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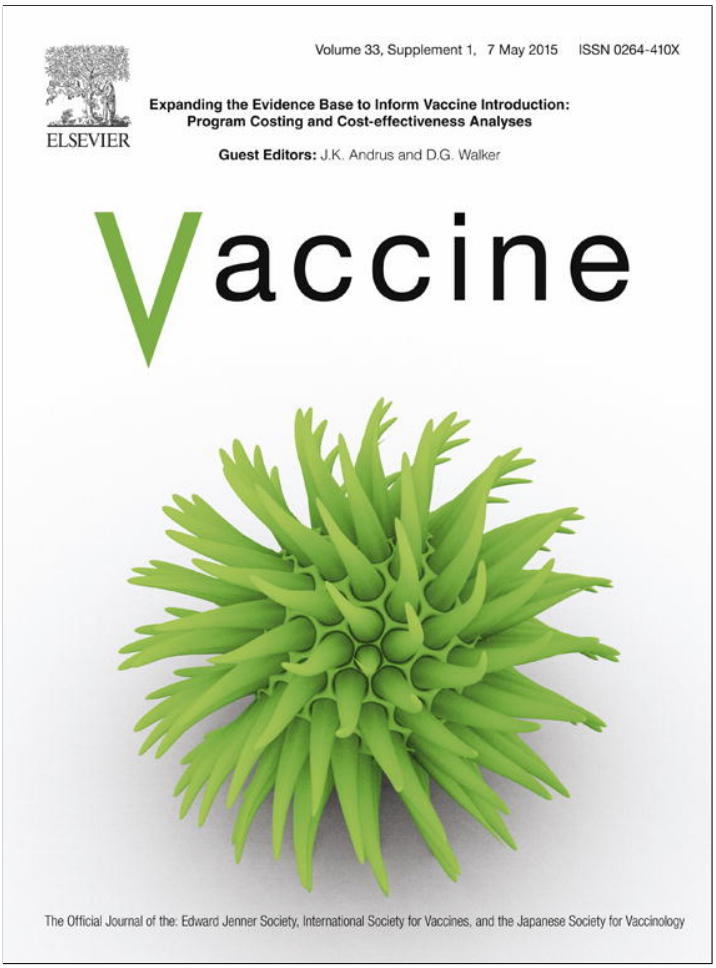

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Expanding the Evidence Base to Inform Vaccine Introduction: Program Costing and Cost-effectiveness Analyses

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The studies published in this supplement feature work conducted by prominent researchers and investigators in the field of vaccine economics, PAHO/WHO Member States, other WHO Member States outside of PAHO that received training from the PAHO ProVac Initiative and other partners that comprise the EPIC (EPI Costing and Financing of Routine Immunization and New Vaccines) group. All this work was made possible by financial support from the Bill and Melinda Gates Foundation. The views expressed herein are those of the authors and do not necessarily reflect the official policy or position of the Bill and Melinda Gates Foundation or the Pan American Health Organization.

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Publication information: Vaccine (ISSN 0264-410X). For 2015, volume 33 (52 issues) is scheduled for publication. Subscription prices are available upon request from the Publisher or from the Elsevier Customer Service Department nearest you or from this journal's website (http://www.elsevier.com/locate/vaccine). Further information is available on this journal and other Elsevier products through Elsevier's website: (http://www.elsevier.com). Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis. Issues are sent by standard mail (surface within Europe, air delivery outside Europe). Priority rates are available upon request. Claims for missing issues should be made within six months of the date of dispatch.

USA mailing notice: *Vaccine* (ISSN 0264-410X) is published 52 times a year by Elsevier Ltd. (The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK). Periodicals postage paid at Jamaica, NY 11431 and additional mailing offices. USA POSTMASTER: Send change of address to *Vaccine*, Elsevier Customer Service Department, 3251 Riverport Lane, Maryland Heights, MO 63043, USA. AIRFREIGHT AND MAILING in USA by Air Business Ltd., c/o Worldnet Shipping Inc., 156-15, 146th Avenue, 2nd Floor, Jamaica, NY 11434, USA.

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Printed by Henry Ling Ltd, The Dorset Press, Dorchester, UK

Vaccine

Volume 33 Supplement 1 2015
VACCINE 33 (Suppl 1) S1/A1–S1/A254 ISSN 0264-410X www.elsevier.com/locate/vaccine

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Vaccine 33S (2015) A1

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Foreword

Strong national immunization programs in the Americas have paved the way for the elimination of vaccine preventable diseases, while simultaneously strengthening the capacity and infrastructure of national health systems. Globally, vaccines together with other public health interventions have also greatly reduced childhood mortality. In an effort to sustain these advances, the World Health Assembly approved the Global Vaccine Action Plan (2010–2020), which aims to ensure the delivery of vaccines to all peoples. While this aspirational goal may be more easily achievable in the Americas, other Regions continue to struggle to improve vaccination coverage and overall health systems strengthening in support of immunization services. It is evident that robust, transparent decision-making structures and processes are essential to aid policymakers in reaching the best possible decisions with respect to new vaccine adoption and other associated technical issues.

Over the last ten years, the Pan American Health Organization's ProVac Initiative has worked with countries to promote the development and use of evidence as the basis for decision-making regarding new vaccine introduction. In weighing introduction decisions, the ProVac Initiative has collaborated with national multidisciplinary teams from Ministries of Health to develop needed information on the cost-effectiveness and cost-benefit that new vaccines could offer. More recently, ProVac has supported countries to acquire a better understanding of the investment requirements as well as the running costs to support sustainable vaccine introduction, over the short, medium and long-term.

To celebrate ProVac's ten-year anniversary, this supplement features country-led research to support real-time policymaking, including, inter alia, cost-effectiveness, program costing, and analyses of financial flows. It highlights the work undertaken by partner organizations collaborating in the ProVac International Working Group, as well as the Bill and Melinda Gates Foundation-led Expanded Program on Immunization Costing and Financing (EPIC) project. Leading researchers and policymakers have contributed perspectives on the challenges and opportunities in this area.

We are very pleased to publish this second supplement with *Vaccine* on useful data for policymakers and program managers in the immunization community.

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http://dx.doi.org/10.1016/j.vaccine.2015.02.001
0264-410X/© 2015 Published by Elsevier Ltd.

Vaccine 33S (2015) A2–A3

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Perspectives on expanding the evidence base to inform vaccine introduction: Program costing and cost-effectiveness analyses

Over the past decade, the Pan American Health Organization's (PAHO) ProVac Initiative has worked with countries to promote the development and use of evidence for immunization policymaking [1]. This supplement features examples of ProVac's country-led research and other partner efforts in this area with an emphasis on analyses of cost-effectiveness, program costs and financial flows. The findings from these studies represent one important outcome of a broader objective to strengthen and institutionalize national capacity to generate, assess, interpret and use local data in the decision making process. Achieving this broader objective has always been a guiding principle of ProVac's work [2].

Due to the success of ProVac, PAHO has received numerous requests for similar support from countries outside of the Americas Region. Therefore, in 2011, the ProVac International Working Group was formed with the aim of transferring the ProVac Initiative's methods and tools to other WHO regions [3]. The International Working Group includes the Agence de Médicine Préventive (AMP), the United States' Centers for Disease Control and Prevention (CDC), the Program for Appropriate Technologies in Health (PATH), PAHO, the Sabin Vaccine Institute, and World Health Organization headquarters and its regional offices for Africa (AFRO), Eastern Mediterranean (EMRO) and Europe (EURO). A total of 17 countries in these three regions received training from the International Working Group over a two year period resulting in nine cost-effectiveness studies [3].

The impact of ProVac's mission to increase national capacity to make evidence-based immunization policy is difficult to quantify. However, cost-effectiveness analyses in this supplement demonstrate the quality of evidence a national team can produce for their own decision making use when given access to flexible tools and training. Nine studies were supported through the ProVac IWG platform and results from Albania, Croatia, Egypt, Georgia, Iran, Kenya, Senegal and Uganda are featured in this supplement [4–10]. Another six studies featured in this supplement were from countries in the PAHO Region, including Argentina, Belize, Brazil, Honduras, Paraguay and Peru [11–16]. They were all led by national health professionals and stakeholders.

These analyses provide an important update to the cost-effectiveness literature on new vaccines from a diverse set of country contexts. With the exception of one cost-effectiveness analysis developed in a high-income country setting (Croatia) with no access to affordable vaccine prices, the findings from the cost-effectiveness research support the previously published evidence that pneumococcal conjugate, rotavirus and HPV vaccines represent good value for money, where disease burden is substantial and/or treatment costs are relatively high and the vaccines can be procured at an affordable price. All primary results from these analyses were subjected to sensitivity analyses to examine the robustness of the findings to changes in the values of key inputs and assumptions. For example, these analyses often considered vaccine price trends over time and other technical or programmatic uncertainties (i.e. booster doses, herd immunity and delivery strategies). Since many countries that received support from the ProVac IWG will graduate from Gavi subsidies in the coming years, these additional analyses were useful to explore the impact of price changes in the cost-effectiveness results. While the results are subject to uncertainty, the conclusions were stable.

The supplement also highlights a recent multi-country study on the costs and financing of routine immunization and new vaccines (EPIC) [17]. The EPIC study included six countries: Benin, Ghana, Honduras, Moldova, Uganda and Zambia. This work represents the first systematic evaluation of costs in countries with a baseline of routine immunization, while also estimating the incremental cost of new vaccines (pneumococcal and rotavirus) to the routine system [18].

The EPIC studies are unique in both the breadth and depth of the data collected from over 300 primary health care facilities across the six countries. An important outcome of this work was the development and use of a Common Approach to costing [17], as well as the creation of a community of practice around cost and financial analysis of immunization. The costing studies allow us to not only describe the range of total and unit costs of routine immunization (RI) [18–21], but also to evaluate more systematically the determinants of costs and productivity [22,23]. Finally, each country team undertook a financial mapping of the total resources available for routine immunization by source [24,25]. This work will be used to improve budgeting and planning of national immunization programs. The evidence will also be used to inform advocacy aimed at greater domestic resource mobilization.

Finally, leading researchers, decision makers and donors comment on the development and use of the data featured in this supplement from their perspective. The four commentaries highlight the following themes (1) the potential role of cost-effectiveness analysis in price negotiation; (2) the continued need for models and methodological approaches that can be adapted for use in low resource policy settings; and (3) the juxtaposition of supporting country-level decision making in the context of donor priority setting [26–29]. From Thailand's Health Intervention and Technology Assessment Program's (HITAP) perspective, cost-effectiveness data is critical in price negotiation for countries,

http://dx.doi.org/10.1016/j.vaccine.2015.01.001
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like Thailand, that do not have access to donor subsidies or innovative financing mechanisms [26]. We see how the HITAP approach could easily be adapted in a context like Croatia, where PCV was found to be not cost-effective at the current assumed price of US$30-35 [8]. Decision support systems as a fundamental underpinning to making better choices with public monies are described from a decision scientist's perspective in 'The ProVac Initiative and evolving decision'support' [27]. As we've seen with the implementation of ProVac, these systems require a long-term investment and commitment to building institutions that require and support an evidence-based approach. We have only just begun with immunization programs but the lessons from the ProVac Initiative may serve to guide future work in promoting health technology assessment across the health sector. Lastly, Gavi and the immunization program manager from Honduras, a Gavi-graduating country, share perspectives on the increasing importance of priority-setting at country level for effective immunization policy and the support that Gavi-eligible countries may need today in order to enter into the near-term graduation from Gavi support [28,29]. All commentaries combined offer an insight into developing a forward thinking approach to the use of evidence for immunization decision making.

We hope the reader finds that this collection of articles provides useful insight into the work required to help countries strengthen their capacity to make evidence-based policy decisions. Accelerating national policy development on new vaccines adoption, together with rapid deployment of vaccines when appropriate, will contribute to saving more lives more quickly.

Disclaimer

The studies published herein include but are not limited to work conducted by the Pan American Health Organization's ProVac Initiative, the ProVac International Working Group and the EPIC study with financial support from the Bill and Melinda Gates Foundation (grant no. OPP50788). The views expressed in each article are those of the authors alone and do not necessarily reflect the official policy or position of the Bill and Melinda Gates Foundation or the Pan American Health Organization.

Conflict of interest statement

None declared.

Acknowledgments

We greatly appreciate the coordination and support provided by Gabriela Felix and Cara Janusz of the Pan American Health Organization.

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Vaccine 33S (2015) A4–A5

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/vaccine

Commentary

Gavi's balancing act: Accelerating access to vaccines while ensuring robust national decision-making for sustainable programmes

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Since its creation in 2000, Gavi, the Vaccine Alliance has leveraged its public–private structure – bringing together governments, UN agencies, private sector and civil society – to make new and underused vaccines more affordable and accessible to people in lower-income countries. Prior to the creation of Gavi, the world's lowest-income countries endured the greatest burden of vaccine preventable diseases yet had limited access to new vaccines readily available in wealthier countries. For example, in 2000, over 60% of high-income countries were providing Hepatitis B vaccine in their national immunisation programmes. In the same year among low-income countries, where the burden of hepatitis B was highest, less than 10% had introduced this vaccine.

Gavi has an ambitious mission to significantly expand access to a range of new and under-used vaccines over a relatively short period of time. With cost barriers largely removed, lower-income countries have embraced the opportunity to seek support for the introduction of life-saving vaccines. Since the initial Gavi-supported introductions of monovalent Hepatitis B vaccine in 2001, the picture has evolved significantly. Gavi currently offers support for 11 vaccine programmes including human papillomavirus, inactivated polio vaccines, Japanese encephalitis, measles, meningitis A, oral cholera vaccine, pentavalent, pneumococcal conjugate, rubella, rotavirus, and yellow fever. Applications for vaccine support have surged and it is expected there will be more than 280 Gavi-supported vaccine programmes in 71 countries by the end of 2015.

However, beyond the "quick win" of successfully launching a new, heavily subsidised vaccine, effective scale-up and sustained programme implementation require strong political will and long-term investments [1]. Gavi thus has an important responsibility to ensure that decisions to adopt new vaccines are locally owned and rooted in strong commitment that will last beyond the duration of its financial support. A challenge of Gavi's mission is balancing the urgent need to address preventable death and disease with life-saving vaccines that are available today with the need to ensure a robust decision-making process.

In this commentary, we reflect on the evidence-informed global-level process that Gavi uses to select vaccines that meet the public health needs of low income countries, as well as translation of these globally-identified priorities into sustainable programmes rooted in locally-owned introduction decisions.

Gavi uses a demand-driven funding model and offers support for a variety of vaccines. Support is awarded in response to countries' requests through a centrally managed application process. Before countries are invited to apply for vaccine support, Gavi determines which vaccines to make available through the development of a Vaccine Investment Strategy (VIS). This global strategy is renewed every five years to identify new priority vaccines for inclusion in Gavi's portfolio. The first VIS was produced in 2008 and the second in 2013. The VIS process brings together disease experts, implementing country representatives, manufacturers and other Vaccine Alliance partners to inform a comprehensive comparative analysis of potential vaccine opportunities for countries meeting Gavi's eligibility requirements.[1] A key consideration is whether Gavi has a comparative advantage in helping to overcome barriers to accessing a vaccine of public health importance. All Gavi countries share a limited ability to pay for vaccines as they have relatively low gross national incomes per capita (GNI p.c.) and therefore limited resources available for immunisation expenditures. Beyond this common barrier, Gavi countries have diverse needs. The VIS aims to identify vaccine investments with significant benefits for a significant number of countries (e.g. pneumococcal conjugate and rotavirus vaccines), or for which Gavi's support fills a unique gap (e.g. support for the oral cholera vaccine stockpile in part to incentivize global supply). It excludes vaccines with lower value-for-money based on the projected health impact and cost of the vaccine, and considers local implementation feasibility as well as global factors such as Gavi's ability to influence pricing. The 2008 VIS identified human papilloma virus (HPV), rubella, Japanese encephalitis and typhoid vaccines to be added to the portfolio of Gavi supported vaccines. The 2013 VIS identified expanded support for yellow fever mass preventive campaigns and investment in the global stockpile of cholera vaccines as new priorities. The Gavi Board deferred a decision on a malaria vaccine which was still undergoing clinical trials and will consider the case for this vaccine

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[1] Gavi's current (2014) eligibility threshold is set at a Gross National Income level of $1580 this is from 2015per capita (according to World Bank data for the latest available year.

http://dx.doi.org/10.1016/j.vaccine.2014.12.051
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if and when the lead candidate is licensed and recommended for use by WHO in late 2015.

Gavi's VIS approach serves as an initial global filter to prioritise vaccines for Gavi support. However, national governments still have to decide whether and when introduction of a vaccine from the Gavi 'menu' is justified. Essential to Gavi's operational model is a country-driven approach, whereby national governments make decisions to introduce a vaccine and then request support from Gavi. Gavi supports partners to develop normative guidance and provide technical assistance to countries on evidence generation and synthesis, including economic evidence, to help inform national decisions on new vaccine introduction. For example, Gavi's Hib Initiative supported the Hib-Rota-PCV decision support model 'TRIVAC', utilised in the cost effectiveness studies reported in this issue [2,3] as well as studies published elsewhere [4,5].

Gavi also recognises the need to strengthen local institutions at the heart of the decision-making process and supports Vaccine Alliance partners and SIVAC (Supporting National Independent Immunization and Vaccine Advisory Committees) to provide technical and coordination assistance to national structures, such as Inter-Agency Coordinating Committees (ICCs) and National Immunization Technical Advisory Groups (NITAGs),[2] to inform and facilitate government decisions and policy making related to national immunisation programmes.

In addition, Gavi's application process aims to reinforce principles of transparent, government driven and partner supported decision-making for new vaccine adoption. For example, new vaccine applications must be aligned with comprehensive Multi-Year Plans for immunisation (cMYPs), demonstrate the government's commitment to meet mandatory co-financing requirements and be rooted in Health Sector Strategic Plans. Countries with a NITAG or other relevant technical advisory body are required to report on their decision-making process and recommendation for the new vaccine introduction. Finally, all applications submitted to Gavi must be approved by an ICC or Health Sector Coordinating Committee (where relevant), signifying agreement by in-country partners and be signed by the national ministers of health and finance.

The Gavi model requires governments to share in the cost of Gavi-supported vaccines with the aim of fostering greater programme ownership and financial sustainability. From the time of introduction, governments are required to co-finance a small portion of the vaccine cost. As countries reach higher income levels this share goes up while Gavi's support decreases. Upon crossing the eligibility threshold, governments enter a five-year transition during which they rapidly scale up their contributions to take on the full financing of Gavi supported vaccines.

As countries expand their national immunisation programmes by adding more vaccines, governments need to consider the increasing budgetary impact of cumulative co-financing obligations and the anticipated cost of vaccines when they are no longer subsidised by Gavi. In addition, a clear understanding of the non-vaccine operational costs at various levels of immunisation programmes – particularly the facility level – is required. Several studies in this issue provide insight to improve the knowledge base of comprehensive immunisation programme costing while highlighting the importance of more precise estimates for accurate budgeting and resource mobilisation [6–9].

To inform considerations of the future cost of vaccines, Gavi is scaling up efforts to increase country awareness of the varying market prices and cost profiles of Gavi-supported vaccines, both at the time of new vaccine applications and as countries approach the transition to self-financing. Likewise, additional support to create and strengthen national advisory bodies such as NITAGs is being provided.

While all of these efforts are important to ensure that vaccine introduction decisions are evidence-based and country-owned, Gavi recognises that more needs to be done to engage local stakeholders and strengthen capacity for decision-making in the context of rapidly expanding immunisation programmes. The Pan American Health Organization's (PAHO) ProVac initiative has played a path-finding role to improve local capacity to carry out economic evaluations and Gavi welcomes efforts to leverage lessons and expertise of institutions such as Agence de Medicine Preventive, PATH, the Sabin Vaccine Institute and the US Centers for Disease Control and Prevention for expanded support to other regions of the world. Lessons from middle and lower-middle income countries on the use of health technology assessments to prioritise health investments will also help to inform areas of potential future collaboration and South-to-South exchanges of experiences.

Strengthened country capacity to access and evaluate evidence and to independently decide to introduce a vaccine – or not – is paramount to country-owned immunisation programmes. With ever-increasing competing priorities in the health sector, value-for-money considerations to inform vaccine introduction decisions are more important than ever. This need will likely be accentuated with vaccines in the pipeline targeting more localised disease burden or with lower vaccine effectiveness, for example future vaccines against malaria and dengue. The unprecedented increase in access to new vaccines in lower-income countries over the past decade necessitates increased support for national-level decision-making processes to better ensure sustainability of expanding immunisation programmes. This will be a major focus of Gavi's next strategic period 2016-2020.

Conflict of interest

The authors have no conflict of interest.

The content of this article represents the personal views of the authors and so does not reflect the official position of the GAVI Alliance.

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Vaccine 33S (2015) A6–A7

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Commentary

Perspectives on the development and use of economic evidence for immunization decision-making in a developing country

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Honduras first established the Expanded Program on Immunization (EPI) nearly 40 years ago and it rapidly became a priority disease prevention program. In the early years of the program, five vaccines were offered in the basic national schedule (Bacillus Calmette-Guérin [BCG], polio, diphtheria–pertussis–tetanus [DPT], measles and tetanus toxoid). Beginning in 1997, the Secretary of Health initiated an accelerated vaccine introduction process, transitioning from the traditional EPI vaccine schedule to an expanded schedule including new and underutilized vaccines. Today, the national immunization program in Honduras includes a schedule of fifteen vaccines.

1. Evidence generation and decision-making on new vaccines

During the period of 1979 to 2003, decisions on the introduction of vaccines followed recommendations from the Pan American Health Organization (PAHO) and the World Health Organization (WHO), taking into consideration data on the local epidemiological profile and burden of disease. In parallel to the decision-making process, Honduras' Secretariat of Health (SoH) prepared financial sustainability plans in the context of the EPI's five-year strategic plan and annual work plans to identify resource needs and potential financing sources. At the time, these instruments were sufficient for decision-making and national priority setting regarding the adoption of additional vaccines.

With the arrival of new, more expensive vaccines, Honduras sought to formalize the decision-making process with a more systematic technical consultation at the national level. To this end, the National Advisory Committee on Immunization (NACI) was created in 1999 [1]. This Committee has played an important role in the introduction of new vaccines. Importantly, it provides recommendations to the SoH as inputs for political discussions about the sustainability and feasibility of adoption of these vaccines that often are many times more expensive than the traditional childhood vaccines. To date, Honduras has introduced new vaccines such as the rotavirus vaccine (RV) and the pneumococcal conjugate vaccine (PCV).

For each of these new vaccine introduction decisions, the NACI and SoH have considered a number of evidence inputs to guide the decision-making process. Since 2004, the NACI and SoH systematically consider technical, political and programmatic aspects regarding new vaccine introduction in Honduras. Of these, the most relevant are political priority; burden of disease; availability of safe, high-quality and effective vaccines; as well as the economic and financial sustainability analyses of vaccine introduction to the national schedule. In the case of the rotavirus vaccine, the private sector had developed an economic evaluation in 2006 that was considered by the health authorities. In following years, Honduras sought to generate evidence from within the SoH to inform decisions and therefore the EPI requested technical cooperation from PAHO's ProVac Initiative to develop cost-effectiveness studies on new vaccines. Evaluations of the PCV and HPV vaccines were conducted in 2009 and 2013, respectively. Support from the ProVac Initiative has been crucial for the development of locally derived evidence providing a credible input into decision making for the Honduran SoH. The evidence on cost-effectiveness of PCV vaccine was used in the 2011 decision-making process. The study on HPV in 2013, concluding that vaccine introduction would represent a highly cost-effective intervention to prevent cervical cancer in Honduras, is currently being used in the national decision making process [2,3].

2. Opportunities and challenges to ensure the sustainable introduction of new vaccines

The Honduran government has a high-level commitment to guarantee free, universal vaccination for its entire population throughout the life cycle, as reflected in its legislation and state management processes. Since the creation of the EPI, the SoH has financed the purchase of vaccines and safe injection supplies, ensuring sustainable supply at the national level. This budget line has been supported since 1998 with the establishment of the "Act to Purchase Vaccines through the PAHO Revolving Fund" [4]. Today, the purchase of vaccines continues to be a protected budget line by the Finance Secretariat (FS) and the SoH.

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http://dx.doi.org/10.1016/j.vaccine.2014.12.048
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Honduras has been eligible for support from Gavi, the Vaccine Alliance, since 2000 due to its status as a low-income country based on the GNI per capita. The country first received financial support in 2003, as well as significant subsidies for introducing the rotavirus vaccine in 2008 and the pneumococcal vaccine in 2010. The window of opportunity from Gavi for new vaccine support has accelerated the country's ability to incorporate new vaccines into the national schedule. The World Bank recently reclassified Honduras as a lower middle income country [5]. Because of this reclassification, in 2012, the country began a gradual process of graduation from Gavi support. As a result, in 2016, the Government of Honduras will assume 100% of the costs associated with new vaccine introduction and no will longer qualify for other windows of opportunity from Gavi. The country has secured gradual incremental government co-financing for both vaccines (RV and PCV) as of 2012. Ongoing advocacy from SoH with the FS and the existing legal framework have been critical in this process.

However, the country currently faces challenges related to the cost of vaccine procurement and operational activities for the introduction of new vaccines. To meet the challenge of securing sufficient financing to fund operational activities, the legislative authorities passed the "Vaccine Act of the Republic of Honduras" in January 2014 [6]. It is expected that the law will ensure the sustainability of traditional, new and underutilized vaccines. This law went into effect on 26 March 2014 and its regulation is in process, helping to ensure implementation. The EPI conducted a study in 2013 to determine the costs of immunization in the country and to map the available funding sources [7,8]. These data will contribute to developing strategic plans and resource mobilization activities with the aim of achieving 100% of domestic financing for essential EPI needs.

Recently, SoH authorities announced a decision to introduce HPV in the national schedule to target adolescent girls. Introduction plans are underway. Despite the announcement of the technical decision, analyses regarding budget impact and available fiscal face for expansion of the existing routine program are still a key criterion for implementing the vaccine because of the current fiscal crisis facing the country, which is a clear challenge to sustainability. The FS is actively involved in identifying financing sources to support the introduction of HPV. National experience demonstrates that the accelerated introduction of new and underutilized vaccines requires the availability of many different kinds of evidence (e.g. cost-effectiveness, disease burden) as wells as different instruments (e.g. vaccine legislation) to ensure its sustainability. It also requires a clear vision of how to address challenges brought on by a fiscal crisis and ways to ensure the sustainability of the entire program.

Going forward, advocacy at the highest political level will be required in order to expand the fiscal space for immunizations. Leadership across the health sector is needed to identify and allocate resources effectively from disparate revenue sources within the health system. Civil society could play a key participatory role in this dialogue, in the context of prioritizing investment for high-impact health interventions such as immunization towards universal health access and coverage strategies.

3. Conclusion

The financial sustainability of new vaccine introduction remains a challenge in the face of a fiscal crisis, where new vaccines have to compete with other health system priorities, even if the vaccine being considered for introduction is expected to contribute to the reduction of the morbidity and mortality of a public health problem. The introduction of new and underutilized vaccines in a developing country as based on the experience of Honduras requires wide-reaching analyses of technical, political and programmatic aspects for decision-making. The economic criterion is essential for decision-making given the high costs of new vaccines. Evidence generation through studies of cost-effectiveness and financial analyses that contribute to introduction sustainability are also required.

Conflict of interest

None declared.

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Vaccine 33S (2015) A8–A10

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Commentary

The ProVac initiative and evolving decision support

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Many of the papers in this supplement give results of cost-effectiveness studies. One of the lessons learned from ProVac has been that the most pressing need, particularly in middle and lower-income countries, is not so much for new methods of capturing ever more elusive forms of cost or benefit, but for building and strengthening the decision support systems (DSS) within which economic analyses are, or should be, embedded. The underlying principle is that supporting decision-making groups with the tools to do their own analyses is better than global or regional one-size-fits-all guidance, or contracting out to consultants. The hope is that in the longer term this approach will benefit public health decision-making more generally. This is very much in line with WHO initiatives following the Mexico Statement in 2005 [1], which included the following: 'health policy, public health, and service delivery should be based on reliable evidence derived from high quality research'. One such initiative is the Evidence Informed Policy Network (EVIPNet [2]) and the tools linked to it such as SUPPORT [3]. As well as tools, country-level structures such as NITAGs [4], IICCs [5] and NRAs [6] have emerged which provide the fora for collaborative and evidence-based decision-making.

The ProVac contribution to this has many of the characteristics of a decision support system (DSS) [7]. It provides a structure for gathering and evaluating data; and it provides models or analytic techniques which are interactive and easy to use by non-computer people, and can respond flexibly to changes in the decision-making environment.

The database element provides country-specific data, much of it quality graded, from a variety of public sources on demography, disease burden, GDP per capita, etc.; data on health services costs, health service utilisation, vaccine coverage, vaccine effectiveness, and vaccine programme costs; a facility for producing tables and graphs; online training materials, guidelines and methods for data collection; and model documentation. Users are encouraged to review and understand the shortcomings of the data and correct errors before using them for modelling. They can search interactively and create tables by filtering on the basis of data quality and geography, but cannot specify and run completely new analyses of raw data.

ProVac also includes other elements that are not always recognised as parts of a DSS, but have proved critical. One is a network of researchers in universities in the region who located, compiled and assessed the quality of local data, and supplied it to the database. The other is an infrastructure of facilitators, training materials and workshops. These are described in more detail elsewhere in this supplement [8,9]. Introductory workshops had 100+ participants, and aimed show people working in the field how they might use their own data on e.g. vaccine coverage and disease surveillance to support a decision they would trust. These were followed by much smaller workshops in which national teams scrutinised their data and carried out the relevant analyses.

However the focus in this paper is on the modelling. In recent years there has been a great deal of activity in infectious disease modelling, but the approach and intent of much of this might be characterised as 'scientific' (about how the world is) rather than decision-oriented (about what we ought to do). There have also been some striking developments in the field of decision support modelling, but the amount of work on vaccine modelling from a decision support perspective has been limited.

Table 1 (adapted from Sanderson and Gruen [10]) suggests some differences between scientific and decision support modelling, which have a number of implications:

- *Estimation vs preference/valuation*. There is an important distinction between estimation ('expert' judgement made necessary by gaps in knowledge, either about the nature of relationships between variables or about the values of model parameters) and valuation (the relative importance of, or preference given to, different types of benefit or criteria of success). In strictly scientific models estimation is generally something to be avoided, by e.g. limiting the scope of the model, and valuation not an issue. In decision-making on the other hand, estimation may be inevitable because the scope of the problem is defined by the decision to be made, and valuation is also inevitable unless one option is best for all outcomes. The only question is whether preferences should be explicit elements of the model, or kept outside it and dealt with less formally. Either way, such judgements should be made not by modellers or technical experts, but by whoever has the authority to make the decision.
- *Consensus*. In general the assumption in scientific modelling is that there is only one 'true' answer to an estimation question. In high-level decision-making by contrast, there are usually several

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http://dx.doi.org/10.1016/j.vaccine.2014.12.049
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Table 1
Scientific and decision-driven modelling.

	Scientific	Decision-driven
Starting point	What can we find out about X? (e.g. values of transmission parameters)	What should be done about X? (e.g. should we add this vaccine to the EPI?)
Task	Fit model/predict/learn/revise	Explore policy options and scenarios
Inputs	Scientific evidence Assumptions/hypotheses	Scientific evidence Estimates, preferences/values, consensus, attitudes to risk
Output	Understanding of causal chains Inconsistencies in the data Plausibility of hypotheses Important gaps in knowledge	Pros and cons of options for different outcomes Robustness of choices to scenarios/preferences Important gaps in knowledge

decision makers or stake-holders involved, often with very different backgrounds and interests. Differences of opinion about what outcomes are important are to be expected. There may also be differences of opinion or confusion about the nature of the causal chains between decision and outcome, and about what options are considered acceptable. It is commonly assumed that decision-makers want to maximise the chances of a good outcome, but many would rather minimise the chances of a bad outcome. All this makes for an insecure foundation for modelling. One response has been the development of 'problem structuring' methods [11] which seek to clarify preferences, options and causal chains, thus fostering mutual understanding and ideally, consensus. However in the case of ProVac there has been little call for this. The questions and options have been clear enough: whether or when to introduce a new vaccine. The decision makers have tended to share a broad concern for reducing the burden of disease, although some have combined this with a concern for efficient use of resources and some, for equity. The nature of the causal links is also fairly clear in qualitative terms (eg vaccines prevent disease) if much less so in quantitative terms (eg the amount of disease prevented).

- *Scenarios & risk*. Uncertainty in decision models may arise not just from imprecision of data on observable phenomena, but also because outcomes depend on events yet to come, including decisions by other 'players'. For example will there be effective new treatments for vaccine preventable diseases, new patterns of transmission through pathogen mutation, and/or sharp shifts in vaccine prices? Exploring the implications of different scenarios or 'futures' is thus an important role for decision-support modelling.
- *Interactive/responsive*. With this reliance on estimates and suspect data, uncertain futures, and differences of viewpoint among decision-makers about valuations and risk, claims that a decision-support model gives 'the right answer' are difficult to justify. A more useful criterion is whether a model is good enough to answer 'what if?' questions, in which outcomes are predicted conditional on the available data plus different sets of assumptions. Given the often large number of possible scenarios, interactive use of models in exploratory or search mode is much more instructive and engaging for decision makers than relying on reported or published analyses. One could say that the point lies more in the process than in the answer. For this purpose, web-based models are increasingly popular, but the ProVac approach has been to use Excel-based models in facilitated workshops. These avoid a tendency on the part of users to plunge straight into the model taking unreliable data on trust, and allow facilitators to provide support tailored to individual needs. They also provide model developers with valuable feedback on their efforts.
- *Levels of complexity*. To begin with the ProVac models were quite simple, but learning on both sides has led to new features being added as the need for them became clear. Excel is an environment that is familiar to most decision makers, and those with the inclination can dig around and scrutinise the formulae. However users vary from country to country, and between types of committee or stakeholders (NITAGs, ministers of health/finance, parliament, etc.), in terms of their starting knowledge and interest in learning about epidemiology, economics and modelling. Ideally decision-support models would be accessible at a variety of levels of user expertise and engagement.

This suggests that decision-support models need all the attributes of scientific models and then some more. In practice the need to be user-friendly and interactive may mean compromises in scientific validity. The key shortcoming of the TriVac [12] models from the scientific point of view is that they are not dynamic. Transmission of infection is not modelled endogenously, and risk does not depend explicitly on contemporary incidence. The problem is that some of the parameters in dynamic models are generally unobservable, so searches have to be made for sets of parameter values that allow the model to fit observed data. Sometimes there are thousands of combinations of parameter values that provide a reasonable fit [13]. In other circumstances it may be hard to find any. This means that running models of this kind interactively tends to be cumbersome at best. The way forward seems to be to develop scientific and decision-support models in parallel, and to use results from scientific models to validate and improve decision-support models. For example CerviVac drew on results from a much more complex model [14] used as a look-up table.

Next steps for TriVac. The plan is to develop a new model (UniVac) that can be used at a number of levels. Starting at the most simple, it will provide a variety of options (e.g. delayed vaccination, waning vaccine efficacy, herd immunity, serotype replacement, and differential coverage in different risk groups), which users can select where relevant and/or as they become more familiar with the model. Within this, one option will be a micro-simulation transmission model behind the same interface. This will provide much more flexibility but at the cost of responsiveness, and we expect limited use of this facility by decision-making teams. However it will provide a standard for testing and validation of simpler versions, and a tool for exploring what is lost by different types of model simplification.

Going further: synthesis. As the use of what-if models becomes more sophisticated and numbers of outcome variables and scenario/sensitivity analyses proliferate, making sense of the sheer numbers of model results can become a challenge. A number of tools have been developed to help with this. Multiple criteria decision methods can help with option shortlisting and selection where there are many criteria, especially when there are many options as well. Decision theory and game theory models may help, depending on decision-makers' attitudes to risk and their willingness to attach probabilities to scenarios, and utilities to outcomes. So far

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we have not felt it appropriate to include these in ProVac but if a taste for rigour takes root among at least some members of the decision-making teams, the time for such methods will come.

Conflict of interest

The author has no conflicts of interest to declare.

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Vaccine 33S (2015) A11–A12

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Discussion

A learning experience from price negotiations for vaccines

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1. Context

Vaccines are regarded as one of the most successful health measures to date and there is no doubt that vaccination is ideal for health decision makers, health practitioners, and the public because it is a preventive measure that is in most cases – once provided – effective in the long-term. However, although there have been a number of newly developed vaccines available in the market over the past few decades, many of them have not been widely taken up, especially in low- and middle-income countries (LMICs), which comprise approximately 80% of the world population. Many scholars have found that the affordability of vaccination is among other important constraining factors, including a lack of local policy-relevant information for making decisions and political prioritization of vaccination or vaccine-preventable disease [1].

As a result, the GAVI Alliance was established to ensure equitable access to new and underused vaccines by negotiating for significantly lower prices compared to the market price. However, these negotiated prices are provided only to eligible GAVI countries. In addition, the UNICEF Supply Division introduced a vaccine procurement program to make some vaccines available for GAVI ineligible countries at a relatively low cost by tapping into economies of scale through a call for tender. However, some vaccines, such as PCV and rotavirus, are still unaffordable for some countries, which result in relatively low uptake through UNICEF. Similarly, the Pan American Health Organization's (PAHO) Revolving Fund negotiates vaccine prices for countries in Latin America [2]. While these initiatives are regarded as effective methods for price negotiation, limitations persist; for example, countries with different levels of economies, such as Haiti and Chile, pay the same vaccine costs under this regional price negotiation.

For countries that are unable to procure vaccines at affordable prices through the above mentioned mechanisms and instead anticipate price drops in vaccines over time, evidence indicates that price drops are usually less than expected [3]. This leads to unnecessary delays in vaccine adoption by countries. As a result, vaccine price negotiation is very important, although vaccine price negotiation principles and processes at the country level are either not practiced or well documented in literature. This paper aims to discuss the experiences of medicine price negotiations in Thailand with the aspiration of adapting these experiences to vaccine price negotiation.

2. The experience of medicine price negotiation in Thailand

The Thai government has systematically established price negotiation mechanisms for medicines, which is recognized as a successful example in an LMIC. The government can introduce previously unaffordable medicines into public programs from the process and make its universal healthcare coverage scheme sustainable. The success of this process can be attributed to three core principles:

1. Establishing reliable and manageable process and mechanism.

   Price negotiation is often seen by the public as a mysterious and endless process that industry uses to lobby decision makers to introduce new technologies. Therefore, it is important to make the price negotiation process trustworthy and manageable by being transparent about who is responsible for the negotiation, how to manage potential conflicts of interest, and what the timeline is for each step of the process. For example, the Thai government established the Working Group on Price Negotiation, comprising multiple stakeholders such as representatives from health insurance agencies, academics, and health professionals, under the national body responsible for designing the pharmaceutical reimbursement list in Thailand [4]. The working group members need to declare conflicts of interest and publicly document the process and information used.

   The working group begins the process of price negotiation once the national body has expressed interest in a particular medicine without yet committing to include the medicine in the reimbursement list. This makes price negotiation more meaningful and effective because industry is aware that the government has not yet decided on inclusion of the particular medicine. This is contrary to common practice in many countries, which conduct price negotiations after the decision has already

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http://dx.doi.org/10.1016/j.vaccine.2014.12.050
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Box 1: Experience of using evidence to lower the price of HPV vaccine in Thailand.

In 2007, when two companies were applying for Human papillomavirus vaccine (HPV) licensing in Thailand, the Thai government knew that the vaccine could have a potential role to reduce the high burden of cervical cancer. The Health Intervention and Technology Assessment Program (HITAP) was requested to conduct an economic evaluation and budget impact analysis in order to inform the government about the introduction of the vaccine as part of public health programs in Thailand. The findings were revealed in 2009, showing that at the price of US$450 per course (three doses), HPV does not represent good value for money for public investment. The report indicated that the price of the vaccine needed to be reduced by approximately 60% in order for the vaccine to become cost-effective at the threshold of 1 Gross Domestic Product/capita/Quality-adjusted Life Year gained [5]. The results were made publicly available and the government decided not to include the vaccine, rather emphasizing cervical cancer screening (a comparator to the vaccine in this study) as a preventive measure. The two companies examined the report and agreed with the findings. Three months later, the companies reduced the price of the vaccine as per the recommendation of the report [6]. Although the government still has not included the vaccine in the public program as of 2014 due to high budget implications, Thai households benefited from the significant price reduction in the private market, from US$450 to US$200 per course. This illustrates how evidence can persuade the private sector to reconsider price strategies of vaccines in a country.

been made to adopt a particular medicine, giving industry the advantage.

2. Making evidence-based price negotiation.

   Although many people recognize price negotiation as an art rather than a science, the Thai experience suggests that price negotiation can be more effective with evidence-based negotiations (see example in Box 1). The working group always requests for economic analyses from health technology assessment (HTA) agencies on value for money and potential budget impact of introducing new medicines in the reimbursement list. If the medicine does not represent good value for money, the working group will request for an assessment to be carried out on the price at which the medicine would become good value for money. Although in other countries the reference prices of medicines in similar classes or in other settings are often used, information on value for money and budget impact analyses that incorporate the costs and benefits of introducing new medicines in comparison to other alternatives as well as the size of the problem signify whether the medicine is necessary and affordable. Using this information ensures that the working group negotiates for medicines that are conclusively needed by the population.

3. Creating incentives for industry.

   While the above two principles may seem stringent, it is necessary to recognize the importance of industry's innovations and productions for health systems. Therefore, in negotiating prices it is critical to create incentives to lower prices as well as ensure the sustainability of industry. Thailand has created incentives by committing to procuring large amounts of products so that the company can still make profits from lower price margins and increased quantity of products sold. This issue has been taken very seriously by the Thai government in introducing and adopting a "one choice" policy for medicine negotiations, which means that the winner of the request for tender is entitled to providing medicines for all public health providers.

3. Conclusion and challenges

The three principles mentioned above are likely to be applicable for vaccine price negotiation, although it has some challenges. For example, the market for newly developed vaccines is more likely to be a monopoly or oligopoly compared to the medicines market due to the lack of alternatives. Another challenge is that there are fewer available vaccines compared to medicines, resulting in mechanisms that are put in place that are not used often; therefore, price negotiation for vaccines may need to be part of medicines price negotiation. The difficulty is that vaccines and medicines are different in many ways, including the need for special supply chain and logistics for vaccines that should be included as part of vaccine procurement. Similarly, price negotiation plays a role in vaccine procurement.

As long as affordability is a major factor in making vaccines available in public programs, vaccine price negotiation will become a more important and significant process. As such, it is important to make the price negotiation process more effective than it is currently. Thus, global organizations, both public and private, and academics should provide better support and conduct more research in order to increase scientific evidence as well as document the process for better implementation of vaccine price negotiation.

Acknowledgements

The Health Intervention and Technology Assessment Program (HITAP) is funded by the Thailand Research Fund under the senior research scholar on Health Technology Assessment (RTA5580010), the National Health Security Office, the Health System Research Institute and the Bureau of Health Policy and Strategy, Ministry of Public Health. The findings, interpretations and conclusions expressed in this article do not necessarily reflect the views of the above funding agencies.

HITAP's international unit was established with support from the Thai Health-Global Link Initiative Project (TGLIP), the international Decision Support Initiative (funded by the Bill & Melinda Gates Foundation and the Department for International Development, UK (NICE 849)), and the Rockefeller Foundation to provide technical assistance on health intervention and technology assessment for governments of low- and middle-income countries.

Conflict of interest statement: Yot Teerawattananon is a member of the sub-committee for the development of the National List of Essential Medicines. Nattha Tritasavit has no conflict of interest.

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Vaccine 33S (2015) A21–A27

Contents lists available at ScienceDirect

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ProVac Global Initiative: a vision shaped by ten years of supporting evidence-based policy decisions

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ARTICLE INFO

Keywords:
ProVac Initiative
Cost-effectiveness
Economic evaluation
NITAG
Evidence-based decisions
Vaccines

ABSTRACT

Introduction: The Pan American Health Organization (PAHO) created the ProVac Initiative in 2004 with the goal of strengthening national technical capacity to make evidence-based decisions on new vaccine introduction, focusing on economic evaluations. In view of the 10th anniversary of the ProVac Initiative, this article describes its progress and reflects on lessons learned to guide the next phase.
Methods: We quantified the output of the Initiative's capacity-building efforts and critically assess its progress toward achieving the milestones originally proposed in 2004. Additionally, we reviewed how country studies supported by ProVac have directly informed and strengthened the deliberations around new vaccine introduction.
Results: Since 2004, ProVac has conducted four regional workshops and supported 24 health economic analyses in 15 Latin American and Caribbean countries. Five Regional Centers of Excellence were funded, resulting in six operational research projects and nine publications. Twenty four decisions on new vaccine introductions were supported with ProVac studies. Enduring products include the TRIVAC and CERVIVAC cost-effectiveness models, the COSTVAC program costing model, methodological guides, workshop training materials and the OLIVES on-line data repository. Ten NITAGs were strengthened through ProVac activities.
Discussion: The evidence accumulated suggests that initiatives with emphasis on sustainable training and direct support for countries to generate evidence themselves, can help accelerate the introduction of the most *valuable* new vaccines. International and Regional Networks of Collaborators are necessary to provide technical support and tools to national teams conducting analyses. Timeliness, integration, quality and country ownership of the process are four necessary guiding principles for national economic evaluations to have an impact on policymaking. It would be an asset to have a model that offers different levels of complexity to choose from depending on the vaccine being evaluated, the availability of data, and the time frame of the decision.
Conclusion: Decision support for new vaccine introduction in low- and middle-income countries is critical to maximizing the efficiency and impact of vaccination programs. Global technical cooperation will be required. In the future, PAHO and WHO have an opportunity to expand the reach of the ProVac philosophy, models, and methods to additional regions and countries requiring real-time support. The ProVac Global Initiative is proposed as an effective mechanism to do so.

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1. Introduction

New vaccines prevent disease and save lives, but their high costs raise issues about value for money and affordability in developing countries. Evidence on the costs and benefits of introducing a

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http://dx.doi.org/10.1016/j.vaccine.2014.12.080
0264-410X/© 2015 Published by Elsevier Ltd.

new vaccine is needed to support sustainable and rational decisions about the adoption of vaccines, as well as the subsequent planning to roll out a new vaccine once a decision has been made. The Pan American Health Organization (PAHO) created the ProVac Initiative in 2004 with the goal of strengthening the country-level technical capacity to make evidence-based decisions on new and under-utilized vaccine introduction in Latin America and the Caribbean, with a focus on economic evaluations [1]. (The term ProVac stands for promoting evidence-based decisions about vaccine introductions.)

The ProVac Initiative was formalized in 2006 in response to a PAHO governing body request for increased technical assistance in evaluating the evidence for new vaccine introduction [2]. The initiative has a specific focus on establishing and building the technical capacity of national multi-disciplinary teams to perform economic studies [3]. In 2010, ProVac established a network of Regional Centers of Excellence (CoE), academic institutions that have helped to gather regional evidence and develop methodological guidelines and tools [4]. In 2012, following increased demand for ProVac tools and methods outside of the PAHO Region, an International Working Group (IWG) was formed to pilot-test the implementation of ProVac in the African, Eastern Mediterranean, and European regions. The IWG included PAHO, the World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC), PATH, Agence de Médecine Préventive (AMP), and the Sabin Vaccine Institute (Sabin). Results from this pilot are described in detail elsewhere in this supplement [5]. In 2013, PAHO member states more explicitly stated the need for support in PAHO's Directing Council Resolution CD52.R14. The mandate requests specific support for (1) institutionalization of evidence-based decision-making process for new vaccine introductions, (2) integration of costing and planning performed by the Expanded Program on Immunization (EPI), and (3) expansion of the evidence base beyond cost-effectiveness. The mandate is aligned with the overall PAHO research policy and constitutes a practical and effective first step toward a health-technology assessment (HTA) approach.

The ProVac approach has involved a clearly defined country-led process for developing evidence to inform decisions on the uptake of pneumococcal conjugate, rotavirus, and human papillomavirus (HPV) vaccines that increase ownership and trust in the results by national authorities, as shown in government websites and press releases [6,7]. Technical working group teams led by the ministries of health present the results of nationally owned cost-effectiveness, program-costing, and financing analyses to national authorities to aid technical evaluation of new vaccines and decisions about whether to adopt them. In more than 10 years of working directly with immunization programs, PAHO has learned many lessons about the infrastructure and processes that national immunization programs need for adequate evaluation of quality cost-effectiveness data or other economic data as part of the decision package. These lessons may offer some insight into strengthening a broader, health-sector approach to developing and using economic evaluations for making decisions about adopting health products and technology.

The vision for the ProVac Initiative was described by Andrus and colleagues in 2007 [1]. The operational implementation was described in detail by the ProVac team in 2010 [3]. This article will provide an update to describe the Initiative's progress in its first 10 years of existence and will evaluate this progress to identify best practices and recommendations to guide future efforts.

2. Methods

Since the project's inception, process indicators have been routinely reviewed to monitor and document progress toward achieving the goal of strengthened national capacity around evidence-based decision-making for new vaccines. These process indicators were initially proposed in the project design phase. The planning and monitoring tools describe the proposed links between planned activities, outputs, and results. But they also help track progress, document achievement of milestones, and identify anything that needs to be revised in future phases of the project. Some additional indicators (marked with an asterisk '*') have been developed in the course of implementation.

These process indicators quantify the immediate output of the Initiative's capacity-building efforts, including:

- Number of persons trained through regional workshops.
- Number of national ProVac teams formed.
- Number of ProVac-supported studies completed.
- Number of tools and instruments developed for country use.
- Number of national immunization technical advisory groups (NITAGs) strengthened through the creation or improvement of standard operating procedures (SOPs).
- Number of total analyses conducted by national teams that had already completed a previous analysis*.

This information was compiled and is presented as a descriptive summary in this article. We also critically assess how improving the process and infrastructure for decision-making has resulted in more countries adequately assessing available evidence and acting on it for decisions. Other qualitative information complements this analysis to predict the sustainability of these capacity-building efforts.

3. Results

Since 2004, ProVac has conducted 4 regional workshops that averaged more than 100 participants each and in which more than 20 countries were represented. Workshops have focused on training to develop cost-effectiveness data on Pneumococcal conjugate vaccine (PCV) (2008), rotavirus vaccine (2010), and HPV vaccine (2011), as well as immunization program-costing analyses (2013). Additionally, the ProVac IWG conducted 3 regional workshops outside the PAHO Region in 2012 and 2013. All these workshops have been essential to raising awareness about the use of economic evaluations for decision-making in health and to stimulating demand for national economic evaluations of new vaccines.

Each workshop resulted in several countries requesting technical support to conduct a country-led ProVac study. The few countries that did not request support following a regional workshop already had strong local institutional capacity to develop and implement cost-effectiveness models with the help of national universities, or already had considered the introduction of the vaccine that was discussed at the workshop. The requests were typically received by PAHO vis-a-vis PAHO country offices and the ProVac Initiative then supports the country's ministry of health in convening a multidisciplinary national study team (i.e., the ProVac study team). The national teams coordinate with ProVac, its national immunization technical advisory group, and national immunization program. In total, ProVac has supported the creation of 15 national teams in the following PAHO countries: Argentina, Bahamas, Belize, Bolivia, Brazil, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Jamaica, Nicaragua, Paraguay, Peru, and Uruguay. In addition, the ProVac IWG supported the creation of national teams in 9 countries outside the PAHO Region: Albania, Azerbaijan, Croatia, Egypt, Georgia, Iran, Kenya, Senegal, and Uganda.

All 24 national ProVac teams have completed at least one economic evaluation to contribute to a national decision-making

Table 1
Published ProVac country studies of Latin America and the Caribbean: characteristics, results, and policy implications.

Country	GAVI Eligibility	Vaccine	Schedule	Vaccine price over analysis time horizon (year 1) –> (last year)*	% Reduction of deaths	Net costs**	DALYs averted	ICER	GDP pc (year)	CEA result	%scenarios with ICER <3xGDPpc (Total CE/Total evaluated)	Country decision	Justification for single product evaluation
Argentina	Not eligible	RV1	2	$7.50 (2012) –> $6.25 (2021)	70.80%	$24,923,806	6,440	$3,870	$9,090 (2011)	Highly cost-effective	93% (13/14)	RV1 introduced in 2015.	N/A (both products were evaluated)
		RV5	3	$5.15 (2012) –> $4.29 (2021)	79.20%	$16,894,756	7,000	$2,414		Highly cost-effective	93% (13/14)		
Belize	Not eligible	HPV	3	$13.79	63.60%	$69,605	162	$429 (societal perspective)	$4,795 (2012)	Highly cost-effective	100% (10/10)	Decision pending.	Model does not allow for product comparison.
Brazil	Not eligible	HPV	3	$13.19	43.40%	$51,167,398	6,677	$7,663	$8,121 (2012)	Highly cost-effective	100% (20/20)	HPV4 introduced in 2014.	Model does not allow for product comparison.
Honduras	Eligible	HPV	3	$13.45	61.80%	$4,029,588	4,349	$926	$1,918 (2012)	Highly cost-effective	95% (19/20)	Decision pending.	Model does not allow for product comparison.
Paraguay	Not eligible	PCV10	2 + 1	$14.85	27.60%	$47,474,013	12,328	$3,851	$2,516 (2009)	Cost-effective	90% (18/20)	PCV10 introduced in 2012 due to increased cost savings and procurement through PAHO Revolving Fund	N/A (both products were evaluated)
		PCV13	2 + 1	$20.00	32.60%	$69,126,188	14,106	$4,901		Cost-effective	85% (17/20)		
Peru	Not eligible	PCV10	2 + 1	$14.24 (2012) –> $9.70 (2031)	34.30%	$363,268,692	226,370	$1,605	$6,573 (2012)	Highly cost-effective	100% (19/19)	PCV13 introduced in 2012,	N/A (both products were evaluated)
		PCV13	2 + 1	$16.34 (2012) –> $11.13 (2031)	47.40%	$408,264,249	313,119	$1,304		Highly cost-effective	100% (19/19)		

Note: Study results in this table reflect the government perspective unless noted otherwise. With the exception of vaccine prices, all dollar amounts shown here have been rounded to nearest USD.

* TRIVAC model for PCV and RV has ability to evaluate stacked cohorts to assess trends such as vaccine price declines; CERVIVAC model used for HPV only allows evaluation of one single girl cohort.

** All benefits and costs were discounted 3% in the base case, except for Brazil and Costa Rica, which used 5% discount for costs and benefits.

process on new vaccines. Several countries ($n = 6$) have completed two or more studies with the support of ProVac technical assistance and tools. The lengthiest study required 16 months to complete and the shortest studies were completed in barely a month; the average time was 6 months and the median was 5 months. The key issues determining the length of a study were local pressure to have evidence ready in time for a decision and the availability of quality inputs, two of the four principles for relevant economic evaluations, identified by the ProVac Initiative (described below) [9]. Both instances where the ProVac studies were conducted in a month were in islands of the Caribbean where local data were already available and there was pressure to finish the studies quickly to ensure that they could be used to inform a decision that had to be made before the end of the year.

In total, results from 24 nationally owned cost-effectiveness analyses (PCV = 9, Rota = 2, HPV = 11) and two EPI costing and financial analyses in LAC have been presented to national authorities to aid decision-making, including both NITAGs and high-level authorities at ministries of health and several of them have been published in peer reviewed journals (table 1). Similarly, the ProVac IWG has supported 9 analyses on the introduction of vaccines (4 for PCV and 5 for rotavirus vaccines), as well as the communication of the results to high-level decision-makers in the respective countries. Based on the currently available data on new vaccine introduction status, all Latin American and Caribbean (LAC) countries that requested support for a PCV or rotavirus cost-effectiveness analysis (CEA) have introduced or plan to introduce the vaccine. Cost-effectiveness analyses on HPV vaccine have not yet been followed by final decisions likely because the analyses had only recently been completed, and because vaccine prices remain high at time of analysis.

By the end of 2013, ProVac had received 43 official requests from 27 countries for support to develop an economic analysis (table 2); 16 were from LAC and 11 from other regions. Twenty requests were for a CEA of PCV, 5 for a CEA of rotavirus vaccine, 12 for a CEA of HPV vaccine and 6 for an EPI cost analysis. Eleven of the requests are still unfunded for 2014 and 2015; ProVac and the partners are working collaboratively to mobilize funds to support these pending requests. About half of the unfunded requests are from ProVac teams that have already received training and are familiar with the tools and another half are a result of unmet demand for training and tools in the IWG pilot regions of Africa, Eastern Mediterranean, and Europe [5].

A number of tools, training programs, and guidance instruments have been developed under the ProVac Initiative umbrella since 2004. All tools were field tested, reviewed by expert groups and then launched at ProVac regional workshops to promote them among potential users and test their capacity to respond to real policy questions at country-level. These enduring products of the initiative include:

- An On-line Immunization and Vaccines Economics and Statistics data repository (OLIVES) and other technical materials.
- A model to evaluate the impact and cost-effectiveness of Hib, rotavirus and pneumococcal vaccination (TRIVAC) [8].
- A model to evaluate the impact and cost-effectiveness of cervical cancer screening and HPV vaccination (CERVIVAC).
- A model to estimate the cost of the EPI program and to estimate the incremental cost and budget impact of adding new vaccines (COSTVAC) [9].

ProVac has also created instruments for data collection on pneumococcal, rotavirus and HPV-related disease diagnosis and treatment costs.

In addition to its framework for supporting country-led economic evaluations, the ProVac Initiative has prioritized the establishment and strengthening of NITAGs. These advisory bodies play a critical role in guiding an objective and transparent decision-making process for immunization policy by providing independent recommendations grounded in evidence to Ministry of Health [10]. As technical advisory committees, NITAGs are one of the key audiences for the cost-effectiveness results generated by ProVac national teams. Since 2004, 16 countries have established a NITAG or received NITAG training from the ProVac Initiative on evidence-based decision-making [11]. Two of these countries have revised their standard operating procedures with guidance from the PAHO NITAG guideline [12,13]. The CDC, the US Advisory Committee on Immunization Practices (ACIP) and the Sabin Vaccine Institute have been crucial partners in these efforts.

Table 2
ProVac cost-effectiveness analysis requested, in progress, and completed.

Country	Study	Status
ProVac in Latin America and the Caribbean		
Argentina	CEA HPV	In progress
	CEA PCV	Completed
	CEA rotavirus	Completed
Bahamas	CEA HPV	Completed
	EPI COSTING	Request received
Belize	CEA HPV	Completed
	EPI COSTING	Request received
Bolivia	CEA HPV	Completed
	CEA PCV	Completed
Brazil	EPI COSTING	In progress
Costa Rica	CEA HPV	Request received
	CEA PCV	Completed
	CEA rotavirus	Request received
Ecuador	CEA HPV	Completed
	CEA PCV	Completed
El Salvador	CEA PCV	Completed
Guatemala	CEA HPV	Completed
	CEA PCV	Completed
	CEA rotavirus	Completed
Honduras	CEA HPV	Completed
	EPI COSTING	Completed
Jamaica	CEA HPV	Completed
Nicaragua	CEA PCV	Completed
Paraguay	CEA HPV	Completed
	CEA PCV	Completed
Peru	CEA HPV	Request received
	CEA PCV	Completed
	EPI COSTING	Request received
Suriname	EPI COSTING	Request received
Uruguay	CEA HPV	Completed
Venezuela	CEA PCV	Request received
ProVac IWG		
Albania	CEA PCV	Request received
	CEA rotavirus	Completed
Azerbaijan	CEA PCV	Completed
Botswana	CEA PCV	Request received
Egypt	CEA Hib	Completed
Iran	CEA rotavirus	Completed
Senegal	CEA rotavirus	Completed
Croatia	CEA	Completed
	PCV	
Georgia	CEA	Completed
	PCV	
Tunisia	CEA	Request received
	PCV	
Kenya	CEA rotavirus	In progress
Uganda	CEA rotavirus	In progress

4. Discussion

The main aim of ProVac is to strengthen country-level capacity to make informed decisions about the introduction of new vaccines.

Consequently, the adoption of a new vaccine is not its ultimate goal. ProVac does not push the introduction of new vaccines with advocacy messages or tools; rather, it advocates for evidence to guide governments in making priority setting decisions. But introducing new vaccines is, to a certain extent, an undeniable measure of the impact of ProVac, particularly when the vaccine in question has been proven to be cost-effective in a variety of country contexts.

In this regard, at least 3 of every 4 decisions supported with ProVac studies resulted in the introduction of a new vaccine. Furthermore, all of the decisions supported with the TRIVAC model resulted in the introduction or plans for a 2014 introduction of PCV or rotavirus vaccine in LAC. Since the CERVIVAC analyses are more recent, their impact on HPV vaccine introduction is yet to materialize. Some of the countries that did not conduct a ProVac study in LAC (such as Colombia, and Mexico) have existing technical capacity to conduct studies without the capacity-building support ProVac provides. Other countries may not have deemed it necessary to conduct an economic evaluation before introducing a new vaccine because other evidence (e.g., WHO recommendations) strongly promoted introduction into the national schedule.

This suggests that initiatives such as ProVac, which put the emphasis on sustainable training and direct support for countries to generate evidence themselves, can help accelerate the introduction of the most *valuable* new vaccines. Experience indicates that some challenges need to be addressed in the future to make the most of the international and national efforts involved and thus maximize impact on the decision-making process.

Key lessons learned from ProVac's experiences providing technical support to countries can be summarized as follows:

4.1. Lessons about regional networks of experts

The ProVac Initiative has created a network of ProVac Centers of Excellence in the PAHO Region, a group of academic institutions with the aim of developing tools and practical guides for country use. In a phase two we intend to broaden the network of ProVac collaborators. In addition to experts from regional universities, collaborators will include key ministry of health and NITAG professionals, and experts from international, regional, and local agencies. The regional network will serve as an advisory and expert panel, reviewing ProVac's models and guidelines to provide a regional "reality check." The network will also provide peer review for publications and the results of country studies, offer technical support to national teams on specific issues, and promote regional exchanges and collaboration.

The participation of regional collaborators and the active involvement of NITAGs give the ProVac core team greater understanding of the regional context. Supporting regional academics and national advisory bodies is part of the capacity-building process for countries, exposing them to large-scale global initiatives with enhanced peer-to-peer exchanges while improving ProVac's ability to create useful and practical tools and methods.

4.2. Lessons about the technical support provided to countries

In these first 10 years of implementing ProVac, the lessons around providing technical assistance to countries to develop country-led cost-effectiveness analyses have led to the definition of four key principles for increasing the potential impact of economic evaluations on policymaking: Timeliness, Integration, Quality and Ownership/ Institutionalization (Box 1).

Box 1: Principles for national economic evaluations with impact on policymaking	Description
Timeliness	Economic analyses and other pieces of evidence are most useful when the results are ready to respond to a specific policy question. ProVac experience demonstrates that CEAs that intend to inform an adoption decision are often used as advocacy instruments if results arrive too late. On the other hand, there were several instances where CEA results were useful for decision makers that needed additional evidence to defend a decision already in place
Integration	Economic analyses need to be adequately contextualized and complemented with all the necessary information to answer a relevant policy question, even by adopting an HTA approach when feasible
Quality	Results from an economic evaluation require quality inputs. Part of this process is evaluating the quality of evidence and ProVac experience demonstrates the utility in doing this at the local level. Poor quality data leads to poor quality results and, worst yet, poor decisions
Ownership/ institutionalization	The development of an economic analysis needs to be owned by nationals, for them to understand its limitations, to interpret its results correctly, and to trust it enough to let them influence their decision. National ownership and institutionalization of the process leads to more rapid and better informed policy decisions

In our experience, these four principles for high-impact economic evaluations interact closely with each other, and all four are needed for an economic evaluation to have real impact on national decision making. These principles were defined from observing many unexpected outcomes from the ProVac process at country level that contributed to 'added-value' for conducting a cost-effectiveness analysis. In other words, these unexpected process outcomes (examples summarized in Table 3) demonstrated that there are benefits of conducting a country-owned economic evaluation that go far beyond obtaining results from the analysis, making the effort to hand over the process to country teams even more worthwhile.

Finally, after an economic evaluation is concluded, countries often grapple with other unanswered questions, particularly if the analysis only assessed the value of a single health intervention. We therefore propose to support comparative analyses with different layers of model complexity (UNIVAC, see below).

4.3. Lessons on cost-effectiveness models for country use

Learning from the extensive technical support provided to countries throughout the years, and to ensure that the four principles for relevant economic evaluations are followed in the future, ProVac has envisioned a new single cost-effectiveness model framework, UNIVAC. UNIVAC will build on the modelling work to develop TRIVAC and CERVIVAC. It will be a single, flexible and consistent framework that can be quickly adapted to the needs of a particular vaccine and particular country. A single flexible model will also allow for head-to-head comparisons of different vaccines as well as non-vaccine health interventions, enhancing the model's usefulness in real-life public policy decisions.

The availability of data often varies from country to country, so there is a need to tailor models to the available local data. It would be an asset to have a model that offers different levels of complexity to choose from depending on the vaccine being evaluated, the availability of data, and the time frame of the decision.

Table 3
Published ProVac country studies of Latin America and the Caribbean: additional benefits from the ProVac approach.

Country	Additional benefits from ProVac approach
Argentina	Acting staff has developed three CEAs with ProVac and quickly adapts tools to country needs as a result of the staff member's honed technical skills with ProVac tools. MOH EPI established salaried position to support vaccine policy research as an input to NITAG discussions and MOH policymaking
Belize	High documented out-of-pocket costs and minimal access to treatment services for cervical cancer in country during study promoted actionable dialogue among key actors
Brazil	Collaboration between a regional academic center of excellence working with ProVac and the Brazilian MOH offered unique opportunity to bridge between academia and real time policymaking
Honduras	Working group established between EPI and cervical cancer groups to develop an HPV CEA study and still continues to meet to promote inter-programmatic approach to HPV introduction and screening infrastructure strengthening
Paraguay	Paraguay MOH EPI emitted ministerial decree to support evidence-based approach to policy development for this study and in the future based on the ProVac experience
Peru	The existing national health institute in charge of conducting economic evaluations worked closely with the EPI ProVac team and relationships were strengthened for future collaborative studies

4.4. Lessons on international comparisons of national cost-effectiveness data

The studies conducted have each adhered to recognized standards for economic evaluations of vaccines [14] and a consistent model has been used for each vaccine. There are, however, several reasons why the base-case results presented by different countries may not be directly comparable. For example, two of the LAC studies used a 5% discount rate (Brazil, Costa Rica) rather than 3%. Five countries presented head-to-head vaccine evaluations (PCV10 vs. PCV13) while others focused on a single vaccine. Some countries considered a longer time horizon than others (four countries used 10 years rather than 20). And while most countries considered both a government and societal perspective, a few countries presented only a government perspective, some presented just the societal, and one presented 3 different perspectives. In addition, there was variation in the year of vaccine introduction and the year in which costs were presented, as well as country-specific assumptions about herd effects, waning, inclusion or exclusion of sequelae costs, and inclusion or exclusion of lost productivity.

These variations make direct comparisons of model results between countries challenging. However, such comparisons are not the aim of the ProVac Initiative. Rather, each study is tailored to country circumstances and the concerns of its decision-makers, which is important to national credibility and ownership and ultimately usefulness of the study results in the decision. The ability to incorporate decision-makers' preferences, the perspectives that are most relevant to the country, and data that reflects the local context makes it possible to construct a base-case scenario that national teams understand and feel confident defending. Thus, while this limits the scope of country-to-country comparisons, it allows for more effective ownership and transfers of knowledge to national teams–and, crucially, produces better local acceptance when results are presented to national committees.

4.5. Lessons for a way forward: The ProVac Global Initiative

Building upon ProVac's 10 years of experience, we propose creating a ProVac Global Initiative with several innovative characteristics. Priority areas over five years include:

- Strengthen infrastructure for decision-making.
  1. *At the global level*: Establish ProVac core teams in all WHO regional offices to provide a regional focal point for economic evaluations of vaccines and potentially broader HTA studies.
  2. *At the regional level*: Create regional networks of experts to review models and data, and to work with national teams.
  3. *At the national level*: Form ProVac national multidisciplinary teams to conduct economic and financial analyses, including cost-effectiveness, comprehensive EPI costing, expenditure tracking, and financial-flows analyses.
- Expand the current suite of economic tools (TRIVAC, CERVIVAC, COSTVAC) to support country-level policy needs in the future, such as vaccines for dengue, meningococcal, malaria, hepatitis A, and cholera.
- Use regional workshops and direct country support to focus training on generating evidence for sustainable introduction of new vaccines and allocation of EPI resources.
- Support national teams as they conduct cost-effectiveness, impact and financial analyses.
  1. Interpret results and create alternative scenarios.
  2. Effectively communicate results to decision-makers.
  3. Provide peer review.
- Support to NITAGs and policymakers with policy briefs and capacity building efforts.

5. Conclusion

PAHO's work to strengthen evidence-based immunization policy in the Americas with the building of capacities to generate, interpret and incorporate economic evidence in the decision making process has clearly contributed to a positive shift in policymaking for immunization programs. The fact that all 14 published cost-effectiveness analyses in this supplement alone were led by national teams is a good indicator of the degree of genuine country involvement and a reflection of the success of the initiative. Other country teams have sought publication elsewhere or are currently preparing articles for submission [15]. The lessons learned during the 10 years of the Initiative in the Americas will guide future implementation. The ProVac Global Initiative is proposed as an effective mechanism to provide support to national governments for generating sustainable technical capacity for evidence-based decisions on new vaccines.

Conflict of interest statement

AS reports having previously received a research grant and travel support from Pfizer Inc. All other authors declare that they have no conflict of interest.

Acknowledgement

We would like to acknolwedge the financial support from The Bill and Melinda Gates Foundation through grant number: OPP50788.

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Vaccine 33S (2015) A28–A33

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Evidence-based decision-making for vaccine introductions: Overview of the ProVac International Working Group's experience

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ARTICLE INFO

Keywords:
Immunization program
Economic evaluations
Cost-effectiveness analysis
Evidence-based policy
Immunization policy

ABSTRACT

Introduction: Pan American Health Organization's (PAHO) ProVac Initiative aims to strengthen countries' technical capacity to make evidence-based immunization policy. With financial support from the Bill and Melinda Gates Foundation, PAHO established the ProVac International Working Group (IWG), a platform created for two years to transfer the ProVac Initiative's tools and methods to support decisions in non-PAHO regions.
Methods: In 2011, WHO Regional Offices and partner agencies established the IWG to transfer the ProVac framework for new vaccine decision support, including tools and trainings to other regions of the world. During the two year period, PAHO served as the coordinating secretariat and partner agencies played implementing or advisory roles.
Results: Fifty nine national professionals from 17 countries received training on the use of economic evaluations to aid vaccine policy making through regional workshops. The IWG provided direct technical support to nine countries to develop cost-effectiveness analyses to inform decisions. All nine countries introduced the new vaccine evaluated or their NITAGs have made a recommendation to the Ministry of Health to introduce the new vaccine.
Discussion: Developing countries around the world are increasingly interested in weighing the potential health impact due to new vaccine introduction against the investments required. During the two years, the ProVac approach proved valuable and timely to aid the national decision making processes, even despite the different challenges and idiosyncrasies encountered in each region. The results of this work suggest that: (1) there is great need and demand for technical support and for capacity building around economic evaluations; and (2) the ProVac method of supporting country-owned analyses is as effective in other regions as it has been in the PAHO region.
Conclusion: Decision support for new vaccine introduction in low- and middle-income countries is critical to guiding the efficient use of resources and prioritizing high impact vaccination programs.
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1. Introduction

According to a study on the global burden of childhood pneumonia and diarrhea, estimates of annual childhood mortality due to rotavirus-associated diarrhea are 192,000 globally, and another 411,000 children younger than 5 die each year from pneumococcal disease [1]. Additionally, 266,000 women died prematurely in 2012 from cervical cancer caused by human papillomavirus (HPV) [2]. Vaccines to prevent these priority diseases offer opportunities to make substantial gains in health, oftentimes at a relatively lower cost than other preventive strategies. However, the relative value of many new vaccines may depend on variables that

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http://dx.doi.org/10.1016/j.vaccine.2014.10.090
0264-410X/© 2015 Published by Elsevier Ltd.

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vary greatly between and within countries; consequently, policy decisions to introduce new vaccines require an evidence base that reflects national conditions.

Using the Pan American Health Organization (PAHO) ProVac Initiative's framework for promoting evidence-based decision-making, the International Working Group (IWG) was created in 2011 to help strengthen national capacity for evidence-based decisions regarding the introduction of new vaccines in developing countries in regions other than Latin America and the Caribbean (LAC). This article is an introductory overview of the work conducted by the IWG. More details about this work will be covered in other publications within this special Vaccine supplement.

2. Background

In 2004, PAHO created the ProVac Initiative. Since then, the ProVac Initiative has trained high-level technical staff from ministries of health from over 25 countries in the Latin America and Caribbean (LAC) region on the use of economic evaluations in the decision-making process for introducing new and underutilized vaccines to prevent rotavirus diarrhea, pneumococcal disease, and human papilloma virus (HPV) infection. ProVac has also supported 21 country-owned cost-effectiveness analyses on rotavirus, pneumococcal conjugate, and HPV vaccines to inform national decision-making processes in LAC.

Implementing the ProVac Initiative in the Americas has yielded a number of valuable lessons and tools for supporting countries in making evidence-based decisions around the introduction of new vaccines. Specifically, multidisciplinary country study teams that collect data and do analysis have used TRIVAC (the integrated childhood vaccination cost-effectiveness model for rotavirus, pneumococcal conjugate, and *Haemophilus influenzae* type b [Hib] vaccines) to ensure that immunization policymakers in LAC recognize study results and weigh their outcomes in decisions about whether to introduce a new vaccine [3].

Over the years, PAHO has received requests from technical cooperation organizations and countries outside of the LAC region to implement ProVac tools and methods. Under the umbrella of the ProVac IWG, PAHO worked closely with organizations involved with global immunization activities – Agence de Médecine Préventive (AMP), United States' Centers for Disease Control and Prevention (CDC), Program for Appropriate Technology in Health (PATH), the Sabin Vaccine Institute, and WHO headquarters, regional and country offices – to leverage lessons learned in the Americas for use in other regions.

It was decided to form the ProVac IWG to serve as the mechanism to bring together the above organizations because IWG would:

- Provide a unique platform to channel requests for technical assistance from developing countries around economic analysis for new vaccines and for adjustments/updates to existing ProVac tools and methodologies.
- Improve coordination among relevant parties supporting evidence-based decisions about introducing vaccines in developing countries—which in turn clarifies roles, responsibilities, and collaborations that help to avoid overlap and maximizes efforts.
- Increase the flexibility of the ProVac tools and methods, helping to ensure their appropriate use in different epidemiological and geographical contexts.
- Generate and encourage the publication of evidence to promote greater consistency between regions, both in the use of standardized methods and tools, and in the country-led evidence-based approach, too.

3. Methods

In 2011, WHO regional offices and partner agencies met at PAHO headquarters to establish the ProVac IWG, as a platform to transfer ProVac's framework and experience (including its tools, methods, and training exercises that support making evidence-based decisions about introducing new vaccines) in selected countries in Africa, the Eastern Mediterranean and Europe—regions where IWG partners have strong existing networks. In 2012, IWG received support from the Bill and Melinda Gates Foundation for two years, during which the technical cooperation focused on low- and middle-income countries. These are regions where the burden of rotavirus, pneumococcal and cervical cancer is greatest and where countries are challenged by limited capacity to build evidence bases to support the decision-making process for introduction of new vaccines. The work focused on support to countries facing decisions about introduction of pneumococcal conjugate vaccine and/or rotavirus vaccine using the TRIVAC impact and cost-effectiveness model.

During the two years, PAHO served as coordinating secretariat, and partner agencies played implementing or advisory roles. AMP provided direct technical support to selected countries in the Eastern Mediterranean (EMR) and Europe (EUR); PATH did the same in Africa (AFR). Both partner agencies received training from PAHO as well as subsequent support from the WHO headquarters and regional offices. Sabin Vaccine Institute supported AMP's and PATH's capacity-building activities at country level with their expertise in effectively communicating evidence for informed decision-making; the CDC provided advisory support on epidemiological data quality. The IWG leveraged existing country relationships and subject matter expertise to support the rollout of this framework in nine countries. The countries were selected according to the following criteria: (1) interest from the ministry of health or an official request to conduct an economic evaluation, (2) a pending decision regarding a new vaccine introduction, and (3) a partner presence in the country.

The ProVac IWG had three main objectives: (1) transferring tools, methods, and lessons learned in the Americas to other regions to support national decisions about new vaccine introduction, (2) building national capacity for using economic analyses in low- and middle-income countries around the world, and (3) providing direct technical support collecting data and conducting economic analyses to inform immunization policy in low- and middle-income countries. Details and follow-up on the objectives are elaborated below.

Considering differences in data availability, data quality, and new vaccine policy questions that exist between WHO regions, the ProVac IWG collaborated to adapt the tools used in the Americas for use to support national-level decision-making about the introduction of new vaccines in developing countries in the WHO Regions of AFR, EMR and EUR. This included revising input parameters of the model (as needed) and translating the ProVac tools and methods to French and Russian. A number of improvements to TRIVAC were also made as a result of direct feedback from countries involved in the IWG. These include: (1) greater clarity in the way inputs were organized —e.g., dose-specific vaccine efficacy and assumptions about vaccine timeliness (on-time, delayed) and age restrictions (age-restricted or unrestricted); (2) improved pop-up explanations and workshop materials designed to suit a wider geographical audience; (3) improved graphical output; (4) greater flexibility to customize the type of diseases considered by the country team—e.g., pneumonia admissions, X-ray-confirmed pneumonia, or clinical pneumonia, etc.; (5) development of features to help users calculate a plausible case fatality ratio and understand how it was derived—i.e., combining a top-down (proportional mortality) estimate of deaths with a bottom-up (incidence-based)

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estimate of cases; (6) increased scope of the OLIVES on-line data repository—e.g., incorporating evidence from outside the Americas on vaccine type coverage, waning vaccine protection etc.; and (7) the addition of two new language options for users of the model—i.e., Russian and French.

National capacity to perform economic analyses to inform new vaccine introduction is considered limited in most developing countries. To address this challenge and ensure that the IWG's tools helped a greater number of public health decision-makers, IWG partners organized regional workshops to provide training on basic concepts of health economics and disease epidemiology, and on the use of ProVac tools for economic analyses. Regional workshops provided national public health professionals with a broad understanding of how to collect and critically assess data, conduct analyses, interpret results, and contextualize findings in light of other relevant criteria for deciding on whether to introduce a new vaccine.

ProVac IWG partner-led regional workshops used PAHO's TRIVAC model as a practical training tool. TRIVAC is an Excel-based, cohort model that provides users with a friendly, stepwise template to collect data for each model parameter [3]. It evaluates the incremental program costs, health benefits gained, and disease-associated costs averted from introducing vaccines that prevent Hib, rotavirus, and pneumococcal infection.

Although the regional workshops were the primary method for training national people on using ProVac tools, the ProVac Centers of Excellence also developed training materials on health economics and evidence-based decision-making in the Latin American region [4]. The training materials, which explained the key concepts required for understanding the tools and how to use them, were provided to country teams and discussed in regional workshops.

The ProVac Initiative promotes capacity-building as an overarching principle to ensure long-term sustainable impact. As stated above, the IWG supported this concept by helping to form multidisciplinary country teams to use ProVac tools, carry out data collection, conduct analysis, and communicate study results to policymakers. The majority of these study teams were appointed by the Ministry of Health; they included participation from WHO regional and/or country immunization staff, Expanded Programme on Immunization (EPI) managers, and relevant experts from ministries of health and academic centers (health economists, epidemiologists, pediatricians, public health and immunization experts). In each country, a ministry of health focal point or a national consultant was also identified to coordinate the study activities. These teams served as technical working groups to support deliberations on the introduction of new vaccines by National Immunization Technical Advisory Groups (NITAGs), where these exist. IWG partners provided ongoing technical support throughout the study, with in-country visits to initiate and support the study and a final visit to review databases, address any methodological challenges, and assist in interpreting the results for decision-making purposes.

CDC partners led technical reviews and provided recommendations regarding epidemiological data on rotavirus and pneumococcal disease. After data collection, multidisciplinary country teams critically assessed the data and conducted the analyses. With support from the whole ProVac IWG, AMP led studies in EMR and in EUR. Similarly, PATH led studies in AFR, complementing work previously conducted in other African countries. The current supplement showcases a more detailed description of AMP's experience, as well as country-led publications from the three regions studied [5–12].

In most cases, the evidence is only as good as the methods used to communicate. The Sabin Vaccine Institute led an effort to develop a communication and advocacy strategy to be applied in study countries to ensure that the evidence generated through ProVac studies reaches stakeholders and decision-makers. The institute developed a practical guide and several templates to help multidisciplinary national teams to package their evidence into concise and practical materials so that the evidence relevant to the decision process could be effectively communicated to a range of stakeholders. The strategy involved these steps:

- Analyze the country's existing decision-making process for introducing new vaccines.
- Identify stakeholders and their roles in the decision process.
- Identify relevant evidence that should be used to properly inform the decision.
- Address common questions about cost-effectiveness and its role in the decision-making on new vaccine introduction.
- Create concise and effective technical presentations based on data from the economic analysis performed.
- Construct key messages and provide supporting evidence to accompany the results of the economic analyses.
- Draft policy briefs that include the national economic analysis and other relevant criteria for decision-making.
- Draft technical reports, including more detailed information about the economic evaluation that was conducted.

4. Results

Economic analyses represent one component of a broader policy framework for evidence-based decisions regarding the introduction of new vaccines. PAHO's ProVac introduction policy framework [13], which considers technical, programmatic, and social criteria, has helped guide countries to use economic analyses in the context of other relevant decision criteria to ensure that a comprehensive policy analysis is conducted to ground decisions in evidence. The ProVac IWG promoted the use of the same framework.

ProVac IWG held both an initial and final meeting during the 2-year period. The initial meeting served as a platform for the IWG partners to agree on specific activities and for PAHO to train implementing partners on the TRIVAC model and ProVac methods; the final meeting was to evaluate the IWG's outcomes. This allowed the incorporation of improvements in the TRIVAC model to accommodate the needs of countries outside the LAC region. Those improvements included adding two new language options (French and Russian), a designated area for manual calculations, and updated default data.

A total of 59 national professionals from 17 countries received training through IWG's regional workshops. Each partner had existing regional ties in one or more of these regions and the workshops complemented their ongoing regional work.

AMP led regional workshops on the use of economic analyses to inform decisions around the introduction of pneumococcal conjugate vaccines in EUR and EMR in 2012 and 2013 respectively; WHO headquarters, regional, and country offices provided support. Similarly, PATH led a workshop on conducting cost-effectiveness analyses of new vaccine introductions, focused on the rotavirus vaccine in AFR in 2013. This workshop in AFR complemented two previous workshops PATH had organized on the use of economic analyses in 2011 (funded by other sources). The regional workshops targeted EPI managers, national health economists, and other relevant ministry of health professionals working in the area of vaccine-preventable diseases. During the workshops, country teams that were conducting their own cost-effectiveness studies within the ProVac IWG shared their experiences; this helped achieve the ProVac objective of capacity-building.

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Table 1
Countries and people trained through workshops and through direct technical support.

	EUR region	EMR region	AFR Region
Countries trained through workshops	Albania Croatia Estonia Georgia	Egypt Islamic Republic of Iran Iraq Jordan Lebanon Tunisia	Botswana Kenya Nigeria Senegal South Africa Uganda
Number of national people trained through workshops	18	20	20
Countries that received direct technical support	Albania Azerbaijan Croatia Georgia	Egypt Iran	Kenya Senegal Uganda
Number of national people trained through direct technical support	52	28	11

The IWG provided direct technical support to nine countries[1] to develop cost-effectiveness analyses and inform decisions on pneumococcal conjugate or rotavirus vaccines [see Table 1]. Seven of those nine countries had received training as part of the above-mentioned regional workshops. After considering the cost-effectiveness results obtained and taking into account other criteria considered relevant, countries either made the decision whether or not to introduce the new vaccine that had been evaluated, or the countries' NITAGs or equivalent advisory bodies used the new evidence and made recommendations to their respective ministries of health [see Table 2 for country-specific information.]

Where data gaps or weaknesses were identified from national sources, the national team presented recommendations to their authorities to strengthen surveillance and health information systems (HIS).

The resources needed for supporting EUR consisted of the partner's staff time and travel costs, workshop participants' travel and per diems, and translation of materials into French and Russian. In EMR and AFR, in addition to all these expenses, a small amount of funds was also required to convene internal working group meetings within each of the countries, to cover coffee breaks, and as a financial incentive for nationals to attend the meeting (which was not necessary in EUR). Lessons learned in the EUR and EMR regions include (1) the need for a well-balanced multidisciplinary team in the country to carry out the cost-effectiveness analysis (CEA), including all relevant specialties and institutions, (2) the importance of involving all stakeholders from the start of the study so that study results are accepted by all parties, and (3) the necessity of providing a regional approach which encourages peer-to-peer interactions between countries that builds esprit de corps among investigators and embraces intellectual development.

Partners working in the AFR region faced different challenges including a more complex country selection process. They also learned that having a country office where the study is being conducted and holding regional workshops before beginning country analyses are critical elements for success of the work. A specific lesson learned from AFR was the importance of beginning these studies well in advance of policymaking timelines that are advanced by the Global Alliance for Vaccines and Immunization (Gavi).

5. Discussion

Many of the countries supported through the ProVac IWG are moving away from donor-funded immunization programs. As such, they have an increasing interest in weighing value against the financial cost of adopting the new vaccine. The ProVac approach to conducting country-owned economic evaluations can be a valuable and timely aid to this national decision-making process, although the unique challenges encountered in each region require further consideration. For Gavi-eligible countries, conducting a country-level CEA is not a current prerequisite for funding and so the dynamics and motivations vary. A cost concern with regard to a new vaccine's affordability is more pertinent. Despite this, we consider the process of generating and collecting data required for a cost-effectiveness study relevant to Gavi-eligible countries: It promotes a culture for evidence-based decision-making while also helping the government evaluate the long-term strategic planning and sustainability of the new vaccine being considered for introduction.

Similar to ProVac's experience in the Americas, one of the key problems we faced in these countries was lack of national-level data on important information such as disease burden and serotype distribution. This often led to using regional data or international estimates for these parameters. One lesson learned is that countries prefer national data, but this requires they anticipate this and that they have surveillance systems in place well before the analysis is conducted, or that they perform focused studies that provide reliable, quality national data. When this has not happened, the question of what constitutes a good surrogate often arises. Examples include regional estimates and data from bordering countries. The variable national technical expertise on subject matter and on how to set up these studies is another lesson to highlight, and indicates the need for regional WHO offices and other partners help them build such capacity.

Sustainability or "nationalization" of the process is yet to be documented in these regions. The Americas has had several experiences of countries performing further studies with significantly less support from the ProVac team [14], but this is yet to happen in the IWG regions where the ProVac support is more recent.

As will be further reinforced in the specific related publications in this supplement, the experience suggested that (1) there is great need and demand for technical support and for capacity-building to conduct economic evaluations at the national level in the regions where the work took place, and (2) the ProVac method of supporting country-owned analyses through extensive training, direct support, and promotion of country ownership of process and results could become as effective in other regions as it has been in the PAHO region if it is properly adapted to the regional context. This collaboration is one of several experiences where regions with more advanced immunization programs transfer successful initiatives to other regions. More international and regional funding mechanisms for cross-regional sharing are needed to maximize the impact of existing initiatives and prevent having each region "reinvent the wheel."

The leveraging of expertise of the partner agencies proved useful. The PAHO ProVac team, which includes the modeling team at the London School of Hygiene and Tropical Medicine (LSHTM) and a core team of international consultants, provided its years of experience developing tools and trainings specifically for country teams and supporting country-led economic analysis, and provided a coordinating role for the group. PATH offered a strong health economics expert team, and also had disease epidemiology

[1] The nine countries were: Albania, Azerbaijan, Croatia, Egypt, Georgia, Iran, Kenya, Senegal, and Uganda.

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Table 2
Country studies' characteristics, results and policy implications.

Country	Gavi eligibility 2014?	Vaccine	Schedule	Vaccine price	% Reduction of deaths	Net costs**	DALYS averted	ICER	GDP per capita***	CEA result	Country decision	Justification for single product evaluation
Kenya	Eligible	RV1	2	$0.20	46%	$50,000,000	1312,920	$38	$942	Highly cost-effective	Introduction scheduled July 2014	RV1 has vial monitor
Senegal	Eligible	RV1	2	$0.20	42%	$17,570,000	190,280	$92	$1,040	Highly cost-effective	Introduction planned 2014	Country preference
Uganda	Eligible	RV1	2	$0.20	40%	$52,000,000	1509,030	$34	$572	Highly cost-effective	Introduction planned 2016	Country preference
Albania	Graduated	RV1	2	$8.50	68%	$1910,000	950	$2,011	$4,149	Highly cost-effective	Introduction planned for 2015	N/A (comparative analysis)
		RV5	3	$8.50	68%	$4790,000	950	$5,042	$4,149	Cost-effective		
Georgia*	Graduating	PCV10	3 + 0	$3.50	30%	$2300,000	1,438	$1,599	$3,602	Highly cost-effective	Introduced in 2014	Global shortage of PCV13
Croatia	Not eligible	PCV10	3 + 0	$ 30.00	58%	$42,508,000	540	$78,649	$13,227	NOT cost-effective	Not introduced	N/A (comparative analysis)
		PCV13	3 + 0	$35.00	58%	$50,250,000	540	$92,973	$13,227	NOT cost-effective		
Egypt	Not eligible	PCV13	3 + 0	$14.24	42%	$1068,600,000	272,878	$3,916	$3,187	Cost-effective	No decision yet	Interested in PCV13 as it covers more serotypes circulating in Egypt
Iran	Not eligible	RV5	3	$10.00	65%	$219,640,000	76,591	$2,868	$4,763	Highly cost-effective	Decision to introduce; year of introduction pending	Pentavalent vaccine available for Iran. RV5 vaccine price negotiated

Note: Study results in this table reflect the government perspective.
* In 2013, there was a global shortage of PCV13. Countries only had the option of evaluating PCV10 for immediate introduction.
** All benefits and costs were discounted 3% in the base case. All figures shown here have been rounded up/down.
*** Of the year of the analysis.

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experts available to provide support. AMP provided effective training techniques. CDC provided important subject matter expertise on epidemiological and surveillance data. WHO headquarters and regional offices provided convening power and global immunization policy expertise. The Sabin Vaccine Institute offered useful and practical tools for communicating results to national authorities.

This experience demonstrated again the critical importance of establishing national multidisciplinary teams for the country to gain ownership over the process and its results. User-friendly, scientifically robust decision-support tools are needed in resource-constrained and/or data-sparse settings and the ProVac tools are an option for filling this gap. The IWG work also confirmed that having a focal point from within the ministry of health or other national institution who is assigned to lead and coordinate the study, rather than hiring an external consultant, is likely more sustainable in the long term and more effective in national-capacity development. However, this could prove challenging, given the more limited time that ministries of health and sometimes even WHO regional or country office staff have to provide support—especially in high-risk regions overwhelmed with emergency or dire health situations as well as with international technical cooperation activities such as in AFR. In the future, it will be necessary to find a more systematized way to deal with country demand for technical cooperation and to prioritize the countries. Finally, as shown in Table 2, technical support to strengthen capacity on economic evaluations of vaccines can be resource-intensive. Combining innovative ways of interacting with local technicians and decision-makers through distance learning with high-quality, easy-to-use tools is necessary for a sustainable approach going forward.

6. Conclusion

A nationally based, evidence-driven decision process for new vaccine introduction in low- and middle-income countries is critical to guiding the efficient use of resources and prioritizing high-impact vaccination programs. It is the antithesis of the top-down approach. This experience demonstrated that the ProVac method for capacity-building – which includes using workshops to promote the socialization of general concepts and tools, providing direct support to countries after an official ministry of health request has been received, convening a multidisciplinary team, and fostering strong working relationships between NITAG, ministry authorities, and the team conducting the analysis – can be implemented successfully in countries outside of the LAC region.

The ProVac method provides an opportunity to get multiple national stakeholders to sit at the same table, which enhances the evidence-based decision-making process at country level. Several agencies are well-suited to provide this technical assistance and coordination at the global level will be required. ProVac IWG partners have expressed their interest in continuing to collaborate on this important work. Going forward, both PAHO and WHO may have an opportunity to coordinate the expanded reach of the ProVac toolkit and decision-support methods to additional regions and countries requiring real-time support.

Contributors

This was a group effort led by the ProVac IWG Secretariat at the PAHO, with considerable contributions from IWG's partners: AMP, LSHTM, PATH, Sabin Vaccine Institute, the CDC, and WHO headquarters. This work was guided and overseen by Dr. Jon K Andrus, Deputy Director of PAHO and principal investigator of the ProVac Initiative.

Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

We would like to acknowledge the financial support provided by the Bill and Melinda Gates Foundation through grant number OPP1032888 to create the IWG and the two-year activities it conducted. We also acknowledge the relevant contributions provided by Liudmila Mosina, WHO EURO; Amos Petu, WHO AFRO; and Irtaza Chaudhri, WHO EMRO.

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Vaccine 33S (2015) A34–A39

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Strengthening national decision-making on immunization by building capacity for economic evaluation: Implementing ProVac in Europe

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ARTICLE INFO

Keywords:
Advisory committee
Health economics
Economic evaluation
Evidence-based policy
Immunization policy
New vaccines

ABSTRACT

Background: For many years, low- and middle-income countries have made efforts to strengthen national decision-making on immunization. The Pan American Health Organization (PAHO) ProVac Initiative was established to help expedite the use of evidence-based decision-making around new vaccine introduction. This initiative provides training in user-friendly cost-effectiveness models and supports the development of country-led economic evaluations. Due to the success of the ProVac Initiative in the Americas, and following requests from countries from outside the Americas, the Bill & Melinda Gates Foundation funded a two-year pilot effort to expand the initiative to other world regions. Called the ProVac International Working Group (IWG), this endeavor took place in 2012 and 2013. It was coordinated by PAHO and carried out in collaboration with several international partners, including the Agence de Médecine Préventive (AMP), London School of Hygiene & Tropical Medicine (LSHTM), Program for Appropriate Technology in Health, Sabin Vaccine Institute, United States Centers for Disease Control and Prevention, and the World Health Organization (WHO). In the WHO European Region, technical support was provided by AMP, in close collaboration with the WHO Regional Office for Europe and other ProVac IWG partners.
Methods: In 2012, AMP, the WHO Regional Office for Europe, and other partners held a training workshop in Dubrovnik, Croatia, for 31 participants from four countries of the WHO European Region. The aim was to train health professionals in standard methods of economic evaluation and to assess regional demand for economic studies to support decision-making on immunization. AMP and the other organizations also supported four national cost-effectiveness studies in the WHO European Region. The assistance included country visits and support over a period of six months, the establishment of multidisciplinary teams of experts, ongoing training on the TRIVAC decision-support model for new-vaccine economic analysis, review of local evidence, recommending key data inputs, and support in presenting results to national decision makers.
Results: National cost-effectiveness studies were conducted in four countries: Albania (rotavirus vaccine [RV]), Azerbaijan (pneumococcal conjugate vaccine [PCV]), Croatia (PCV), and Georgia (PCV). All four countries improved their estimates of the burden of disease preventable by the new vaccines. National advisory bodies and ministries of health obtained economic evidence that helped Albania and Croatia to make decisions on introducing the new vaccines. Azerbaijan and Georgia used economic evidence to confirm previously made preliminary decisions to introduce PCV and make corresponding financial commitments. The study helped Albania to obtain access to affordable prices for rotavirus vaccines through participation in the UNICEF procurement mechanism for middle-income countries. Croatia was able to define the PCV price that would make its introduction cost-effective, and can use this figure as a basis for price negotiations.
Discussion: Despite some challenges due to competing national priorities, tight budgets for immunization, and lack of available national data, the ProVac IWG helped to build capacity of national health

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http://dx.doi.org/10.1016/j.vaccine.2014.12.073
0264-410X/© 2015 Published by Elsevier Ltd.

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professionals, support decision-making for the introduction of new vaccines, and promote utilization of economic evidence for making decisions on immunization. This type of strong collaboration among international partners and countries should be scaled up, given that many other countries in the WHO European Region have expressed interest in receiving assistance from the ProVac IWG.

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1. Background and regional context

New vaccines, such as rotavirus and pneumococcal vaccines, have the potential to prevent deaths and reduce disease burden. However, the national decisions to introduce new vaccines need to be strongly justified because the vaccines are expensive and often lead to a substantial increase in the cost of immunization programs. The ministries of health should carefully consider the financial aspects of such introductions, including evidence on cost-effectiveness of the new interventions. Therefore, many low- and middle-income countries have expressed a need for support in obtaining local evidence on cost-effectiveness of new vaccines as well as building capacity in interpreting and communicating this type of evidence to national decision makers.

To respond to these needs in the Americas, the Pan American Health Organization's (PAHO) ProVac Initiative was created in 2004 to strengthen national technical capacity to make evidence-based immunization policy. The ProVac Initiative produced models for cost-effectiveness analysis (CEA), conducted regional training workshops, and provided direct technical support to individual nations. This approach and the experience in the Americas have been described elsewhere [1].

Due to the success of the ProVac Initiative in the Americas, countries from other world regions requested help in building capacity in economic evaluation in order to strengthen their national decision-making processes for immunization. In response, the Bill & Melinda Gates Foundation funded a two-year pilot project called the ProVac International Working Group (IWG). This effort, which took place in 2012 and 2013, was coordinated by PAHO and carried out in collaboration with international partners that included the Agence de Médecine Préventive (AMP), London School of Hygiene & Tropical Medicine (LSHTM), Program for Appropriate Technology in Health (PATH), Sabin Vaccine Institute, United States Centers for Disease Control and Prevention (CDC), and World Health Organization (WHO). The mandate of this group was to implement ProVac tools and methods in countries in the WHO African, Eastern Mediterranean, and European regions.

AMP, in collaboration with WHO regional offices, implemented the ProVac tools and methodology in six countries, four in the WHO European Region and two in the WHO Eastern Mediterranean Region. Joint WHO and AMP workshops were conducted in both of these regions to raise countries' awareness of the need to use evidence to support decision-making and of the availability of the ProVac IWG support as well as to briefly train the countries on health economic evaluation.

This article focuses on the experience of implementing ProVac in the WHO European Region. The experience and lessons learned from the Eastern Mediterranean Region with AMP and from the African Region with PATH can be found in an article by Jauregui et al. [2].

2. Methods

2.1. The use of the ProVac Initiative methodology and tools

AMP and WHO benefited from the successful development and use of ProVac tools and methodologies in the Americas, and applied them in the WHO European Region. AMP, in collaboration with WHO, trained the country teams on two levels. First, the general ProVac approach was explained to the teams, insisting on the importance of transferring the skills and the knowledge to the teams, to enable country capacity-building and ownership of the project results. Second, the tools themselves were presented.

The main tool used was the TRIVAC model. TRIVAC is a decision-support model developed by the LSHTM, and it had been used by the ProVac Initiative in Latin America for many years [1]. It is built in Excel and can be used by countries to conduct CEAs of vaccines that prevent disease caused by three pathogens: rotavirus, pneumococcus, and *Haemophilus influenzae* type b.

The TRIVAC model has three particular characteristics that facilitate training in countries. First, it is a transparent model that shows data inputs, calculations, and results, thus allowing analysts to understand the steps that lead to the results. Second, a range of results are displayed that can be used as evidence for decision-making. These results include the number of cases, hospitalizations, and deaths averted; number of fully vaccinated children; cost of the immunization program; and cost of health services avoided. Third, the Excel software is globally available and user-friendly. With TRIVAC, people from many countries and backgrounds, independent of their knowledge of models and software, can conduct an economic evaluation with the appropriate data [3].

2.2. A regional training workshop

In October 2012, AMP and the WHO Regional Office for Europe held a regional training workshop, in the city of Dubrovnik, Croatia, on the cost-effectiveness of the pneumococcal conjugate vaccine (PCV). The aim of the workshop was to train health professionals, increase the countries' knowledge on the use of economic evaluation to inform new-vaccine introduction policy, improve countries' capacity to conduct country-owned CEAs, and assess regional demand for economic studies. Thirty-one participants from four countries (Albania, Croatia, Estonia, and Georgia) attended. The PCV component of the TRIVAC model was used as a basis for workshop exercises.

After the workshop, three of the four countries that participated (Albania, Croatia, and Georgia) submitted official letters to the WHO Regional Office for Europe, asking to be included in the ProVac IWG. Estonia did not present a request because data on cost-effectiveness of new vaccines became available from studies conducted by that country's University of Tartu. However, the ProVac IWG did also support a national study in Azerbaijan, which made a request to WHO in 2012.

2.3. A multidisciplinary national working group

A common priority for AMP and the WHO Regional Office for Europe was to use CEAs to strengthen decision-making in immunization policy and to ensure the sustainability of vaccine introduction. Therefore, emphasis was given to maximizing the commitment and support of existing advisory bodies in the country (National Immunization Technical Advisory Group [NITAG] or interagency coordination committee [ICC]) as well as other stakeholders involved in decision-making (ministry of health, ministry

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of finance, WHO country office, and United Nations Children's Fund).

At the national level, AMP and the WHO Regional Office for Europe utilized the ProVac approach in helping each country create a national team of experts from diverse organizations and with multiple areas of expertise, such as epidemiology, infectious disease, finance, pediatrics, and economics. This multidisciplinary team of experts was responsible for collecting the appropriate data for the CEA. The team included staff from such institutions as the respective ministry of health (MoH), the institute of public health, the main university hospital, and the NITAG. The coordinator and leader of this team was a national focal point, previously designated officially by the MoH. AMP and the WHO Regional Office for Europe encouraged the inclusion of candidates who could devote at least half of their time to the ProVac IWG, since they would be in charge of conducting the studies. AMP and WHO strongly advised the selection of a focal point already in position with a relevant immunization policy-making organization, in order to ensure that the capacities learned would endure in the country. If the national focal point was already an employee of the national immunization program, this would help guarantee country ownership of the study and thus sustainability of the process.

2.4. A six-month country-led study process

AMP, the WHO Regional Office for Europe, and the other ProVac IWG partners worked with countries for an average of six months. This included two or three in-country visits lasting two or three days each. The first visit aimed to raise awareness on the project and to ensure commitment from authorities and to train the focal point and the multidisciplinary team on economic evaluation and the TRIVAC model. The second visit focused on assessing data collected to populate the model. The third visit consisted of validating final data, interpreting results, undertaking scenario analysis, and assisting the team in preparing a presentation for national stakeholders. This three-visit approach allowed a close follow-up with the national team by international experts who could provide needed assistance.

With this approach, many national authorities were brought into the CEA process. In Albania, for example, the study results were presented to the NITAG, ICC, MoH, institute of public health, red cross albania, health insurance institute, national drug control center, and UNICEF. National teams were also encouraged to publish an article on their study in a peer-reviewed journal.

2.5. Support from the ProVac International Working Group

The ProVac IWG brought together different actors, different institutions, and different areas of expertise to jointly work on the undertaking. AMP was in constant communication with the other partners to share and gain from their experiences and expertise. For example, the partners suggested improvements to the TRIVAC model and the ProVac methodologies. The needs and level of development of the non-PAHO countries were different from those of the PAHO nations. AMP provided feedback to the LSHTM and PAHO on making the tools more useful and tailored to the countries' circumstances. CDC experts helped the countries validate the data used for their study models and provided the best available evidence on the efficacy of vaccines and the burden of disease at both the regional and international level.

3. Results

With the 53 Member States in the WHO European Region, the ProVac IWG effort was aimed at middle-income countries, which have to bear the full cost related to introducing new vaccines. Some of these countries have been able to receive support from Gavi, the Vaccine Alliance (Gavi),[1] but they have had to co-finance an increasing proportion of the price of new vaccines, starting at 20% and ending with the full price within four years.

Even with initial support from Gavi, the introduction of vaccines doubles or triples the cost of immunization programs in middle-income countries and requires either increasing the overall MoH budget or redistributing funds from other programs within the MoH. The resources available for public health programs in these countries are limited, and ministries of health face a number of competing priorities. Therefore, economic evidence to help decide if introducing new vaccines should be prioritized along with other public health programs has been particularly important for middle-income countries. Additionally, the CEA results, along with other evidence, could help policy and decision makers to advocate to the ministries of finance for allocation of additional funds. Further, in Croatia, the CEA conducted with ProVac IWG support was the country's first economic evaluation in the area of infectious disease prevention and control; this effort has helped build economic evidence into the nation's decision-making process.

In all four countries, the CEA studies provided an opportunity to use national surveillance statistics and global estimates to review the data on the burden of the diseases preventable by the new vaccines. For example, the CEA team in Albania estimated the burden of rotavirus gastroenteritis using data from rotavirus sentinel surveillance and national mortality statistics. The Croatian team conducted analysis of data from their national infectious disease notification system and reviewed publications related to the distribution of pneumococcal serotypes in their country. The teams in Azerbaijan and Georgia critically reviewed data from population-based passive pneumonia and meningitis surveillance. The ProVac IWG helped these teams to better understand the potential biases in these estimates and provided alternative WHO estimates to use in scenario analysis.

The work also improved the understanding of the financial implications that these diseases hold for public health systems. The CEA teams in all the countries estimated a frequency of hospitalizations and outpatient visits due to diseases that could be prevented by the new vaccines, along with the potential resulting cost savings in the health care and treatment provided by governments.

3.1. Two Gavi graduating countries: Azerbaijan and Georgia

In 2010, Azerbaijan and Georgia applied for Gavi support to introduce PCV. The applications were submitted in order to use the last opportunity to receive Gavi support because both countries were due to lose their Gavi eligibility status in 2011. However, those two countries' decisions to introduce new vaccines were still at a preliminary stage. In 2010, due to global constraints in new-vaccine supplies, it was not known when pneumococcal vaccines would become available for these countries. Therefore, the MoH decisions and corresponding financial commitments needed to be reconsidered and confirmed at a later stage. In addition, in Azerbaijan, in accordance with local regulations, prior to the introduction of the new vaccine, the MoH had to obtain approval of its decision from the Cabinet of Ministers.

In both of the countries, the national advisory bodies provided scientific recommendations to support final decisions on introducing PCV based on evidence related to the burden of pneumococcal

[1] The Global Alliance on Vaccines and Immunization (GAVI) was established by the Bill & Melinda Gates Foundation in late 1999. (Recently, the organization changed its name to Gavi, the Vaccine Alliance [Gavi]). Gavi's mission is "saving children's lives and protecting people's health by increasing access to immunization in poor countries." More information is available at: http://www.gavialliance.org.

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Table 1
Summary of data and results of the cost-effectiveness analysis for each country.

Country	Albania		Azerbaijan	Georgia	Croatia	
Vaccine(s)	RV1	RV5	PCV10	PCV10	PCV13	PCV10
Estimated price of vaccine (per dose)	$8.5	$8.5	$3.5	$3.5	$35	$30
GDP/capita	$3707	$3707	$7490.5	$3508	$13,227	$13,227
$US per DALY averted from a government perspective	$1935	$4954	$66	$1599	$87,053	$73,642
Result	Highly cost-effective	Cost-effective	Highly cost-effective	Cost-effective	Not cost-effective	Not cost-effective

diseases, efficacy and safety of PCV, programmatic feasibility of introduction, and acceptance of the new vaccine by medical workers and the population. However, policymakers needed additional economic evidence to make sure that the vaccine introductions should be prioritized among other public health interventions, confirm their preliminary decision to introduce pneumococcal vaccine, and warrant the allocation of additional funds.

The MoHs were also going to use the CEA results to advocate with the Ministry of Finance for additional funds to ensure timely provision of increasing co-financing payments as well as sustainable financing of PCV vaccination after the end of the Gavi support. The lack of local expertise in health economics and economic evaluation prompted the MoHs to request support from the WHO Regional Office for Europe, which in turn requested support from the ProVac IWG.

In Azerbaijan, the CEA results indicated that introducing PCV10 would be highly cost-effective (Table 1). The results helped the MoH of Azerbaijan to confirm its decision to introduce pneumococcal vaccine. The results were also included in the request submitted to the Cabinet of Ministers, contributing to their final approval and to introduction of PCV in December 2013. The MoH has expressed an interest in further studies using the TRIVAC model and methodology, including for a comparative analysis of the 13-valent PCV and for a CEA of the HPV vaccine.

In Georgia, the results of the study indicated that introducing PCV would be highly cost-effective (Table 1) [5]. The MoH confirmed its preliminary decision to introduce pneumococcal vaccines and made corresponding financial commitments. The pneumococcal vaccine was introduced into the national immunization schedule in November 2014.

3.2. Two middle-income countries: Albania and Croatia

In the middle-income nations of Albania and Croatia, the national advisory bodies recommended introducing new vaccines into the routine immunization schedule. However, the MoHs requested additional economic evidence to make a final decision to introduce new vaccines and to ensure that allocating additional funds would be justified.

In Albania, the national immunization program and the ICC discussed introducing the rotavirus vaccine. They concluded that introduction was justified, given the burden of disease, vaccine characteristics, and public health considerations. However, final recommendations to the MoH were dependent on additional evidence indicating that introducing rotavirus vaccination would be cost-effective. Therefore, the MoH asked the WHO Regional Office for Europe and AMP for support in conducting an economic evaluation.

The ProVac IWG CEA results indicated that introducing vaccination against rotavirus in Albania was either cost-effective or highly cost-effective,[2] depending on the vaccine (RV1 or RV5) and on the perspective chosen (governmental or societal) (Table 1) [6]. Based on these results and other relevant evidence (such as safety, efficacy, burden of disease, and acceptance), the ICC (which served as a national advisory body) recommended the MoH introduce the vaccine into the country's immunization schedule. The MoH accepted the ICC recommendation. However, the introduction of rotavirus vaccine in Albania has been scheduled for 2015 because in 2014 the country planned to introduce IPV as part of implementing the Polio Eradication and Endgame Strategic Plan. The ProVac IWG economic evaluation helped to better the understanding of how vaccine price influences cost-effectiveness. The analysis also prompted the MoH to request that the UNICEF procurement division include Albania in its initiative to support middle-income countries in accelerated introduction of rotavirus vaccines.

Croatia was a middle-income country when it was selected to participate in the ProVac IWG. In July 2012, Croatia became a high-income country, in accordance with the World Bank classification.[3] Similar to Albania, the NITAG in Croatia discussed recommendations on PCV introduction, but final recommendations were pending additional economic evidence that could help to prioritize the introduction of PCV among other public health interventions. Support to conduct a CEA came from the WHO Regional Office for Europe and the ProVac IWG. One objective of the CEA was to assess if introducing PCV vaccine would be cost-effective, taking into account the high vaccine price set by the manufacturers. The Croatian government had cost effectiveness estimates from pharmaceutical company studies but wanted to have an independent source of information.

The CEA results indicated that introducing pneumococcal vaccine into the routine immunization program in Croatia would not be cost-effective, based on the costs and benefits to children aged <5 years (Table 1) [7]. This was true for both PCV13 and PCV10. The major parameters affecting the incremental cost-effectiveness ratio (ICER) were the high price of the vaccine and the relatively low mortality due to pneumococcal diseases. The MoH decided to postpone PCV introduction until the vaccine's price is reduced.

This CEA work was one of the first MoH-led cost-effectiveness studies in Croatia. It was also the first time in the country that a decision on introducing a new immunization intervention took into account economic evidence. The evaluation stimulated interest in improving existing analyses (such as on incorporating health benefits for older age groups) and in generating similar economic evidence each time a new vaccine is considered. The multidisciplinary team has recommended that the MoH make routine use of economic evaluations to support decisions and prioritization of public health interventions.

4. Discussion

The ProVac IWG enabled advisory bodies (NITAGs or ICCs) in four countries to develop evidence-based recommendations to the ministries of health on making or confirming preliminary decisions

[2] Based on the threshold of >1 GDP per capita to >3 GDPs per capita established by the WHO's Commission on Macroeconomics and Health. For more information please, see: http://www.who.int/choice/costs/CER_thresholds/en/.

[3] For additional information, visit the World Bank website, at: http://www.worldbank.org/en/country/croatia.

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on introduction of rotavirus and pneumococcal vaccines. The CEAs provided the ministries with additional economic evidence that helped them to prioritize the introduction of the new vaccines among other public health programs.

In Albania, for example, following the CEA, introduction of rotavirus vaccine was recommended by the ICC. The MoH accepted the ICC recommendation, and introduction is planned for 2015. In Georgia and Azerbaijan, preliminary decisions made in 2010 (in order to not lose an opportunity to receive Gavi support) were confirmed by the ministries of health, and relevant financial commitments were made. PCV was introduced in Azerbaijan in December 2013 and in Georgia in November 2014. In Croatia, the MoH made a decision not to introduce PCV until the vaccine price decreases to a level where the introduction becomes cost-effective.

Overall, the transparency of the TRIVAC model developed by LSHTM allowed the process of producing evidence and its value to be demonstrated and understood by a variety of national experts and national authorities. Importantly, all four ProVac IWG country teams recommended that economic evaluations become a routine approach in making decisions and prioritizing public health interventions.

A second notable effect was capacity-building. The national focal points were trained on economic evaluation and on the TRIVAC model, using a learning-by-doing approach. The focal points were active workers in the field and in institutions surrounding vaccination decision-making processes. In Albania, the focal point worked at the Institute of Public Health; in Azerbaijan, he was head of the MoH department for immunization; in Croatia, he was the EPI manager; and in Georgia, the focal point worked at the Department of Communicable Disease Surveillance. This choice of focal points encouraged sustainability because the skills gained through the ProVac IWG process remained in those institutions, rather than being lost as when an external consultant leaves.

AMP and the IWG partners also trained the multidisciplinary teams on the TRIVAC model and on the process of economic evaluation in general. In addition, the members of national advisory committees were trained to better understand the methodology of economic evaluations and to properly interpret the results of CEAs. They learned how to use the economic evidence to develop recommendations on new vaccines and how to communicate the results of CEAs to policymakers and decision makers.

A third benefit was that the CEAs helped the countries to conduct thorough analyses and better estimate the burden of disease by combining locally available data and the results of global estimates. The ProVac IWG helped the national teams to better understand the limitations of and properly interpret their national surveillance and statistics data. The studies provided estimates that helped the ministries of health to better understand the financial burdens that diseases preventable by new vaccines impose on the health care system. The countries were also able to define the price that would make introducing the new vaccines cost-effective.

A fourth noteworthy outcome came at the regional level. AMP and the WHO Regional Office for Europe applied the ProVac IWG methodology in a standardized way in all four countries in order to provide consistent support, but also to enable the nations to help each other through peer-to-peer exchanges and to build long-lasting regional collaborations. Indeed, the focal point from Georgia attended the final country visit of the AMP team to Azerbaijan, to see the work to be done there and to observe the work of its national team in action.

In June 2014 the WHO Regional Office for Europe conducted a regional meeting where the methodology and results of the CEAs conducted with ProVac IWG support were shared with other middle-income countries. The participants achieved common agreement on the important role of economic evidence in justifying the introduction of expensive new vaccines. They also discussed using CEA results to prioritize introducing new vaccines and to advocate for additional funding to cover the cost. Many of the countries expressed their interest in obtaining WHO Regional Office for Europe support in conducting similar economic evaluations. The Regional Office is going to extend the peer-to-peer exchange implemented within ProVac IWG by having trained specialists from Azerbaijan, Georgia, or Croatia participate in evaluations planned for the Republic of Moldova and Uzbekistan.

While the ProVac IWG effort has had a clear impact on the individual countries and the WHO European Region overall, some ongoing challenges must be mentioned. A major constraint for the countries involved was the lack of available national data on disease burden and cost of treatment of diseases preventable by new vaccines. This was especially true for the nations that do not implement laboratory-based invasive bacterial diseases surveillance or countries that have recently been through substantial health system reforms. This limitation affected the results of the CEAs since the countries sometimes had to rely on global estimates, international data, or expert opinions. For example, Georgia went through a change in the financing of its health care system, so it was difficult to obtain cost data. Of course, these approximations were assessed as much as possible in the scenario analyses that were done as part of the CEAs.

Table 1 briefly summarizes the data and results across the four nations, and more detailed information and results are available in a set of country-specific articles [5–7] and in table 2 of the ProVac IWG overview piece [2].

It is difficult to make comparisons among the four country studies described in this paper. Three of the studies focused on PCV, and one dealt with RV. Two of the nations are Gavi graduating countries; one is a middle-income nation, and one is a middle income nation which became a high-income nation during the study (Croatia). In addition, assumptions, perspectives, and scenarios were customized to each country context to ensure the results were meaningful for national decision makers.

All of these factors make it hard to compare results across the countries. In particular, the source of evidence varied depending on the parameter considered. For example, the source of health care cost estimates ranged from expert opinion in one country to a carefully conducted costing study in another. The PCV studies also presented a range of results. In Croatia, PCV was not found to be cost-effective in the base case or in most alternative scenarios, but the analysis did not include the additional, indirect benefit that herd immunity would have for older individuals. Neither Georgia nor Azerbaijan considered this factor, but the case for vaccination was still clear in those two countries. The difference in Croatia is that it has a much higher GDP per capita and a much lower mortality rate in children. Thus, the case for vaccination is less clear, and the next step will be to assess the potential importance of the benefits for older individuals.

5. Conclusion

The ProVac experience gained by PAHO in the Americas was shared with AMP and the WHO Regional Office for Europe and its partners, and then applied to the WHO European Region. This type of cooperation should be scaled up. The strong collaborations among the ProVac IWG partners and the countries in the WHO European Region have been very fruitful, and they should be continued. In addition, many other countries in the WHO European Region have expressed interest in receiving assistance from the ProVac IWG. The way forward is to make sure that all those countries receive the support they need to implement economic

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evaluations and promote evidence-based decision-making for vaccines and other health interventions.

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Acknowledgments

The authors would like to thank the focal points and multidisciplinary teams in Albania, Azerbaijan, Croatia, and Georgia for their time and valuable contributions to the ProVac IWG effort and to this article.

For their contributions to the ProVac IWG, the authors recognize many persons from the Agence de Médecine Préventive, including Alfred Da Silva, Philippe Stoeckel, Brad Gessner, Aline Munier, Antoine Durupt, Chloé Thion, Sabrina Gaber, Anais Colombini, Jean-Bernard Legargasson, Andrée Diakité, Aude Bruyas, Coline Laugraud, Alexandre Blake, Carlos Lara, and Viktor Galayda. Similarly, appreciation goes to Kamel Senouci from WHO and to Anushua Sinha from Newark University Hospital.

For their assistance in implementing this effort, the authors would like to thank all the ProVac IWG partner organizations (and some of their specific representatives), including the Pan American Health Organization (Barbara Jauregui, Cara Janusz); London School of Hygiene & Tropical Medicine (Colin Sanderson); Program for Appropriate Technology in Health; Sabin Vaccine Institute (Christopher Nelson, Diane Coraggio); United States Centers for Disease Control and Prevention (Rana Hajjeh, Ben Lopman, Manish Patel, Umesh Parashar, Tamara Pilishvili), WHO headquarters (Raymond Hutubessy, Miloud Kaddar), WHO regional offices, and WHO country offices.

Appreciation also goes to science editor Bill Black for his help on the manuscript.

Conflict of interest statement: The authors have no conflict of interest to declare. The current manuscript was supported by the ProVac IWG, which is funded entirely by a grant from the Bill & Melinda Gates Foundation.

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Vaccine 33S (2015) A13–A20

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Costs and financing of routine immunization: Approach and selected findings of a multi-country study (EPIC)

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ARTICLE INFO

Keywords:
Costs
Financing
Routine immunization
Productivity
Low-income

ABSTRACT

Background: Few detailed facility-based costing studies of routine immunization (RI) programs have been conducted in recent years, with planners, managers and donors relying on older information or data from planning tools. To fill gaps and improve quality of information, a multi-country study on costing and financing of routine immunization and new vaccines (EPIC) was conducted in Benin, Ghana, Honduras, Moldova, Uganda and Zambia.
Methods: This paper provides the rationale for the launch of the EPIC study, as well as outlines methods used in a Common Approach on facility sampling, data collection, cost and financial flow estimation for both the routine program and new vaccine introduction. Costing relied on an ingredients-based approach from a government perspective. Estimating incremental economic costs of new vaccine introduction in contexts with excess capacity are highlighted. The use of more disaggregated System of Health Accounts (SHA) coding to evaluate financial flows is presented.
Results: The EPIC studies resulted in a sample of 319 primary health care facilities, with 65% of facilities in rural areas. The EPIC studies found wide variation in total and unit costs within each country, as well as between countries. Costs increased with level of scale and socio-economic status of the country. Governments are financing an increasing share of total RI financing.
Conclusions: This study provides a wealth of high quality information on total and unit costs and financing for RI, and demonstrates the value of in-depth facility approaches. The paper discusses the lessons learned from using a standardized approach, as well as proposes further areas of methodology development. The paper discusses how results can be used for resource mobilization and allocation, improved efficiency of services at the country level, and to inform policies at the global level. Efforts at routinizing cost analysis to support sustainability efforts would be beneficial.

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1. Introduction

Vaccines are one of the best buys in public health [1,2] and a good candidate for government financing [3]. Historically, the cost per fully immunized child (FIC) with measles, polio, DTP, and BCG vaccines ranges from less than $3 to $22, with variation between countries by facility type and ownership, volume of vaccines administered, wastage rates, type of delivery strategy, and input prices [4,5–11][1]. Unit costs generally decline as output increases, but there is scant evidence on whether unit costs will rise as coverage increases beyond 80% [1,12,13].

Currently, all GAVI-eligible countries have introduced pentavalent vaccine into their routine immunization (RI) programs[2]. Rotavirus, pneumococcal, and HPV vaccine introductions also are on the rise worldwide [14]. Total and unit costs of RI have increased with the introduction of new vaccines [15–17] but many of these studies have relied on secondary estimates of costs and financing. Secondary sources have been shown to underestimate the cost of

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[1] DTP refers to the diphtheria–tetanus–pertussis vaccine and BCG is the Bacillus Calmet–Guerin vaccine that protects against tuberculosis.

[2] The pentavalent vaccine is a combination vaccine preventing pertussis, tetatnus, diphtheria, hepatitis B, and haemophilus influenza type b.

http://dx.doi.org/10.1016/j.vaccine.2014.12.066
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Table 1
EPIC study country characteristics (2011).

Country	DTP3 coverage level (WUENIC) (%)	Total doses (million)	GNI per capita	Infant population
Benin	85	3.7	$720	348,577
Ghana	91	9.5	$1,420	1011,012
Uganda	80	11.9	$470	1326,826
Zambia	81	4.8	$1,180	567,320
Moldova	93	0.68	$1,980	47,537
Honduras	91	3.8	$2,030	177,733

Sources: WHO-UNICEF Best Estimates (who.immunization.org); EPIC study reports; World Development Indicators, Ministry of Health Reports.

national immunization programs [11] and reliability of secondary sources has been questioned [18].

Facility-based costing surveys have the potential to more fully capture the costs and financing of immunization through more detailed analysis of input use. Given the pace and breadth of new vaccine introduction and universal coverage goals highlighted in the Global Vaccine Action Plan [19], as well as the emphasis by the global community on Universal Health Coverage (UHC), there is a critical need for updated cost and financing estimates for RI and new vaccine introduction. Understanding the costs of existing coverage levels is a first step toward adequate planning and budgeting for GVAP and UHC goals. Potential cost variation at the facility level merits further exploration, as such analyses can identify areas of program efficiency and value for money.

2. Objective and scope of the EPIC studies

This paper describes the methods, selected findings and policy focus the EPI Costing and Financing (EPIC) studies conducted between 2012 and 2013 in Benin, Ghana, Honduras, Moldova, Uganda and Zambia, supported by the Bill & Melinda Gates Foundation (BMGF). The purpose of the EPIC studies was to provide countries and the global community with updated and detailed cost estimates of RI programs with pentavalent vaccine in the schedule, as well as the incremental costs of other new vaccines.

The EPIC studies were conducted by the Pan American Health Organization (Honduras); Curatio Foundation International (Moldova); Health and Development Africa (Uganda and Zambia); and Agence pour la Medicine Preventive (Ghana and Benin). Each organization selected countries that had introduced pneumococcal and/or rotavirus vaccines in either 2011 or 2012 as part of their response to a Request for Proposals (RFP) issued by the BMGF. The RPF focused attention on determining facility-level total and unit costs, and reasons for their variation; financial flow analysis of the RI program; new vaccine introduction cost; and, comparisons with other economic information and planning estimates. All studies received ethical clearance from respective governments.

The EPIC studies estimated RI costs from a government perspective. RI was defined as immunization services provided on a regular basis either in public or non-governmental organization (NGO) facilities, or through community outreach services. The study excluded the cost of supplementary immunization activities (SIAs), and private, for-profit facilities. Introduction costs of HPV vaccines also were excluded as these were being evaluated elsewhere [20,21].

The studies benefited from advice of Steering Committee members[3] and inputs from partners through the GAVI Alliance Immunization Financing & Sustainability Task Team[4]. In addition to building the evidence-base, this exercise strengthened capacity of researchers and fostered collaboration between government, researchers, and international experts, ultimately developing a community of practice.

Table 1 compares the characteristics of the EPIC countries. Coverage of the third dose of DTP vaccine (used as a proxy in this study for fully vaccinated child) ranged from 80% in Uganda to 93% in Moldova [22]. Two of the countries are low-income (Benin and Uganda); two countries are categorized as intermediate countries by GAVI (Ghana and Zambia); and two countries will graduate from GAVI support in the next few years (Moldova and Honduras). The infant target population ranges from less than 200,000 (Honduras) to nearly 1.5 million (Uganda).

3. Methods and common approach

Because EPIC studies were carried out by different organizations, a Common Approach was developed to harmonize and standardize methods for cost and financing estimation [23].

3.1. Costing of routine immunization (RI)

The EPIC studies evaluate both the economic and financial costs of the routine immunization program[5]. Costing utilized an ingredients-based approach to data collection on quantities of inputs used, unit prices, and proportion of time or use for immunization, similar to other immunization costing methods [25–28].

The study evaluated **recurrent inputs** by line items such as personnel, vaccines, syringes and other supplies, per diem, fuel and transport, cold chain maintenance, maintenance of other equipment, and operating costs; and **capital inputs**, such as cold chain, vehicles, computers, and other capital inputs. In addition, the study examined costs by activity classification: facility-based service delivery, outreach, record-keeping and HMIS, supervision, training, social mobilization, supply chain and logistics, program management, surveillance, and other. A matrix between line items and activities was developed to facilitate analysis (Fig. 1).

[3] Steering Committee members included Carol Levin (University of Washington); Ulla Griffiths (London School of Hygiene and Tropical Medicine); Raymond Hutubessy (WHO); Stephen Resch (Harvard School of Public Health); and Mike Hanlon (Institute for Health Metrics).

[4] IF&S TT members participating providing feedback on the study included Santiago Cornejo and Marya Paytna (GAVI Secretariat); Claudio Politi (WHO/HQ); Gian Gandhi and Tom O'Connell (UNICEF); Mike McQuestion (Sabin Institute); Niyazi Cakmak (WHO EURO); Amos Petu (WHO ESA); Alexis Saytalou (WHO WCA); Claudia Castillo (PAHO).

[5] Economic costs represent the opportunity cost associated with using inputs in the routine immunization program as compared to their next best use. Financial costs refer to financial outlays made to support routine immunization. An economic cost analysis estimates the annualized value of capital investments and the value of donated goods and labor time; whereas, a financial cost estimate is based on the financial outlay for capital equipment and excludes the value of donated goods and services.

Line Item/ Activity	Routine Facility-based Service Delivery	Record-Keeping & HMIS	Super-vision	Outreach Service Delivery	Train -ing	Social Mobiliz-ation& Advocacy	Surveill -ance	Cold Chain Mainten -ance	Vaccine Collection, Distribu-tion Storage	Program Manage-ment	Other
Salaried Labor											
Volunteer Labor											
Per Diem- Travel Allowances											
Vaccines											
Vaccine Injection & Safety Supplies											
Other Supplies											
Transport/ Fuel											
Vehicle Maintenance											
Cold Chain Energy Costs											
Printing											
Utilities, Communication											
Other Recurrent											
Cold Chain Equipment											
Vehicles											
Lab Equipment											
Other Equipment											
Other Capital											
Buildings											

Fig. 1. Matrix of costing line items and activities for routine immunization. *Source*: Brenzel, L. Common Approach for the Costing and Financing Analyses of Routine Immunization and New Vaccine Introduction Costs (EPIC). Working Paper, Mimeo (2014).

Costs were based on a multi-stage, stratified random sample of public and NGO primary health facilities in each country to obtain a representative sample (Table 2). The sampling frame was based on a purposive selection of regions, followed by random selection of districts [29]. Within each district, facilities were randomly selected from a complete list of facilities, with oversampling of rural facilities to better understand their cost structure.

Sample size was estimated based on a two-stage sampling technique with correction for proportions, and a level of error of 10%, leading to a target sample size of approximately 50 facilities per country. There was some variation in approach, with the Honduras study having a sample of 71 facilities, and the Benin study 46 facilities. The EPIC studies resulted in a total sample of 319 facilities, of which 65% were in rural areas.

Data collection was accomplished using a standardized questionnaire that was adapted and pretested in each country [23]. Data were collected on the total quantities of inputs, unit prices, facility outputs, facility characteristics, useful life of equipment and vehicles, and other factors to enable allocation of shared inputs to routine immunization. Labor time for RI was assessed through a cascade of time-related questions:

- How many days per week does this staff usually work at this health facility?
- How many hours per week does this staff usually work at this health facility?
- What portion of these hours is spent on all routine immunization related activities?
- What proportion of time is spent on each routine immunization activity (as specified in Fig. 1)?

Other approaches to estimate labor time and costs, including time and motion studies and weekly activity diaries exist [30], but these options were not pursued given time and resource constraints, and potential for other biases to be introduced. While there are challenges in eliciting time responses from personnel, study teams incorporated validation techniques during field surveys to minimize bias.

Other shared inputs, such as transport and vehicles, were allocated to RI on the basis of the share of distance traveled by vehicles. Building space was allocated based on the share of facility area used for RI activities including storage of vaccines. Questionnaires were used to obtain output information and qualitative data on facility management. In addition, administrative, managerial, and program-related outputs (doses and children vaccinated) and inputs such labor time, per diem, transport, vaccine storage and distribution, supervision, and management were collected at district, regional and national levels using standardized, pre-tested questionnaires.

Table 2
EPIC studies facility sample by country.

Country	Total Facilities	Rural	Urban
Benin	46	26	20
Ghana	50	38	12
Honduras	71	31	40
Moldova	50	42	8
Uganda	49		
Zambia	53	38	15
Total	319	175	95
Percent (%)		65	35

Source: EPIC country reports, 2014. *Note:*the Uganda sampling frame was done on the basis of facility type.

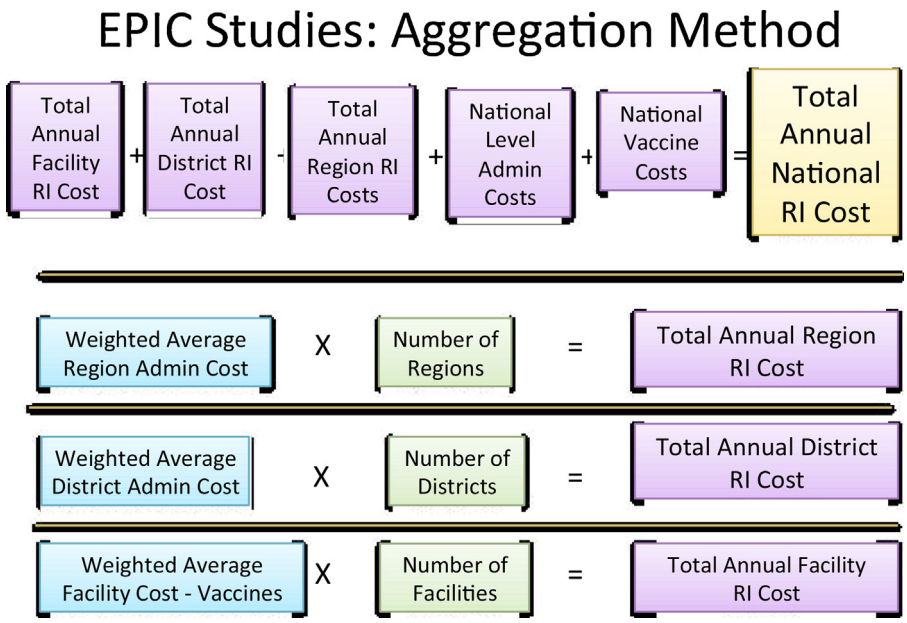

Fig. 2. Cost aggregation method for the EPIC studies. *Source*: Brenzel, L. Common Approach for the Costing and Financing Analyses of Routine Immunization and New Vaccine Introduction Costs (EPIC). Working Paper, Mimeo (2014).

Each study recruited and trained enumerators to administer questionnaires, and pre-testing was a form of hands-on training. Each study team included field supervisors who regularly verified survey responses. Emphasis was on maintaining high quality and reliability of information collected.

An Excel-database tool developed for analysis of facility-level data the EPIC studies [24][6]. This tool mimicked the facility questionnaire to facilitate data entry and estimated total and unit costs (per dose, child, and FIC) in both local currency units and $US 2011[7]. The database tool included validation checks to ensure data were entered properly and that answers were within a plausible range. The database tool also allowed for export of summary data into statistical software for further analysis. All facility results were weighted based on sampling weights, and capital costs were annualized based on useful life and a 3% discount rate.

While the EPIC studies emphasized evaluation of facility cost variation, there was a need to generate national total and unit costs for policy recommendations. The approach was based on use of weighted average facility and administrative level costs. Facility, district, and regional costs were added to total national vaccine and RI program costs to generate the total national RI cost (Fig. 2)[8]. Other methods including statistical approaches were described in the Common Approach and will be explored in the subsequent phase.

3.2. Costing of new vaccine introduction (NUVI)

Costing new vaccine introduction drew from the WHO Guidelines for estimating incremental costs of introducing new vaccines into the national immunization system [31], supplemented by methods used in recent studies [20,21,32,33]. The time period for costing new vaccine introduction is important to distinguish. For the EPIC studies, expenditures for capital equipment to fill gaps in the routine program six months prior to new vaccine introduction and up to six months after the initial period of introduction were evaluated, unless otherwise designated by the EPI manager.

Studies estimated a series of incremental costs of new vaccines from a governmental perspective (Table 3). I**ncremental economic costs** that valued additional time and use of cold chain capacity, donated goods and services would be useful for evaluating cost-effectiveness of NUVI. **Incremental financial cost** estimation, relevant for planning and budgeting for NUVI, relied on a different approach to capital evaluation and excluded donated goods and service. **Incremental fiscal costs** measured financial outlays to benchmark costs against needed subsidies.

Costs were disaggregated into one-time investments, and ongoing NUVI costs. Investment costs were defined as those specific to the introduction event, such as initial training and social mobilization events. These were annualized and discounted using estimates of useful life of training (2–3 years) at a 3% rate. The WHO Vaccine Volume Calculator was used to estimate additional cold storage requirements o [34]. Ongoing costs of NUVI were defined as the additional recurrent costs to the RI program, including labor costs and maintenance.

3.3. Financial flows for routine immunization

The EPIC studies measured the total financial envelope available for immunization, tracing flows from all sources to their intended use. All sources of financing, their relative importance, and purpose of support were evaluated. Information was collected from national and sub-national government, donor agencies (in-country and headquarters), non-governmental organizations, and other sources. The approach did not evaluate expenditures as these would be somewhat duplicative of the financial cost estimates previously generated. In addition, evaluating financial flows allows the government and partners to see the total available resources, whether they were actually spent or not. Expenditures are dependent upon the effectiveness and efficiency of public expenditure management systems and donor processes and procedures, and would under-estimate the total resources available for a program.

[6] The Moldova team developed a separate Excel-based analytical tool, and the Honduras team used the CostVac Tool, which was further developed under the EPIC studies.

[7] FIC refers to a fully immunized child or those who have received the third dose of the pentavalent vaccine.

[8] An alternative approach using the results of the determinants analysis was used in some studies, but the results were found to be similar to the averaging approach.

Table 3
Cost estimation for new vaccine introduction for the EPIC studies.

Line item	Economic costs	Financial costs	Fiscal costs
Salaried labor	Included to represent opportunity cost of time of existing staff involved in NUVI (FT and % of time)	Labor costs of new staff hired to accommodate NUVI	Included if new staff needs to be hired
Volunteer labor	Economic Value Included	Excluded	Excluded
Per diems	Included	Included	Included
Vaccines	Economic value of vaccines utilized	Financial costs of purchased vaccines	Financial cost of purchased vaccines
Vaccine injection supplies	Economic value of utilized supplies	Financial cost of purchased supplies	Financial cost of supplies
Transportation and other transport costs	Economic value included	Included	Financial cost of fuel and other transportation
Cold storage costs	Economic value of current cold chain volume – and/or – economic value of additional cold storage equipment and supplies purchased for NUVI (discounted annualized share of total cost)	Financial costs of additional cold storage equipment and supplies purchase for NUVI using straight-line depreciation	Payment of additional cold chain purchase for NUVI
Vehicles	Economic value of vehicle use for NUVI activities	Purchase of vehicles for NUVI	Purchase of vehicles for NUVI

Source: Brenzel, L. Common approach for the costing and financing analyses of routine immunization and new vaccine introduction costs (EPIC). Working Paper, Mimeo (2014).

Table 4
Sample Coding of Health Care Functions for RI and NUVI for the EPIC Studies.

Classification of health care functions HC (functions)		
Code	Sub-code	Description
HC.1		Curative care
HC.6		Preventive care
	HC.6.1	Information, education and counseling programs
	HC.6.1.1	*Social mobilization, advocacy*
	HC.6.2	Immunization programs
	HC.6.2.1	*Facility-based routine immunization service delivery*
	HC.6.2.2	*Outreach routine immunization service delivery*
	HC.6.2.3	*Training*
	HC.6.2.4	*Vaccine collection, storage and distribution*
	HC.6.2.5	*Cold chain maintenance*
	HC.6.2.6	*Supervision*
	HC.6.2.6	*Program management*
	HC.6.2.7	*Other routine immunization program activity*
	HC.6.5	Surveillance
	HC.6.5.1	*EPI Surveillance*
	HC.6.5.2	*Record-keeping and HMIS*
HC.7		*Governance and health system financing and administration*
HC.99		Not disaggregated

Source: Brenzel, L. Common approach for the costing and financing analyses of routine immunization and new vaccine introduction costs (EPIC). Working paper, Mimeo (2014).

Complementary facility costing information at was paired with analysis of funding flows as needed.

The System of Health Accounts coding [35,36] was used to analyze financial flows in a harmonized manner across the six countries. These codes were disaggregated further to be consistent with the matrix of line items and activities developed for the Common Approach (Table 4)[9]. Data collection was facilitated through standard pre-tested data collection formats, and analysis was conducted using an Excel-based tool. Countries were encouraged to collect and analyze data for more than one year to evaluate trends. All findings were converted to $2011. Each team produced a mapping of financial flows for RI.

3.4. Health facility RI productivity performance

The EPIC studies focused on a comparison of facilities through a graphical analysis where facilities were plotted into quadrants according to high/low unit cost per dose based on median values (*X*-axis) and high/low doses administered (*Y*-axis). These plots revealed a spread of facility types across the performance spectrum. These plots could be used to identify those facilities with the same level of output but widely different costs. Facilities that can provide the same level of output for less cost could be interpreted as being more efficient. Additional productivity indicators such as doses administered per full-time equivalent; wastage rates for different vaccines; and, drop-out rates, were compared across facilities. Statistical analysis also sought to uncover the possible reasons for variation in performance levels to provide information to managers on how to improve performance and efficiency of service delivery.

4. Selected findings of the EPIC studies

We report some of the findings from the EPIC studies across countries to illustrate trends. Additional detail and analysis can be found in other manuscripts in this Supplement. First, there is a wide range of total facility immunization economic costs within the country samples, with nearly 200-fold differences in Moldova and 60-fold differences in Uganda. Benin had the smallest range between high and low cost facilities. Second, differences in total facility cost between countries are related to variation in wage rates and labor time spent on immunization. Fig. 3 illustrates the main cost drivers of facility costs for the EPIC studies and shows that the proportion of labor costs appears to

[9] The SHA codes are organized around the following: (1) Revenues (Financing Sources-FS): classifies funding sources at country level; (2) Health Care Financing (HF): classifies intermediary financing agents; Health Providers (HP): classifies funding by type of facility; Health Care Functions (HC): classifies RI activities; Health Care Provision (FP): classifies RI line item.

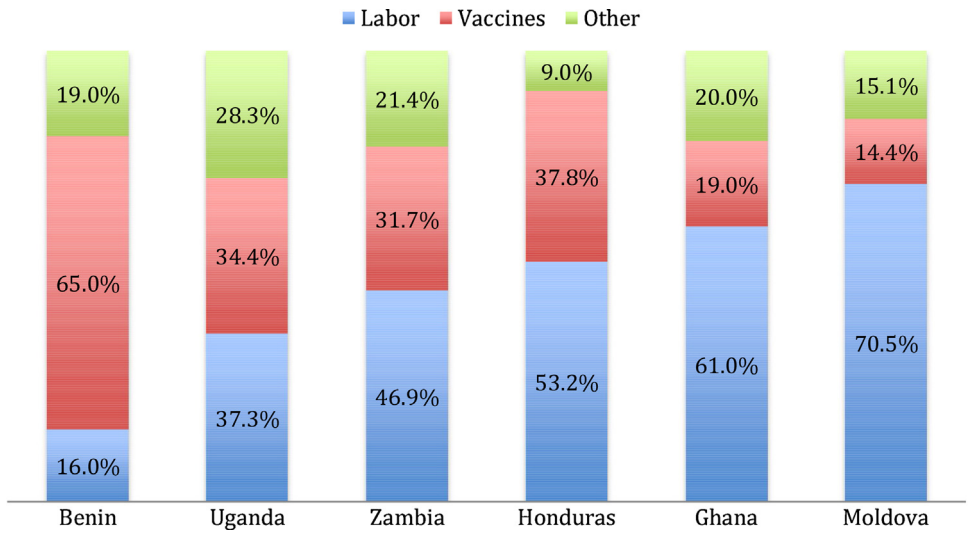

Fig. 3. Cost drivers at facility level for the EPIC studies. *Source*: author's calculations.

be related to level of economic development. In Moldova, 65% of total facility cost was for labor. Ghana has a relatively high labor share because of the role of volunteer labor (5% of total cost) and higher wage rates. All of the countries had a similar immunization schedule (pentavalent, oral polio, measles and BCG vaccines).

Third, average unit costs of RI at the facility level are higher than previously estimated. Table 5 shows the cost per dose ranges from $2 in Benin to $18 in Moldova, and the cost per infant varies from $19 to over $300. The cost per FIC ranges from $25 to $332, with an average of $46.50 in low income countries (Benin and Uganda), and $58.50 in socio-economically intermediate countries (Ghana and Zambia). The average cost/FIC for countries in Africa is $46.50. In Moldova, non-labor cost per dose is $6 compared to $18 with labor, and the non-labor cost per infant is $112 compared to $317. More detailed examination of cost variation will be undertaken in the next phase of EPIC.

The majority of total national RI costs was for service delivery with an average of 15% for administration and management costs above the facility-level. Moldova, which had the highest immunization coverage, had an above-facility share of 18%. Further investigation as to the relationship between management and immunization performance would be useful.

Finally, governments in the EPIC study sample are financing approximately 70% of the RI program on average, ranging from 45% in Benin and Uganda to 95% in Moldova. Total available financing ranged from approximately $9 million to $50 million in 2011.

5. Policy conclusions and lessons learned

The EPIC studies provide a unique set of high quality data on RI program costs, updating the evidence-base to include pentavalent vaccines in the immunization schedule. The studies reveal that governments are financing a larger total amount and share of RI than previously estimated [17]. The major cost drivers continue to be labor, followed by vaccines.

The EPIC studies also showed a wide range in facility-level total costs within countries, as well as variation in unit costs between countries. The extent of this variation may mean it is no longer possible to refer to a single point estimate of unit costs. Further analysis of factors contributing to cost variation can be useful for

Table 5
Facility-based routine immunization economic costs and national-level financing ($2011).

Country	Facility Weighted Average					Share of above facility costs (%)[b]	Total available financing (m)[c]	Share of government financing (%)
	Routine immunization economic cost	Cost/dose	Cost/infant	Cost/infant ($PPP)	Cost/FIC[a]			
Benin	$14,994 ($6,026–$50,472)	$2	$19	$42	$25	6	$10.12	45
Uganda	$23,470 ($1,911–$112,753)	$5	$20	$61	$44	16	$34.3	45
Ghana	$16,460 ($4,385–$99,789)	$5	$36	$78	$51	12	$50	85
Zambia	$28,286 ($6,260–$64,019)	$7	$60	$123	$66	26	$38.9	82
Honduras	$12,069 ($2,165–$221,235)	$8	$113	$217	$128	14	$49.1	64
Moldova	$11,943 ($565–$112,548)	$18	$317	$672	$332	18	$8.8	95

Source: authors' calculations rounded to nearest whole number.
[a] FIC = fully immunized child represented by number of children receiving the third dose of DTP-containing vaccine.
[b] Reflects administrative and program management costs at higher than facility levels.
[c] Figures reflect total resources potentially available and not actual expenditures made.

identifying ways in which performance of the RI program can be improved [38].

In all countries, the value of labor time represented an important share of total costs, ranging from 19% in Benin to 65% in Moldova. Labor time is a shared cost and data collection required enumerators to probe to determine both the allocation to immunization, and within immunization, the allocation to various activities. Because of the exclusive focus on immunization, time allocations may be overestimated relative to other services. Future studies could explore alternative methods, such as diaries or observation, or estimate time allocations (and costs) across the full range of services provided.

While most of the study teams followed the methods described in the Common Approach, there was some variation due to Ministry of Health requests. The sample size of 50 facilities was intended to be as representative as possible, with a reasonable level of power. Facility surveys are costly to conduct, and analysis can be time consuming. Achieving the right balance between feasibility and generalizability is important. Further work regarding facility sampling for costing studies and approaches for routine cost data collection and analysis are needed.

The policy implications of having accurate cost and financing information are several. For instance, these data can be used to improve planning of resource requirements and financing needs at the country level. Understanding the incremental delivery costs associated with new vaccine introduction will be important for updating donor policies related to subsidizing new vaccine introduction, and for domestic and external resource mobilization for routine programs.

The EPIC studies have provided much-needed information on the costs and financing of RI. The study design aimed to generate a representative sample for each country, though the results can only be interpreted as indicative for other settings. Further investigations are warranted, as there were no studies from Eastern Mediterranean, Southeast or East Asian countries in the first wave. Further analysis could be undertaken with the existing data sets both within country and across countries, particularly with respect to evaluation of productivity and determinants of costs. Finally, there is scope to refine the methods and make them useful for regular data collection and analysis by the national immunization program.

Conflict of interest statement

The authors declare no conflict of interest. The EPIC studies and preparation of this manuscript were supported by the Bill & Melinda Gates Foundation. However, the views expressed represent those of the authors only.

Acknowledgements

We would like to thank all of the members of the study teams who provided inputs into the development of the methods and approaches used for the EPIC studies. The contributions of Steering Committee members, most notably Carol Levin and Ulla Griffiths, were critical to the successful outcome of the EPIC studies. Finally, we appreciate the comments of two independent reviewers.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.066.

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Vaccine 33S (2015) A40–A46

Contents lists available at ScienceDirect

Vaccine

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Costs of routine immunization and the introduction of new and underutilized vaccines in Ghana

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ARTICLE INFO

Keywords:
Ghana
Immunization
Costs
Underutilized vaccines
Fully immunized child

ABSTRACT

Background: Limited knowledge exists on the full cost of routine immunization in Africa. Ghana was the first African country to simultaneously introduce rotavirus, pneumococcal and measles second-dose vaccines. Given their high price, it would be beneficial to Ghanaian health authorities to know the true cost of their introduction.
Methods: The economic costs of routine immunization for 2011 and the incremental costs of new vaccines were assessed as part of a multi-country study on costing and financing of routine immunization known as the Expanded Program on Immunization Costing (EPIC). Immunization delivery costs were evaluated at the local facility, district, regional, and central levels. Stratified random sampling was used for district and facility selection. We calculated the allocation of nationwide costs to the four health-system levels.
Results: The total aggregated national costs for routine immunization – including vaccine costs – equaled US$ 53.5 million during 2011 (including central, regional, and district costs); this equated to US$ 60.3 per fully immunized child (FIC) when counting vaccine costs, or US$ 48.1 without. National immunization program delivery costs were allocated as follows: local facility level, 85% of total national cost; district, 11%; central, 2% and regional, 2%. Salaried labor represented 61% of total costs, and vaccines represented 17%. For new vaccine introduction, programmatic start-up costs amounted to US$ 3.9 million, primarily due to salaried labor (66%). The mean facility-level cost per vaccine dose administered in a routine immunization program was US$ 5.1 (with a range of US$ 2.4–7.8 depending on facility characteristics) and US$ 3.7 for delivery costs.
Discussion: We identified a high cost per fully immunized child, mostly due to non-vaccine costs at the facility level, which indicates that immunization program financing – whether national or donor-driven – must take a broad viewpoint. This substantial variation in overall costs emphasizes the additional effort associated with reaching children in various settings.

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1. Introduction

Multiple additional vaccines are currently being introduced into routine immunization programs in countries that are eligible for funding from the Global Alliance for Vaccines and Immunization (GAVI). However, many countries are unable to raise sufficient resources, both domestic and external to achieve their objectives [1]. Furthermore, the full cost of new vaccines, plus their distribution and storage costs, remains high for many governments [2] and support for new vaccines in many developing countries remains overwhelmingly dependent on GAVI financing [3]. In addition, new vaccine introduction costings tend to overlook non-vaccine costs [4,5].

In the African region, Ghana has been a leader in introducing new vaccines into routine immunization programs, expanding from 7 vaccines in 2002 to 12 vaccines in 2013. Ghana was one of the first countries to introduce the pentavalent vaccine (in 2002). Most recently, it has simultaneously introduced pneumococcal conjugate vaccine (PCV), rotavirus vaccine, and measles second-dose (MSD). It has also made substantial investments to ensure new vaccine delivery such as cold chain capacity expansion.

Nevertheless, costs have not been fully assessed, and have focused mainly on resource requirement projections. The latest official information available can be extracted from the 2010–2014

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http://dx.doi.org/10.1016/j.vaccine.2014.12.081
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Table 1
Final sample selected by district and location.

District	Urban				Rural			
	Sampled urban facilities	% of total urban facilities sampled	Facility type and ownership	Catchment population (average)	Sampled rural facilities	Facility type and ownership	% of total rural facilities sampled	Catchment population (average)
Asante Akim South	2	100%	Government clinic; Government hospital	18,906	5	Government CHPS[a]; Government clinic; Government health center (3)	42%	9431
Atwima Mponua	1	100%	Government hospital	122,398	5	Government CHPS; Mission clinic; Mission health center; Government health center (2)	55%	15,325
Ga West	4	50%	Government hospital; Government CHPS; Government clinic (2)	16,011	4	Government CHPS (2); Government clinic (2)	44%	10,351
Bunkpurugu Yunyoo	1	100%	Mission hospital	31,074	5	Government CHPS (2); Mission health center; Government health center	55%	6958
Kassena Nankana	2	100%	Government hospital; Government health center	16,358	8	Government CHPS (6); Government clinic; Government health center	40%	4075
Wa Municipal	1	100%	Government clinic	63,673	12	Government CHPS (7); Government health center (4); Government clinic	43%	6123

[a] CHPS, community health-based planning and services facilities.

comprehensive multi-year plan (cMYP) [6]. The estimate of the projected cost for routine immunization in 2011 was US$ 32 million [6]. A costing study by Levin et al. [7] conducted in 2000 estimated the total cost for routine immunization at US$ 5.1 million, corresponding to US$ 9.7 for each fully immunized child (FIC) – i.e., three doses of diphtheria-tetanus-pertussis (DTP), hepatitis B, and *Haemophilus influenzae* type b (Hib) – and a cost of US$ 0.26 per capita, adjusted for inflation.

This study was part of the Expanded Program on Immunization Costing (EPIC), a multi-country analysis of the costs and financing of routine immunization programs and new vaccine introduction, which was supported by the Bill and Melinda Gates Foundation. The project encompassed Benin, Ghana, Honduras, Moldova, Uganda, and Zambia. This manuscript focuses exclusively on the costs of routine immunization and new vaccines introduction.

2. Methods

The study evaluated the national routine immunization program in 2011 and new vaccine introduction in Ghana from the perspective of the government health service. The following vaccines were part of Ghana's routine immunization schedule in 2011: Bacillus Calmette-Guerin (BCG), pentavalent DTP-hepatitis B-Hib, polio, measles first-dose, yellow fever, and tetanus toxoid (for pregnant women), which represent nine doses per FIC (see Appendix 1). With the introduction of pneumococcal conjugate vaccine, rotavirus, and measles second-dose in 2012, the number of doses increased to 15 per FIC.

A multi-stage, stratified random-sampling approach was used to select a representative sample of six districts and 50 primary healthcare facilities. Districts were classified according to their urban and rural location, the number of pentavalent doses administered in 2011, and population density.

Within selected districts, facilities were stratified based on facility type, ownership (non-government or government), and rural versus urban status (see Table 1). Four types of facilities were included in the analysis: (1) reproductive and child health (RCH) units of district hospitals, (2) health centers (HC), (3) clinics, and (4) community-based health planning and services facilities (CHPS) [8].

RCH units are located in urban areas within the district hospital compounds and focus on maternal and child curative and preventive care. HC provide basic curative care, disease-prevention services, and primary health care [9]. They are located in urban or rural areas, serve as the reference facility for the sub-district, and supervise the community-level facilities. Clinics provide similar services to HC. CHPS are the lowest level of service delivery and serve as first-line health facilities. CHPS provide interventions in small facilities and also provide outreach services to communities, mostly in rural areas. The sample size of 50 facilities corresponds to an error margin of 12% and a confidence level of 90% [5].

Methods were based on internationally accepted approaches [10,11], drawing upon a common methodological approach [5]. For each sample facility, total routine immunization facility costs were estimated by combining expenditure data and information on input quantities and unit prices. Recurrent and capital inputs, including shared and specific inputs, were allocated to immunization activities (see Table 2). Vaccine costs were estimated from records on doses utilized, including wastage.

The cost of vaccines and supplies was allocated to facility-based delivery or outreach, based on the proportion of doses administered in each strategy. New vaccine introduction costs were estimated through specific questions from the sample of facilities, districts, and regions, as well as from the central Expanded Programme on Immunization (EPI). Expenditure reports at the central level were reviewed to complement the data collection. For the different antigens in the schedule, the prices per dose were: US$ 0.07 for BCG, US$ 3 for pentavalent, US$ 0.13 for polio, US$ 0.19 for measles, and US$ 0.66 for yellow fever. For the new vaccines, the prices per dose were: US$ 7.00 for pneumococcal vaccine,[1] US$ 2.42 for rotavirus, and US$ 0.19 for measles second-dose. Vaccine prices were collected from the UNICEF supply division price datasets.

Personnel costs, estimated from the percentage of total working time spent on routine immunization activities, were collected in

[1] Source: http://www.unicef.org/supply/files/PCV.pdf.

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Table 2
Delivery costs (i.e., excluding vaccines) and main cost drivers (inputs, activities) of routine immunization in Ghana.

Level	Weighted average total cost (US$, 2011)	Distribution of aggregated costs	Line item cost driver (four largest items in total cost at given level)	Activities (four largest items in total cost at given level)
Facility (n = 3044)	12,153	85%	Salaried labor (82%) Volunteer labor (6%) Vehicles (5%) Transport/fuel (3%)	Record-keeping & HMIS (17%) Facility-based delivery (15%) Outreach service delivery (15%) Social mobilization (14%)
District (n = 170)	25,285	11%	Salaried labor (38%) Overhead, utilities, com° (15%) Buildings (13%) Vehicles (13%)	Program management (18%) Surveillance (17%) Supervision (14%) Social mobilization (12%)
Region (n = 10)	92,858	2%	Salaried labor (39%) Cold chain energy costs (18%) Vehicles (13%) Cold chain equipment (8%)	Vaccine coll., dist. & storage (38%) Program management (17%) Supervision (11%) Surveillance (9%)
Central (n = 1)	702,727	2%	Cold chain equipment (25%) Salaried labor (18%) Overhead, utilities, com° (13%) Other recurrent (12%)	Vaccine coll., dist. & storage (38%) Social mobilization (22%) Program management (15%) Supervision (10%)

each facility through staff interviews. Total facility routine immunization economic costs and unit costs are reported in US$, 2011. Recurrent costs included salaried labor, volunteer labor, transport vaccines, energy costs, and overhead. Capital costs included cold chain equipment, vehicles, and buildings. All capital costs were annualized and discounted at 3%. To obtain a national estimate of RI costs, the weighted facility, district, or regional cost was multiplied by Ghana's total number of facilities (3044), districts (170), or regions [10], respectively. Vaccine costs were added to this figure as were national EPI costs. Local currency units were converted in 2011 US$ (1 US$ for 1.54 Ghanaian Cedi according to official annual exchange rate from central bank).

To estimate the incremental cost of new and underutilized vaccine introduction (NUVI), the analysis focused on the additional activities and resources that would not have occurred if the new vaccines had not been introduced. This was based on interviews at all levels and document reviews [5,12–14]. In 2012, Ghana simultaneously introduced the 13-valent, 3-dose PCV; live oral monovalent G1P8; 2-dose rotavirus vaccine; and measles second-dose vaccine. According to the vaccine introduction plan, the time period for the analysis started in August 2010 (central level only) and ended approximately 5 months later, after most of the major additional activities (social mobilization, training, supervision, and surveillance) had occurred at all levels. Economic costs represented the incremental opportunity cost of NUVI, while fiscal costs represented the additional financial requirement for the new vaccines. Economic costs assessed both start-up costs (additional activities and investment) and ongoing incremental costs of routine activities over the year of introduction. Costs associated with staff time for vaccine administration were treated as ongoing costs, as were cold chain equipment costs. The average time spent (full time equivalent per dose) to administer the vaccines in each facility (facility-based and outreach) was extracted from the routine immunization costing of 2011.

Reported costs included costs per infant population, total population, total dose administered (or incremental new vaccine doses) and FIC. FIC was defined as receipt of the third dose of pentavalent DTP-hepatitis B-Hib vaccine (a proxy that does not capture all antigens), as derived from facility immunization records. For the facility analysis, the infant population was defined as the number of children in the catchment area of the facility who were younger than 1 year old; for the nationwide analysis, the infant population in the national census estimate was used [15]. Total cost captured all costs and delivery costs as a portion of the total cost, excluding vaccines and supplies.

3. Results

The total national aggregated RI costs amounted to US$ 53.4 million in 2011, accounting for 5.21% of general government expenditure on health and 0.14% of the gross domestic product [16]. The aggregated RI cost per routine dose administered was US$ 5.7 (total doses administered: 9,464,165). In comparison, the cost per FIC was US$ 60.3 (the number of children that received a third dose of DTP-HepB-Hib: 887,086) [17]; the cost per infant population was US$ 52.9 (the infant population: 1,011,012); and the cost per capita was US$ 2.1 (the per capita count: 25,275,293).

The distribution of routine immunization costs by input type is shown in Fig. 1. Recurrent line items accounted for 91% of those costs; of that, salaried labor was the primary cost.

Table 2 shows delivery costs and main cost drivers (inputs and activities) of routine immunization in Ghana. Delivery costs, excluding vaccines, were substantial (US$ 43.4 million) and mostly borne at the facility level (85%). Facilities mainly used financial resources for service delivery, record keeping, and social mobilization. District offices focused the use of their resources on program management, supervision, and surveillance; in contrast, offices at central and regional levels focused on vaccine collection and storage, as well as program management.

3.1. Facility-level costs for routine immunization

Table 3 shows the total annual costs in 2011 US dollars for total outputs and unit costs at the facility level, by facility type and

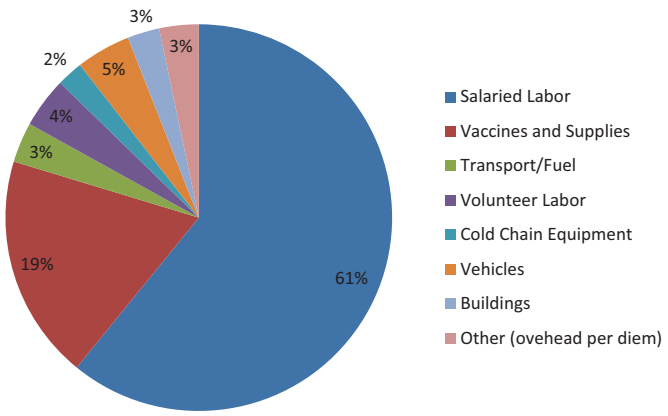

Fig. 1. Distribution of routine immunization costs in Ghana, by input type (2011).

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Table 3
Annual total costs, total outputs and unit costs at facility level by facility type in Ghana (US$, 2011).

	CHPS rural *N* = 19	CHPS urban *N* = 1	Health center rural *N* = 14	Health center urban *N* = 3	Clinic rural *N* = 6	Clinic urban *N* = 3	RCH urban *N* = 4
Average total cost	12,833	11,017	23,098	22,238	13,501	11,413	26,743
Standard deviation	*593*	–	*679*	*4953*	*1023*	*2418*	*3692*
Delivery total cost	11,030	6429	14,537	14,364	11,000	9393	16,425
Standard deviation	*394*	–	*510*	*2973*	*579*	*1841*	*2330*
Outputs							
Routine doses administered	1604	3024	4195	6078	3925	5276	11,119
Standard deviation	*79*	–	*196*	*581*	*720*	*1452*	*1241*
FIC (children receiving DTP3)	136	443	545	549	365	245	695
Standard deviation	*5*	–	*26*	*62*	*55*	*52*	*84*
Unit costs							
Per routine dose administered	8.00	3.64	5.51	3.66	3.44	2.16	2.41
Per FIC (children receiving DTP3)	94.16	24.87	42.41	40.50	36.94	46.66	38.49
Unit delivery costs							
Per routine dose administered	6.88	2.13	3.47	2.36	2.80	1.78	1.48
Per FIC (children receiving DTP3)	80.94	14.51	26.69	26.16	30.10	38.41	23.64

CHPS = community health-based planning and services facilities, RCH = reproductive and child health facilities,. FIC = fully immunized child.

location. Within the sampled facilities (11 urban and 39 rural), the cost per unit of output was US$ 5.07 per routine dose administered, US$ 51.26 per FIC, US$ 36.11 per infant population, and US$ 1.50 per capita. The average delivery cost per dose varied by the type of facility, and among facilities of the same type, the cost also varied depending on whether the facility was rural or urban. Similarly, the unit cost per FIC decreased with facility type.

Across all facilities, the main facility-level cost driver was salaried labor, which contributed 60% of total facility costs and an average of 1.76 full time equivalent (FTE). However, the average FTE varied substantially depending on facility type; RCH had an average FTE (3.00) that was almost double the FTE of HC (1.57) and CHPS (1.69). The other critical cost components were 26% for vaccines and injection supplies, 5% for volunteer labor, and 2% for transportation and fuel. Capital costs represented 7% of total facility costs; of that, vehicles accounted for 4%, buildings accounted for 2%, and cold chain equipment accounted for 1%. The proportion of costs attributed to volunteer labor was higher in CHPS (6.3%), as was the proportion of costs due to transport and fuel.

Facility costs also differed depending on whether the facility had an urban or rural location. Although the average total cost was higher in urban areas, the unit cost per dose administered was lower in urban facilities (US$ 3.17) than rural ones (US$ 5.78). The difference in the urban and rural cost per dose was confirmed for each facility type and was related to the volume of services provided.

Fig. 2 shows the routine unit cost per dose and delivery cost per dose by type of facility. Although rural and urban facilities had a similar cost structure by activity, the cost of facility-based service delivery was substantially higher in urban areas (33% for urban; 20% for rural). In all facility types, facility-based and outreach delivery activities (cost of vaccines, transport, and staff time for vaccine administration) were the three main cost drivers. Outreach was the primary cost driver in health centers (33% of overall costs), clinics (27%) and CHPS (20%), while facility-based delivery was the primary cost driver in RCH units (46%).

3.2. New vaccines introduction costs

Economic startup delivery costs (i.e., during the introduction period at the different levels) amounted to US$ 3.9 million, of which salaried labor costs accounted for 66%, or US$ 2.6 million (see Table 4). Ongoing costs (including cold chain, salaries for vaccine administration, and vaccines utilized) were US$ 22.7 million, or 85% of the total. Overall, total costs (both start-up and ongoing) were driven by vaccines (70%), labor (18%), and cold chain (7%)

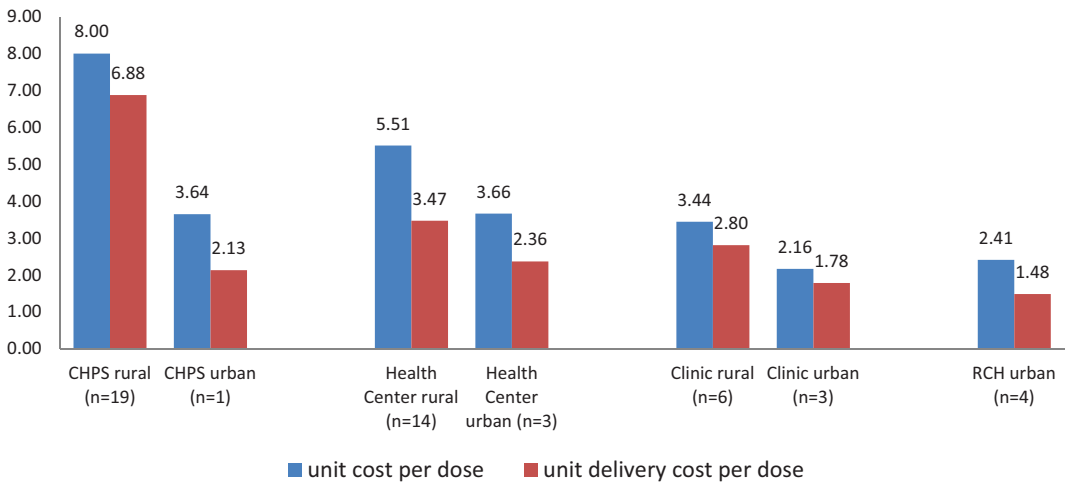

Fig. 2. Routine unit cost per dose and unit delivery cost (Delivery cost per unit of output is a portion of the total cost (excluding vaccines and supplies costs)) per dose according to facility type (US$, 2011). CHPS, community health-based planning and services facilities; RCH, reproductive and child health facilities.

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Table 4
Start-up costs, ongoing costs, and fiscal costs for new vaccine introduction in Ghana.

Line item	Economic costs, US$		Fiscal costs, US$	
Start-up costs				
Salaried labor for introduction-related activities	2,634,785	7.92%	28,389[a]	0.09%
Other recurrent expenses[b]	552,413	2.07%	552,413	1.67%
Building overhead, utilities, communication	164,461	0.62%	157,007	0.48%
Per diem and travel allowances	101,403	0.38%	101,356	0.31%
Volunteer labor	89,231	0.33%		
Transport/fuel	69,130	0.26%	92,191	0.28%
Printing	25,229	0.09%	25,229	0.08%
New cold chain equipment	149,853	0.56%	1,531,426	4.64%
Vehicles	90,073	0.34%	584,000	1.77%
Other capital	27,021	0.10%	100,000	0.30%
Other	52,723	0.20%	52,723	0.16%
Ongoing costs				
Salaried labor for new vaccines delivery	2,117,351	7.92%	–	–
Vaccines and supplies	18,800,058	70.36%	29,813,420	90.24%
Cold chain energy cost	296,204	1.11%	–	–
Cold chain equipment utilization	1,549,177	5.80%	–	–
Total start-up economic costs *per doses administered*	3,956,321 *1.22*	14.81%	–	–
Total ongoing economic costs (delivery) *Per doses administered*	3,962,732 *1.23*	85.19%	–	–
Total economic delivery cost *Per doses administered*	7,919,053 *2.45*			
Total fiscal costs	–	–	33,038,153	100%

[a] Hiring coordinator for introduction of new vaccines.
[b] Studies, new vaccines pilot, launch, and surveillance of adverse event following immunization (AEFI).

(see Appendix 3). The value of time spent by personnel for vaccine administration in facilities was significant. The cost for new vaccines delivery was higher in outreach, with US$ 1.2 million and US$ 0.9 million for facility-based delivery. The total ongoing incremental economic costs during the year of introduction represented 42% of routine immunization costs in 2011. The delivery cost per dose administered amounted to US$ 2.42, with US$ 1.22 for start-up and US$ 1.23 for ongoing (see Table 4 and Appendix 4). The cost per dose of new vaccines purchased was equivalent to US$ 5.13. The cost of new vaccine purchases represented a three-fold increase in total vaccine costs compared to routine infant vaccine costs in 2011, mostly driven by PCV costs.

4. Discussion

Our EPIC study represents one of the most thorough attempts to evaluate the costs of national routine immunization programs in Ghana and in other countries for the companion studies from this issue [5, 28-31]. In Ghana, we found that total national costs and costs per FIC were high due mainly to delivery costs, and within non-vaccine costs mainly to employee salaries. Most non-vaccine costs were incurred at the facility level. Costs varied by a factor of three depending on the facility type and rural versus urban locations.

Previous studies evaluating routine immunization costs per FIC in Cameroon and Ghana put these at US$ 12.73 [18] and US$ 9.7 [7], respectively. Our study result of US$ 60.3 per FIC was, respectively, 4.7 [18] and 6.2 [7] times higher. The higher values could be related to one or a combination of factors including changes in immunization schedules, a greater reliance on outreach-based services through CHPS, a greater volume of services related to rising coverage levels in a growing population, and significant increases in ministry of health (MOH) staff salaries [19]. The Ghana 2010–2014 cMYP for an identical schedule assessed the cost per FIC at US$ 36.4 in 2011 [6]. Furthermore, previous costing analyses are not directly comparable to these results as they could have under-represented or not reported specific cost categories, thus contributing to lower estimates (as well as highlighting the need for a consistent and validated costing methodology). Based on this difference, we think that true immunization costs are likely to be much higher in Africa than generally appreciated.

Delivery routine immunization costs represented 81% of total routine immunization costs, which were almost entirely borne at the facility level. This may result in these costs (and the associated government contribution) being under-appreciated by external donors, since donors deal primarily with the national level and national governments. As African countries experience increased economic activity with rising per capita GDP and as they graduate from GAVI funding, their national governments will need to account for these costs to sustain immunization programs.

The high share of salaried labor identified in this study was consistent with the salaries and benefits that account for more than 60% of total public health expenditure in Ghana [9]. It was, however, higher than findings from a review [20] that found personnel costs totaled 45%. The larger proportion of personnel costs can be explained by the methodology that accounted for actual FTE spent on routine immunization activities (rather than standard estimates as in the comprehensive multi-year plans) at all levels, and the increase in salaries. The costs of salaried labor may increase as a proportion of overall immunization programs as national GDPs rise,

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and as vaccine prices decline due to more manufacturers entering the market.

The higher unit cost of the mostly rural CHPS underlines the additional expense associated with reaching children in these settings [21]. That greater expense can be ascribed to more dispersed or more difficult to reach populations and that requires more effort to vaccinate; outreach often involves house-to-house immunization, more manpower, and greater fuel costs per vaccinated child. Earlier studies have found that below-target investments exist for capital items in CHPS in Ghana [19]. These were consistent with our finding that the proportion of capital costs in total facility costs is smaller in CHPS than in health centers. The smaller investment in CHPS is explained by the services they deliver (basic health care) and the fact they have only recently been created. Where facility-level performance was good, such as has been documented for record-keeping [10], this came at a cost, as evidenced by the substantial economic contribution of record-keeping for routine immunization. The lower unit cost (per FIC or per dose administered) in facilities that delivered proportionally more doses was consistent with findings from other companion studies [30,31]. A facility-based costing study in Peru also found substantial variations depending on facility type [22]. We found evidence that some sub-national expenses were not always accounted for in the new vaccine introduction plan [14]. By contrast, the simultaneous introduction of multiple vaccines has reduced some incremental costs such as training, supervision, and surveillance, which would have cost more if the vaccines had been introduced at separate periods. These benefits were identified in the last programmatic review [17]. For example, the total incremental economic cost for the three vaccines was US$ 1.06 per capita in Ghana, whereas another incremental costing study in Gambia found US$ 0.89 per capita (PCV vaccine only) [26]. We also found that most important ongoing incremental non-vaccine costs related to cold chain expansion, as identified in other studies [25,26].

This study has limitations, with general assumptions made to overcome data availability issues or reduce the data collection burden. Expenses for cold chain maintenance were only available at a central level, as EPI is responsible for cold chain maintenance at all levels. The daily allowance for national immunization days was used to estimate volunteer labor costs, which may overestimate the volunteer labor costs compared to local wages. We did not have data on the actual useful life years of vehicles or cold chain equipment by district or facility, and instead relied on data from the national level. For personnel relating to new vaccine delivery, the average time spent per dose to administer the vaccines in each facility (facility-based and outreach) was extracted from the routine immunization costing and applied to the number of doses of new vaccine administered in the year of introduction. This potentially could have resulted in overestimating the time needed to administer the vaccine. In addition, lower expenses and limited availability of funds compared to budgets could imply the non-realization of planned activities and consequently lower the cost of immunization.

Our study has several policy implications because study results provide evidence for cMYPs, GAVI policies, and the development of national health insurance plans regarding health system costs of delivering immunization – all of which continue to be poorly understood [27]. Accounting for all immunization costs when looking at financial sustainability will be increasingly important: The challenge for many countries in coming years will be to sustain their immunization programs following new vaccines introduction. Our results indicate areas where previous cMYPs underestimated the total US$ 53.4 million costs [23,24], namely personnel costs, transportation, and volunteers. Notably, this includes facility-level delivery costs, and the implications of current and future local salaries. In addition, governments should further evaluate the large difference in costs per FIC by facility type to identify areas for increased efficiencies. Local-level staff should assess the sustainability of current levels of volunteer labor and the implications of this assessment for immunization budgets. Lastly, Ghana and other countries must ensure that immunization activities remain equitably distributed, including hard-to-reach populations, by ensuring that budgets account for the substantially higher cost of delivering services to these populations.

Contributors

A common methodological approach and generic questionnaire was developed by the Bill and Melinda Gates Foundation (BMGF). JBLG adapted the questionnaire to the Ghana context following a pre-test of the questionnaire and meetings with Ghana EPI staff and the MOH. JBLG conducted the cost analysis, and report and manuscript writing. MA was in charge of survey implementation and data entry, supervised the interviewers, and provided input on sampling. FN was the interface between the country's health authorities and Agence de Médecine Préventive (AMP), presented the project to national authorities, including the Ethics Committee, facilitated administrative implementation, and provided feedback on study documents, sampling process, data interpretation, and manuscript writing. BG provided technical guidance at each step of the project, and reviewed the study report and manuscript. AC recruited the core team, oversaw the project development and implementation, supervised all scientific work, provided technical guidance on the methodology, guided data analysis and interpretation, and reviewed the scientific study report and article. All authors agreed on the final draft. Policy implications and recommendations were discussed during a workshop dedicated to this study with Ghana Health Service and EPI in Accra.

Acknowledgments

We would like to acknowledge the following individuals who contributed to the study: The Ghana Health Service, in particular, KO Antwi-Agyei (Ghana Health Service/EPI), John Frederick Dadzie (Ghana Health Service/EPI), and Dan Osei (Ghana Health Service, PPME), who facilitated and provided guidance for study implementation and analysis. We would also like to acknowledge the interviewers who collected the data: Gustav Togobo, Irene Hamba, Seth Adjei, Bernard Achampong, and Vida Gyasi. Darwin Young (BMGF consultant) developed the cost calculation tool. Logan Brenzel and Damian Walker (BMGF consultants) supervised the study. Steering committee members Carol Levin (University of Washington), Ulla Griffiths (London School of Hygiene and Tropical Medicine), Mike Hanlon (University of Washington), Raymond Hutubessy (World Health Organization), Stephen Resch (Harvard University), and Santiago Cornejo (GAVI) provided input in the overall study.

Conflict of interest: JBLG, BDG and AC work for the AMP, which receives unrestricted funding from Sanofi Pasteur and grant-specific support from Crucell, Sanofi Pasteur, Pfizer, Merck, and GlaxoSmithKline.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.081.

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Vaccine 33S (2015) A47–A52

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Cost analysis of routine immunisation in Zambia

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ARTICLE INFO

Keywords:
Routine immunisation
Costs
Sustainability
EPI
Africa

ABSTRACT

Background: This study aimed to inform planning and funding by providing updated, detailed information on total and unit costs of routine immunisation (RI) in Zambia, a GAVI-eligible lower middle-income country with a population of 13 million.
Methods: The exercise was part of a multi-country study on costs and financing of routine immunisation (EPIC) that utilized a common, ingredients-based approach to costing. Data on inputs, prices and outputs were collected in a stratified, random sample of 51 facilities in nine districts between December 2012 and March 2013 using a pre-tested questionnaire. Shared inputs were allocated to RI costs on the basis of tracing factors developed for the study. A comprehensive set of costs were analysed to obtain total and unit costs, at facility and above-facility levels.
Results: The total annual economic cost of RI was $38.16 million, equivalent to approximately 10% of government health spending. Government contributed 83% of finances. Labour accounted for the lion's share (49%) of total costs followed by vaccines (16%) and travel allowances (12%). Analysis of specific activity costs showed that outreach and facility-based services accounted for half of total economic costs. Costs for managing the program at district, provincial and national levels (above-facility costs) represented 24% of total costs. Average unit costs were $7.18 per dose, $59.32 per infant and $65.89 per DPT3 immunised child, with markedly higher unit costs in rural facilities. Analyses suggest that greater efficiency is associated with higher utilisation levels and urban facility type.
Conclusions: Total and unit costs, and government's contribution, were considerably higher than previous Zambian estimates and international benchmarks. These findings have substantial implications for planners, efficiency improvement and sustainable financing, particularly as new vaccines are introduced. Variations in immunisation costs at facility level warrant further statistical analyses.
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1. Introduction

Accurate, detailed information on costs of routine immunisation (RI) programmes is critical to inform policy, planning, management and funding of countries' Expanded Programmes on Immunisation (EPI) [1]. While comprehensive multi-year plans (cMYPs) provide planners and funders with estimates of current and future EPI resource requirements, they are not generated from facility-level information [2]. Periodic studies using facility-level surveys would generate more robust costing data which is increasingly important in a context of intensified competition for health financing along with introduction of new, relatively expensive vaccines.

A number of studies in the last two decades examined costs and financing of RI with traditional vaccines [3–8]. Multi-country studies suggest considerable variations between countries and possible changes in both unit costs and in levels of government funding for programmes [8,9]. However, the number of studies examining RI program costs has dwindled since 2000, although costs of new

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http://dx.doi.org/10.1016/j.vaccine.2014.12.040
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vaccines have enjoyed increased attention [10–12]. The literature suggests that previous analyses of RI costs should be interpreted with caution due to changes in vaccines, prices, health system costs, service delivery models and contexts and methodological inconsistencies [13].

Thus there is limited knowledge about the costs of RI in African countries. Zambia required updated understanding of RI costs to reflect introduction of single-dose liquid Pentavalent vaccine in 2007, in the context of challenges in achieving full immunisation coverage above 80% across all districts [15,16][1] and ahead of phasing in new vaccines (PCV, rotavirus and measles second-dose) from 2012.

2. Objectives

The study aimed to comprehensively describe RI economic and financial costs to inform planning, management and funding. Specific objectives were to generate estimates of facility-based delivery costs of RI and to identify factors that may affect programme costs and productivity which can be explored in further analyses.

3. Methods

The investigation followed a common methodology (Common Approach) developed for the multi-country EPIC study, adapted to reflect Zambia's context and data availability [13].[2] The study examined all costs related to routine immunisation, defined as services provided regularly as part of the government programme at facilities, outreach sites and Child Health Weeks, but excluding supplementary immunisation activities. A sample of 51 facilities was randomly selected proportional to numbers of facilities within strata of facility types – Rural Health Centres (RHCs) and Urban Health Centres (UHCs) – across nine districts in three provinces which were purposively selected to be representative of typical contexts across Zambia. These strata are used in Zambia's health system planning, and the sample included 36 of Zambia's 1037 RHCs (which serve populations of approximately 10,000 in rural areas), and 15 of the 228 UHCs, (serving 30–50,000 people in urban or peri-urban settings) [17]. The strata include hospital associated health centres, which provide PHC for communities near hospitals. Costs were analysed by line item and 11 standard EPI functions [13]. Semi-structured questionnaires were used to obtain data on RI activities and associated costs from staff and managers at facility, district, provincial and national levels.

An ingredients-based, 'bottom-up' approach was used to analyse all relevant immunisation economic and financial costs at the facility and higher levels of the health system. A step-down approach to allocating total programme costs was not used, but specific, shared costs were allocated to RI using a set of allocation factors and assumptions, such as share of staff time or square metres of facility space used for RI. Significant shared costs included those of human resources (HR), vehicles, buildings and utilities. HR costs were allocated according to the share of staff time spent on immunisation. (see Appendix A for details of costing).

The economic cost of capital items was discounted using a 3% discount rate, while the financial costing depreciated capital costs on a straight line basis. Volunteer labour was included in economic but not financial costs.[3] Costs are reported in 2011 US$ ($1 = ZK4787) but HR costs reflect substantially higher 2012 pay scales to facilitate interpretation in the current context.

Data were captured in Excel and transferred to a costing database for further cleaning, analysis and production of unit costs. Unit costs for UHC and RHC were weighted according to the proportion of doses delivered at each site. Unit costs for district and higher levels were calculated using the same approach. The total national cost of RI was calculated by applying the weighted average unit costs by facility type to the total number of doses administered in UHC and RHC in Zambia in 2011. Differences in facility costs were demonstrated with scatter plots. Natural log transformations of variables were used where data showed high variation.

Several limitations may have affected accuracy of results. Allocation of staff time to RI activities relied on interviewee estimates in each site, not direct observation, due to time and resource constraints. However, triangulation was used to check plausibility and consistency of estimates. Quality of record keeping at the facility, district and central level was variable and required additional assumptions to be made in analysis of vehicle use and vaccine wastage rates.

Table 1
Aggregated total RI economic costs by expenditure line item and level of health system in Zambia ($, 2011).

	Cost (US$, 2011)	% of total
Expenditure line item		
Salaried labour	18,861,822	49.4
Per diem & travel allowances	4,389,987	11.5
Vaccines	6,167,984	16.2
Vaccine injection & safety supplies	185,702	0.5
Other supplies	297,187	0.8
Transport/fuel	2,348,864	6.2
Vehicle maintenance	420,650	1.1
Cold chain energy costs	119,545	0.3
Printing	77,645	0.2
Building overhead, utilities, communication	1,075,464	2.8
Cold chain equipment	568,066	1.5
Vehicles	2,007,144	5.3
Other Equipment	557,284	1.5
Buildings	1,085,278	2.8
TOTAL economic cost	**38,162,622**	**100**
Level of health system		
Facility (incl. vaccines)	31,156,342	82
District	5,385,501	14
Provincial	937,609	2
National	683,170	2

4. Results

4.1. Total costs of RI and major contributors

Table 1 summarises the aggregated national total economic costs of RI in Zambia by line item, function and level of the health system. The total cost in 2011 was estimated at $38.16 million. Items funded by government were estimated to contribute 83% of this total.

The largest line item cost was labour, amounting to 49% of the total facility RI cost. Vaccines contributed to 16% to the total, followed by 12% for travel allowances and 6% for transport and fuel. Together these items contributed 83% of total costs. Capital items, mainly vehicles, buildings and cold chain equipment, contributed 11% of total costs. Cold chain equipment costs comprised 1% of the total.

[1] To 2012, full immunization was defined as receiving BCG, OPV3, DTP-HepB-Hib3, and Measles 1.

[2] See Brenzel L, Young D, Walker DJ. Costs and financing of routine immunization: approach and selected findings of a multi-country study (EPIC). Vaccine 2015, http://dx.doi.org/10.1016/j.vaccine.2014.12.066, [in press] for a link to the Common Approach [14].

[3] The financial costing does not indicate cash flows. The Common Approach referred to these as fiscal costs, which were not calculated for RI.

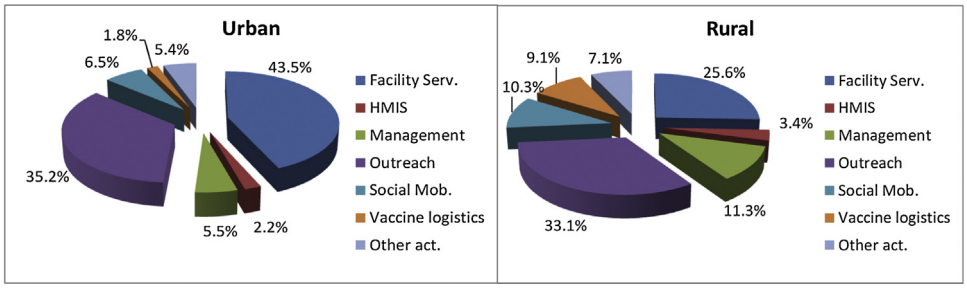

Fig. 1. Urban and rural health centre economic cost of RI by function in Zambia ($ 2011).

Table 2
Average facility level total economic costs of RI by line item and service volumes by facility type in Zambia (Weighted averages, US$, 2011).

	Urban Health Centres	Rural Health Centres	All facilities	% of total
Sampled facilities (n)	15	36		
Salaried labor	13,381	13,209	13,276	46.9
Per diem & travel allowances	1,907	2,671	2,369	8.4
Vaccines	16,044	3,912	8,708	30.8
Vaccine injection supplies	487	116	263	0.9
Other supplies	275	64	147	0.5
Transport/fuel	361	1,454	1,022	3.6
Vehicle maintenance	2	194	118	0.4
Cold chain energy costs	142	72	99	0.4
Sub-total recurrent	**32,599**	**21,692**	**26,002**	**91.9**
Cold chain equipment	379	363	369	1.3
Vehicles	3	1,066	645	2.3
Other equipment	735	389	526	1.9
Building	726	752	742	2.6
Sub-total capital	**1,843**	**2,570**	**2,282**	**8.1**
Total facility RI cost	**34,441**	**24,262**	**28,284**	**100.0**
Total child doses	13,325	2,974	7,066	
Total DTP3 vaccinated children	1,271	330	702	
Targeted infants	1,868	319	931	
Catchment population	44,156	7,536	22,013	

When contributions of each level of the health system to total RI costs were analysed, facility level costs dominated (82%). However, district level costs (14%) were substantial, related mainly to vehicles to support facilities or collect vaccines, and district immunisation staff and operational overheads (see Appendix A).

The contribution of line items to total national RI economic costs was similar to the facility level (see Table 2), but vaccines contribute a substantially higher proportion (30.8%) of facility level costs. Total financial costs, which omitted volunteer health workers and discounting of capital items, were approximately 3% less than economic costs.

Outreach and facility-based service delivery were the two most costly RI activities. Their combined cost was 52% of the total, and included large costs of labour and vaccines. Social mobilisation, programme management, supervision and vaccine distribution each contributed 8–10% of total costs, and 37% altogether.

4.2. RI economic costs at facility level

The costing highlighted major variation in total costs and unit costs of facilities between RHCs and UHCs. The average total cost of RI was $24,262 and $34,441 per annum at RHC and UHC respectively (Table 2). Vaccines accounted for most of this difference, and a much larger share of total economic costs in UHCs (47%) than RHCs (16%). The average costs of labour were similar despite their different outputs, and labour contributed a larger share for RHCs (54%). The mean staff time spent on immunisation ranged from 7.53 min per dose in high volume facilities (>19,000 doses p.a.) to 50 min in low volume sites (mean 2739 doses per annum).[4] Travel costs contributed markedly more in RHCs than UHCs, both for travel allowances (11% vs. 6%) and other transport-related costs (6% vs. 1%).

The contribution of different RI activities also varied between UHCs and RHCs (Fig. 1). For both, routine facility-based and outreach services accounted for most costs, followed by social mobilization. However, in UHCs facility-based immunisation comprised 44% of costs vs. 35% for outreach. In RHCs this was reversed: outreach accounted for 56% of doses, and contributed more costs (33%) than facility based services (26%). RHC social mobilisation costs were also higher.

Unit costs showed further variability between UHCs and RHCs (Table 3). For example, the national weighted average unit cost per DTP3 vaccinated child was $65.89 at facility level, but the total unit cost per DTP3 child was $87.14 in RHCs, compared to $33.38 in UHCs. Most of the difference was explained by labour costs ($32 of the variation), and travel-related allowances and costs ($12).

Scatter plot analyses suggested a relationship between higher total costs of facilities and increasing service volumes. Similarly, when facilities' unit costs per dose or per DPT3 child were compared, it was apparent that they declined as service volumes increased (Fig. 2). With some exceptions, UHCs had higher volumes and operational efficiency than average, while RHCs had lower numbers of doses and efficiency. Below a threshold of approximately 700 DPT3 children (or 10,000 doses) per annum, the unit

[4] This time allocation seems high, but is nevertheless consistent with the model of outreach services.

Table 3
Average total economic unit costs by facility type in Zambia (Weighted, $, 2011).

Unit costs Sampled facilities (*n*)	Urban Health Centres 15	Rural Health Centres 36	Weighted average
Cost per dose	3.73	9.43	7.18
Cost per dose – delivery costs only	2.43	8.07	5.84
Cost per DTP3 vaccinated child	33.38	87.14	65.89
Cost per targeted infant	22.85	83.17	59.32
Cost per capita	0.97	3.52	2.51

cost per dose appears to rise more rapidly as volumes fall. Beyond the threshold of around 700 DPT3 children, increasing service volumes did not result in much further decline in unit costs.

There was also wide variation in both total and unit costs *within* facility types. Particularly among RHCs with lower service volumes, sites with similar outputs had very different costs. Within the RHC stratum several facilities deviated markedly from average. These outliers had unusually low numbers of children attending, high levels of outreach activity involving high numbers of staff, or high transport costs to reach remote vaccine collection or outreach sites.

The large staff contribution to unit cost variation was explored further. Quadrant analysis indicated clear increases in doses per full time equivalent staff (FTE) involved in immunisation in facilities with larger number of doses and attendance (Fig. 3). However, high variation persisted, particularly between RHCs. There is no clear indication of why some facilities cope with substantially less staff than others for a similar number of doses.

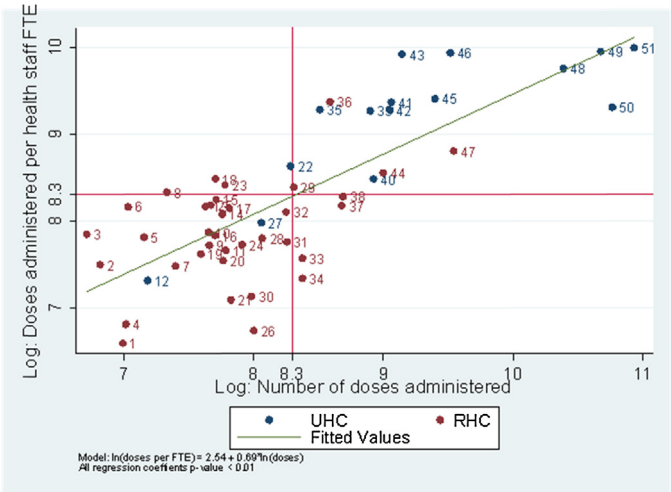

Fig. 3. Doses per full time equivalent staff providing immunisation compared to annual number of doses administered at each RHC and UHC sampled in Zambia.

5. Discussion

Results of this study provide detailed, up-to-date reference values for planners and managers of RI and other PHC services, as well as important perspectives on several aspects of costs.

5.1. Comparison to benchmarks

The estimates of Zambian total unit costs of $66 per child that received DPT3 and $59 per targeted child are considerably higher than previous estimates of average costs from other countries. Studies in the 1990s up to 2000 tended to suggest average cost per child fully immunized with DPT, BCG, polio and measles of around $20 [3–8]. Analysis of 50 FSPs in 2008 revealed an average cost per child of $17 [9].[5] For 56 cMYPs developed between 2004 and 2012, the average costs were $21 per child and $28 per fully immunized child, although wide variation between regions was noted [10].

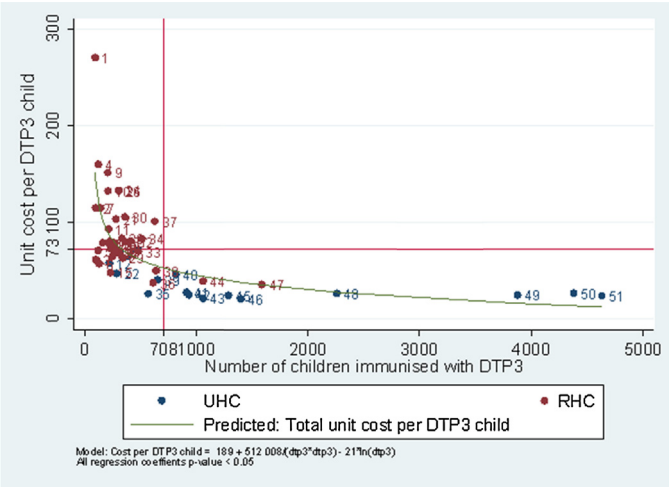

Fig. 2. Total unit cost per DTP3 child compared to number of children immunised with DPT3 at UHCs and RHCs in Zambia.

The study supports observations that health system costs and capacity will be increasing considerations in low- and lower-middle income countries in coming years [18]. The updated, more comprehensive assessment of staff costs seems to be the main explanation for Zambia's higher costs, although factors such as wastage, coverage and vaccination completion rates may also contribute to differences. Results provide a new reference point for labour costs after remuneration increases aimed at strengthening human resources for health, as well as confirming labour intensity of immunisation programmes found by previous studies [19].

Findings also show the relative importance of other delivery costs and vaccines in the current context. Even if all staff costs are removed, Zambian unit costs remain close to higher previous unit cost estimates. But vaccines contributed only one-third of non-staff costs or $12.20 (UHC) to $13.38 (RHC) per DPT3 child, suggesting limited potential of further conventional vaccine price reductions to affect total EPI costs. Management and supervision also accounted for a relatively high share of total cost. Expansion of the EPI, including new vaccines introduction, should carefully consider the possibility of significant incremental burdens on management capacity. Vehicles and cold chain equipment are critical to immunisation delivery and often a major focus of EPI planning, but are actually relatively small components of total economic costs.

Total costs in Zambia, as well as contributions of key line items and functions, are notably different to expenditures reported for the base year of the Zambia cMYP 2012–2016 [15]. Compar-

[5] It should be noted that in 2008 most countries had not introduced pentavalent but were using tetravalent vaccine (DTP-Hep B) instead. This partly explains cost differentials.

isons between the costing study and the cMYP are limited by the differences in their purpose, methodology and underpinning assumptions. However, total costs in the cMYP were $33.81 million (2010) compared to $38.16 million in the study. The most substantial differences were in study estimates for costs of staff ($8.2 million above the CMYP), vehicles and fuel ($2 million higher) and travel allowances ($8 million lower). The differences illustrated potential for similar studies to contribute unit and total cost estimates, and other data, which can refine the inputs and assumptions of cMYPs.

This study also indicates a higher level of government contribution (83%) to RI funding than previous benchmarks, largely due to more comprehensive costing of human resources. Previous analyses of FSPs and cMYPs suggested that governments provided an average of 42% and 56% of immunisation costs [8,9] while Zambia's cMYP estimated that government contributed 76% of RI funding. The new estimate of total RI cost represents 5.4% of Zambia's total expenditure on health and 10% of government health expenditure. The country, which has a severe, generalised HIV epidemic, is already challenged to fund more than the $388 million (55%) share of health spending that it contributed in 2011 [20]. Study results could thus influence decisions around targets for funding by GAVI and other partners.

5.2. Unit and total facility cost variations

High variability in total and unit costs within facility types presents a challenge to managers and planners. Cost profiles indicated that Zambian efficiency improvement efforts should prioritise the largest contributors to total RI costs, namely labour, vaccines and travel allowances, as well as outreach activities. They may benefit from stronger management of staff allocations and productivity, travel and outreach activities and stock and wastage. Weaknesses of stock management observed at all levels of the system are a concern, particularly if more expensive new vaccines are introduced.

Despite extensive measurement of health sector efficiency and productivity in high-income countries [21] and pressing health care resource constraints, there are few evaluations of efficiency in African health systems[22], and of RI specifically [23,24]. Several, costing studies have found that factors such as service volume, number of immunisation sessions, immunisation strategy and prices affect total vaccination program cost [9,10,21–23,25,26]. Others have shown a strong, negative association between scale of services and unit costs [19]. A statistical analysis of immunisation costs in PHC facilities in India found a significant positive association between total facility cost and not only the number of doses administered, but also production factors such as type of vaccination strategy [25].

The descriptive information presented in this paper has limitations for identifying determinants of costs and efficiency. However, it seems to support the association of utilisation with facilities' total costs and efficiency measures. Furthermore, the type of facility also appears to be associated with efficiency. As illustrated by examining line item and activity costs, the facility type may to some extent be considered a proxy for service delivery strategy (e.g. facility based vs. outreach) or context (e.g. travel requirements).

The strong tendency of small and rural sites to have higher unit costs appears to corroborate the observation in Burkina Faso that small PHC services need a minimum staff complement and infrastructure, and have less flexibility to adjust staffing to workloads below a threshold level of service volumes [22]. Most Zambian facilities have immunisation days that require a nurse to attend, but numbers of children presenting for immunisation vary. Closing low utilisation health care facilities is typically not an option to improve unit costs as it compromises equity and coverage targets. Thus, improving utilisation (for immunisation and/or other PHC services) and understanding the determinants and barriers to service uptake become key issues to utilise capacity better. Availability of spare capacity is also likely to be higher in small, low volume facilities. This may be relevant to assessing capacity needs when new vaccines or other services are introduced, or coverage is increased.

Of note, most large Zambian PHC facilities have similar unit costs and are likely to function at close to maximum capacity, so their opportunities for further improvement in efficiency may be limited. However, investigation of the large variations in unit costs among facilities within RHC and UHC strata and at similar levels of output, suggested that small facilities with high cost per dose typically had higher staff allocations and costs for similar service volumes. The reasons for differences in staffing for similar workloads were not clear, but this suggests potential to allocate staff more efficiently between facilities and functions within facilities.

For planning and budgeting purposes, the study finding of high variation of costs indicates that using average total or unit costs of UHCs and RHCs to estimate costs of new facilities or increasing coverage may not be accurate enough. An approach that establishes benchmarks for different facility types, based on both the type of facility and expected attendance volumes, may have potential to be more useful. Unit costs could be a good predictor of total immunisation costs for facilities above the threshold of around 700 DPT3 children or 10,000 doses. But below this threshold it seems desirable to consider total facility costs and specific circumstances when predicting costs, due to high variation in unit costs.

The above observations present hypotheses for planners and funders about factors that may be important determinants of unit costs and total facility costs of immunisation services. However, the apparent associations of facility type and outputs *per se* with unit and total costs will benefit from further analysis as they may not be strong enough for optimal planning. Underlying factors such as catchment population, remoteness, staff mix, proportion of services delivered through outreach and community demand factors such as poverty may affect unit and total costs in ways that are not reliably identified in descriptive data presented here.

Further multivariate statistical analyses may thus show associations of costs with various independent variables that can assist in predicting total facility and programme expansion costs. Some examples exist of statistical analyses of PHC and immunisation program costs and efficiency to inform this next step [22,23,25].

6. Conclusions

Total and unit costs of RI in Zambia, and government's contribution, were considerably higher than previous Zambian estimates and benchmarks for developing countries. Large variations in costs at facility level were associated with service volumes, facility type, staffing and travel costs in particular. Many EPI managers report that they have inadequate information on costs at facility and higher levels in the system for planning and forecasting. Costing studies and support may assist countries to strengthen cMYP estimates and programme management.

Study findings have substantial implications for planners, efficiency improvement and sustainable financing, particularly as new vaccines are introduced. Further, multivariate statistical examination of RI cost determinants is desirable. Consideration of immunisation costs in the context of comprehensive PHC services, rather than as a vertical programme, could also refine strategic responses.

Competing interests

The authors declare that they have no competing interests.

Declarations by authors

The authors declare that they have reviewed and approve the manuscript. CS, CC, AK, LB and TG were involved in design of the study. The research was implemented and data cleaned and analysed by CS, CC, EM, SB, LM, ZN and KM. The article was written by AK and CC, with support and review by LB, EM and CC.

Acknowledgements

The study was funded by the Bill and Melinda Gates Foundation, and supported by GAVI and World Health Organisation (WHO). The findings and conclusions contained within this article are those of the authors and do not necessarily reflect positions or policies of the Bill & Melinda Gates Foundation or other partners. Managers, planners and staff of the EPI Programme of Ministry of Community Development and Mother and Child Health, the Ministry of Health, and development partners provided key inputs and advice in designing and collecting data for the study. The support and advice of Damian Walker, Darwin Young, the EPIC Steering Committee and GAVI IF&S members are also acknowledged.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.040.

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Vaccine 33S (2015) A53–A59

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Examining the cost of delivering routine immunization in Honduras

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ARTICLE INFO

Keywords:
Cost and cost analysis
Immunization
New vaccines
Honduras
Latin America

ABSTRACT

Background: Many countries have introduced new vaccines and expanded their immunization programs to protect additional risk groups, thus raising the cost of routine immunization delivery. Honduras recently adopted two new vaccines, and the country continues to broaden the reach of its program to adolescents and adults. In this article, we estimate and examine the economic cost of the Honduran routine immunization program for the year 2011.

Methods: The data were gathered from a probability sample of 71 health facilities delivering routine immunization, as well as 8 regional and 1 central office of the national immunization program. Data were collected on vaccinations delivered, staff time dedicated to the program, cold chain equipment and upkeep, vehicle use, infrastructure, and other recurrent and capital costs at each health facility and administrative office. Annualized economic costs were estimated from a modified societal perspective and reported in 2011 US dollars.

Results: With the addition of rotavirus and pneumococcal conjugate vaccines, the total cost for routine immunization delivery in Honduras for 2011 was US$ 32.5 million. Vaccines and related supplies accounted for 23% of the costs. Labor, cold chain, and vehicles represented 54%, 4%, and 1%, respectively. At the facility level, the non-vaccine system costs per dose ranged widely, from US$ 25.55 in facilities delivering fewer than 500 doses per year to US$ 2.84 in facilities with volume exceeding 10,000 doses per year. Cost per dose was higher in rural facilities despite somewhat lower wage rates for health workers in these settings; this appears to be driven by lower demand for services per health worker in sparsely populated areas, rather than increased cost of outreach.

Conclusions: These more-precise estimates of the operational costs to deliver routine immunizations provide program managers with important information for mobilizing resources to help sustain the program and for improving annual planning and budgeting as well as longer-term resource allocation decisions.

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1. Introduction

Implementation of the Expanded Program on Immunization (EPI) in Latin America and the Caribbean (LAC) has been broadly successful. Vaccination has been responsible for much of the reduction in childhood mortality since the 1980s, and the LAC nations are on track to achieve Millennium Development Goal 4 [1]. At the beginnings of these EPI programs, the routine delivery of childhood vaccines, including Bacillus Calmette-Guérin (BCG), diphtheria–tetanus–pertussis (DTP), oral polio (OPV), and measles (M), cost no more than US$ 20 per fully immunized child. Today, the cost of vaccines alone to complete the recommended schedules in most LAC countries far exceeds this cost [2]. There are newer, more expensive vaccines, including ones to prevent severe pneumonias, meningitis, and diarrheas in children, as well as the human papilloma virus (HPV) that causes cervical cancer in women. These new vaccines have demonstrated a favorable cost-effectiveness profile, but they often require a doubling or tripling of the budget envelope for their adoption into the routine program [3]. Additionally, the health system costs associated with delivering vaccines are likely increasing due to the infrastructure investments required

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http://dx.doi.org/10.1016/j.vaccine.2015.01.016
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to incorporate new vaccines and a broadening of the program to include population groups beyond children [4].

Concern about growing costs has triggered an interest in strengthening capacity to track and analyze immunization costs, cost-effectiveness, budget impact, expenditures, and outcomes in order to promote greater operational efficiency and sustainability. This trend has been especially true for countries that are approaching a transition away from donor support. Honduras is one of six LAC countries that receive new-vaccine subsidy support from Gavi, the Vaccine Alliance, which is a public–private partnership that works to increase access to new vaccines in the poorest nations of the world. In 2011, Gavi support subsidized 42% of the total cost of vaccines used in Honduras' national immunization program [5]. But, like all other LAC countries supported by Gavi (except Haiti), Honduras is "graduating" from Gavi eligibility due to economic growth and will soon face a higher, "graduated" cost for the newly adopted vaccines. For Honduras and its Gavi graduating peers, understanding the cost of routine immunization in the context of Gavi graduation is critical for planning and program sustainability.

In 2012–2013, the Honduran Ministry of Health (MoH) undertook a study to estimate the costs of the routine immunization program for the year 2011. The study was carried out in collaboration with PAHO's ProVac Initiative, which is a capacity-building effort to strengthen evidence-based decision-making concerning immunization policy [6]. This study was part of the Bill and Melinda Gates Foundation's EPI Costing and Financial Flows (EPIc) project, a study of the cost and financing of national immunization programs in six countries. Research teams in the EPIc network developed common methodological guidance and actively worked to harmonize their studies with this guidance [7]. This article reports the total and unit costs of routine immunization delivery in Honduras in 2011 and describes these costs in the context of programmatic performance and efficiency. A companion article in this special supplement to *Vaccine* explores financing for immunization services in Honduras in the same year [8].

1.1. Routine immunization in Honduras

In Honduras, the recommended schedule of childhood vaccines includes the traditional ones of BCG, Hepatitis B (HepB) infant dose, OPV, DTP/HepB/Hib, and measles–mumps–rubella (MMR), plus two recent additions, pneumococcal conjugate vaccine (PCV) and rotavirus vaccine (RV). The national immunization program also includes vaccines for other populations and diseases, including Tetanus–diphtheria (Td), yellow fever, influenza, and booster doses of DTP (Table 1). Additionally, there are assessments underway to evaluate introducing the HPV vaccine as soon as 2015 [9].

Among countries of the Americas in the same income grouping, Honduras' immunization program is considered a success story. With the help of sustained vaccination coverage above 90% in targeted risk groups, mainly children under 5 years old, Honduras has been free of polio since 1981 and measles since 1989 [10]. Recently, Gavi recognized Honduras for its notable achievement of reaching 98% coverage of the target population with the rotavirus vaccine within two years of the vaccine's introduction into the routine schedule [11]. In 2011, Honduras reported that all children under the age of 2 years were fully vaccinated with all the recommended routine vaccines, with the exception of PCV13, which had been newly introduced in the middle of that year. However, population coverage of childhood vaccines in Honduras saw a slight downward trend after adjustments to the official denominator estimates in more recent years [18]. When using municipal-level denominators that do not account for migration, coverage gaps appear to persist in vulnerable populations and difficult-to-access areas. Security problems in the country have compounded the problem of suboptimal coverage in some districts [12]. Nonetheless, the estimates available indicate coverage has been very high overall for many years [10].

The MoH delivers over 90% of all vaccinations in Honduras. The national immunization program has its central administrative offices in the capital, Tegucigalpa. Regional offices in each of Honduras' 20 sanitary regions oversee service delivery activities as well as organize and operate the supply chain. At the municipal level, one health facility is designated as the "lead" facility for EPI, and has some administrative role in managing immunization in the municipality's health facilities.

The vast majority of immunization service delivery occurs in three types of health facilities: (1) hospitals; (2) CESAMO [*Centro de Salud con Médico y Odontólogo*] health centers, which are typically found in more densely populated areas; and (3) CESAR [*Centro de Salud Rural*] health centers, which are mostly found in rural areas. Immunization in hospitals is limited to newborn application of BGG and hepatitis B doses (70% of all births occur in hospitals). Therefore, the bulk of immunization activity occurs in CESAMO and CESAR health centers.

2. Methods

The methods for this study were guided by the "common approach" methodology for the EPIc multi-country study [7], which aimed to harmonize approaches between the six study sites regarding the sampling protocol, scope and categorization of costs, preferred data sources and assumptions, and study perspective. In Honduras, we retrospectively estimated the economic costs of the government-administered routine immunization program for 2011, from a societal perspective that valued the opportunity cost of all resources consumed in the delivery of immunization except patient time and expenses (e.g., for transportation to clinics).

The routine immunization program is defined as the routine activities to deliver vaccines to the recommended target populations in Honduras. These routine activities include health facility-based vaccination, outreach activities, and the annual periodic intensification of routine immunization (PIRI) through mass social mobilization (which overlaps with Vaccination Week in the Americas). The annual total number of doses applied in the routine program includes those applied in-facility and out-of-facility, but excludes doses applied to achieve a supplemental non-routine program goal, such as vaccination of adult risk groups with the pneumococcal polysaccharide vaccine supply that Honduras received as a donation in 2011. To facilitate comparison to other countries in the EPIc study, we also present the portion of program cost for delivering immunization to children up to 1 year of age (see Supplementary Appendix 1). All costs, other than for vaccines and syringes, were collected in the local currency, lempiras, and converted to 2011 US dollars, with the official exchange rate of 18.8915 lempiras to US$ 1.00. Vaccines and syringe purchase records were already in US dollars. All capital costs were annualized, with a three percent discount rate [13].

Data were collected on resource use and costs at the central, regional, and municipal program administrative levels as well as at health facilities. Eight of the country's 20 sanitary regions were selected purposefully by the EPI to represent a range of settings in terms of the level of urbanization, socioeconomic status, and geography. Two of the selected regions are geographically small, but very populous metropolitan regions (Tegucigalpa and San Pedro Sula). The six other selected regions are more characteristic of the country as a whole. Within the 8 regions, we gathered data from each regional EPI office. In addition, using a multistage probabilistic design, we collected information from a sample of 31 rural (CESAR)

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Table 1
Recommended vaccination schedule in Honduras for children, adolescents, and risk groups, with relevant costing data.

Vaccine	Doses recommended (number primary doses + booster)	Target group schedule (month)	Price per dose (US$, 2011)	Wastage (%)
BCG	1	0	$0.10	68
Hepatitis B (HepB)	1	0	$0.23	0
Oral polio (OPV)	3 + 1	2, 4, 6, 18	$0.21	18
Pentavalent (DTP + HepB + Hib)	3	2,4,6	$3.19	1
Pneumococcal conjugate, 13-valent (PCV13)	3 + 1	2, 4, 6, 18	$7.00[a]	7
Rotavirus	2	2, 4	$2.50[a]	2
Diphtheria–tetanus–pertussis (DTP)	2	18, 48	$0.18	19
Measles–mumps–rubella (MMR)	1	18	$1.60	3
Tetanus–diphtheria (Td)	1	Risk groups	$0.08	24
Yellow fever (YF)	1	Risk groups	$0.67	40
Influenza	1	Risk groups	$3.60	21
Inactivated polio (IPV)	NR[b]	Risk groups	$5.50	–

[a] GAVI prices; all other prices are referenced from PAHO Revolving Fund [19].
[b] Not reported.

facilities and 40 urban health facilities (CESAMOs and hospitals) participating in the routine delivery of public sector vaccinations.

First, from each of the six non-metropolitan regions, three municipalities were selected without replacement and with probability proportional to the size of population under 1 year old. Then, in each municipality, the facility designated as the "lead" facility for EPI in the municipality was selected, as was one non-lead CESAMO and one CESAR. The facilities were selected by simple random sampling within these three strata. Most lead facilities were CESAMOs, but in three cases the lead facility was a hospital. In some instances a municipality did not have a non-lead CESAMO or non-lead CESAR to select, and in these cases, a facility of the other type was selected instead. The probability of selection for each facility was calculated using a Monte Carlo simulation in which 10 million samples were drawn, and the probability of selection equaled the fraction of samples containing the facility. After separating the doses applied in the two metropolitan regions from the rest of the regions, characteristics of the selected vaccination delivery sites are similar to other facilities in the sampling frame that were not selected and other facilities outside of the frame, including the ratio of urban to rural sites and the mean number of doses applied by health facility type (Table 2).

2.1. Data collection

Survey instruments were developed, tested, and then administered at all 71 health facilities and eight regional offices selected in early 2013 (Supplementary Appendix 2). Data was entered in EpiInfo7 (U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, USA) and exported to Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA). Structured interviews were conducted with staff at the national immunization program offices in Tegucigalpa to capture costs at the central level, and then this information was analyzed in the ProVac COSTVAC tool, also developed in Microsoft Excel. COSTVAC was piloted previously in Colombia and Bolivia and is described elsewhere [14].

Surveys at all levels captured information on labor, cold chain, vehicles, travel and per diem allowances, buildings, and other recurrent and capital costs. When resources were shared between the routine immunization program and other health service delivery activities, only the proportions of each shared resource reported as used by the immunization program were valued. Additionally, data on vaccine, injection supplies, and other supplies and costs (including international freight and handling) were collected at the central office. A bottom-up costing approach was used for these commodities, in which the total number of vaccine doses delivered to patients was multiplied by the average price per dose paid for vaccines in 2011, including transaction costs (insurance and fees), excluding transfers (e.g., import duties), and accounting for reported vaccine-specific wastage rates. For the base case scenario, the unit price of Gavi-subsidized vaccines included both the portion of cost paid by Gavi and the portion paid by the Honduran government. The cost of syringes and supplies was similarly based on the number of vaccine doses delivered and unit prices, but, assuming 5% wastage. Because the vaccine doses and associated vaccination supplies such as syringes, cotton, bandages, and rubber gloves are typically imported and have well-documented standard costs, we categorized this group of resource use as its own category, "Vaccines and Supplies." All other categories of resources required to deliver the immunization program are referred to as "system costs" (i.e., non-vaccine costs). These system-cost inputs (labor, equipment, vehicles, per diem and travel allowances, buildings, etc.) were apportioned across 12 principal immunization program planning components used to develop annual and multiannual plans in the Latin America and Caribbean region to understand the activity-based cost structure of the program (Box 1).

2.2. Data analysis

After a modest correction factor was applied to account for differences between the sampled and non-sampled municipalities, the inverse of the probabilities of selection was used as *analytical weights* in the data analysis. Total costs were derived by extrapolating the *weighted* average system cost per dose estimated for the sample, accounting for sample design, to all health facilities in Honduras. We excluded the administrative costs identified at the two metropolitan regional offices (Tegucigalpa and San Pedro Sula), which were substantially higher than the costs in the other regions surveyed. We then averaged the administrative cost per dose identified at all other regional offices and applied this average to non-sampled regional offices in the country in order to estimate costs for this level. These extrapolated cost estimates were then summed with the central-level costs to construct an estimate of the total economic cost of the routine immunization program in Honduras for 2011.

Weighted average total facility-level system costs and weighted average facility-level system costs per dose were estimated for each type of health facility. System cost per dose was calculated at each level by dividing total immunization system costs at each level by total doses delivered in 2011.

We estimated the total cost per fully immunized child (FIC) by summing both the vaccine cost and system cost required to complete the recommended national schedule for 1-year-old children, which includes seven vaccines (14 doses in total). The estimate of vaccine and injection supply cost per FIC included transaction costs, injection supplies, and wastage for relevant vaccines. System cost

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Table 2
Characteristics of sampled and non-sampled administrative offices and health facilities administering the routine immunization program in Honduras.

Characteristic	Sample		Frame	Nationwide
Number of central office	1		1	1
Number of regional offices	8		8	20
By type: non-metropolitan	6		6	18
By type: metropolitan	2		2	2
Number of health facilities	71		784	1535
By type: CESAMO	37		211	412
By type: CESAR	31		526	1020
By type: hospital	3		14	30
By type: other	0		31	73
Total population under 1 year old	63,632		102,709	177, 733
Total doses applied	541,862		2450891	4104,310
	Metro	*Non-metro*		
Mean doses applied by type: CESAMO	15,104	4792	6822	5270
Mean doses applied by type: CESAR	1926	1089	1160	1182
Mean doses applied by time: hospital	20,133	20,646	24,390	16,671
Fraction of total doses applied during PIRI*	0.0988		0.0972	0.0927
Fraction of total doses applied to children under 1 year old	0.6149		0.6416	0.6498

* PIRI = periodic intensification of routine immunization.

Box 1: Definitions of EPI planning and budgeting components in PAHO region.

EPI component	Cost definition
Political priority, advocacy and legal basis	Time and resources dedicated to advocacy and policy, including developing legal frameworks for immunization.
Planning and coordination	Time and resources dedicated to managing, planning, and budgeting and coordinating at all levels of the program.
Vaccines and supplies	Includes all vaccines and safe injection supplies.
Cold chain	Time and resources dedicated to installing, maintaining and using the cold chain, which encompasses vaccine storage and distribution.
Training	Time and resources developing, administering and/or participating in training and continuous learning opportunities.
Social mobilization	Time and resources dedicated to community level mobilization to raise awareness about vaccination, including television spots, information and education campaigns, and importantly resources dedicated to support the Jornadas Nacionales de Vacunación.
Other operating costs	Time and resources dedicated to other recurrent and capital costs of the immunization program, for example printing and office furniture.
Monitoring and supervision	Time and resources dedicated to local level staff to perform supervision visits and meetings in order to monitor coverage and other performance indicators.
Surveillance, vaccine safety and laboratories	Time and resources dedicated to epidemiological investigation of Adverse Events Following Immunization (AEFI) and VPD outbreaks.
Information systems	Time and resources dedicated to record keeping and reporting data between programmatic levels.
Research	Time and resources dedicated to operational research.
Evaluation	Time and resources dedicated to evaluating program performance at sub-national and national level.

per FIC was estimated for each vaccine by multiplying each recommended dose by the mean system cost per dose at each level of the program. Additional results specific to the cost of vaccinating children up to 1 year old were calculated to facilitate comparison between the study in Honduras and other EPIC country studies. All statistical analysis were conducted in STATA12.

3. Results

3.1. Total costs of routine immunization in Honduras

The total cost to deliver the routine immunization program in Honduras for 2011 was US$ 32.5 million. Vaccines and other supplies represented a large share of the costs, amounting to 25%. However, labor was the largest cost category, accounting for about half of the total cost (Table 3). Excluding vaccine and injection supplies, about three quarters of the costs are incurred at the health facilities. Only 14% and 9% of system costs occur at the regional and central offices, respectively. About 55% of all doses in the routine immunization program are delivered to children up to 1 year old. Analysis of program costs for this population is described in Supplementary Appendix 2.

Labor costs are substantial at all levels, but the activities supported by these costs range widely among the different program levels. Activities to support program management, including planning and coordination, supervision, monitoring and evaluation, and research, are consistently a large share of total labor across levels. In contrast, vaccine administration and social mobilization are more substantial at the facility level. At the regional offices, labor costs are mostly associated with program management, cold chain, and surveillance activities. Other labor costs that represent administrative and support activities, such as for drivers and secretaries, carry a larger share of the costs at the central level.

Expenses to support the launch of a new vaccination in April 2011, against pneumococcal disease, were also surveyed. Besides the cost of procuring the vaccine and needed supplies for the two new vaccine programs (around US$ 4.8 million, assuming GAVI prices of US$ 7 per PCV dose and US$ 2.50 per rotavirus dose), nationwide trainings and revision of vaccination manuals represented the only other incremental costs identified for the 2011 study period. These costs totaled US$ 142,300. The survey of costs at the facility level did not reveal any incremental costs solely related to incorporating the new vaccine.

Leading up to the introduction of rotavirus vaccine in 2009 and in anticipation of future PCV13 introduction, Honduras had invested substantially in the cold chain infrastructure to ensure adequate capacity for both rotavirus and PCV13. However, our study did not gather data on the cost of these investments, which occurred prior to the 2011 study period.

3.2. Unit costs and costs to fully vaccinate a child

In 2011, more than 4 million doses of vaccine were delivered to protect children, adolescents, and adults against 14 vaccine-preventable diseases. The mean system cost per dose to deliver the vaccines was US$ 5.97, of which 78% occurred at the facility level. When accounting for the stratification by facility type in the sample design, the facility-level system cost per dose delivered ranges from US$ 1.58 (95% CI: US$ 1.23–1.92) in hospitals to US$

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Table 3
Total cost of the routine immunization program in Honduras (2011 US dollars, in thousands).

Category	Facility	Regional	Central	All levels
Capital costs				
Vaccine and supplies	$0	$0	$0	$0
Labor	$0	$0	$0	$0
Volunteers	$0	$0	$0	$0
Cold chain	$625	$176	$12	$813
Vehicles	$53	$44	$65	$162
Buildings	$613	$104	$17	$734
Other	$28	$10	$103	$141
Total	$1319	$334	$197	$1850
Recurrent costs				
Vaccine and supplies [a]	$0	$0	$7990	$7990
Labor	$15,404	$1800	$449	$17,653
Volunteers	$713	$0	$0	$713
Cold chain	$357	$70	$30	$457
Vehicles	$60	$71	$21	$152
Buildings	$220	$0	$6	$226
Other	$1021	$1046	$1381	$3448
Total	$17,775	$2987	$9877	$30,639
Total costs				
Vaccine and supplies [a]	$0	$0	$7990	$7990 (25%)
Labor	$15,404	$1800	$449	$17,653 (54%)
Volunteers	$713	$0	$0	$713 (2%)
Cold chain	$982	$246	$42	$1270 (4%)
Vehicles	$113	$115	$86	$314 (1%)
Buildings	$833	$104	$23	$960 (3%)
Other	$1049	$1056	$1484	$3589 (11%)
Total	$19,094	$3321	$10,074	$32,486 (100%)

[a] *Note*: Total vaccine costs reflect the following assumptions: (1) PCV13 and rotavirus price per dose consider GAVI-manufacturer price agreements of US$ 7.00 per dose and US$ 2.50 per dose, respectively, and (2) vaccine and supply costs for PPV23 (2011 donation) were excluded.

Table 4
Weighted average delivery cost per dose, by facility type (2011 US dollars).

Facility type	Obs.	Mean	SE	95% CI LB	95 CI% UB
CESAMO	37	$4.56	$0.60	$3.34	$5.77
CESAR	31	$7.68	$1.75	$4.16	$11.21
Hospital	3	$1.58	$0.17	$1.23	$1.92

Table 5
Weighted average delivery cost per dose, by facility output category (2011 US dollars).

Facility size (no. of doses)	Obs.	Mean	SE	95% CI LB	95% CI UB
Huge (≥10,000)	16	$2.84	$0.40	$2.03	$3.66
Large (5000–9999)	4	$4.63	$1.67	$1.28	$7.97
Medium (1500–4999)	20	$5.05	$0.85	$3.34	$6.75
Small (500–1499)	27	$9.28	$0.83	$7.61	$10.96
Tiny (<500)	4	$25.55	$2.02	$21.48	$29.61

7.68 (95% CI: US$ 4.16–11.21) in rural vaccination posts (Table 4). Regardless of facility type, facility-level system cost per dose was strongly (negatively) correlated with volume of doses delivered (Table 5). Facilities delivering fewer than 500 doses per year have the highest system cost per dose, at US$ 25.55 per dose (95% CI: US$ 21.48–29.61). In contrast, the facilities delivering 10,000 or more doses per year have the lowest system cost per dose, at US$ 2.84 (95% CI: US$ 2.03–3.66).

Focusing just on the cost of fully immunizing a child up to 1 year of age, we calculated that the cost per FIC was US$ 132.24. Of this cost, US$ 48.67 (37%) is for vaccine and injection supply and US$ 83.57 (63%) is for system cost (Table 6). Since the total cost at regional and facility level accounts for the sample design, and is extrapolated based on facility volume, type, and location, the cost per dose represents a national average. Assuming the vaccine and delivery costs associated with the number of doses for completing the recommended schedule for the new rotavirus and pneumococcal conjugate vaccines, roughly 20% of the cost per FIC is associated with these vaccinations in 2011.

4. Discussion

Applying a rigorous methodology that included systematic data collection from a representative sample of health facilities

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Table 6
Cost per fully immunized child (FIC) at age of 1 year in Honduras (2011 US dollars).

Vaccine	Doses/U1 FIC	Cost/dose	Total cost
BCG	1	$0.10	$0.10
Hepatitis B	1	$0.23	$0.23
Oral polio	3	$0.21	$0.63
Pentavalent	3	$3.19	$9.57
Rotavirus	2	$2.50	$5.00
PCV 13	3	$7.00	$21.00
MMR	1	$1.60	$1.60
Vaccine only	14		**$38.13**
With safety box and injection supplies			$46.01
With wastage	17.11		**$48.67**
All other resources employed for delivery (labor, cold chain, infrastructure, etc.) by dose			
	Central administration	$0.51	$7.12
	Regional administration	$0.81	$11.33
	Facility delivery	$4.65	$65.13
	Total for delivery		**$83.57**
Total economic cost per fully immunized child			**$132.24**

Bolded values represent intermediate calculation. The sum of the last two bold values gives the total.

and regional EPI offices, this study generated comprehensive, detailed, and precise estimates of resources actually used to deliver the national immunization program of Honduras. The study further benefited from the use of the COSTVAC tools developed by PAHO's ProVac Initiative and collaboration with the community of immunization-costing experts convened for the large EPIc project. The results have direct utility for policymakers in Honduras as they carry out strategic planning for sustaining and improving the national immunization program. Additionally, the information adds another dimension to assessments of program performance, and provides useful baseline information for cost-effectiveness analysis and resource tracking over time.

In addition to being useful for policymakers and stakeholders in Honduras, the study also generated three key insights that are beneficial more generally. First, the study contributes to a growing literature showing that the "system costs" of high-quality immunization programs, particularly labor costs for vaccine delivery, are significant, and should not simply be ignored. In many low- and middle-income settings, including Honduras, health sectors are rapidly expanding both the coverage and scope of services provided. However, the capacity of the health workforce is often a binding constraint on production. Greater awareness of the current use of scarce human resources by different activities of the health sector should aid efforts to align existing resources with health priorities and inform strategies to increase resources.

Second, this study shows that system costs of immunization programs at the facility level range widely, and that these costs are tightly correlated with the number of vaccine doses delivered. Similar findings on the range in unit costs in different health service settings have been reported for Peru [15] and for many other developing countries [16]. Additional studies are required to determine how much of the observed range at the facility level is unavoidable, and how much represents an opportunity to improve efficiency. However, this study suggests that achieving high coverage in sparsely populated areas will require more resources per dose delivered than in urban areas. The less densely populated areas may have somewhat lower wage levels, but they face fixed costs associated with ensuring that services are geographically accessible to populations in these areas. With an increasing number of municipalities registering DTP3 coverage rates below 80% in Honduras [12], more resources may be needed to achieve the goal of extending the benefits of immunization to all persons [17].

Third, this study is the first to estimate the economic cost of annual vaccination campaigns in conjunction with costing of a routine immunization program. In Honduras, as in many other LAC countries, these periodic campaigns mobilize a very large portion of workers in the health sector as well as government workers in other sectors, plus numerous volunteers, for a period of two to three weeks at a time. This massive community effort is responsible for delivering about 8% of the doses in Honduras, and it is believed to be critical to achieving high population coverage and maintaining the public perception of vaccination as an essential health intervention. Despite the important programmatic benefits that campaign activities provide for completing childhood schedules and other targeted goals, these annual drives are resource-intensive, and many of the resources consumed should be accounted for in the annual budgeting process. While our study does not measure the opportunity cost of these campaigns in terms of the health and other services foregone, it does value the time of all workers and volunteers (as well as other inputs) consumed during the campaigns. These factors should be taken into consideration for future planning efforts.

The study has several limitations. First, the study's design allows for standard statistical inference regarding the economic costs of vaccination in the eight regions surveyed. However, those regions were not selected at random. Therefore, our estimation of total national cost required the additional assumption that facilities in regions outside the sample frame are not systematically different from facilities of similar size and type in the sampled regions. Because of this, uncertainty in our estimates is somewhat greater than what is reflected in the reported confidence intervals. Secondly, labor cost at the facility level may have been overestimated due to a reporting bias. Although the interview method and interviewer training were designed to minimize this type of bias, we did not have a gold standard with which to validate the method or measure the bias, if present. Additionally, in most cases, the person in charge of immunization at the health facility reported her or his estimate of the fraction of the time each worker spent on immunization activities. Although they were encouraged to, and often did, solicit information from other health workers at the facility during the interview, it is reasonable to assume that the measure of health worker time allocated to immunization is imprecise. Ideally, future studies would validate the method by comparing it to time-motion study or other more rigorous measurement methods. Third, the societal perspective of this study did not measure household costs associated with time and travel costs for vaccination. Fourth, our study was not able to allocate system costs to deliver specific vaccines, though it is possible that certain vaccine types require more or fewer resources. Finally, the correlates of total facility costs identified in this study are consistent with other published findings of facility-level cost drivers.

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However, having further information on the relationship between coverage (or other program performance measures) and total costs would help to refine recommendations on programmatic efficiencies.

We expect much of the information collected will be useful in routine budgeting as well as in strategic planning for new vaccine introduction, program quality improvement, and optimization of cost-efficiency. However, care must be taken in those efforts. Our estimates are from one historical year, and secular trends in unit costs and other contextual factors may necessitate updating or making adjustments to the results of this study for use in the future. Additionally, some of the costs we report have no corresponding financial transaction (e.g., volunteer time), and not all of the costs for immunization are accounted for in the immunization program's budget. Indeed, facility-level labor is a major input that is generally not included in the immunization budget. Finally, we did not estimate the marginal system cost of increasing coverage or the marginal system cost of adding a new vaccine to the routine immunization schedule. In the planning for marginal increases in scope or scale of the immunization program, we would not recommend naively assuming that additional doses would have system costs equal to the average system cost measured in this study. Nonetheless, in the context of planning for such increases, having the information from this study is far better than having no systematic, comprehensive information about resource use.

5. Conclusions

The study shows that even with the addition of new, more expensive vaccines to the routine schedule, system costs account for the majority of the resources used in the delivery of Honduras' national immunization program. System costs per dose delivered range widely among facilities, with the costs being most strongly correlated with the number of doses delivered. The study contributes key information to enable better mobilization and management of resources for immunization. Integrating the type of costing data collected in this study with other program performance measures will enable more accurate resource planning and identification of opportunities to improve cost efficiency.

Acknowledgements

We would like to extend our deepest thanks to the top notch data collector team that visited all 71 health facilities and eight regional offices. The team of public health professionals that serve in management at the national and regional levels in Honduras dedicated a substantial amount of time for interviews and data gathering, and for this we are ever grateful. We also are indebted to the other EPIc country teams and EPIc steering committee members for their constructive feedback and reviews of the data and technical reports. And, finally, we would like to thank Logan Brenzel and Damian Walker for their support and guidance in this process. This study was kindly financed by the Bill and Melinda Gates Foundation (OPP1032888).

Authors' contribution: CJ, IMB, CC, GF & SR designed and implemented the study. LM, ID, IMB, GF & CC supported data collection. All authors contributed to data analysis and write up. All authors approved final manuscript for publication.

Conflict of interest: The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.01.016.

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Vaccine 33S (2015) A60–A65

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Costs of routine immunization services in Moldova: Findings of a facility-based costing study

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ARTICLE INFO

Keywords:
Routine immunization
Costs
Moldova
Cost-effectiveness
Sustainability

ABSTRACT

Objective: Available estimates on how much it costs to provide routine immunization services are outdated. This study attempts to address gaps in evidence by evaluating the total economic and unit costs of delivering routine immunization (RI) services in Moldova as part of a multi-country study on the costs and financing of routine immunization (EPIC).
Methods: This cross-sectional study is based on a multistage stratified random sample of fifty primary health care facilities. Data on inputs, prices, and outputs were collected retrospectively for 2011 and analyzed using an ingredient-based costing approach in Excel and SPSS®.
Results: The average total annual facility cost for RI was $11,943 ranging from $565 to $112,548 and labor cost was the main driver of routine immunization costs contributing 65%, followed by capital costs – 16.3% and the cost of vaccines and injection supplies accounting for 9%.

The average cost per dose was $18.3, the cost per child was $316.6 and the cost per fully immunized child was $332.3. The results show considerable variation in the costs of routine immunization services across facility type and depending on a facility scale i.e. annual doses administered.
Conclusions: The study shows that the cost of fully immunizing a child in a middle-income country is much higher than previous estimates. These results will be used by the government for better planning and financing of routine immunization services, leading to greater sustainability.
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1. Introduction

Vaccination against childhood communicable diseases through the Expanded Program on Immunization (EPI) is one of the most cost-effective public health interventions [1]. By reducing mortality and morbidity, vaccination can substantially contribute toward achieving the Millennium Development Goal of reducing under-five mortality among children by two-thirds between 1990 and 2015 [2].

The costs and financing of national immunization programs have been evaluated since the 1980s as part of the *Universal Childhood Immunization* Initiative [3]. However, currently available information is out-dated and new knowledge on the full economic costs of routine immunization programs is important to inform both global and national policies and practice.

Our study evaluates the total economic and unit costs of the immunization program in the Republic of Moldova as part of a multi-country study supported by the Bill and Melinda Gates Foundation and aimed at evaluating the costs of routine immunization programs and new vaccine introduction. It is expected that our study results will contribute to building a new evidence-base that will provide valuable inputs into the development of national and global policies, as well as contribute to better planning and management of the national immunization program in Moldova.

2. The national immunization program in Moldova

The current plan for the national immunization program in Moldova covers the period 2011–2015 and guarantees free immunization against ten infectious diseases: poliomyelitis, diphtheria, tetanus, pertussis, hepatitis B, measles, mumps, rubella, tuberculosis, and Haemophilus influenza type B. Based on this program Moldova plans to increase DTP 3 coverage up to 94% and 95% in

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http://dx.doi.org/10.1016/j.vaccine.2014.12.034
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2014 and 2015 respectively, although country already reports high DPT3 coverage rate that is above 90% [4,5].

Routine immunization services[1] are delivered primarily through primary health care (PHC) facilities. In urban areas, *Family Medicine Centers* (FMC) serve a population of between 40,000–80,000 and 440–880 infants. In rural areas, *Health Centers* (HC) cater to 4500 inhabitants and around 50 infants; *Family Doctor Offices* (OFD) serves between 900–3000 inhabitants and about 10–33 infants; and, small *Health Offices* (HO) cover up to 900 residents and 5–8 infants. All facilities with the exception of HOs are staffed with doctors and nurses, while most of HOs only employ nurses. Private facilities, though growing in number, do not engage in the delivery of the routine immunization services funded by the state. In all PHC facilities, immunization is delivered as a fixed strategy and no outreach activities are carried out. Consequently, costs captured in this study only pertain to the fixed strategy.

3. Materials and methods

This is a cross-sectional facility-based costing study, which examines total and unit costs of routine immunization and describes cost drivers and cost variation across facilities in Moldova.

3.1. Facility sampling

The study was based on a representative sample of PHCs selected based on multistage, stratified random sampling. In the first stage, the total number of vaccine doses delivered in 2011 was used to stratify 37 districts into three strata: districts with low, medium and high vaccine doses administered per annum. Stratification was based on tercile groups derived through simple frequency analysis on annual doses administered. After stratification two districts were chosen in each stratum using simple random sampling approach, resulting in 6 districts in the sample.

In the second stage, PHC facilities were randomly selected from a complete list of facilities stratified by urban and rural location within each sampled district. Proportions of urban/peri-urban and rural facilities from the total number of facilities were estimated, and used to calculate the number of rural and urban/peri-urban facilities to be sampled. One peri-urban facility was randomly selected in each sampled district and three urban facilities were randomly selected from the capital city. Rural facilities were selected using systematic random sampling. Consequently, the final sample consisted of eight urban/peri-urban and 42 rural facilities, represented by five FMCs, 10 HCs, 23 OFDs and 12 HOs. This sample was drawn from 1318 facilities involved in the delivery of immunization services.

Data collection in facilities took place from October 3rd 2012 to January 14th 2013 using standardized, pre-tested and structured questionnaires. Data were collected by experienced data collectors and included interviews with facility administrators and health workers involved in immunization, facility observation, and record review.

3.2. Cost analysis

The data for the routine EPI were collected retrospectively for 2011 calendar year and converted into $US 2011 using the current exchange rate for the year. Cost calculations were based on common approach methodology for the costing and financing analysis of routine immunization program [6,7] and costing guideline for comprehensive Multi-Year Plan (cMYP) [8]. Costs of all inputs were captured using an ingredients approach listing all inputs by activity and quantities and prices for each input element [9,10].

The cost data included a comprehensive list of capital[2] as well as recurrent expenditure items. Capital costs were analyzed using a 3% discount rate [11] and country specific useful life years for different capital items were applied [12].

The cost of labor included salaries and other allowances for the staff involved in the EPI and were calculated based on a self-reported percentage of time spent by staff on different immunization activities.

The cost of vaccines and syringes was calculated for each vaccine separately. The number of doses used included both doses administered (for all vaccines in the schedule) and doses wasted, which allowed estimating vaccine-specific and overall facility level wastage rates [11].

Cold chain costs were calculated by inventorying the number and type of cold chain equipment and the World Health Organization (WHO) product information sheets [13] informed the prices. Cold chain energy costs were based on energy consumption characteristics from the WHO *Products Information Sheets* and local unit price of 0.095 $US/kw/h was applied.

For those costs not exclusive to immunization, the following allocation methods were used: cost of vehicles and vehicle maintenance was allocated based on the proportion of km traveled for routine immunization out of total km traveled in 2011; building costs were allocated based on the proportion of square meters designated for routine immunization (where vaccines are administered, stored) out of total facility space. More details about the costing, unit prices are available from elsewhere [12] A table of key assumtions/cost allocation methods is provided in the Annex.

Estimated costs were converted into the *cost per dose* delivered, cost per *Fully Immunized Child* (FIC) and *cost per infant*. For the purposes of our study the Fully Immunized Child denotes a child less than one year of age who received three doses of DTP vaccine (DTP3). Although this definition differs from what is being formally used in Moldova,[3] it is useful for international comparability of costs.

Excel software was used for calculation of various cost elements and unit costs for a facility. These calculated variables were transferred to SPSS version 19.0 for further statistical analysis.

Throughout the paper, unless otherwise noted, we present total economic costs of the routine immunization services on a facility level in 2011 $US at the current exchange rate. The costs and cost variations are presented by urban–rural location, type and scale of a facility using *T*-test for statistical significance.

4. Results

4.1. Total facility costs and observed cost variation

The total facility level immunization costs in the sample varied from $565 to $112,548, with a mean of $11,943 and median $US3822. Log transformed variables reveal a positive linear correlation between total facility level costs and total doses delivered ($r = 0.95$, $p < 0.01$).

Fig. 1 shows that total facility cost varies by facility type, with costs increasing with facility size (HOs to FMCs). Variation within facility type is not large with the exception of FMCs where costs range from $28,335 to $112,548 (mean $62,902). Two facilities

[1] Routine immunization services are defined as those immunization services or activities that are conducted regularly as part of the national program.

[2] Capital items include buildings, vehicles, cold chain equipment and office equipment.

[3] FIC in Moldova denotes a child less than one year of age who received three doses of DTP-Hib-Hep B, one doses of BCG, one doses of Hep B, three doses of OPV and one doses of MMR vaccines.

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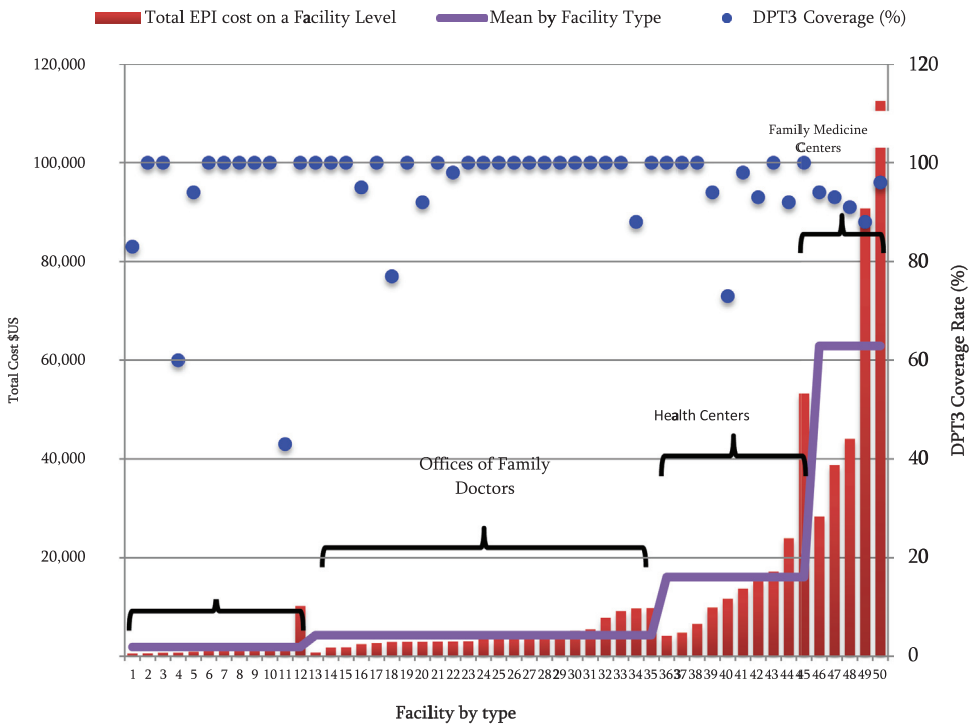

Fig. 1. Total costs by type of facility and DTP3 coverage (%).[6]

within each of the HOs and HCs have significantly higher costs compared to their peers. Both of these facilities were found to be high performing ones delivering more doses annually and achieving higher coverage rates. The figure also shows that while the majority of facilities achieve high DTP3 coverage rates, a few underperforming facilities contribute to a lower average DTP3 coverage rate in the sample – 94.8%. HCs and OFDs had higher coverage rates (98.1–97.8%, respectively), while HOs have the lowest rates on average (90.2%). The study also found that the facility total cost correlates with the number of infants covered by the facility ($r = 0.95$, $p < 0.01$).

4.2. Total facility cost structure

Analysis revealed that the share of labor costs increases with facility size and scale (defined as total doses delivered in 2011), and is the main driver of immunization costs. Labor cost accounted for 65% of the total facility immunization cost for the sample, ranging from 55% in lower scale to 73% in higher scale facilities. Close to 87% of labor inputs are spent on four critical immunization functions/activities: routine service delivery (29.8% of the time), program management (23.5%), recordkeeping and health management information (17.1%), and social mobilization (16.7%) (see Fig. A1 supplied in Annex for more details).

Capital costs are the second biggest contributor to total facility immunization costs. The share of recurrent and capital costs differed across facilities as well. Namely, the share of capital costs was lowest in FMCs – 10.3% and highest in HOs – 22.8%, with the average across all sampled facilities being 16.3% (see Table 1). Furthermore, in the facilities with higher scale, the share of capital costs was around 9.3%, while in a low scale facility it reached 23.1%. Vaccine and injection supplies only accounted for 8.72% of the cost (range: 8.3–14.42% by facility type and 8.04–10.63% by facility scale).

4.3. Facility unit costs and their variation

A range of unit costs was evaluated for this study, including cost per dose, cost per infant, and cost per FIC and amounted to $US6.4, $US112.3 and $US117.8 respectively. Differences between urban and rural facilities are presented in Table 2. These differences (both with and without shared labor costs) are not statistically significant. Also differences in the unit costs captured between types of facilities did not reveal statistical significance. However, when shared labor costs were removed, the cost per dose was $3.10 in the sample of FMCs, increasing to $8.50 per dose in the sample of HOs, which became statistically significant ($p < 0.01$).

Fig. 2 shows a negative relationship between facility scale and unit cost for the facilities in the sample: larger facilities have lower unit costs in general.

The only significant influence, although with marginal statistical significance ($p < 0.1$) was between unit costs and facility scale and only for the cost per FIC and/or cost per infant. The statistical significance of scale influence increased when shared labor costs were removed from unit cost estimates (see Table 2).

4.4. Unit costs and facility level immunization program performance

Fig. 3 shows the relationship of facility unit costs and performance measured as DPT3 coverage rate.[4] HOs with the lowest DPT3 coverage rates spend a comparable amount per dose delivered as OFDs and HCs. The amounts of non-labor inputs are highest in HOs

[6] The fact that the denominators of target population differ by facility type the low coverage rates at smaller facilities mean fewer individuals compared to bigger facilities.

[4] To calculate DPT3 coverage rate we used number of children receiving three doses of DTP (or DTP containing vaccine) under the age one divided by the number of children under one in the facility catchment area, determined through facility records.

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Table 1
Cost structure by facility type and facility scale.

Item	Facility type				Facility scale			
	FMC	HC	OFD	HO	Low	Medium	High	Total
Recurrent cost (%) of total	**89.7**	**88.7**	**85.4**	**77.2**	**76.9**	**87.7**	**90.7**	**83.7**
Salaried labor	70.4	73.2	68.1	54.4	55.5	71.4	73.3	65.1
Vaccines and injection supplies	14.4	8.2	8.8	8.3	8.1	8.6	10.6	8.7
Utilities and communications	2.7	4.8	5.9	8.5	8.3	5.1	5.0	6.4
Printing	1.1	0.5	0.1	0.0	2.4	1.5	0.5	1.7
Cold chain energy	0.1	0.5	0.5	1.8	1.4	0.5	0.2	0.8
Other recurrent	1.0	1.5	2.0	4.2	1.2	0.6	1.1	1.0
Capital cost (%) of total	**10.3**	**11.3**	**14.6**	**22.8**	**23.1**	**12.3**	**9.3**	**16.3**
Building	7.1	5.8	9.2	15.3	15.2	7.5	5.7	10.3
Cold chain equipment	0.2	0.8	2.3	4.6	4.5	1.6	0.6	2.7
Other capital costs	3.0	4.7	3.1	2. 9	3.4	3.2	3.0	3.3
Total (%)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
Unit cost per dose, US$	**10.4**	**19.4**	**18.5**	**18.7**	**20.5**	**18.3**	**14.5**	**18.4**

Table 2
Facility unit costs by type of facility, location and facility scale.

Unit cost $US	Facility type					Facility location				Facility scale				Total
	FMC	HC	OFD	HO	Sig.	Rural	Semi-urban	Urban	Sig.	Low	Medium	High	Sig.	
Total cost per dose	10.4	19.4	18.5	18.7	*.338*	18.6	14.5	13.1	*.561*	20.5	18.3	14.5	*.190*	**18.3**
Total cost per Infant	143.9	322.9	338.7	296.5	*.249*	325	207	165	*.279*	331.5	352.8	216.1	*.059*	**316.6**
Total cost per FIC	155.1	328.8	347.2	332.2	*.285*	340	222	180	*.290*	357.5	359.7	231.2	*.078*	**332.3**
Total cost w/o labor per dose	3.1	5.2	5.9	8.5	*.009*	6.6	4.0	3.7	*.226*	9.1	5.2	3.9	*.000*	**6.4**
Total cost w/o labor per Infant	42.6	88.5	110.6	138.7	*.152*	116	56	47	*.232*	157.3	99.8	57.4	*.003*	**112.3**
Total cost w/o labor per FIC	45.9	89.9	113	152.4	*.083*	122	60	51	*.216*	167.3	101.7	61.6	*.001*	**117.8**
N weighted	**55**	**190**	**708**	**365**		**1238**	**54**	**26**		**489**	**556**	**273**		**1318**
N unweighted	**5**	**10**	**23**	**12**		**42**	**5**	**3**		**16**	**18**	**16**		**50**

and lowest in FMCs and largely determined by variable use of capital. HCs spend the highest amount per dose delivered, but also achieve the highest coverage rates. FMCs seem to be the most efficient facilities being able to deliver immunization at the lowest cost per dose by using labor and non-labor inputs effectively. Finally, while HCs spend the highest amount per dose they spend the least (after FMCs) on non-labor inputs.

5. Discussion

The study helped estimate average unit cost per dose delivered in 2011 ($18.3) and cost per FIC ($316.6). These figures are higher than what has been previously reported in the literature [9,14–16] and also higher than the figures used in the cMYP–191 $US per FIC [8]. Though cMYP underestimated shared costs by 32% and capital costs by 61%, but recurrent costs were overestimated by almost 44% [12].

Our study shows that the labor inputs are significant contributor to a unit cost and consequently to the overall immunization program cost. These findings are comparable with the evidence documented elsewhere i.e. immunization program being labor intensive [2,9,16]. Furthermore, the study captured the breakdown of labor inputs on various functions, not easily available from other studies, showing that four activities on a facility level determine

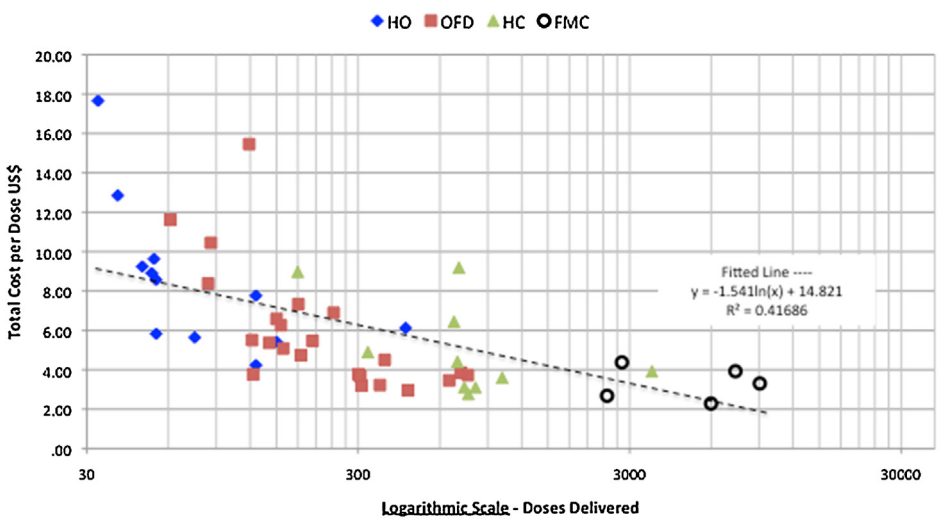

Fig. 2. Total cost without labor per Dose by facility scale.

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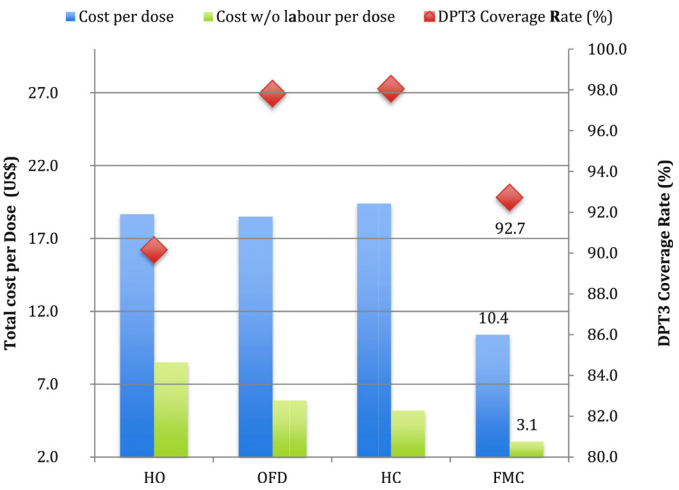

Fig. 3. Total cost per dose and DTP3 coverage rate by type of facility.

close to 87% cost of labor inputs for immunization. The government of Moldova is focused on increasing health system efficiency. These findings suggest that reducing staff time spent on immunization could help increase efficiency of the program and it could be achieved either through task shifting [17][5] i.e. delegating certain immunization related tasks from doctors to nurses, or through reducing time spend on management and/or recordkeeping functions. The latter could be achieved with the help of computer based HMIS, which is currently being developed. Adequate modules for immunization program planning and management along with the modules for record keeping offer potential for reducing staff time spent on these functions, conditioned that PHC modules of the HMIS are developed with this objective in mind.

We have also seen variable use of capital by facility type and by scale. Namely, larger facilities (i.e. FMCs and HCs) and facilities with a greater scale are able to use capital more effectively. The influence of the capital becomes significant when shared labor costs are excluded and when variable use of capital becomes critical determinant of the costs. The level of scale is associated with lower unit costs, and supports the available global evidence [15,18]. Consequently increasing the scale of a facility (by merging smaller ones into larger ones, where possible) could help reduce the program unit costs. Although this may as well increase distance to a facility and may negatively affect immunization coverage rates.

Furthermore, vaccines and vaccine supplies were found to be the third most important cost driver of the immunization costs on a facility level. Consequently reducing vaccine prices, which currently are double the prices of UNICEF supplied vaccines [19], could be the strategy for the country to consider. Furthermore, Moldova is graduating from the GAVI Alliance in 2016 and country is contemplating reforming its immunization program and decentralizing vaccine procurement responsibilities due to the nature of the national public finance regulations. Our study shows that the cost of vaccines is critical element of the immunization program and needs to be well managed. Therefore centralized model for vaccine procurement could be more effective, while decentralization of this function may drive vaccine prices up and could increase overall program cost.

[5] Task shifting is the name given to a process of delegation whereby tasks are moved, where appropriate, to less specialized health workers. By reorganizing the workforce in this way, task shifting presents a viable solution for improving health care coverage by making more efficient use of the human resources already available.

Finally, we have seen that Moldova achieves high immunization coverage rates compared to other countries in the region [20]. However, differences exist when coverage rates are examined by facility level. Namely, HOs that are equipped only with nurses and located in small villages have the lowest DPT3 coverage. However, due to a very small number of infants – 7 (95%CI: 6.7–7.9) in the facility catchment area this low coverage translates into at most one child missing its third dose of DPT. HCs along with OFDs achieve higher DTP3 coverage rates compared with others. It could be assumed that relatively small size of the catchment population and having doctors on staff probably allows these facilities to better identify, plan and follow-up infants and consequently achieve higher DPT3 coverage. While FMCs also have doctors on staff, due to the large size of the catchment population, they may face additional complexities in finding, following and immunizing a child. In light of this increasing DPT3 coverage could be achieved by placing more importance on FMCs, where immunization program performance is the second poorest after HOs – 92.7%. Improving performance of these facilities seems more feasible on several counts: they have better staffing and more human resources, they have more infants and improving their performance would have greater impact on the national coverage rate. Also, due to their ability to deliver most cost-efficient immunization services it may be less costly option for the national budget. However, this strategy raises urban–rural equity concerns. To mitigate these concerns, it seems necessary to focus managerial efforts on significantly underperforming rural facilities, where coverage rates are below 80% and provide supportive supervision or other assistance that will be necessary.

While the study provides valuable evidence, its strength and limitations should be kept in mind. Namely, this is the first facility-based costing study of immunization services conducted in Moldova and provides rich data that could be used in the national planning as well as for benchmarking results of future research. The sample size at 50 facilities was relatively small and excluded maternity homes, where BCG and Hepatitis B birth dose is administered, so that total and unit costs may be slightly underestimated. Nevertheless, maternities only provide two out of 22 doses in the immunization schedule and are larger in size compared with the facilities in our sample, so that maternities would be expected to deliver immunization at a lower cost. Consequently, our underestimations are expected to be small. Secondly, our definition of the FIC is not fully compatible with the national definition used in Moldova. Consequently, careful interpretation is needed when comparing with the findings from other national as well as internationally available data. Finally, labor cost estimates could be affected by recall bias related to a time spent on immunization activities, although efforts were made to minimize this bias by organizing group discussions at the facility to reach consensus among staff.

6. Conclusions

Our findings could inform policy discussions within Moldova around increasing immunization coverage rates while running the program more efficiently and sustainably. At the same time increasing coverage rates through sustainable financing is a global concern, well beyond Moldova. Our study noted variations in total immunization costs and unit costs at the facility level and variation in the facility performance measured by DTP3 coverage rate. The analysis allows hypothesizing that characteristic of a facility may have influenced achieved DPT3 coverage rates. However available evidence also indicates that immunization coverage rates are as well dependent on socioeconomic characteristics of the population [21–23] on their proximity to health facility [24,25] etc. Therefore, it

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would be valuable to evaluate other context specific determinants (e.g. population and geography characteristics) in a multivariate model to establish causal links between the factors determined by our bi-variate analysis for the facility performance and costs. Such research could provide an additional valuable contribution to the global evidence in addition to this study.

Acknowledgements

This study would have not been possible without the continuous support of the Ministry of Health of the Republic of Moldova, EPI manager, directors of District Public Health Centers and health care providers who gave their time as well as allowed access to facilities and facility records. Therefore, we would like to acknowledge their invaluable support in carrying out this work. We would like to thank Bill & Melinda Gates Foundation for providing financial support. And in particular, we would like to acknowledge the support of Logan Brenzel and Damian Walker, steering committee members and other country teams that commented on an earlier draft of this paper and provided valuable inputs and guidance to the study team.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.034.

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Vaccine 33S (2015) A66–A71

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Determinants of routine immunization costing in Benin and Ghana in 2011

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ARTICLE INFO

Keywords:
Benin
Cost
Economics
Ghana
Immunization
Vaccine

ABSTRACT

Background: Existing tools to evaluate costs do not always capture the heterogeneity of costs at the facility level. This study seeks to address this issue through an analysis of determinants of health facility immunization costs.
Methods: A statistical analysis on facility routine delivery and vaccine costs was conducted using ordinary least squares regression. Explanatory variables included the number of doses administered; proportion of time spent by facility staff on immunization; average staff wage; whether the health facility had enough staff; presence of cold chain equipment; distance to a vaccine collection point; and, facility ownership. Data were drawn from representative samples of primary care facilities in Benin and Ghana (46 and 50 facilities, respectively) collected as part of the EPIC studies.
Results: Weighted average RI immunization facility cost was US$ 16,459 in Ghana and US$ 14,994 in Benin. The regression found total doses administered to be positively and significantly associated with facility cost in both countries. A 10% increase in doses resulted in a 4% increase in cost in Ghana, and a 7.5% increase in Benin. In Ghana, the proportion of immunization time, presence of cold chain, and sufficiency of staff were positively and significantly associated with total cost. In Benin, facility cost was negatively and significantly related to distance to the vaccine collection point. In the pooled sample, facilities in capital cities were associated with significantly higher costs.
Conclusions: This study provides evidence on the importance of the level of scale in determining facility immunization cost, as well as the role of availability of health workers and time they spend on immunization in Ghana and Benin. This type of analysis can provide insights into the costs of scaling up immunization services, and can assist with development of more efficient immunization strategies.
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1. Background

Like most Sub-Saharan African countries, Benin and Ghana have improved immunization performance during the past decade. According to the 2011 Ghana Multiple Indicators Cluster Survey, coverage of pentavalent vaccine (DTP–HepB–Hib) was 92.1%, while measles, yellow fever and neonatal tetanus immunization coverage were lower at 88.5%, 88.3% and 70.3%, respectively [1]. In Benin, a 2007 EPI Review found 81% administrative coverage for the pentavalent vaccine compared to 67% obtained through surveys [2]. Both countries have introduced new vaccines with GAVI support (pneumococcal, rotavirus or measles second dose) (Table 1).

Existing tools to assess routine immunization (RI) costs (such as the comprehensive multi-year plan) do not capture heterogeneity in facility costs. This is an important limitation as previous studies have demonstrated wide variation in facility cost that would contribute to national program costs and performance [3 ref: Walker]. The current manuscript seeks to address this issue by analyzing determinants of RI costs at facility level. Results from this type of analysis can support development of more targeted interventions to improve immunization program efficiency.

2. Methods

2.1. Data collection

The current evaluation is based on a representative, stratified random sample of 50 facilities in Ghana and 46 facilities in Benin.

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http://dx.doi.org/10.1016/j.vaccine.2014.12.069
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Table 1
Routine childhood immunization vaccine schedule and age of administration in Benin and Ghana.

	Ghana	Benin
Traditional and underused vaccines (routine immunization cost analysis)		
Bacillus Calmette-Guérin (BCG)	Birth	Birth
Oral poliovirus (OPV)	Birth, 6, 10 and 14 weeks	Birth, 6, 10 and 14 weeks
Diphtheria–tetanus–pertussis–hepatitis B–*Haemophilus influenzae* type b	6, 10 and 14 Weeks	6, 10 and 14 Weeks
Measles	9 Months	9 Months
Yellow-fever	9 Months	9 Months
New vaccines (NUVI analysis)		
Pneumococcal conjugate* (13-valent)	6 Weeks, 10 weeks, 14 weeks (introduced April 2012)	6 Weeks, 10 weeks, 14 weeks (introduced July 2011)
Rotavirus*	2, 6 and 10 Weeks (introduced April 2012)	Not introduced
Measles second dose*	18 Months (introduced February 2012)	Not introduced

* Not included in facility routine immunization costs in 2011.

In Ghana, districts were classified according to urban and rural location, number of pentavalent doses administered in 2011, and population density. Four rural districts (high and low number of doses administered by high and low population density) and two urban districts (high and low doses administered) were selected. Facility types included reproductive and child health (RCH) units of district hospitals; health centers (HC); community health planning and services facilities (CHPS); and clinics. CHPSs serve as first-line health facilities providing direct interventions as well as outreach services to mostly rural communities. Many CHPSs tend to require more manpower and fuel per vaccinated child than other health facilities. While costs may be higher, they tend to deliver fewer vaccine doses than other facilities, and have higher unit costs [4 ref: Le Gargasson et al. in this Supplement].

In Benin, eight districts were selected based on population density, pentavalent doses administered and geographic zone. Within the 14 total selected districts, immunization facilities associated with immunization programs were stratified by type (district hospital, health center, clinic, community health center); ownership (non-governmental or government); and rural versus urban location. The average urban health facility covered a total population of approximately 20 to 40 thousand versus 8 to 15 thousand for the average rural health facility. Table 2 describes the sample of health facilities included in this analysis.

Forty percent of health facilities in the Ghana sample were CHPSs, while an equivalent type of health facility did not exist in the Benin sample (Appendix 1). This difference in health structure composition and distribution limits direct comparison of costs between Ghana and Benin. Benin had a higher average number of doses delivered per facility, and did not use volunteers to conduct RI activities (Tables 3 and 4).

Data were collected using standardized, pre-tested questionnaires. Total RI facility economic costs were estimated based on input quantities and prices as per a common methodological approach developed for the EPIC studies and global costing guidelines [6,7]. Vaccines administered were collected from facility monitoring records. Economic costs of inputs were allocated to the different immunization activities (cf. Appendix 2 for definitions) based on factors in the common approach. A fully immunized child (FIC) was defined as children receiving the third dose of pentavalent (DTP–hepatitis B–Hib) vaccine derived from facility immunization records. Weighted average costs were estimated using facility sampling weights.

In Ghana, the study protocol was submitted to the Ghana Health Service Ethical Review Committee and the study was authorized in December 2012. In Benin, the study was exempted from an Internal Review Board (IRB) process. Standard confidentiality procedures were implemented to protect the identity of study informants including password-protected computer entry.

2.2. Strategy for the treatment of joint cost

In most of the surveyed health facilities, resources were shared between different vaccination delivery strategies (facility-based or outreach), and between vaccination and other health services. For personnel, paid labor was estimated based on the percent of total working time spent on a range of immunization activities, such as record-keeping, vaccine administration, outreach, program management, among others. Vaccine costs were allocated to outreach or facility-based service delivery based on the number of doses administered within each strategy. For transportation and vehicle costs, the number of kilometers obtained from vehicle log books or estimated response was used to determine share of costs. Costs for overhead, utilities and communication were estimated based on the total facility or administration expenses for these items, multiplied by the ratio of the number of patients receiving the third DTP dose and the sum of outpatient visits and inpatient admissions. In Ghana, the daily allowance for national immunization days was used to estimate volunteer labor costs.

2.3. Cost determinants model

According to economic theory, costs are a function of quantities, prices, quality, and other environmental factors [8–10]. For this study, facility immunization RI cost is represented in the following reduced form equation:

$$\log(CQ_i) = \beta_0 + \beta_1 \times \log(\text{Doses}_i) + \beta_2 \times \log(\text{Time}_i) + \beta_3 \times \log(P_i) + \beta_4 \times Z_i.$$

In this linear model, CQ_i is the total facility immunization cost (including vaccine cost); Doses_i represents the total doses administered to RI (quantity measure); Time_i reflects the proportion of time spent on immunization by facility staff; P_i is the average wage of staff (proxy price measure); and Z_i reflects other environmental and quality factors that could influence cost. One measure of quality was based on answer to the question "Do you have enough staff to perform routine immunization well?" Other variables included type and ownership of the health facility, location of the facility, whether cold chain equipment was present in a facility, distance of the facility (km) to the nearest vaccine collection point, and existence of volunteers.

Variables in the regression equations were transformed into logs base 10. The coefficients on the explanatory variables can be interpreted as the effect a particular variable would have on total facility cost. Alternative model specifications were conducted for this analysis to examine the effects of different control variables in the regression. Ordinary least squares (OLS) regressions were

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Table 2
Final sample selected by district and location in Ghana and Benin.

District	Sampled urban facilities	% Of total urban facilities sampled	Average population covered by one facility	Sampled rural facilities	% Of total rural facilities sampled	Average population covered by one facility
	Urban			Rural		
Ghana						
Asante Akim South	2	100	18,906	5	42	9431
Atwima Mponua	1	100	122,398	5	55	15,325
Bunkpurugu Yunyoo	1	100	31,074	5	55	6958
Ga West	4	50	16,011	4	44	10,351
Kassena Nankana	2	100	16,358	8	40	4075
Wa Municipal	1	100	63,673	12	43	6123
Benin						
Akpro	2	25	20,082	3	50	11,402
Cotonou 2-3	5	100	44,239			
Cotonou 1-4	5	100	35,618			
Dassa Zoumé	2	25	24,035	4	100	8041
Parakou N'Dali	1	40	35,955	3	25	11,260
Porto Novo	3	46	23,292	5	16	12,113
Savalou banté	1	22	26,624	4	100	15,602
Tchaourou	1	57	27,909	5	100	14,514

Table 3
Descriptive Analysis of the continuous regression variables for Benin and Ghana.

Characteristics (in average)	Ghana		Benin		*P*-value
	Weighted mean	Std. err.	Weighted mean	Std. err.	
A. Immunization cost by facility, including vaccine costs (USD)	16,459.38	1624.02	14,993.99	1563.07	$P < 0.0001$
B. Immunization cost by facility, excluding vaccine costs (USD)	12,153.01	1041.89	5344.62	425.76	$P < 0.0001$
C. Proportion of staff time for routine immunization (%)	34.67	2.74	40.07	3.74	$P < 0.0001$
D. Routine doses administered in 2011	3244.52	411.47	8120.86	882.37	$P < 0.0001$
E. Total number of staff per facility	12.20	1.97	15.52	2.41	$P < 0.0001$
F. Number of campaigns in 2011	2.21	0.31	4.09	0.09	$P < 0.0001$
G. Average wage of staff per facility	432.55	10.94	126.09	7.48	$P < 0.0001$
H. Distance in Km to the vaccine collection point	–	–	15.17	18.4	

conducted using STATA version 12 [11]. In addition to conducting separate regression analyses for each country, a pooled analysis was conducted. This analysis could assess whether relationships between the independent variables and facility cost hold with an improved sample size ($N = 95$).

Post-estimation regression diagnostics were performed to examine the specification, robustness and sensitivity of the various models. A Breush–Pagan test for heterogeneity showed equality of variances. One important assumption for OLS was exogeneity of the output variable (doses). The number of total doses administered was obtained from facility records for 2011. Costs were based on an analysis of inputs rather than government allocation of facility budgets which may influence the level of vaccine administration. For this study, doses delivered are therefore exogenous to facility cost for the period in question.

3. Results

3.1. Statistical description of samples

Facility immunization costs were higher in urban than rural areas in Benin (Appendix 3a). Substantial variation occurred across regions and by facility type. These variations were reduced when vaccine costs were excluded. The distance between health facility and vaccine collection point was larger in rural facilities, and in hospitals. Higher costs were observed in facilities located in Central and Northern regions. Working time dedicated to vaccination was greater in urban areas and hospitals. The average wage was slightly lower in rural than urban areas.

In Ghana, vaccine cost constituted a lower fraction of total facility immunization cost than in Benin. The variation between rural and urban areas, across regions and by facility type remained whether or not vaccine costs were included (Appendix 3b). Facility RI cost was greater in urban areas, and in hospitals. Higher costs also were observed in facilities located in the Northern region. The distance between the health facility and vaccine collection point was larger for rural than urban facilities. Urban facilities also showed greater proportions of working time dedicated to immunization perhaps related to the larger numbers of doses administered. The average wage was slightly lower in rural than in urban areas, and increased from lower to higher-level health facilities (CHPS to hospitals).

Most facilities in both countries were government-owned (Table 4) and used public electricity. The largest differences

Table 4
Descriptive analysis of the categorical regression variables for Benin and Ghana.

Variable	Ghana (%)	Benin (%)	*P*-value (%)
Government-owned	95	91	0.422
Existence of cold chain equipment in the facility	68	100	$p < 0.0001$
Collection of user fees	54	0	$P < 0.0001$
Use of volunteer labor for immunization	84	0	$P < 0.0001$
Whether facility manager felt he had enough staff to perform routine immunization well	65	46	0.099

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Table 5
Results of the regression analysis of facility RI cost in Benin and Ghana.

Variable	Ghana			Benin			Two countries
	(M1)	(M2)	(M3)	(M1)	(M1)	(M2)	(M1)
	$N = 48$; df. = 42; R^2-adj. = 0.412	$N = 48$; df. = 42; R^2-adj. = 0.512	$N = 48$; df. = 36; R^2-adj. = 0.472	$N = 45$; df. = 39; R^2-adj. = 0.868	$N = 43$; df + 37; R^2-adj. = 0.902	$N = 43$; df. = 34; R^2-adj. = 0.898	$N = 93$; df. = 84; R^2-adj. = 0.507
A. Total doses administered to RI (entered into the model as a log value)	**0.359**** (3.26)	**0.366***** (4.95)	**0.418***** (3.98)	**0.690***** (13.64)	**0.754***** (15.67)	**0.752***** (14.09)	**0.512***** (8.12)
B. Dedication proportion of vaccinating personnel time (entered into the model as a log value)	**0.503**** (2.76)	**0.493**** (2.99)	**0.562**** (3.20)	0.106 (1.40)	−0.0377 (−0.50)	−0.0492 (−0.70)	**0.438***** (4.78)
C. Average monthly wage per facility (USD)—of staff involved in RI (entered into the model as a log value)	0.477 (1.21)	0.129 (0.32)	−0.141 (−0.25)	0.00353 (0.04)	0.0190 (0.29)	0.0250 (0.35)	−0.0156 (−0.09)
D. Enough staff to perform routine immunization well? (Yes = 1/no = 0)	**0.657***** (3.57)	**0.510***** (3.61)	**0.496**** (3.06)	−0.0577 (−0.98)	−0.0747 (−1.45)	−0.0802 (−1.53)	0.203† (1.98)
E. Region (greater Accra in Ghana/Cotonou in Benin = 1; others =0)			−0.187 (−0.70)			−0.0523 (−0.46)	**0.318*** (2.27)
F. Health Facility (CHPS in Ghana/Health Center in Benin = 1/others = 0)	−0.0484 (−0.23)		−0.104 (−0.55)	0.0390 (0.41)		0.0855 (0.86)	−0.118 (−0.97)
G. Ownership (govt. = 1/CHAG/NGOs = 0			−0.153 (−0.56)				
H. Urban = 1/rural = 0			−0.0459 (−0.19)			−0.0147 (−0.15)	−0.0221 (−0.16)
I. User fees (yes = 1/no = 0)			0.0149 (0.09)				
J. Cold chain equipment in facility (yes = 1/no = 0)		**0.481**** (3.13)	**0.480**** (2.77)				
K. Existence of Volunteers supporting immunization (yes = 1/no = 0)			0.284 (1.22)				
L. Distance in Km to the vaccine collection point (entered into the model as a log value)					−**0.128***** (−5.48)	−**0.129***** (−3.78)	
M. Dummy for country (1 = Ghana, 0 = Benin)							0.436† (1.74)

t Statistics in parentheses.
† $p < 0.1$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

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between countries were user fees were only collected in facilities in Ghana[1], and approximately one-third of facilities in Ghana did not have cold chain equipment. Table 3 shows the aggregated national RI cost based on weighted averages. The weighted average facility RI with and without vaccine in Ghana was US$ 16,459 and US$ 12,153, respectively. Costs for Benin were lower at US$ 14,994 with vaccine costs, and US$ 5345 without vaccine costs. This confirms the previous observation that vaccine costs take a much higher share of immunization cost in Benin than Ghana. On average, Ghanaian facilities had fewer fully immunized children, total doses delivered, health staff dedicated to immunization, and immunization campaigns. However, wages were higher in Ghana which can partly explain the difference in the weighted average facility cost between the two countries.

3.2. Regression models for total economic RI costs

The regression models had overall good explanatory power for the facility data in Ghana, and higher explanatory power for facilities in Benin. In both countries, total doses were positively and significantly associated with facility RI cost. A 10% increase in doses implies an increase of facility RI cost of 3.7% and 7.5% in Benin and Ghana, respectively. This relationship was maintained in the pooled analysis (Table 5).

In Ghana, the proportion of time spent on vaccination, sufficiency of staff, and presence of cold chain equipment were significantly and positively associated with facility cost. An increase of 10% working time for vaccination will increase the facility cost by 5%. Immunization costs of the facilities having enough staff or cold chain equipment were on average 50% higher.

In Benin, distance in km to vaccine point was significantly and negatively associated with facility RI cost, such that a 10% increase in the distance to the vaccine point was associated with 1.3% decrease in facility RI cost. This result seems counter-intuitive, as one would expect distance to influence travel cost. However, another interpretation is that remote facilities have lower levels of inputs (and possibly lower quality of care) and hence, lower costs. The proportion of time and wages were not significantly associated with facility costs.

The pooled analysis confirmed the positive and significant relationship of facility cost with administered doses and proportion of working time. Facilities located in urban areas were significantly and positively associated with facility RI cost. Finally, RI facility costs were 44% higher in Ghana.

4. Discussion

Few statistical studies have looked at the determinants of routine immunization costs at facility level. For the Ghana analysis, the proportion of time spent was positively associated with total facility RI cost, though RI costs were not significantly associated with wage rates. In a setting where payment for human resources remains low, this suggests that productivity of human resource plays a more important role, at least for immunization program costs. The relationship with the proportion of time spent on routine immunization in Ghana is consistent with an earlier study, based on hours worked by village nurses [4].

In Ghana and Benin, facility immunization cost also was positively associated with the average number of total doses administered to RI. The relationship between the number of total doses administered and facility costs was found in another study conducted in India by Brenzel et al. [4].

Walker et al. [5] found considerable variations in facility immunization costs in Peru according to region and facility type. Vaccine wastage also was reported as a predictor of immunization costs. However, information on wastage rates was incomplete or inconsistent in both Ghana and Benin and could not be evaluated in this study. The current study did not find significant effects of location and facility type independent of the effects of vaccine doses.

The study found a positive relationship between the quality of immunization services, represented by sufficiency of staff and presence of cold chain equipment, and facility RI cost. The costing study reflected the actual state of service delivery in facilities and not a normative estimate of best practice. Therefore, it would be expected that facilities with more and better inputs would have a higher cost.

The study had several limitations. First, the relatively small sample size per country may have led to bias in coefficient estimation. The pooled analysis resulted in a slightly higher effect of doses than in the Ghana sample alone, and a lower effect than the Benin sample alone. Second, factors other than input quantity and price will influence facility costs. While other variables were included in the various model specifications, variables such as corruption or staff training, which capture the behavior of health workers, were absent. Third, unit costs were not directly comparable between the two countries due to different types of facilities and health system structure. Some potentially important variables, such as vaccine wastage and vaccine stock-outs were not available to examine their impacts on facility RI cost.

Some of the tracing factors used in allocation of shared facility costs could potentially overestimate the true costs for routine immunization. In addition, use of the daily allowance for national immunization days to estimate volunteer labor costs may overestimate the latter when compared to local wages. When compared to potential financial costs, facilities where vaccines represent a higher share of the economic costs are likely to have a lower financial cost/economic cost ratio (for example, district hospitals and Health Centres in Ghana).

Regarding policy implications, the recent expansion of CHPS facilities (located closer to rural populations) in Ghana led to additional operating costs at the service delivery level. However, from a household perspective, CHPS expansion should reduce travel and opportunity costs for users. The impact on total societal costs is unknown. Even if negative, there may be a social or ethical benefit in transferring costs from the rural poor to the local health system.

In conclusion, this study identifies factors associated with RI facility cost in two West African countries. These data should allow countries in the region to make some assessment of the impact of various strategies on overall costs. In terms of future research, these results also highlight the importance of full costing approaches in economic evaluations due to the significant contribution of human resource costs to total cost. The use of all resources (full costing) has been underestimated [5] or not considered in other studies. In addition, studies with a larger sample size might allow fuller evaluation of some potentially important variables.

Contributors

CA conducted the statistical and regression analysis, developed the database and wrote the first draft of the manuscript. XX and JBLG provided input into statistical, regression analysis, conducted data analysis, interpretation and wrote parts of the manuscript. LK and FN provided input for data interpretation and discussion and reviewed the manuscript. AC recruited the core team, oversaw the project development and implementation, and reviewed the scientific study report and the article. BDG provided senior scientific support, supervised the scientific work and oversight to the project.

[1] User fees were not for immunization services specifically but for other services in the health facility.

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Role of the funding source

This project was funded by the Bill and Melinda Gates Foundation. The funding source for this study provided technical support and reviewed study documents and manuscript.

Conflict of interest statement

JBLG, XX, CA, BDG and AC work for the Agence de Médecine Préventive, which receives unrestricted funding from Sanofi Pasteur and grant-specific support from Crucell, Sanofi Pasteur, Pfizer, Merck, and GlaxoSmithKline.

Acknowledgements

The Benin Ministry of Health for facilitating the study implementation.

Darwin Young (Consultant, BMGF) for developing the cost calculation tool, Logan Brenzel (senior program officer, BMGF) for study supervision, technical support and final review

Damian Walker (Consultant, BMGF) for study supervision.

Steering committee members for their input into the overall study including Carol Levin (University of Washington, Seattle, WA, USA), Ulla Griffiths (London School of Hygiene and Tropical Medicine, London, United Kingdom), Mike Hanlon (University of Washington, Seattle, WA, USA), Raymond Hutubessy (World Health Organization, Geneva, Switzerland), Stephen Resch (Harvard University), Santiago Cornejo (GAVI, The Vaccine Alliance, Geneva, Switzerland).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.069.

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Vaccine 33S (2015) A72–A78

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The drivers of facility-based immunization performance and costs. An application to Moldova

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ARTICLE INFO

Keywords:
Routine immunization
Productivity
Costs
Middle-income country

ABSTRACT

Objective: This paper identifies factors that affect the cost and performance of the routine immunization program in Moldova through an analysis of facility-based data collected as part of a multi-country costing and financing study of routine immunization (EPIC).

Methods: A nationally representative sample of health care facilities (50) was selected through multi-stage, stratified random sampling. Data on inputs, unit prices and facility outputs were collected during October 3rd 2012–January 14th 2013 using a pre-tested structured questionnaire. Ordinary least square (OLS) regression analysis was performed to determine factors affecting facility outputs (number of doses administered and fully immunized children) and explaining variation in total facility costs.

Results: The study found that the number of working hours, vaccine wastage rates, and whether or not a doctor worked at a facility (among other factors) were positively and significantly associated with output levels. In addition, the level of output, price of inputs and share of the population with university education were significantly associated with higher facility costs. A 1% increase in fully immunized child would increase total cost by 0.7%.

Conclusions: Few costing studies of primary health care services in developing countries evaluate the drivers of performance and cost. This exercise attempted to fill this knowledge gap and helped to identify organizational and managerial factors at a primary care district and national level that could be addressed by improved program management aimed at improved performance.

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1. Introduction

Cost-effectiveness of immunization programs is well documented worldwide within developed and developing country settings [1–5]. Although strong steps have been taken globally to expand immunization coverage rates, the progress is not sufficient in many countries and several issues are still pending on the international agenda: how to identify and reach out to non-served population? Which new vaccines need to be considered in an improved vaccination calendar? What are the costs of including them (both non-served population and new vaccines) in the current immunization plans?

As in many other health care services, strategies of immunization programs and their cost structures cannot be replicated from one country to another. Population density, their location and accessibility along a territory, distribution of health care services and population characteristics (health habits and education) all have strong influence on costs of delivering vaccination services [6,7]. Vaccine procurement mechanisms, status of cold chain and managerial capacity also influence success of vaccination initiatives. Global evidence on what determines cost of immunization and how much is necessary for developing countries to deliver these services is still inconclusive. Our study aims at contributing additional evidence around the topic of immunization costs and productivity determinants, by using the facility level costing data from Moldova.

Particular studies on cost determinants for immunization programs provide rich insights about relevance of particular factors under specific scenarios. Bishai et al. [8] analyzes average costs and DTP3 coverage, by using a fifty-country panel data from 2000 to 2003 arising from WHO and GAVI sources. They prove the presence of strong economies of scale in the provision of immunization coverage. Also using facility data, Robertson et al. [9] calculated average costs per Fully Immunized Child (FIC) in Gambia, which further contributed to the argument of decreasing costs with scale. In the same direction, Kahn et al. [10] based on immunization centers in Dhaka,

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http://dx.doi.org/10.1016/j.vaccine.2014.12.041
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Table 1
Summary statistics, unweighted sample.

Variables	Obs.	Mean	Std. Dev.	Min.	Max.
Fully immunized child (FIC)	50	60.88	135.16	1	714
Total number of doses administered	50	895.20	1844.43	33	9060
Total economic cost, facility level	50	11,942	21,743	565	112,548
Total economic cost, facility + district level	50	12,502.23	22,404.94	627.75	115,062
Total economic cost, facility + district + national level	50	12,663.11	22,723.92	641.27	116,657
Share of staff time spent in the facility for immunization in % (FTE)	50	1.32	2.01	0.2	10.20
Total working hours	50	51.22	12.12	8	71
Total facility square meters	50	577.76	1173.18	20	5820
Cold chain capital index (cold chain economic cost at facility level, in USD)	50	72.86	22.20	7.79	136.14
Hourly wage, mid career nurse (USD)	50	1.82	0.16	1.45	2.28
Refrigerator unit price (USD)	50	0.76	0.36	0.01	2.13
Total number of infants in the facility catchment area	50	66.06	149.98	1	810
Share of population with university education in %	50	6.46	5.38	2.90	24.40
Dummy facility type (=1 if FMC)	50	0.10	0	0	1
Dummy doctor at the facility (=1 Yes)	50	0.88	0.33	0	1
Dummy facility location (=1 if Urban)	50	0.06	0.24	0	1
Distance from the facility to the vaccine collection point	50	19.60	13.14	0	50
Overall wastage rate in % (from total number of doses administered)	50	17.01	8.89	4.90	36.90

Bangladesh, calculated average cost of FIC during the year 1999. Results prove decreasing costs with population scale, and identified the relevance of community support in reaching higher coverage.

Creese et al. [11] looked at costs per FIC in Indonesia, Philippines and Thailand, analyzing 1978/79 facility level data. Bi-variate analysis across institutions and countries found significant rural–urban differences in input prices as well as in population accessibility to the services. Walker et al. [12] looked at disaggregated immunization costs per budgetary line in three Peruvian districts and calculated average expenses per FIC. Findings show significant differences across urban and rural locations, as well as among types of facilities, suggesting the presence of geographical access barriers in reaching with immunization.

Particular goal of this paper is to identify production and costs determinants on a facility level as well as on a district and national level.[1] Understanding productivity and cost determinants will help in identifying key arguments to improve allocative efficiency in resources utilization looking for reaching the still non-reached population. Are input prices relevant to determine immunization cost structures? Are facility types a relevant factor in the design of a vaccination campaign? What is the relevance of scale (number of children to be immunized) at the moment of selecting the immunization activity plan? Ordinary least square (OLS) method was applied to a traditional cost function structure, recognizing a multivariate influence of different factors on Moldovan immunization costs, where production variables as well as population and health system characteristics participate in the definition of total costs, at the facility, district and national levels.

2. Methods

Out of 1318 health care facilities delivering immunization services in Moldova across 37 districts, the research team sampled 50 institutions, combining districts with urban and rural locations, as well as capturing diversity of health service providers, more details on sampling are described elsewhere [13]. Details about costs and cost elements are also available from the full study report [14].

The survey allowed capturing facility performance indicators (fully immunized child and number of total doses administered), human resource characteristics and their participation in the immunization activity (hours worked on immunization activities, presence of doctor in the health center), as well as a facility specific scale factors (total square meters per facility, cold chain).

Beyond this information, the facility-based dataset was enriched with data about input prices, and socio-economic characteristics (number of infants in a catchment area, average household income, education level of families, etc.).

Table 1 summarizes descriptive statistics for un-weighted sample of facilities. (See Table 5 in the Annex for a glossary of variables).

The estimation strategy considers a sequence of two steps. The first step analyzes determinants of main production indicators/outputs: what explains the number of FIC and the total number of doses administered on a facility level? In order to

[1] Facility level costs include only facility specific cost and do not take into account costs incurred outside the facility such as costs of district and national public health centers; district level costs comprised by the facility specific costs and costs of district public health centers that were allocated down to a facility level and the national level costs consist of facility, district and national costs.

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answer these questions, we looked at variables related to inputs: human resources and facility capacity/specification, corrected by scale variables (number of infants in catchment area), as well as by wastage rates, seen as a proxy for a facility management practices.

Applying a linear production function, immunization outputs take the form:

$$Q_i = A_i + \alpha_1 \times L_i + \alpha_2 \times K_i - \alpha_3 \times W_i \quad (1)$$

where, Q is the output indicator (FIC or number of doses administered) for facility i, L (labor) and K (capital) are production factors, with participation $\alpha 1$ and $\alpha 2$ respectively, and A is the scale of infants present in the catchment area. The production function also depends on the wastage rate (W), which weighted the productivity of each factor.

Applying natural logarithms on the left side of the equation (1) facilitates the use of ordinary least square estimations techniques and the calculus of semi-elasticities in production with respect to a relevant input indicator(s). They allow identifying how output production changes (in percentages) when input each factor is modified by one unit (keeping constant all other factors)[2 3]:

$$\ln Q_i = A_i + \alpha_1 \times L_i + \alpha_2 \times K_i + \alpha_3 \times W_i \quad (2)$$

The second estimation step proposes to answer: what determines the cost of immunization services? For this purposes we use the Total Economic Cost at a facility level as well as at district and national levels as dependent variables.

The costs model implemented is based on a traditional cost structure CQ _i = w_i.K_i + r_i.L_i, expressed in natural logs, adding contributions from the literature on hybrid costs models, where prices, quality-driver and demand side characteristics interact [15,16], in the form:

$$\ln CQ_i = \ln FIC_i + \alpha_1 \ln w_i + \alpha_2 \ln r_i + \alpha_3 \ln W_i + \alpha_4 \ln P_i \quad (3)$$

where, CQ is the total economic cost for the facility i (i = 1. . .50), w and r are input prices for labor force and infrastructure (as it will be detailed in the next section), FIC captures the effect of the size of the objective population (scale factor) which incorporates the level of inputs involved.[4] W is a proxy of managerial quality (wastage rate) and P introduces the relevance of demand-side variable in the cost structure (i.e. education and income of the population affected by the program).

3. Results and discussion

3.1. First step: production determinants

We proposed two production indicators following the specification in equation (2): "Number of Fully Immunized Children" and "Total Number of Doses Administered" per facility. Although both dependent variables relate to the service production capacity of a facility, the "Number of Fully Immunized Children" involves a quality dimension (it requires children identification, on-time follow-up, etc.).

As fixed facilities – with no outreach activities – are responsible for explaining immunization performance in Moldova, explanatory variables used in the regression are related to health center characteristics: facility level inputs (human resources and infrastructure), proxy variables explaining logistics required for vaccine distribution i.e. distance to vaccine collection site, size of population in a facility catchment area and facility type. In addition, the variable "*wastage rate*" was included as proxy for managerial effectiveness at the provider level.[5]

Table 2 presents the results of this regression. Firstly, human resources are positive and significant related at 1% level on facility outputs, with similar magnitude and relevance in all specifications.[6] Furthermore, two alternative measures of capital were included: facility square meters and the cold chain capital index,[7] intending both to capture productivity issues related to infrastructure. In the case of total number of doses administered, coefficients of both variables show to be significant at 5% level, although their effects on productivity are smaller than those of human resources. Cold chain capital index does not affect FIC but has positive and statistically significant association on the total doses delivered, and its relevance is greater that of square meters.

The number of infants in a catchment population, show to have positive relationship in explaining higher immunization outputs, but its magnitude is lower when their coefficients are compared with those which relates to human resources.

The distance to vaccine collection site and type of medical facility do not have statistically significant influence on productivity. On the other hand, the presence of doctors in the facility has strongest influence on the number of doses delivered and number of FICs produced. All specifications show to be statistically significant at 1% level.[8]

Finally, wastage rate have negative coefficients on both output indicators, statistically significant at 1% level, although with slightly stronger implications for the total number of doses administered.

Beyond the predictive capacity of the model implemented, the obtained R2 might be also the result of the small size of the sample available to pursue the analysis. The same consideration applies to the results reached at the second estimation step.

3.2. Second step: cost determinants

For evaluating determinants of costs we used Eq. (3) described earlier, with two alternative approaches. The first approach used facility-specific scale and input prices variables—specifications (1) through (4) in Table 3, reflecting prices of identified main labor and capital inputs used in vaccination activities, such as hourly USD wages for mid career nurses, unit USD prices for ice packs

[2] Originally, a Cobb–Douglas functional form was considered as a potential specification for the production function, given its relative straightforward reading of coefficients within a log linear equation. However, it assumes constant elasticity of substitution, which imposes a constraint to the estimation. In addition, histograms of both dependent variables used in the econometric implementation (fully immunized children and total number of doses administered) suggest the presence of a semi-log specification. For more details see [14].

[3] Although Poisson and Negative Binomial estimation forms are useful in studying health care related issues (visits to doctors, number of inpatient days, etc.), in our case the dependent variables do not fit into those alternatives: although integer and positive, observations are not concentrated on values 0, 1, 2, etc., and there are not zero values involved (see Table 1 in the paper).

[4] A production function shows the technological relation of inputs to produce a good or service (immunized children, in this case), while cost function is triggered by input prices, given a technological production structure. As the former is an antecedent of the latter, the econometrical implementation instruments a two-step estimation, where the result of the first step is incorporated in the second.

[5] Breusch–Pagan/Cook–Weisberg tests were performed to detect any linear form of heteroscedasticity. Additionally, estimations use robust standard errors to deal with this potential specification problem (Manning and Mullahy [1]).

[6] Nevertheless, the analysis may involve potential issues related to endogeneity. The share of staff time spent on immunization affects the number of fully immunized children that does not reveal that it is possible that health care personnel are responding to demand requirements.

[7] One possible measure of capital in immunization activities is cold chain capacity at the health center. As these devices varies in capacity across facilities, one potential way of capturing the scale of this factor is to use its total costs at the facility, under the assumption that capacity and costs are related.

[8] The facilities studied do not show the presence of correlation between experience (seniority) of the nurses participating in the vaccination team and immunization performance.

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Table 2
Determinants of production.

	Ln FIC			Ln total dose adm.		
Variables	(1)	(2)	(3)	(4)	(5)	(6)
Total working hours	0.0311**	0.0330***	0.0315***	0.0249***	0.0269***	0.0254***
	(0.0121)	(0.0114)	(0.0114)	(0.0087)	(0.0074)	(0.00728)
Total facility square meters	0.000507**		0.000461**	0.000523**		0.000459**
	(0.000219)		(0.000218)	(0.00021)		(0.000204)
Cold chain capital index		0.0109	0.00955		0.0147**	0.0133**
		(0.00717)	(0.00705)		(0.00575)	(0.00555)
Total number of infants in the facility catchment area	0.00636***	0.00577**	0.00547**	0.00538***	0.00444*	0.00413**
	(0.00213)	(0.00273)	(0.00219)	(0.00173)	(0.0023)	(0.00172)
Dummy facility type (=1 if FMC)	−1.708	−0.0152	−1.62	−1.529	0.192	−1.407
	(1.123)	(1.04)	(1.152)	(0.944)	(0.884)	(0.968)
Dummy doctor at the facility (=1 Yes)	0.585***	0.676***	0.627**	0.702***	0.809***	0.760***
	(0.209)	(0.239)	(0.235)	(0.213)	(0.219)	(0.22)
Distance from the facility to the vaccine collection point	0.0036	0.00553	0.00583	−0.000313	0.0025	0.0028
	(0.00882)	(0.00947)	(0.00926)	(0.00655)	(0.0071)	(0.00669)
Overall wastage rate	−0.0387***	−0.0399***	−0.0402***	−0.0460***	−0.0478***	−0.0481***
	(0.0105)	(0.0101)	(0.00963)	(0.0101)	(0.00969)	(0.00899)
Constant	0.703	−0.119	0.0121	3.982***	2.888***	3.018***
	(0.823)	(1.147)	(1.135)	(0.663)	(0.796)	(0.779)
R-squared	0.721	0.714	0.735	0.779	0.787	0.811

Notes: Robust standard errors in parentheses. Significance levels:
* $p < 0.1$.
** $p < 0.05$.
*** $p < 0.01$.

Table 3
Determinants of total economic cost, facility level.

Dep. var.: ln total economic cost, facility level								
Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Ln Fully Immunized Children (FIC)	0.743***		0.743***		0.615***		0.616***	
	(0.0598)		(0.0548)		(0.0749)		(0.164)	
Ln FIC est.		0.815***		0.813***		0.694***		1.720***
		(0.107)		(0.109)		(0.150)		(0.218)
Ln FIC2							−0.000218	
							(0.0297)	
Ln FIC2 est.								−0.139***
								(0.027)
Ln hourly wage, mid career nurse	1.122	1.442**	0.991	1.409**	1.050	1.395**	1.050	1.628*
	(0.981)	(0.532)	(1.024)	(0.569)	(0.986)	(0.593)	(0.999)	(0.619)
Ln refrigerator unit price	0.0502	0.183***	−0.0745	0.152	−0.0651	0.132	−0.0651	0.132
	(0.0823)	(0.0361)	(0.165)	(0.133)	(0.137)	(0.133)	(0.139)	(0.112)
Ln ice pack unit price			−1.033	−0.261	−1.468	−0.667	−1.469	−0.934
			(1.127)	(1.086)	(0.947)	(1.111)	(1.007)	(0.904)
Ln share of population with university education					0.618***	0.447*	0.619**	0.692***
					(0.186)	(0.229)	(0.264)	(0.174)
Ln overall wastage rate					−0.00933	−0.0188	−0.00945	0.210
					(0.175)	(0.200)	(0.181)	(0.156)
Constant	5.526***	5.303***	2.649	4.581	0.842	3.130	0.837	−0.283
	(0.661)	(0.512)	(3.309)	(2.993)	(2.924)	(3.279)	(3.187)	−2.839
R-squared	0.815	0.795	0.821	0.795	0.859	0.811	0.859	0.891

Notes: Robust standard errors in parentheses. Significance levels:
* $p < 0.1$.
** $p < 0.05$.
*** $p < 0.01$.

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Table 4
Determinants of total economic cost, facility + district, and facility + district + national level.

	Dep. var.: ln total economic cost							
	Facility + district level				Facility + district + national level			
Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Ln fully immunized children (FIC)	0.749*** (0.0525)		0.609*** (0.160)		0.750*** (0.0522)		0.608*** (0.159)	
Ln FIC est.		0.818*** (0.106)		1.719*** (0.204)		0.819*** (0.105)		1.717*** (0.202)
Ln FIC2			0.00274 (0.0286)				0.00329 (0.0284)	
Ln FIC2 est.				−0.138*** (0.0255)				−0.137*** (0.0252)
Ln hourly wage, mid career nurse	0.919 (0.989)	1.339** (0.553)	0.979 (0.964)	1.561** (0.610)	0.91 (0.981)	1.331** (0.551)	0.971 (0.956)	1.553** (0.608)
Ln refrigerator unit price	−0.0612 (0.155)	0.167 (0.127)	−0.0490 (0.132)	0.151 (0.106)	−0.0597 (0.154)	0.169 (0.127)	−0.0471 (0.131)	0.153 (0.105)
Ln ice pack unit price	−0.973 (1.075)	−0.197 (1.049)	−1.355 (0.958)	−0.817 (0.870)	−0.967 (1.067)	−0.19 (1.045)	−1.342 (0.951)	−0.804 (0.866)
Ln share of pop'n with university education			0.579** (0.256)	0.661*** (0.168)			0.574** (0.254)	0.658*** (0.167)
Ln overall wastage rate			−0.0205 (0.182)	0.195 (0.150)			−0.0216 (0.182)	0.193 (0.149)
Constant	2.914 (3.151)	4.859 (2.886)	1.350 (3.048)	0.234 (2.723)	2.944 (3.127)	4.893* (2.873)	1.413 (3.025)	0.302 (2.707)
R-squared	0.835	0.806	0.869	0.899	0.838	0.808	0.871	0.900

Notes: Robust standard errors in parentheses. Significance levels:
* $p < 0.1$.
** $p < 0.05$.
*** $p < 0.01$.

and refrigerators, for which data is present and available across all facilities.[9]

In the second approach, in addition to price variables, hybrid specifications were considered, by adding two variables—specifications (5) to (8) in Table 3. The first one relates to a facility management practice associated to efficiency in the use of resources (wastage rates). The second variable accounts for demand-side factors – characteristics of households – (income, educational level, etc.), which may affect demand for health services [17,18]. As potential demand side variables were strongly cross-correlated, we only retained the share of population with university education.

In both cases, the scale factor is the total number of FIC (or FIC estimated).[10] Based on the available evidence, the expectation is that higher scale will require more resources to deliver immunization services and therefore the total facility costs will be higher. However, due to economies of scale, we also expect cost per FIC to decline as the scale increases. The variable FIC^2 (the square of FIC) – if its coefficient is negative and statistically significant – will support that hypothesis.

Results are presented in Table 3. Specifications (1), (3), (5) and (7) show FIC coefficients to be positive and significant at 1% level. Using natural logs in both sides allows identifying product elasticities: 1% change in FIC is related to 0.615–0.743% change in total immunization costs at the facility level. Replacing FIC for its estimated specification (columns 2, 4, 6 and 8) does not change either the significance or the weight of the variable influence on the total cost, which assures robustness of our findings.

Prices of human resources and capital do not show conclusive and strong relevance on the total cost of immunization.[11] Only labor prices – as well as refrigerator prices – reveal statistically significant association when FIC-estimated is used in the regression. On the other hand, ice pack unit prices are not significant under any specification of the model.

Columns (5) to (8) in Table 3 introduce supply and demand characteristics, in addition to input prices.[12] Demand-side variables show their explanatory power (positive and significant at 1% level) over immunization costs on a facility level under any specification. A possible interpretation is that educated people demand higher quality and more services, which is associated with greater cost, as prices coefficients remain similar across facilities. Wastage rate proved not to have significant influence over costs in any specification.

As Fig. 1 shows, total immunization costs increase with scale (FIC or FIC-estimated). However, the slope of the curve provides an argument about potential decreasing costs as long as the number of FIC increases (i.e., total costs' growth rate is decreasing with scale), as it was pointed in the literature. This effect is captured by

[9] A detailed analysis of the costs of the Moldovan immunization program is available in a companion paper [13] and in the full research report [14].

[10] As FIC strongly correlates with demand and supply side variables and to avoid multi-collinearity we used FIC estimated as well. The variable is built based on the estimation of FIC arisen from step one of the model. Replacing coefficients obtained in specification (3) of FIC into the original database leads to a new variable, FIC estimated, allowing to link production decisions with the cost structure.

[11] The Moldovan remuneration scheme at the public health sector relies on fixed salaries, not adjusted to differences in performance. Therefore, vaccination coverage is not related to the implementation of any specific financing rule based on results.

[12] The approach combines supply and demand characteristics into a single reduced-form regression. Nevertheless, additional information, not available at this stage, may allow estimating a system of equations, in order to capture separately both vectors of determinants.

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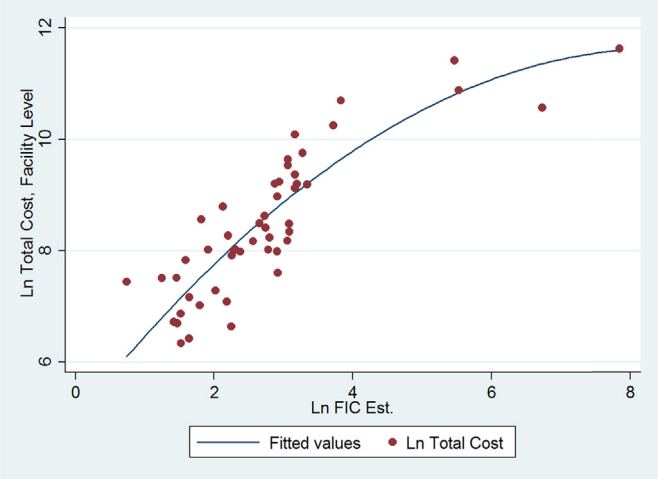

Fig. 1. Total costs by FIC. Estimation at facility level.

introducing variables FIC^2 and FIC^2-estimated, which are the second power of the scale variables used in our cost estimations, as shown in specifications (7) and (8). The new variable has a negative coefficient and is significant at 1% level when used with the FIC-estimated specification, providing statistical support to Fig. 1. The availability of an increased sample of facilities would provide additional evidence to qualify this finding.

Immunization program in Moldova is strongly centralized. Central Government assumes responsibility for salaries, cold chain, and vaccine and syringe provision as single purchaser, leaving limited responsibility over cost management to lower levels, which are responsible for organizing and managing immunization program locally. Therefore, cost determinants are expected to be mainly dependent on health care provider characteristics, where decentralized responsibilities and social factors interact. To evaluate this argument, costs estimation analyses are replicated at district and national levels. Findings of this analysis are presented in Table 4, for facility + district levels – columns (1)–(4) – and facility + district + national levels–columns (5)–(8). The results are consistent with findings presented for a facility level in Table 3, supporting the hypothesis that total costs are mainly affected by the performance at a local facility level and FIC scale factors.

4. Conclusions

By using a representative sample of health care facilities and an econometric model, the paper provides new evidence on an insufficiently explored topic in the literature, addressing a multivariate approach to analyze determinants of immunization production and costs. Under a centralized-fixed, facility based immunization program, human resources are major determinant in producing higher outputs (measured as FIC or as total doses administered). The paper brings also insights about differences in factors' productivity in immunization activities: investments in more time devoted to vaccination tasks and higher professional involvement result to be more relevant than increasing facility capacities, in mainly all production specification models.

Results on immunization costs estimations may contribute to the discussion about the relevance of health system organization in explaining programs' performance. In this case, the Moldova's centralized healthcare system based mainly on population attending to fixed facilities seems to reduce the impact of input prices in the definition of the program cost as a whole, leaving higher relevance to demand characteristics and scale factors. Furthermore, the analysis suggests that costs arising on a district and national level are not relevant in driving total expenditures, and mostly facility level costs determine overall observed variability. Factors operating on a local level – such as managerial efficiency in distribution and utilization of resources – seem to have influenced not only the production of doses administered and children covered, but also their costs.

It will be most interesting to compare our results with those obtained from decentralized systems, where decision making for labor remuneration and/or purchase of inputs is decentralized to sub-national entities and/or facilities.

Finally, the scale of children to-be immunized impacts the production of the program, and affects its costs positively, although decreasingly. This fact suggests that in a scenario of countries with high urbanization rates, costs of covering the immunization gap is relatively lower, providing incentives to scale up not only in scale but also in scope, by involving new antigens.

Conflict of interest

There is no conflict of interest with regard to this study.

Acknowledgments

This paper is part of a multi country study supported by Bill and Melinda Gates Foundation and Curatio International Foundation #21979. The authors acknowledge collaboration of Alfredo Palacios (CEDES), as well as the comments and suggestions provided by reviewers. Particular thanks go to Mike Hanlon, David Bishai, Damian Walker, Logan Brenzel and Jeremy Lauer, and the participants of the meeting organized by the Foundation on immunization costs in Geneva, Switzerland, November 2013.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.041.

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Vaccine 33S (2015) A79–A84

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/vaccine

Mapping financial flows for immunisation in Uganda 2009/10 and 2010/11: New insights for methodologies and policy

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ARTICLE INFO

Keywords:
Financial flows
Mapping
Resource tracking
Immunisation
Donors
Uganda

ABSTRACT

Background: The Global Vaccine Action Plan highlights the need for immunisation programmes to have sustainable access to predictable funding. A good understanding of current and future funding needs, commitments, and gaps is required to enhance planning, improve resource allocation and mobilisation, and to avoid funding bottlenecks, as well as to ensure that co-funding arrangements are appropriate. This study aimed to map the resource envelope and flows for immunisation in Uganda in 2009/10 and 2010/11.

Methods: To assess costs and financing of immunisation, the study applied a common methodology as part of the multi-country Expanded Program on Immunisation Costing (EPIC) study (Brenzel et al., 2015). The financial mapping developed a customised extension of the System of Health Accounts (SHA) codes to explore immunisation financing in detail. Data were collected from government and external sources. The mapping was able to assess financing more comprehensively than many studies, and the simultaneous costing of routine immunisation collected detailed data about human resources costs.

Results: The Ugandan government contributed 56% and 42% of routine immunisation funds in 2009/10 and 2010/11, respectively, higher than previously estimated, and managed up to 90% of funds. Direct delivery of services used 93% of the immunisation financial resources in 2010/11, while the *above* service delivery costs were small (7%). Vaccines and supplies (41%) and salaries (38%) absorbed most funding. There were differences in the key cost categories between actual resource flows and the estimates from the comprehensive multi-year plan (cMYP).

Conclusions: Results highlight that governments and partners need to improve systems to routinely track immunisation financing flows for enhanced accountability, performance, and sustainability. The modified SHA coding allowed financing to be mapped to specific immunisation activities, and could be used for standardised, resource tracking compatible with National Health Accounts (NHA). Recommendations are made for refining routine resource mapping approaches.

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1. Background

Uganda is a low-income country with a population of 34.5 million in 2011 [1]. The Ugandan Expanded Programme on Immunisation (UNEPI) achieved significant performance improvements in the early 2000s. However, performance stagnated after 2007 due to service delivery challenges and districts' varied success in achieving immunisation targets [2]. WHO reported a reduction in DTP3 coverage from 82% to 78% between 2011 and 2012 [3]. The Ugandan

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http://dx.doi.org/10.1016/j.vaccine.2014.12.053
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health care system is funded from public, external development partners and private sources [6,24]. Per-capita health spending was reported to be $10.29 in 2011/12, well below the estimated requirement of $48 for a minimum health package [4,5,25]. The Ugandan public financing management performance report (2008) found public sector financial management had generally credible budgeting processes but weak monitoring of expenditures, budget execution and control, and only average accounting and reporting systems [28] with limited detail on specific programmes and illnesses. The review found that donor funding had poor predictability and provision of financial information, and low proportions were managed by government processes [27]. Other sources also note difficulty in tracking funding, coordinating partner efforts, and ensuring that national health priorities are addressed [4,7].

The Global Vaccine Plan (GVAP) emphasises the need to strengthen the understanding of costs and financing of country immunisation programmes [8]. Resource tracking through methods such as National Health Accounts (NHA) and National AIDS Spending Assessments (NASAs) can improve the efficiency of allocations and the predictability and sustainability of health financing [9,10,20]. Resource tracking for women and children's health is also being promoted to ensure that funding commitments are honoured and results measured [11]. Since 1998 the WHO-UNICEF Joint Reporting Form (JRF) has collected coverage and financial indicators from member states, including the percentage of all expenditures for routine vaccines financed by governments using internal public funds as compared to donor or other funding sources [19]. The Ugandan JFR for 2011 reported that 19% of routine vaccines were funded by the government of Uganda (GOU) [29]. Apart from the JRF, which in many cases tends to have limited reporting on financing indicators [19], there have been few resource-tracking efforts for routine immunisation (RI) funding and spending [12,31]. In Uganda, the comprehensive multi-year plan (cMYP) estimated financing for the national immunisation programme at US$23 per child in 2011 [2,13]. The cMYP provides national estimates but does not examine facility-specific data.

This paper presents a detailed mapping of all government and external funding flows for RI in Uganda in 2009/10 and 2010/11. The study was done as a companion analysis to the detailed facility-costing EPIC studies [30]. The objectives were to:

- Identify and quantify the total envelope of funding available for RI from all sources and evaluate the distribution of the envelope by line items, activity, and health providers.
- Map the funding flows from sources to the ultimate uses of those funds for RI.
- Evaluate differences between the funding envelope and estimated financial costs derived from a companion study [14].

2. Methods

The analysis identified financial and commodity flows for immunisation, and focused on disbursements and flows in 2009/2010 and 2010/2011. The rationale for focusing on funding flows is that they reflect the total funding envelope available for RI, whereas expenditures are a function of the efficiency and effectiveness of government and donor disbursement mechanisms [21]. This mapping represents an alternative way of tracking resource flows specific to RI, defined as facility and outreach-based services providing traditional vaccines,[1] but excluding supplementary immunisation activities (SIAs). Private, for-profit sector financing was also excluded. The methodology was adapted from the NHA approach that uses the System of Health Accounts (SHA) for coding financing sources, agent service providers, and health care functions/activities [20]. The 2011 SHA codes were further disaggregated for the Health Care Functions (HC6.2) to provide a common framework for analysis of immunisation-specific financial flows across the six EPIC countries [16] (see Table 1).

Table 1
Additional disaggregated SHA health care function codes for immunisation mapping in Uganda.

HC.CODE	HC.Description
HC.1	Curative care
HC.6	Preventive care
HC.6.1	Information, education and counselling programmes
HC.6.1.1	*Social mobilisation, advocacy*
HC.6.2	Immunisation programmes (not disaggregated)
HC.6.2.1	*Facility-based routine immunisation service delivery*
HC.6.2.2	*Outreach routine immunisation service delivery*
HC.6.2.3	*Training*
HC.6.2.4	*Vaccine collection, storage and distribution*
HC.6.2.5	*Cold chain maintenance*
HC.6.2.6	*Supervision*
HC.6.2.7	*Programme management*
HC.6.2.8	*Other routine immunisation programme activity*
HC.6.5	Surveillance
HC.6.5.1	*EPI Surveillance*
HC.6.5.2	*Record-keeping and HMIS*
HC.7	Governance and health system financing & admin.
HC.99	Not disaggregated
HC.RI.3	Prevention and public health services
HC.RI.3.3	Prevention of communicable diseases
Cap.Invstmt.	Capital Investment

The inserted dis-aggregated activities are shown in italics.

Data were collected from all government and external sources of immunisation financing or commodities in financial years 2009/10 and 2010/11 using a standardised questionnaire and methods developed for the EPIC studies [15]. The questionnaire was adapted from the NASA and NHA tools, and aimed to collect quantitative financing data linked to sources, agents, service providers and activities of immunisation.[2] Data were analysed based on a matrix of immunisation activities and line items.

The national-level analysis traces UNEPI funding from the ministry of health (MOH) for all national-level activities and EPI staff salaries, as well as for central vaccines funding. Disbursements to Uganda from the secretariat of the Global Alliance for Vaccines and Immunisation (GAVI) for vaccines were channelled through the national medical stores. Public financing for RI at the facility level includes staff salaries and MOH primary health care (PHC) grants to district health offices (DHOs), which cover overhead and operational items such as maintenance, fuel, and supplies. These cater for all PHC services and it was not possible to track immunisation-specific funding apart from village health workers' outreach stipends. Therefore, total funding flows for salaries for district and facility-level RI activities were based on estimates obtained from the detailed costing [14] of a stratified random sample of 52 facilities in 12 districts conducted for the EPIC study in Uganda [30]. For salary and vaccine financing, 60% were allocated to routine facility-based immunisation and 40% to outreach, based on costing study estimates. Salary costs in 2009/10 were 2011 costs deflated by a CPI of 5% [22]. Data are reported using a 2011 exchange rate of 1 US dollar to 2290 Ugandan shillings (US $1:2290 USh). Non-profit organisations that deliver RI services on behalf of the government receive vaccines free of charge from UNEPI, and data were not available on their service volumes or funding. The analysis consequently categorised them as public providers.

[1] BCG; 3 doses of pentavalent diphtheria, pertussis, tetanus, Hepatitis B, *Haemophilus Influenza* Type b; 3 doses of polio; and measles first dose.

[2] Refer to supplementary materials for the questionnaire.

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3. Results

Fig. 1 shows that between 2009/10 and 2010/2011, total financing for RI in Uganda increased from $24.2 million to $32.9 million. In both years, the Ugandan government contributed approximately half of all financing (56.4% and 42.2%, respectively). Funding from the MOH for salaries at the district and the facility level accounted for the largest share of public financing for RI (49% of total spending in 2009/10 and 38% in 2010/11). Inter-governmental transfers at the central level accounted for the remainder of public funding for RI.

Development partners accounted for 43.6% of total RI financing in 2009/10 and 58% in 2010/11, with GAVI as the largest external contributor ($7,962,874 in 2009/10 and $12,540,610 in 2010/11). The expanding role of external financing in 2010/11 was thus due to increased GAVI funding (57% increase) and to a large injection of funds from the Japan International Cooperation Agency (JICA) for equipment to strengthen the RI cold chain before the introduction of the pneumococcal conjugate vaccine (PCV). The estimated real government contribution remained the same in both years, but decreased as a portion of the total due to the increasing external funding in 2010/11.

Fig. 1 also illustrates some volatility of funding from various sources and in total financing for RI, suggesting potential challenges for both domestic resource mobilisation and management of donor financing.

Importantly, this study found that the public sector was responsible for managing 90.5% and 83% of total RI financing in the two years. In 2010/11, the national medical stores managed 41% of immunisation funding through the procurement and distribution of the vaccines (this included the GAVI contribution), while MOH managed 35% for facility-level salaries, and UNEPI managed 7% for its specific coordination, supervision, and support roles. JICA managed its own contribution of cold chain equipment (14%), as did most of the other external sources.

The study found that 93.4% of immunisation funding in 2010/11 was directed towards the service delivery level; the small remaining proportion was spent at the national level or by development partners. At the healthcare provider (HP) level, the bulk of financing was for provision of immunisation services by public entities: UNEPI, DHOs and facilities (Fig. 2), including non-profit facilities that provided immunisation on behalf of the government (except for a few that received identifiable funding from the Red Cross).

In terms of the health care function (activity), Table 2 shows that in 2009/10 and 2010/11, the largest proportion of funding went to routine facility-based immunisation (47% and 43%, respectively), and outreach immunisation (31% and 29%, respectively). Supervision, record keeping, cold chain maintenance, surveillance, training and social mobilisation amounted to 2% or less of the total in both years. However, this probably reflects the difficulty that respondents had in determining funding flows for programme functions, and that some of the non-disaggregated funding might relate to these activities.

Table 2 further shows the factors of production, and that the majority of RI funding was for government salaries (49% and 38% in 2009/10 and 2010/11, respectively), followed by vaccines and supplies (37% and 42%, respectively) which were primarily the GAVI contribution and Uganda's co-financing for pentavalent vaccine. Investments in cold rooms by USAID and cold chain equipment by JICA, which are captured under capital investments, contributed almost 3% in 2009/10 and 13% in 2010/11. The non-disaggregated flows may include some financing for transport and per diem, but it was not possible to identify these details in a top-down mapping exercise.

Table 2
Routine immunisation funding in Uganda by activity and factors of production (2009/10 and 2010/11), US$.

Immunisation activity (Healthcare)													
Line items (Factors of Production)	Facility-based routine service delivery	Outreach routine service delivery	Programme manage-ment	Record keeping & HMIS	Social mobilisation& advocacy	Super-vision	Surveil-lance	Training	Vaccine collection, storage & distrib.	Not disag-gregated	Cold chain maintnce	Capital investmt	Grand Total	% by Line item
US$ (2009/10)														
Cold chain equipment												684,629	684,629	2.8%
Not disaggregated[a]	6844	19,760	283,145		172,435	139,421	183,299	402,154		1,300,307	78,496		2,585,860	10.7%
Per diem						14,446	39,411						53,857	0.2%
Transport	4691		60,731	2809									68,231	0.3%
Vaccines and other goods	5,371,111	3,580,741							6266				8,958,118	37.1%
Wages and Salaries	5,962,705	3,975,137	1,872,315										11,810,157	48.9%
Grand Total	11,345,352	7,575,638	2,216,191	2809	172,435	153,867	222,709	402,154	6266	1,300,307	78,496	684,629	24,160,851	100%
% of Total Healthcare	47.0%	31.4%	9.2%	0.0%	0.7%	0.6%	0.9%	1.7%	0.0%	5.4%	0.3%	2.8%	100.0%	
US$ (2010/11)														
Cold chain equipment												4,374,936	4,374,936	13.3%
Not disaggregated[a]			203		44,017	43,323		178,993		1,566,483			1,833,020	5.6%
Per diem			403,371				70,742						474,113	1.4%
Transport			34,061										34,061	0.1%
Vaccines & other goods	8,300,219	5,365,589											13,665,808	41.5%
Maintenance											191,378		191,378	0.6%
Wages & salaries	6,276,532	4,184,355	1,876,149										12,337,036	37.5%
Grand Total	14,576,751	9,549,944	2,313,784		44,017	43,323	70,742	178,993		1,566,483	191,378	4,374,936	32,910,352	100.0%
% of Total Healthcare	44.3%	29.0%	7.0%	0%	0.1%	0.1%	0.2%	0.5%	0%	4.8%	0.6%	13.3%	100.0%	

[a] Where details of functions or line items were not available, funding was categorised as "not disaggregated". HMIS: Health Management Information System.

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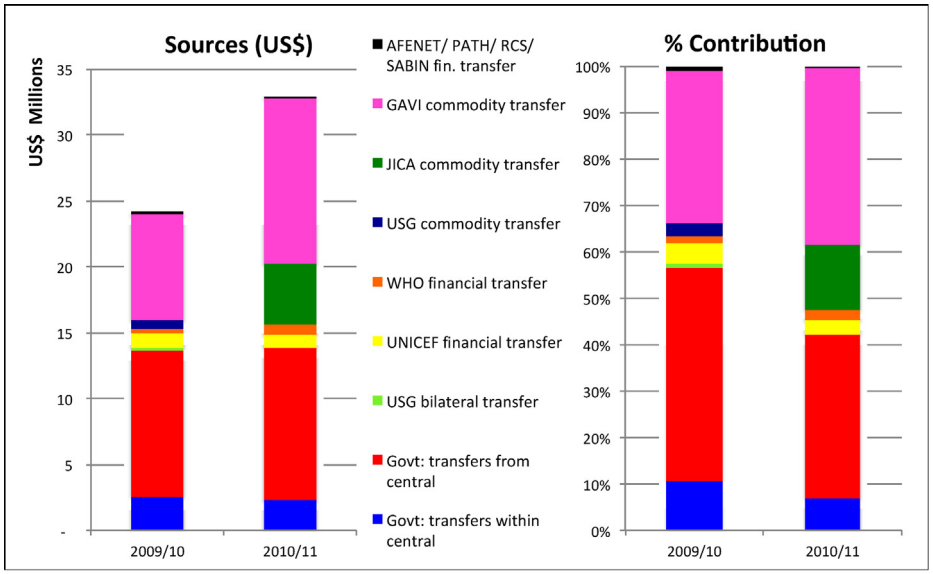


USG: United States Government. AFENET: African Field Epidemiology Network. RCS: Red Cross Society. JICA: Japan International Cooperation Agency.

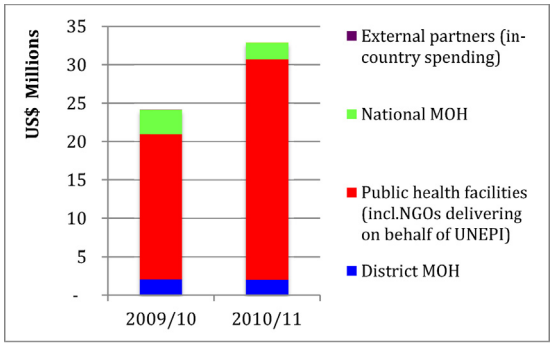
Fig. 1. Sources and percent of contribution of routine immunisation financing in Uganda 2009/10 and 2010/11 ($ millions and %).

4. Discussion

This study presents a comprehensive and rigorous mapping of funding for RI in Uganda, which identified a number of sources, quantified funding for human resources, and – as far as was possible – identified the intended use of the funding for RI activities.

Important findings are that Uganda's government has been providing approximately 50% of total RI financing per year, mainly for health system costs (particularly salaries), as well as contributing to the vaccine costs. In addition, the government is managing the lion's share of resources. These findings may be important when assessing government ownership and leadership of the immunisation programme, and may have implications for sustainability and co-financing strategies.

There are not many similar immunisation-mapping studies for comparison, apart from the WHO-UNICEF JRF data which indicated that the Ugandan government contributed 19% of the vaccine costs in 2011 [29], but that obviously did not capture public spending on salaries. An analysis of financial sustainability plans found that, on average, governments in low-income countries financed 35% of immunisation, and that this percentage had not increased between 2000 and 2006 [17]. A study between 2004 and 2012 of 56 cMYPs from countries at all levels of income also found that governmental spending accounted for around 56% of total RI financing [18]. Another encouraging finding of the mapping was that the majority of funding (93.3%) was spent at the level of service delivery. The remainder, spent at the national level (6.6%) or by the development partners (0.1%), appears relatively small, but data are not yet available from other countries to confirm this.



*UNEPI: Ugandan Expanded Programme for Immunisation.

Fig. 2. Allocation of routine immunisation financing to providers in Uganda (2009/10 and 2010/11, US$ millions).

Nevertheless, the mapping confirmed that development partners still play a key role in financing critical inputs, even before the introduction of new vaccines. GAVI financing for vaccines was pivotal, but other partners' catalytic funding enabled the overall immunisation system to function, including large non-routine expenditures such as for cold chain equipment. The study also found some volatility in flows from different funding sources and in allocations to programme components, as well as the challenge of allocating flows to specific activities. This can lead to difficulties for both funders and managers in ensuring optimal resourcing of the programme.

Comparing the study results with the 2012–2016 cMYP's estimate of anticipated funding sources for 2011 [2] highlighted several issues. The mapping identified additional funders and provided a more comprehensive, updated view of off-budget contributions (see Table 3). Overall, actual mapped contributions in 2010/11 were only $1.2 million (4%) higher than the cMYP estimate, partly due to the larger estimated government contribution to salaries, and the increased GAVI contribution. The other external sources, excluding the JICA contribution for cold chain equipment that was double what was anticipated by the cMYP (probably because the earlier year's commitment rolled over into 2010/11), were US$4 million less than anticipated in the cMYP. This raises questions about reasons for shortfalls and their potential impact on RI and other PHC services.

The mapping exercise also highlighted the potential for mismatches between available resources and the estimated resource needs. The accompanying costing study [14,30] estimated total Ugandan RI economic costs at $40 million in 2011. Excluding the JICA capital investments from this mapping total, the actual available funds mapped were only US$28 million, 29% less than was estimated to be necessary in 2011. However, direct comparisons have limitations; for example, the mapping methodology probably underestimated government funding, particularly on items such as transport, fuel, maintenance and vehicles at the district and facility levels, something that could not be readily identified from integrated primary health spending data. This is a common challenge in health sector resource tracking [20], and limited

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Table 3
cMYP financing estimates vs. mapping funding sources, Uganda (2010/11, US$).

	cMYP finance estimates	Study mapping estimates	Variance between cMYP & mapping	
Funding sources:	2011 (US$)	2010/11	2011	%
Central government	8,437,918	12,738,948	4,301,029	51%
District local government	3,587,818	1,160,718	−2,427,100	−68%
UNICEF	3,423,584	977,401	−2,446,182	−71%
PATH[a]	653,617		−653,617	−100%
WHO	1,584,167	782,344	−801,823	−51%
GAVI	11,746,006	12,540,611	794,605	7%
JICA	2,283,654	4,566,313	2,282,659	100%
Total	31,716,763	32,910,352	1,193,588	4%

[a] USAID/PATH contributed in 2009/10 but not 2010/11. JICA: Japan International Cooperation Agency.

ability to track funding at decentralised levels and underfunding of these items was reported as a major hurdle for RI [23].

The mapping also raises questions around sustainability of Uganda's plans to improve coverage, introduce new vaccines, and ensure system capacity for their delivery. The cMYP estimated that total RI resources requirements would increase by 200% by 2016, driven mainly by new vaccines, but also by most other activities, and by line items. This will require rapid increases in programme financing, well-coordinated funding flows and efficient programming of extra resources. For the foreseeable future, the sustainability of immunisation programmes seems likely to depend on increased partner funding combined with contributions from government. Advocacy efforts aimed at both donors and government will be important to ensure adequate funding, especially with possible reductions in global development assistance. Systematic assessment of the likely fiscal space to support the expanded immunisation is also desirable. The Ugandan government contribution to RI of just $14 million was already equivalent to 9.3% of total government health funding in 2011, and there are also indications of pressure on public funding for health programmes and steadily increasing staff costs [4].

The Uganda study shows that further financial mapping is likely to be valuable for Uganda and other countries to quantify issues around changing funding needs, funding flows and gaps, and to track trends across more years. The study suggests the following for future immunisation resource tracking efforts:

- Full expenditure tracking and costing studies may be desirable, at least to establish baseline parameters and estimate public salary contributions, but these may not be feasible in many countries. Therefore, mapping of financial flows may often be a feasible and cost-effective way to provide priority information for planners, managers and funders.
- Ideally, a single, routine system should accurately capture all funding commitments and contributions from partners, and reconcile government reported figures to plans and donor reports. It should be feasible to establish a system that accurately records all substantial donations, their primary purposes, and actual expenditures at each level of the health system. This is compatible with recommendations for "compacts" between governments and partners to report on commitments and expenditures for women and child health in each country [11], and would allow for more accurate on-going assessment of levels and adequacy of financing flows, as well as absorption bottlenecks [23,26].
- Both resource mapping studies and routine mapping systems will require some extra resources. While no representative data on costs of such systems are available, it is clear that, given the relatively small number of funding sources and implementers of services for immunisation, mapping studies and systems will require far smaller resources than NHAs and NASAs, especially if data collection becomes routinised.
- Furthermore, countries' experience in optimising approaches to routine data collection and analyses for NASAs and NHAs, combined with the relative simplicity of immunisation resource flows, may help to avoid some of the challenges encountered by previous efforts to institutionalise health resource tracking [20]. These have mostly related to difficulties of working within poor public financial information systems, particularly for tracking public health care spending related to specific programmes or interventions.
- The SHA coding system provides a useful framework for collecting and analysing funding commitments and flows. However, the SHA codes required further disaggregation to be meaningful for analysing the components of the RI programme (see Table 1).
- Consideration needs to be given to harmonising cMYP systems with financial information from partners and government at national and sub-national levels. The data collection may not yet be well co-ordinated or complete, hindering the analysis or interpretation for operational and planning decisions. Possible areas for review include cMYP financial classifications and clearer linkages between cMYP resource needs and financing projections.
- Further, detailed financing analyses of priority programmatic area and line items, as well as the identification of potential bottlenecks, delays and fund re-allocations, could enhance funding and programmatic efficiency.
- Other areas for further exploration include sub-national funding flows, and also funding related to non-governmental providers. In Uganda, an estimated 22% of private expenditure for child health is for non-curative services but there has been no assessment of their contribution to immunisation [6].

The resource mapping approach had limitations, although they are unlikely to affect its main conclusions. The analysis mapped funding allocations and did not track actual expenditures, or track funds down to district and service level. The mapping was thus not a full resource tracking and should also not be assumed to provide an accurate reflection of all actual consumed RI spending, which was not its primary intention. However, the identification of the large GAVI disbursement late in 2011 which was largely expended in 2012, illustrates the importance of understanding differences between the approaches, as well as usefulness of multi-year data to interpret mapping results and trends.

5. Conclusion

Results highlight that governments and partners need to improve systems to routinely track immunisation financing flows for enhanced accountability, performance, country ownership, co-funding decisions and sustainability. Comparison of cMYP and mapping estimates of resource needs, gaps, and financing flows showed some variation, particularly related to funding sources. These warrant further assessment and monitoring to ensure key planning and activities function optimally. Introducing new,

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expensive vaccines will involve large costs and increased financial flows, and create new challenges to optimise financing. The modified SHA coding developed here (see Table 1) could be used for standardised, NHA-compatible resource tracking.

Conflict of interest statement

I wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Acknowledgements

The study was funded by the Bill and Melinda Gates Foundation and supported by GAVI and the World Health Organization (WHO). Managers, planners, and staff of the UNEPI, the MOH, and development partners provided key inputs and advice in designing and collecting data for the study. The support of Damian Walker, the EPIC Steering Committee, and GAVI steering committee members are also acknowledged.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.053.

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Vaccine 33S (2015) A85–A92

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Tracking financial flows for immunization in Honduras

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ARTICLE INFO

Keywords:
Resource tracking
Financial flows
Immunization
New vaccines
Honduras
Latin America

ABSTRACT

Introduction: In Honduras, until 2008, vaccine and injection supplies were financed with domestic resources. With the introduction of rotavirus vaccine in 2009 and pneumococcal conjugate in 2011, the country's Expanded Program on Immunization required an influx of resources to support not only vaccine procurement but also investments in cold chain infrastructure and programmatic strategies. This paper examines the origin, allocation, and use of resources for immunization in 2011 in Honduras, with the aim of identifying gaps in financing.
Methods: An adaptation of the System of Health Accounts (2011) codes was used to specifically track resources for immunization services in Honduras for 2011. All financial flows were entered into an Excel database, and each transfer of resources was coded with a financing source and a financing agent. These coded financing sources were then distributed by provider, health care function (activity), health care provision (line item or resource input), and beneficiary (geographic, population, and antigen). All costs were calculated in 2011 United States dollars.
Results: In 2011, financing for routine immunization in Honduras amounted to US$ 49.1 million, which is equal to 3.3% of the total health spending of US$ 1.49 billion and 0.29% of the GDP. Of the total financing, 64% originate from domestic sources. The other 36% is external financing, most importantly Gavi support for introducing new vaccines. This analysis identified potential financing gaps for many immunization-related activities besides procuring vaccines, such as expanding the cold chain, training, social mobilization, information systems, and research.
Conclusions: The funding for Honduras' immunization program is a small share of total public spending on health. However, new vaccines recently added to the schedule with financial support from Gavi have increased the financing requirements by more than 30% in comparison to 2008. The Honduran government and its partners are developing sustainability plans to cover a financing gap that will occur when the country graduates from Gavi support in 2016. Access to lower vaccine prices will make the existing and future program, including the planned introduction of HPV vaccine to adolescent girls, more affordable.
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1. Introduction

Immunization is widely regarded as providing one of the best returns on investment in public health. Nevertheless, the resource needs and, as a result, spending for national immunization programs have grown in Honduras and other countries of Latin America. This is primarily due to the introduction of new, more expensive vaccines, as well as the expansion of the populations benefiting from these vaccines. Established in 1979, Honduras' Expanded Program on Immunization (EPI) has rapidly grown both in terms of the number of vaccines offered in the program as well as the related costs to deliver these vaccines. With financial support from the Gavi, the rotavirus vaccine was introduced in 2009, followed by the pneumococcal vaccine in 2011. Currently, Honduras is considering the introduction of HPV vaccine, which would further increase total financing needs for the program [1].

In 2011, the national health expenditure amounted to US$ 1.49 billion, representing a per capita expenditure of US$ 182 [2] (Table 1). As elsewhere in Latin American and the Caribbean, in Honduras the government has set out to secure domestic financing to support immunization services in order to build

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http://dx.doi.org/10.1016/j.vaccine.2015.01.012
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Table 1
Health, economic and demographic indicators for Honduras.

Indicator	
Total population [3]	8,215,313
Expected births [3]	177.733
Women of childbearing age [3]	2,135,981
Infant mortality rate [3]	24.3
GDP per capita (US$ at current prices) [4]	2156
National health expenditure (million US$) [2]	1494
Public expenditure on health [2]	48.1%
Private expenditure on health [2]	51.9%
Health expenditure per capita (US$) [2]	181.8

a sustainable program in both the short and medium term. The new, more expensive vaccines provide substantial health benefits [5]. However, their higher costs and the reliance on external aid to introduce them make it imperative to carefully track immunization resources [6]. This study aims to map the financial and commodity flows that support immunization services in Honduras. An accurate understanding of the resource flows and available financing for immunization services in a country such as Honduras could empower decisionmakers and planners with information to improve resource allocation and to mobilize funds needed to fill gaps. The country is currently developing sustainability plans in preparation for its graduation in 2016 from Gavi subsidies for the pneumococcal conjugate and rotavirus vaccines. Graduation from Gavi support occurs after a country has surpassed the eligibility criteria of <US$ 1500 per capita GDP [7].

2. Methods

2.1. Conceptual framework and accounting method

Resource tracking is a real-time planning and evaluation tool to understand and assess the flow of resources for health (and, in this case, immunization services) aimed at reaching end users in a country [8]. A more precise description and understanding of these resource flows enables a management team to demonstrate their good stewardship of both domestic and external funding sources as well as to identify any overlap and/or inefficiencies. Additionally, these methods may point to funding gaps and to reasons to support resource mobilization efforts. This analysis focuses on the flow of financing and commodities for the routine immunization program from external, government, and other domestic sources. Following the EPIc Common Approach [9], this analysis adapted the System Health Accounts [10] coding methods for tracking financial flows to

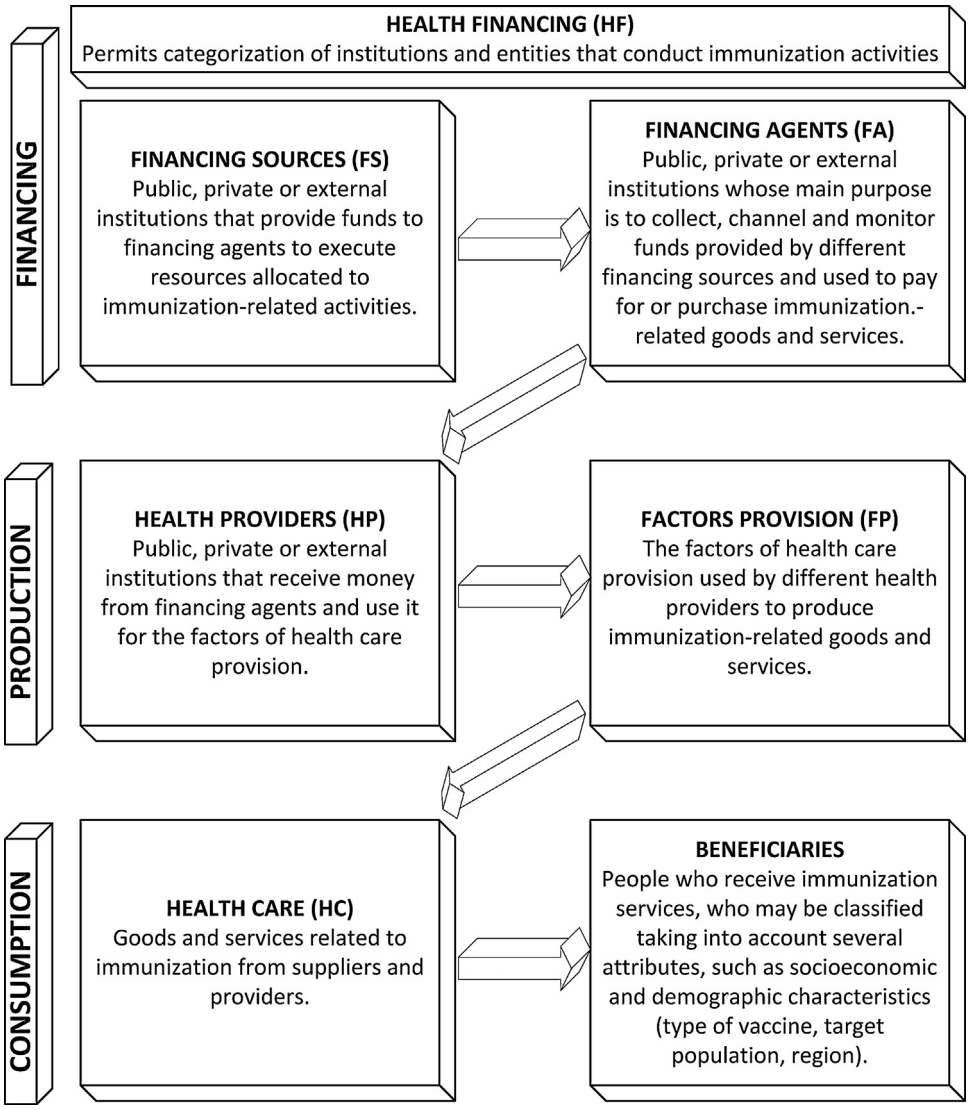

Fig. 1. System of Health Accounts (SHA) 2011 financing, production, and consumption codes [6].

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the context of immunization delivery. This coding system facilitates the identification and categorization of various financing sources, agents, and schemes that subsequently can be distributed between different health care providers, health care functions (similar to EPI planning components or activities) [11] health care provisions (similar to line item classifications), and ultimately beneficiaries by vaccine type and/or region [5,8] [10,12]. Fig. 1 shows the relationship between the different transactional vector categories.

All financial flows identified for the fiscal year 2010/2011 were quantified and coded. This 12-month period began 1 January 2011 and extended to 31 December 2011. EPI financing was evaluated at the national, regional, and local levels. Financing at the local level was, in part, estimated through a survey conducted in a representative sample of health units. More information regarding the sample of health units is described in a companion analysis of costs published in this issue [11]. Information from bilateral and multilateral agencies that provided some type of support to the immunization program, whether in cash or in kind, was also included in the study. Donations in kind were recorded through the use of local appraisals. For example, Project HOPE donated approximately 150,000 doses of the 23-valent polysaccharide (PPV23) vaccine for special risk groups. In this case, the market value of the doses (US$ 17.63 per dose) was considered and subsequently recorded as a financial flow.

The accrual accounting method was used for this study, which refers to identifying all financial transactions or committed budgets that have been transferred in the period in which the value of a good or service was generated [12]. All financial flows were estimated in the local currency, lempiras, and converted to 2011 US dollars at the official exchange rate of 18.8915 lempiras to US$ 1.00. Administrative records from public, private, and foreign institutions were obtained to estimate the total financing amount transferred. In the event that financial records were not adequately detailed to ascertain allocation of the financing source, agent, and scheme to health provider, health care function, health care provision, and beneficiaries, several allocation rules were assumed:

- Health providers (HP), region (REG), vaccine (VAC), target population (POP): Financing records do not provide information to code directly for health provider type, region, vaccine, or target population. As such, the total 2011 financing for immunization was allocated to each of these categories based on the proportion of doses applied by category.
- Factors of health care provision (FP): Most financing records provide sufficient information to classify the transaction by FP. In the event of insufficient information on the record to inform the allocation by FP, records from other institutions with similar expense detail were used to apply an assumption regarding the FP.

Additionally, another series of allocation rules were derived from the facility-based survey that was implemented primarily for the analysis of the cost of delivering routine immunization in Honduras [11]. Financing for Ministry of Health (MoH) staff 100% dedicated to immunization services was easily identifiable in the staff roster. However, staff that share time between immunization services and other public health services were identified in the facility-based sample, and the extrapolations of these costs to the whole country were used. Also, some financing for vehicles, meetings, per diems, and travel allowances at the local level was identified in the facility-based survey.

2.2. Data collection

Several data sources were consulted to identify, quantify, and correctly code all financial flows. Through key-informant interviews, primarily with the immunization program management and key actors in financial management at the Honduran MoH, a mapping exercise was conducted to better understand all potential financial sources and actors in the flow of resources for immunization in the country. With each of the institutions identified in the mapping exercise, in-person interviews and official letters were used to solicit information. Additionally, some facility-level financial sources and flows were identified in the facility-based survey administered primarily for the cost analysis [11].

Specifically, the MoH provided information on payroll, inventories, financial records, and national statistics, among others, at the central and regional administrative levels. The national payroll database provided a listing of all MoH staff dedicating some or all of their work time to immunization services. This database identified the financing source for each employee. The cold chain inventory listing was obtained to determine information on all equipment acquired in 2011, including the location, brand, model, series, operational use, condition, replacement cost, and financing source. A secondary source for equipment information was the national inventory of assets listing, which details all goods and property of the MoH that support immunization services. Vehicles procured in 2011 were identified in this listing. Next, financial transaction records ("F01 forms") were obtained from the MoH budget office to identify, quantify, and code many financial flows related to vaccines, supplies, per diems, travel allowances, and other transfers. This form reports the line item detail, including intended use (activity or health care provision), executing unit, accounting period, financing source, financing agent, and total amount transferred. Finally, national statistics on production (doses applied) by health facility, municipality, region, sector, and antigen were obtained from the National Statistics Bureau. The MoH Management, Planning, and Evaluation Unit provided information on financing from international cooperation partners, including Gavi. Information regarding financing from the U.S. Agency for International Development (USAID) and the Spanish Agency for International Development and Cooperation (AECID) was obtained from the Extending Coverage and Financing Unit in the MoH.

The Ministry of Finance (MoF) provided additional health-related F01 foms detailing financial transactions at the lower administrative levels. The Honduran Social Security Institute provided information on vaccination statistics (doses applied) and payroll. Finally, information was gathered from international organizations to track all resource flows originating outside of the country. PAHO, UNICEF, Gavi, and other multilateral and bilateral organizations as well as NGOs and foundations contributed information regarding their financing of immunization services in Honduras. For example, PAHO provided all purchase invoices for vaccines and other supplies procured through the PAHO Revolving Fund. These invoices detail vaccine prices, quantity, administrative fees, freight, and insurance for each purchase order.

3. Results

In 2011, an estimated US$ 49.1 million in financing was identified for immunization services in Honduras. This equaled 3.3% of total national health expenditures and 0.29% of the GDP for the same year. Fig. 2 details the 2011 financial flows for routine immunization services in Honduras. The mapping of financial flows led to a systematic approach for identifying and quantifying financing from its origin to its intended beneficiary, grouped by region, antigen, and target population. The direction of resource flows among the financing sources, agents, providers, and ultimately beneficiaries is shown by the directional arrows in Fig. 2.

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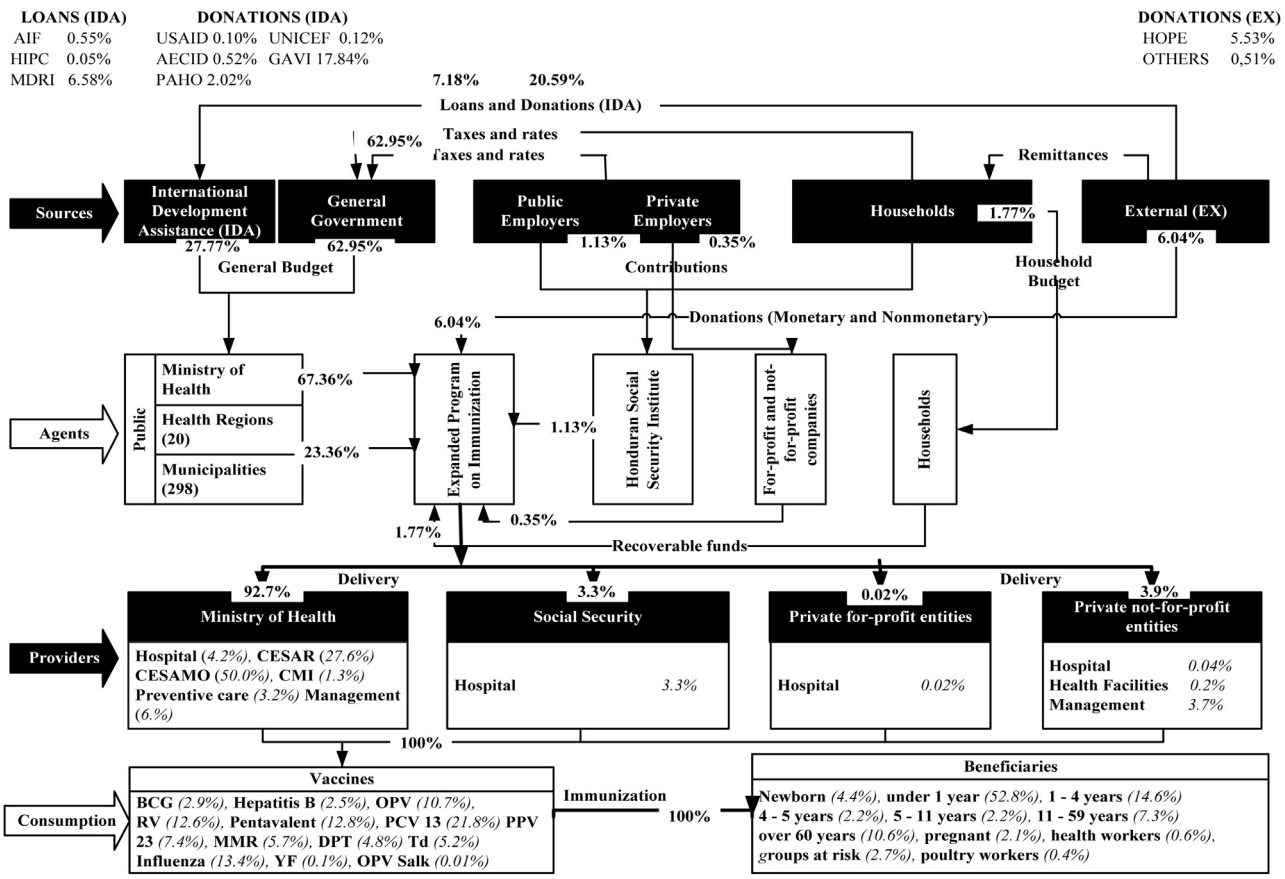

Fig. 2. Mapping of immunization financing flows in Honduras, 2011.

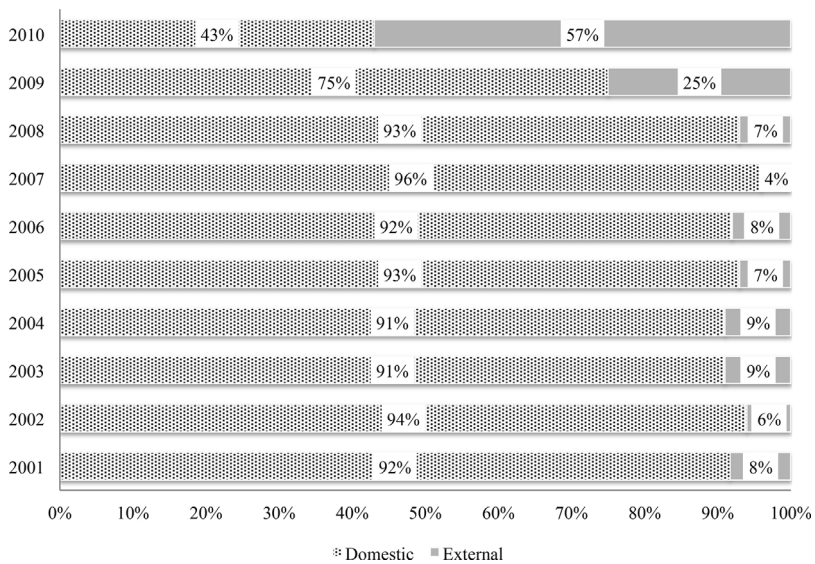

Fig. 3. % Financing of EPI by source (2001–2010).

An estimated 64% of total financing for immunization services originated from domestic revenue schemes, principally taxes and royalties on public and private companies and/or households. External financing (i.e. donations, loans, direct foreign investment) for immunization amounted to 36%, primarily from donations (21% of the total financing) and loans (7% of the total financing). Gavi financial transfers accounted for 17.8% of total financing.

The financing sources for immunization included the central government, public and private employers, households, and international cooperation. These sources were then channeled to the financing agents responsible for allocating the resources to the intended provider. All external financing was redirected to the MoH as the financing agent, at the central, regional, or municipal level.

The EPI, in conjunction with upper leadership at the MoH, makes resource allocation decisions as an important financing agent for

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all immunization services. This agent allocates resources to the service provider level, including all public, social security, and private clinics providing immunization services. Public sector clinics provided 94.5% of the vaccinations in 2011, and they received about 93% of the total available financing for immunization. Of the total financing, 21.8% supported PCV13 vaccinations, with the next largest shares going to influenza (13.4%), pentavalent (12.8%), and rotavirus (12.6%). Finally, financing tagged for beneficiaries is most importantly targeted at those under 1 year old (53%).

Crossing the financing agent codes and the financing source codes illustrates the critical role the government plays in financing and administering financial flows for use in the immunization program (Table 2). By far, the MoH manages and administers the single largest share (67%) of all the financing. At the regional and local government level, a smaller but substantial amount of domestic revenues is managed and administered, approximately US$ 11.1 million or 22% of total financing. Some PAHO resources are directly transferred to the local level, totaling approximately US$ 300,000. This financing is for per diems and travel allowances to mobilize outreach efforts in low-coverage districts. Finally, it is important to note that most other external financing aimed at supporting immunization services in Honduras is earmarked for vaccine and supply purchases. These purchases are executed at the central level; therefore, most financing of external origin, for example Gavi financing, is centralized.

The matrix in Table 3 shows how various financing sources contribute to different resource inputs (i.e. factors of provision (FP)) to the national immunization program. Again, we can see that the government finances approximately two-thirds of the program. The central government primarily finances wages and other employee benefits, including per diems and travel allowances. In contrast, the regional governments finance all vaccines (for both children and other risk groups) as well as the majority of the cold chain equipment acquired in 2011. This finding is of interest because procurement for vaccines and supplies is centralized, while the available financing is located in decentralized accounts. The third largest source of financing is from Gavi, which exclusively finances new childhood vaccines (PCV13 and rotavirus), injection supplies, and a small amount of per diem and travel allowances as well as printing. Loans from international organization, mostly originating from agreements related to the country's status as a heavily indebted poor country (HIPC), finance wages for health workers at the regional level and facility level, as well as safety boxes and some cold chain equipment.

4. Discussion

Throughout the 2000s, Honduras' immunization program relied little on external financing to meet the program's targets. However, external financing for routine immunization services, primarily from Gavi, increased from 7.3% in 2008 to 25% in 2009 and 57% in 2010 (Fig. 3) [13]. With Gavi and PAHO support, rotavirus vaccine was first procured in 2009, and PCV13 at the end of 2010. Additionally, WHO donated pandemic A(H1N1) influenza vaccine to the country during this period.

Despite a decreasing overall share of total financing originating from domestic sources for immunization services, the government of Honduras has increased the fiscal space available for vaccine purchase and strengthening of the routine program in recent years. Legislation first enacted in 1998 has earmarked up to 2% of the budget assigned to the MoH for vaccine and supply procurement. From 2005 to 2008, the budget approved for immunization more than doubled. Both 2007 and 2008 represent atypical years, when a policy change extended routine seasonal flu vaccination to new risk groups, and the elderly, and the

Table 2
Financing Agent (FA) by Financing Source (FS) for routine immunization in Honduras, 2011 US$ in thousands.

		FA 1.1.1	FA 1.2.1	FA 1.3.1	FA 3	FA 4	FA 5	FA 6	Total financing by source
		Ministry of Health	Regional gov't	Social Health Insurance	Private sector	Nonprofit orgs. Serving households	Households	Rest of the world	
FS 1.1.1	Central gov't	$19,757							$ 19,757
FS 1.1.2	Regional gov't		$11,140						$ 11,140
FS 2.1.1.1	USAID	$ 48							$ 48
FS 2.1.1.5	AECID	$ 256							$ 256
FS 2.1.2.3	PAHO	$ 690	$ 300						$ 990
FS 2.1.2.1	UNICEF	$ 57							$ 57
FS 2.1.3	GAVI	$ 8,757							$ 8,757
FS 3	Social insurance			$ 554					$ 554
FS 5	Voluntary prepayment						$ 867		$ 867
FS 6	Other domestic revenues				$ 71	$ 99			$ 171
FS 7	Direct foreign transfers							$2,967	$ 2,967
FSR 1.1	Loans	$ 3,499	$ 23						$ 3,522
Total financing by agent		$33,062	$11,463	$ 554	$ 71	$ 99	$ 867	$2,967	$ 49,084

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Table 3
Financing Source (FS) by Health Care Provision (FP) for routine immunization in Honduras, 2011 US$ in thousands.

		FS 1.1.1	FS 1.1.2	FS 2.1.1	FS 2.1.2	FS 2.1.3	FS 3	FS 5	FS 6	FS 7	FSR 1	Total financing by health provision
		Central gov't	Regional gov't	Bilateral orgs. (USAID, AECID)	Multilateral orgs. (PAHO, UNICEF)	Gavi	Social insurance	Voluntary prepayment	Other domestic revenues	Direct foreign transfers	Loans	
FP 1.1	Wages	$16,620				$ 78	$ 554		$ 74		$3,229	$ 20,555
FP 1.3.1	Per diem	$ 345	$ 485	$ 74	$ 530	$ 123		$ 780	$ 54	$ 123		$ 2,514
FP 3.2.1.1.1	Other vaccines		$ 3,275							$ 2,673		$ 5,947
FP 3.2.1.1.2	Childhood vaccines		$ 5,576			$8,336						$ 13,911
FP 3.2.1.2	Other healthcare goods	$ 12		$ 12	$ 16							$ 40
FP 3.2.2.1	Injection supplies		$ 177			$ 13				$ 8		$ 198
FP 3.2.2.2	Other supplies		$ 100			$ 46				$ 6	$ 23	$ 175
FP 3.3.1	Transport	$ 111	$ 179	$ 4	$ 13	$ 48		$ 54	$ 16	$ 20		$ 445
FP 3.3.2	Maintenance	$ 34	$ 518	$ 33				$ 16		$ 120		$ 720
FP 3.3.3	Printing	$ 10		$ 49	$ 22	$ 11				$ 8		$ 101
FP 3.3.4	Other non-healthcare services		$ 102	$ 80	$ 28	$ 1			$ 0.3	$ 1		$ 212
FP 3.4.1	Utilities and communications	$ 33	$ 46	$ 35	$ 12	$ 17				$ 7	$ 7	$ 158
FP 3.4.2	Other non-healthcare goods	$ 35	$ 2	$ 9	$ 6			$ 18	$ 26	$ 2	$ 65	$ 163
FP 4.1	Cold chain equipment	$ 110	$ 681		$ 12						$ 198	$ 1,001
FP 4.2	Vehicles				$ 4	$ 47						$ 51
FP 4.3	Other equipment			$ 5	$ 61	$ 37						$ 104
FP 5	Other items of spending on inputs	$ 2,447			$ 1							$ 2,448
FP 99	Not disaggregated				$ 340							$ 340
Total financing by source		$19,757	$11,140	$ 303	$ 1,047	$8,757	$ 554	$ 867	$ 171	$ 2,967	$3,522	$ 49,084

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Table 4
Domestic financing gaps by immunization activity in Honduras (2011).

Activity (health care function)	Domestic financing	External financing
Social mobilization	79.5%	20.5%
Facility-based vaccination	84.0%	16.0%
Outreach	82.4%	17.6%
Training	65.0%	35.0%
Vaccine and supplies	51.0%	49.0%
Cold chain	81.0%	19.0%
Supervision and monitoring	75.5%	24.5%
Evaluation	52.7%	47.3%
Program management	84.7%	15.3%
Other operating costs	38.0%	62.0%
Surveillance	77.2%	22.8%
Information system	80.6%	19.4%
Priority policy and legal basis	51.1%	48.9%
Research	96.4%	3.6%
Total	66.2%	33.8%

country launched a massive measles and rubella follow-up campaign to maintain the country free of susceptible persons.

Gavi has provided financing to the EPI since 2004. Through 2010, Honduras received US$ 9.7 million in support for injection safety, for generalized strengthening of immunization services and of the health system more broadly, and for new vaccine introduction, primarily rotavirus. More than 80% of this Gavi support has been directed toward the procurement of new vaccines. In 2011, Gavi financing for immunization in Honduras totaled US$ 8.7 million, an amount that nearly equaled the total financing during the preceding six years. The hike in financing supported the universal introduction of PCV13, the most expensive vaccine in the routine program, as well as efforts to strengthen the immunization information system, including the purchase of computers for the regional level to begin implementing a computerized nominal registry system.

Support from donor partners, particularly Gavi, has strengthened the government's financial capacity to incorporate new vaccines, leading to substantial health gains for children in Honduras. However, Gavi subsidies will expire in 2016, and the government will be fully responsible for paying for the new vaccines, though at a negotiated, greatly reduced price. In addition to gaps in financing of new vaccines, there are other important funding shortfalls for operational activities (Table 4) that need to be more closely assessed for near-term resource mobilization efforts and planning. Domestic resources will need to replace the external sources soon.

For 2011, the EPI reported approximately US$ 21.3 million in expenditures [13]. Vaccine and supply purchases represented over 80% of this amount. This reported expenditure figure only represents the budget managed and executed by the central EPI management, which generally would cover vaccine and supply procurement via the PAHO Revolving Fund as well as training, other meetings, and employee wages and benefits for the management team. Still, this figure does not clarify important and real financing gaps for the same year. The program had received a budget approval in the amount of US$ 25 million. Due to unforeseen revisions to the committed budget (which was financed from both domestic and external resources), the program suffered a financing gap just under US$ 4 million for the same year. This shortfall most severely impacted the acquisition of needed cold chain equipment and vehicles. Nonetheless, the program successfully rolled out the PCV13 vaccine and met nationwide targets for completing childhood vaccination schedules during the two annual national vaccination weeks. Still, many districts suffered from lower coverage in 2011 than in previous years. Further, these financing gaps, particularly for general operations and transport, put the program's operational capacity at serious risk.

Under the incremental co-financing payment agreement with Gavi, Honduras' financial obligation per dose for PCV13 will go from US$ 0.17 in 2011 to US$ 2.17 in 2014. This is a useful mechanism to begin transitioning toward more sustainable, domestic financing streams. However, financing gaps for operational activities, such as transport and cold chain maintenance, may widen because of the government's increased financing responsibility for the new vaccines. In the near and long term, the government's primary strategy to ensure sustainability and to maintain the great progress the program has made in reducing vaccine-preventable diseases is tied to securing 100% of immunization financing from domestic sources. This will be achieved with the commitment of the central government and subnational governments by allocating greater resources, raising existing taxes on some products, and/or imposing new taxes on other products. In 2013, the National Congress of Honduras passed a law earmarking increased domestic funding for immunization services. The new legislation included language to protect financing for general strengthening of the program as well as to procure vaccines and supplies. This law has yet to be published in the official legislative gazette, but this new legislative framework will help secure increased funding that will sustain both vaccine procurement and programmatic strengthening.

5. Conclusion

The cost of Honduras' EPI makes up a small share of the public spending on health. However, new vaccines recently added to the schedule with financial support from Gavi have increased program costs more than 30%. The Honduran government and its partners need to prepare to cover a future financing gap when the country graduates from Gavi support in 2016. Access to lower vaccine prices will make the existing and future program, including the planned introduction of HPV vaccine to adolescent girls, more affordable in the near and long term.

Acknowledgements

We are grateful to the team of public health professionals that serve in management at the national and regional levels in Honduras dedicated a substantial amount of time for interviews and data. We also are indebted to the other EPIc country teams and EPIc steering committee members for their constructive feedback and support. This study was kindly financed by the Bill & Melinda Gates Foundation, Seattle, WA, USA.

Conflict of interest statement: The authors declare no conflicts of interest.

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Vaccine 33S (2015) A93–A98

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

What have we learned on costs and financing of routine immunization from the comprehensive multi-year plans in GAVI eligible countries?

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ARTICLE INFO

Keywords:
Costs
Routine immunization
Financing
Sustainability
Low-income

ABSTRACT

Background: Immunization is one of the most cost-effective health interventions, but as countries introduce new vaccines and scale-up immunization coverage, costs will likely increase. This paper updates estimates of immunization costs and financing based on information from comprehensive multi-year plans (cMYPs) from GAVI-eligible countries during a period when countries planned to introduce a range of new vaccines (2008–2016).

Methods: The analysis database included information from baseline and 5-year projection years for each country cMYP, resulting in a total sample size of 243 observations. Two-thirds were from African countries. Cost data included personnel, vaccine, injection, transport, training, maintenance, cold chain and other capital investments. Financing from government and external sources was evaluated. All estimates were converted to 2010 US Dollars. Statistical analysis was performed using STATA, and results were population-weighted.

Results: Results pertain to country planning estimates. Average annual routine immunization cost was $62 million. Vaccines continued to be the major cost driver (51%) followed by immunization-specific personnel costs (22%). Non-vaccine delivery costs accounted for almost half of routine program costs (44%). Routine delivery cost per dose averaged $0.61 and the delivery cost per infant was $10. The cost per DTP3 vaccinated child was $27. Routine program costs increased with each new vaccine introduced. Costs accounted for 5% of government health expenditures. Governments accounted for 67% of financing.

Conclusion: Total and average costs of routine immunization programs are rising as coverage rates increase and new vaccines are introduced. The cost of delivering vaccines is nearly equivalent to the cost of vaccines. Governments are financing greater proportions of the immunization program but there may be limits in resource scarce countries. Price reductions for new vaccines will help reduce costs and the burden of financing. Strategies to improve efficiency in service delivery should be pursued.

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1. Introduction

Immunization is one of the most cost-effective health interventions for achieving the Millennium Development Goal of reducing deaths among children less than 5 years of age (MDG4) by two-thirds [1,2]. Vaccines provide health benefits not only for the immunized child, but also for the community as a whole through herd immunity. In addition, studies have shown that immunization extends life expectancy and contributes to economic growth [3,4].

Studies show it costs between $17 and $25 to fully vaccinate a child with traditional vaccines. Variation in estimates is related to level of scale, type of delivery strategy, and prices [5–7].[1] Costs of immunization have increased with the addition of new and more expensive vaccines [8]. As of March 2014, almost all low- and middle-income GAVI-eligible countries have introduced pentavalent vaccine; 40 included pneumococcal vaccine; 34 launched rotavirus vaccine [9]. This paper evaluates total and unit cost and financing, of routine immunization based on country-level information from comprehensive multi-year plans (cMYPs) in GAVI-eligible countries.

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[1] The traditional vaccine schedule includes three doses each of oral polio vaccine, and combined diphtheria–pertussis–tetanus vaccine, and a single dose each of measles and Bacillus-Calmette Guerin (BCG) vaccine against tuberculosis.

http://dx.doi.org/10.1016/j.vaccine.2014.12.076
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2. Methods

The cMYP is a planning tool for estimating current and future costs and financing of the national immunization program using a standard method [10]. Baseline year estimates are retrospective. Countries also estimate 5 years of future resource requirements and financing to achieve national immunization program goals, such as introducing new vaccines and ramping up coverage rates. The present analysis is based on 40 cMYPs from GAVI-eligible countries with a baseline year between 2008 and 2011 and projection years until 2016.[2] This timeframe more fully captures plans to introduce Hib-containing, pneumococcal and rotavirus vaccines as compared to earlier estimates [8].[3] These vaccines prevent the majority of preventable child deaths and the global community has coalesced around their widespread introduction through the GAVI Alliance.

The database was structured to evaluate baseline and projection year data, resulting in 6 years of data for each country. Costs included both immunization-specific and health system costs categorized into line items: shared and immunization-specific personnel and per diem; traditional and new vaccines; injection supplies; transport for fixed sites and outreach services; training; social mobilization and advocacy activities; disease surveillance; program management; operational costs (cold chain and other equipment maintenance, building operating costs and utilities); other recurrent costs; cold chain equipment; vehicles; other equipment, including construction of buildings. Delivery costs excluded vaccine and safe injection costs. Information on sources and uses of financing was incorporated. Data on doses utilized, DTP3 coverage rates, and total and target populations were derived from the cMYPs, and used to estimate unit costs.[4] The number of children receiving the third dose of DTP vaccine served as a proxy to estimate the cost per fully immunized child, or FIC [5,6,11,12].

The database contained categorical information on vaccination schedule for each country year: Hepatitis B vaccine (including tetravalent vaccine); Hib-containing vaccine (mostly pentavalent vaccine); Hib-containing and pneumococcal vaccine; or, Hib-containing vaccine, pneumococcal, rotavirus vaccines. No distinction was made for vaccine formulation. A novel approach to assessing the impact of different vaccine schedules on program costs was developed.

Macroeconomic data on gross domestic product, GNI per capita, and government health expenditures also were incorporated into the database [13,14]. Projections of GHE were based on real GDP growth rates. Regional affiliation and GAVI Alliance co-financing groupings were included [9]. As the median baseline year was 2010, all costs and financing was converted into 2010 USD equivalents using the consumer price index [15].

The database of 40 baseline country years and 203 projection country years, for a total of 243 total country years was statistically analyzed using STATA [16].[5] All estimates are population-weighted. This approach represents a small methodological advance over previous analyses of cMYPs.

Financing sources reflect the last source from which financing is allocated. For example, if a bilateral donor channels funds through a multi-lateral agency, the cMYP method attributes financing to the multi-lateral agency and not the bilateral donor. As a result, the cMYP estimate may under-represent some funding sources. In addition, sources of financing are not mutually exclusive, as pooled financing includes funds from the government, bilateral donor agencies, development banks, and other sources.

Table 1
Comparison of regional RI programs in sample cMYPs (baseline year, weighted average).

Region	% DTP3	Target infants	Doses (million)
AFRO ($n = 27$)	84.9%	899,588	12.2
EMRO ($n = 4$)	75.6%	4.7 million	88
EURO ($n = 4$)	86.4%	93,273	1.6
SEARO/WPRO ($n = 5$)	94.3%	3.8 million	107.2
Total ($n = 40$)	86.5%	2.9 million	92.7

Source: author's calculations.

3. Results

3.1. Sample data

The cMYP sample represents a population of 1.02 billion and 30.6 million surviving infants. Most countries are from the Africa region (66%), and 56% have a GNI/capita less than $975. Eighty-five percent of sample countries utilize Hib-containing vaccine in the baseline year. In the projection years, 82% of countries plan to introduce pneumococcal vaccine, and 58% expect to include rotavirus vaccines.

Table 1 summarizes routine immunization program outputs from the sample cMYPs by region for the baseline year. DTP3 coverage varies from 76% in AFRO countries to 94% in SEARO and WPRO countries, with an average of 86.5%. The average number of target infants is highest in EMRO countries, though the number of doses utilized per year is largest for countries in the SEARO and WPRO regions.

3.2. Costs of routine immunization programs

The population-weighted average annual RI cost was $62 million for the baseline year, increasing 86% to $114 million on average for the projection period. Countries in the EMRO Region had the highest average annual RI cost in the baseline year ($86 million), compared to countries in the AFRO region ($22 million). Regional RI cost variation may be related to differences in goals, size of the target population, coverage rates, health system configuration, delivery strategies, and prices.

Fig. 1 illustrates the distribution of RI costs by line item for the baseline year compared to the projection years for the sample. Vaccines are the main cost driver, accounting for more than half of RI cost, rising to 61% of RI cost in projection years. Personnel time represents 22% of RI cost, declining to 15% of RI cost in future years. Cold chain cost, maintenance, and safe injection supplies have relative shares of total cost at 3%, 6%, and 5%, respectively, which are maintained in the projection period.

[2] The sample included the following countries: Afghanistan, Angola, Armenia, Azerbaijan, Bangladesh, Benin, Cameroon, Central African Republic, Republic of Congo, Djibouti, Democratic People's Republic of Korea, Eritrea, Gambia, Ghana, Georgia, Guinea, Guinea Bissau, India, Kenya, Lesotho, Liberia, Mali, Moldova, Mozambique, Niger, Pakistan, Rwanda, Senegal, Sudan (north), Tanzania, Timor L'Este, Togo, Uganda, Yemen, and Zambia. Data from Ethiopia were excluded because of missing information on routine doses.

[3] Most sample countries have or will introduce pentavalent vaccine.

[4] Estimates of doses, coverage and population in the cMYP were used in the analysis to ensure internal consistency in the analysis, as costs reflected the coverage and program goals of the country. Utilizing other estimates, such as WHO–UNICEF Best Estimates would have introduced bias into the analysis and created inconsistencies between inputs and outputs. For the projection years, there are some differences between the cMYP projected coverage rates and those determined retrospectively by WHO and UNICEF.

[5] One outlier observation from Djibouti, Haiti, and Mali ($n = 3$) were removed from the dataset on the basis that total immunization cost was more than two-times the standard deviation.

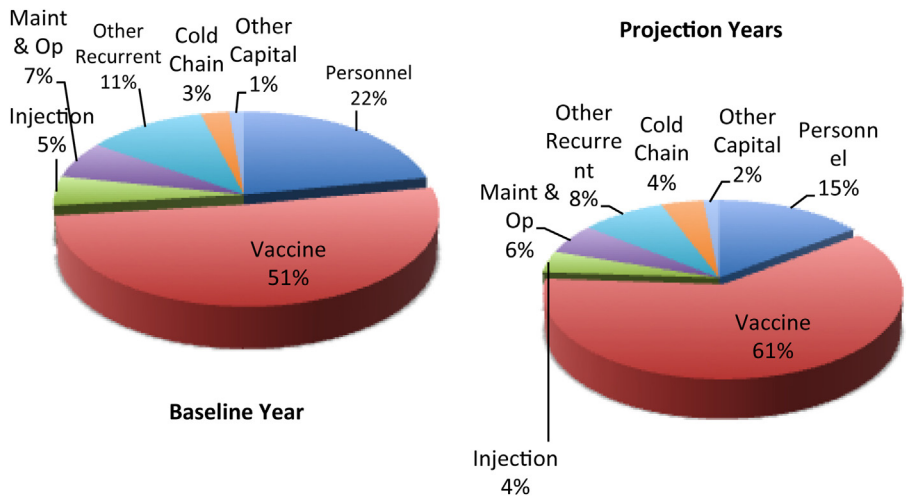

Fig. 1. Comparison of RI cost line items in sample cMYPs.

Source: author's calculations.

Table 2
RI total and delivery unit costs in sample CMYPs (baseline and projection years).

Region	Cost/capita	Cost/dose'	Cost/child	Cost/FIC
Baseline results				
AFRO (n = 27)	$0.92	$2.01	$23.60	$28.00
EMRO (n = 4)	$0.64	$1.29	$18.78	$24.83
EURO (n = 4)	$0.80	$3.00	$56.62	$65.43
SEARO/WPRO (n = 5)	$0.46	$0.68	$22.35	$23.72
Total baseline (n = 40)	$0.67	$1.34	$22.68	$26.72
Non-vaccine delivery costs (n = 40)	$0.31	$0.61	$10.36	$12.06
Projection years results				
Total (n = 203)	$1.30	$2.00	$41.80	$45.16

Source: author's calculations.

Table 3
Financing per infant by source and region in sample cMYPs.

Indicator/region	Total government financing per infant	Government vaccine financing per infant	Government non-vaccine financing per infant
Total baseline (n = 40)	$14	$6	$8
AFRO (n = 27)	$11	$4	$8
EMRO (n = 4)	$8	$3	$6
EURO (n = 4)	$47	$28	$19
SEARO/WPRO (n = 5)	$19	$10	$9
GAVI poorest (n = 22)	$12	$5	$7
GAVI intermediate (n = 9)	$10	$4	$6
GAVI graduating (n = 9)	$23	$12	$11
Total projection years (n = 203)	$18	$9	$10

Source: author's calculations. Results rounded.

3.3. Unit costs of RI

RI unit costs are higher, on average, than what has been previously reported in the literature [1,5–8,12]. Baseline year estimates reveal a cost per dose of $1.34; cost per infant of $23; a cost per fully immunized child (FIC) of $27. Unit costs for the projection period are double baseline values, with a cost per dose of $2, cost per child of $42, and cost per FIC at $45 (Table 2).

There is significant regional variation in these estimates, with unit costs greatest for EURO countries, and least for SEARO and WPRO countries. The analysis reveals a strong inverse relationship between population size and unit cost, but a weaker relationship between costs and country income. Countries classified as 'intermediate' under the GAVI co-financing classification (GNI per capita between $975 and $1500) have lower costs per child and per FIC than either poorer or graduating countries (Table 3).

3.4. Non-vaccine delivery costs

Non-vaccine delivery costs represent 44% of total RI costs in the baseline year, ranging from 37% in EURO countries to 46% for AFRO countries. The importance of delivery costs is also reflected in unit costs: delivery cost per dose of $0.60; delivery cost per child of $10; and, delivery cost per FIC of $12 (Table 2). Countries in the EURO region have the highest delivery costs per infant and per dose, probably related to higher wages of health workers. While vaccines are an important cost element, these results suggest that health systems delivery costs are an equally important factor for understanding cost requirements for immunization programs. Recent

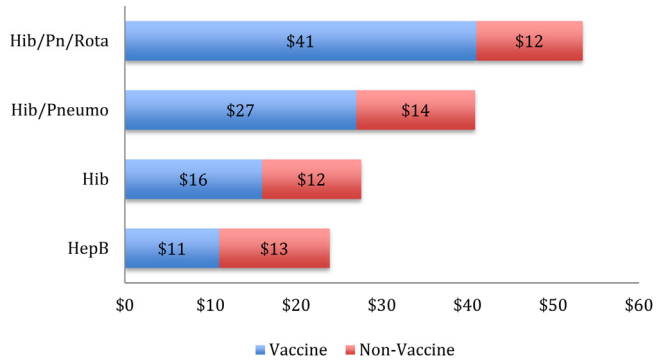

Fig. 2. Effect of new vaccines on cost per infant (baseline and projection year, $n = 243$).
Source: author's calculations.

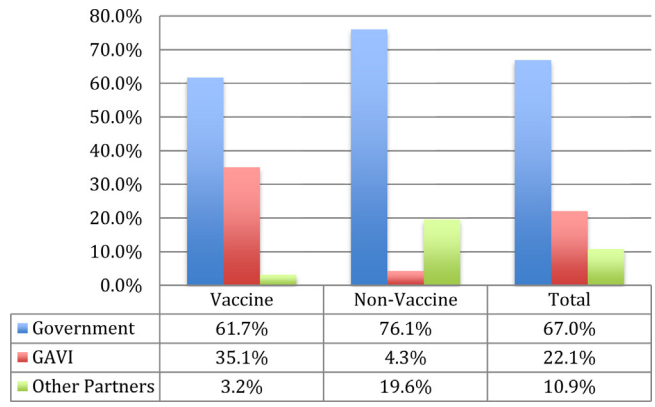

Fig. 3. Share of RI financing by source in 40 cMYPs (population-weighted).
Source: author's calculations.

studies confirm the growing importance of non-vaccine delivery costs and need for strong systems [18,19].

3.5. Unit costs and new vaccines

This study compares total and unit costs of different immunization schedules and finds increasing costs per dose with each new vaccine incorporated. For the baseline year, the average cost per dose in countries with Hepatitis B vaccine is $1. This figure rises to $1.40 for countries with Hib-containing vaccine and to $1.50 for countries with both Hib-containing and pneumococcal vaccines. Adding rotavirus vaccine increases the cost per dose further to $2.70.

Fig. 2 shows the effects of new vaccines on the cost per infant. Vaccine schedules with Hib-containing and pneumococcal vaccines cost $15 more per infant than those with Hib-containing vaccine. Rotavirus vaccine introduction appears to increase cost per child by an additional $12, and this schedule with three new vaccines is 141% higher than a program with HepB vaccine alone. Increases appear to be driven primarily by the cost of the vaccines, as the share of delivery costs to total unit costs steadily declines with each new vaccine in the schedule from 54% (HepB alone) to 22% (schedule with three new vaccines).

3.6. Affordability of the routine program

Total RI costs represent a fraction of gross domestic product (0.1%), but nearly 5% of government health expenditures (GHE) in the baseline year, rising to 8% in projection years. Vaccine costs account for 2.8% of GHE in the baseline year, which is more than double a previously reported benchmark of 1% [20]. The share of GHE appears to increase with the number of new vaccines, from 2% Hepatitis B for schedules, to 13% for schedules with Hib-containing and pneumococcal vaccines.

3.7. Financing of routine immunization

Sources of RI financing for the sample of cMYPs include the government and pooled funds, bilateral and multilateral assistance, the GAVI Alliance, non-governmental organizations (NGOs), private organizations and foundations, and other sources. Countries co-finance a portion of the cost of new vaccine costs supported by the GAVI Alliance, which also provides health systems support to countries.

The study found that government sources account for the largest share of total RI financing (67%) in the baseline year (Fig. 3). GAVI support represents 22% of total RI financing, and financing from multilateral organizations, such as WHO and UNICEF, account for 11% of the total. Higher income countries appear to finance a greater share of their RI program from government sources. The share of government and pooled financing of RI programs is largest for countries in the EURO Region (84%) and smallest for the AFRO Region (43%), for which GAVI support accounts for 38% of financing, and multilateral agencies account for 19% of financing. Governments also finance the lion's share (76%) of delivery costs. The GAVI Alliance finances a small proportion (4%) of delivery costs, most probably through Immunization Services Support (ISS) and Health Systems Strengthening (HSS) support. In projection years, government financing drops somewhat to 59% of total RI financing, and GAVI financing increases to 33%. Both appear related to growth in new vaccine introduction.

Government financing is $14 per infant for the baseline year, rising to $18 per infant in the projection years. Countries in the EURO region have the highest government financing of RI per infant ($47), and EMRO countries the lowest ($8). For AFRO and EMRO countries, government vaccine financing per infant is lower than that for non-vaccine financing. In SEARO/WPRO countries, governments finance roughly equal amounts of vaccine and non-vaccine costs; while, in EURO countries, government financing for vaccines per infant is higher than that of delivery costs.

4. Discussion

This analysis of cMYP data shows that total and unit costs of RI are higher than previously estimated for the baseline year, with projected increases to $45 per FIC related to new vaccine introduction and coverage increases [1,5,8,12]. The analysis also reveals regional variations. Unit costs are lower in countries with larger populations and higher immunization coverage, relating to scale effects. Unit and marginal costs may increase with higher coverage levels (as predicted by economic theory) because of additional efforts required to reach remaining pockets of low coverage. On the other hand, changes in technology or delivery strategy may reduce average costs as greater efficiencies are gained. Additional country-level studies on these relationships will be important.

Non-vaccine delivery costs were found to be an important component (44%) of total RI costs, at $10 per child and $12 per FIC, on average with some regional variation. While the share of delivery costs declined with addition of each new vaccine because of rising share of vaccine costs, the absolute amount increased slightly from $12 to $14 per child indicating that new vaccines have a positive effect on delivery costs. Delivery costs play an important role and should be fully considered during planning and budgeting and reflected in the cMYP [18,19].

In this study, RI and vaccine costs account for much higher shares of GHE than previously estimated, but these ratios also should be evaluated with in-country studies. EMRO countries in the sample have the highest shares and may have particular challenges with program affordability and sustainability. Fiscal space can be expanded through health sector allocation as well as more efficient service delivery.

Governments are committing more, both in absolute terms and as a percent of total financing (67%) to the routine program, up from estimates of 42–56% [8,12]. Government financing of RI has increased from $5.60 per infant to $14 per infant, representing a 150% increase within the past 10 years.

The cMYP provides a wealth of country-level information on immunization program costs and financing for both GAVI-eligible and other countries. The cMYP tool is designed to guide planners on future resource mobilization needs and not for reporting or cross-country evaluation. As such, application of the guidelines and drive for accuracy will vary by country. Conditions over the cMYP period may change and there is uncertainty in projecting costs and financing. Estimates are evaluated for internal consistency by WHO but are not routinely externally validated. For these reasons, the quality and reliability of cMYP data have been called into question. Baseline-year figures are thought to be a more reliable reflection of actual costs and financing [17]. Focus should be on baseline results, with those for the projection years viewed as indicative rather than conclusive.

In 2015, approximately 40 country cMYPs will need to be updated which represents an opportunity to strengthen the quality of cMYP estimates. Additional consistency and plausibility checks could be employed to ensure that all inputs required to support new vaccine introduction, particularly for delivery costs, are factored into the estimates. Distinguishing new vaccine introduction start-up costs with recurrent costs in the tool may be useful. Comparing cMYP cost estimates with GHE could provide useful benchmark for determining whether specific policy objectives are affordable and feasible. RI programs that account for more than 5% of GHE may have substantial challenges in mobilizing needed resources where there are competing priorities for scarce health resources.

Further, information from detailed costing and financing studies, such as the EPI Costing and Financing Studies of RI and New Vaccines (EPIC) studies could serve as benchmarks for cMYP calculations, including those related to labor time, maintenance and supply chain costs, and transport costs per dose of vaccine, among others. Finally, a database of immunization unit costs from published and unpublished literature may serve as a useful reference point for cMYP estimations.

5. Conclusion

This study employed statistical methods to evaluate cost and financing estimates from cMYPs covering a planning period of significant new vaccine introduction. The study found a cost per FIC of $27 and cost per child of $23 on average for the baseline year, with regional variation. Vaccines continue to be the main cost driver, but the role of delivery costs was found to be important. Unit costs are projected to double.

The study showed evidence that total and unit costs increase with additional new vaccines using a new approach that compares vaccine schedules. Country-level, retrospective studies are needed to measure the actual incremental cost (both start-up and ongoing) of new vaccines, and there is a growing literature in this area.

Planning and budgeting for national immunization programs cannot be made in isolation from the rest of the health system. This analysis highlighted potential issues related to affordability and sustainability [21]. Although total government financing levels are expected to increase, government contribution as a share will decline as new vaccines are introduced. There is need to maintain government commitment to financing the RI program as a whole, including traditional vaccines. Ensuring adequate financing for the poorest countries, not only in Africa, but also in the EMRO region should continue to be a priority. Further price reductions for new vaccines will help reduce costs and burden of financing, but focus on efficiency gains will be important [18,19].

Acknowledgements

The author would like to thank the members of the GAVI Alliance Immunization Financing & Sustainability Task Team who provided feedback and advice on earlier versions of the analysis. Special mention goes to Claudio Politi, WHO Immunization, Vaccines, and Biologicals Unit, who provided access to the initial cMYP database.

Conflict of interest: The author declares no conflict of interest. The views expressed in this paper represent those of the author only. Some financial support in preparation of this manuscript and conduct of the analysis was provided the Bill & Melinda Gates Foundation. However, the views expressed represent those of the author only.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.076.

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Vaccine 33S (2015) A99–A108

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Costs of vaccine programs across 94 low- and middle-income countries

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ARTICLE INFO

Keywords:
Costs
Vaccine
Routine immunization
Supplemental immunization activities
Supply chain

ABSTRACT

While new mechanisms such as advance market commitments and co-financing policies of the GAVI Alliance are allowing low- and middle-income countries to gain access to vaccines faster than ever, understanding the full scope of vaccine program costs is essential to ensure adequate resource mobilization. This costing analysis examines the vaccine costs, supply chain costs, and service delivery costs of immunization programs for routine immunization and for supplemental immunization activities (SIAs) for vaccines related to 18 antigens in 94 countries across the decade, 2011–2020. Vaccine costs were calculated using GAVI price forecasts for GAVI-eligible countries, and assumptions from the PAHO Revolving Fund and UNICEF for middle-income countries not supported by the GAVI Alliance. Vaccine introductions and coverage levels were projected primarily based on GAVI's Adjusted Demand Forecast. Supply chain costs including costs of transportation, storage, and labor were estimated by developing a mechanistic model using data generated by the HERMES discrete event simulation models. Service delivery costs were abstracted from comprehensive multi-year plans for the majority of GAVI-eligible countries and regression analysis was conducted to extrapolate costs to additional countries.

The analysis shows that the delivery of the full vaccination program across 94 countries would cost a total of $62 billion (95% uncertainty range: $43–$87 billion) over the decade, including $51 billion ($34–$73 billion) for routine immunization and $11 billion ($7–$17 billion) for SIAs. More than half of these costs stem from service delivery at $34 billion ($21–$51 billion)—with an additional $24 billion ($13–$41 billion) in vaccine costs and $4 billion ($3–$5 billion) in supply chain costs.

The findings present the global costs to attain the goals envisioned during the Decade of Vaccines to prevent millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities. By projecting the full costs of immunization programs, our findings may aid to garner greater country and donor commitments toward adequate resource mobilization and efficient allocation. As service delivery costs have increasingly become the main driver of vaccination program costs, it is essential to pay additional consideration to health systems strengthening.

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http://dx.doi.org/10.1016/j.vaccine.2014.12.037
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1. Introduction

This decade (2011–2020) has been labeled "the Decade of Vaccines" after various country governments and international donors committed to help discover, develop, and deliver vaccines to people in the world's poorest countries. Understanding the full scope of vaccination program costs is vital to ensuring adequate resource mobilization to attain the goals envisioned by the Decade of Vaccines Collaboration. This costing analysis responds to the requests of the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) as part of the Decade of Vaccines Economics (DOVE) project to strengthen methods for estimating and projecting immunization program resource requirements [1]. While the study builds on lessons learned from previous costing exercises, it extends beyond prior efforts by transparently modeling more detailed cost components (vaccine, supply chain, service delivery), exploring enhanced model methods, and providing sensitivity and scenario analyses. By taking a bottom-up approach to cost each component, this analysis identifies specific cost drivers of immunization programs. The aim of this paper is to detail the model structure, input sources, modeling methods, and baseline results of vaccination program costs.

2. Methodology

2.1. Analysis scope

The costing analysis focused on 94 low- and middle-income countries identified by the global vaccine action plan (GVAP) and country eligibility policy of the GAVI Alliance across the Decade of Vaccines, 2011–2020. The GVAP, endorsed by 194 Member States at the World Health Assembly in 2012, centered around low- and middle-income countries that currently or have previously received support from the GAVI Alliance [2]. Based on current GAVI classifications, the 94 countries include 36 low-income countries, 17 intermediate countries, 20 graduating countries, and 21 countries not eligible for GAVI support [3] [2]. A full list of countries is included in the online supplement.

The vaccines included in this analysis are relevant to 18 antigens and encompass immunizations delivered through routine immunization programs and supplemental immunization activities (SIAs). The complete list of vaccines is provided in Table 1.

Introduction years for routine vaccines, the timing of SIAs and the number of vaccine doses annually delivered to each country rely on GAVI's Adjusted Demand Forecast version 9.0 (ADF v9) [4]. The ADF also includes forecasts for introductions of future vaccines, both licensed and unlicensed, in countries' national immunization programs. For the frequency and timing of SIAs for measles, measles–rubella (MR), and measles–mumps–rubella (MMR) vaccinations, forecasts additionally used information from the World Health Organization (WHO) [5]. For SIAs for oral polio vaccine (OPV), forecasts relied on information from the Global Polio Eradication Initiative [6].

As for the model structure, separate methodologies were developed for vaccine, supply chain, and service delivery cost components associated with routine immunization and SIAs. The methodologies and assumptions relied on the most recent information and price data from the GAVI Alliance [3,4,7–11], the PAHO Revolving Fund [12–15], UNICEF Supplies and Logistics [16], as well as country-specific models developed by the HERMES (Highly Extensible Resource for Modeling Event-Driven Supply Chains) Logistics Modeling Team [17,18]. For additional data underlying the model such as population data, immunization coverage rates and economic growth, we relied on datasets validated by third-party multilateral agencies [19–22]. Service delivery cost projections relied primarily on data obtained from country-specific comprehensive multi-year plans (cMYPs) overseen by the World Health Organization [23].

2.2. Costing scope and components

This costing analysis assesses the vaccine costs, supply chain costs, and service delivery costs of immunization programs for routine immunization and for SIAs, consisting of the following components:

Routine immunization:

1. *Vaccine costs:* Costs to procure vaccines, related injection equipment and safety boxes.
2. *Supply chain costs:* Costs for transportation, both immunization-specific and shared[3], including amortization for vehicles, fuel costs, and per diems; costs for storage including amortization for equipment, maintenance, and energy cost; and costs of labor.
3. *Service delivery costs:* Costs of personnel, both immunization-specific and shared[4]; and non-personnel costs including program management, training, social mobilization, surveillance, and other recurrent costs related to vaccination.

Supplemental immunization activities:

1. *Vaccine costs:* Costs to procure vaccines, related injection equipment and safety boxes.
2. *Operational costs:* Cost to deliver vaccines and manage vaccination campaign efforts.

The categorization of costs reflects cMYP classifications and definitions utilized in previous vaccine program analyses [24–26]. All costs are presented in constant 2010 US dollars (US$2010).

2.3. Baseline cost estimations and projections

2.3.1. Routine and supplemental vaccine costs

The costs of vaccines for both routine and SIA delivery strategies encompass: (1) vaccine-specific price per dose (including freight); (2) vaccine-specific injection equipment and safety box price per dose; and (3) the number of required vaccine doses (including wastage and buffer doses), relying on data from the GAVI Secretariat for GAVI-supported vaccines[5] and GAVI Strategic Demand Forecast (SDF)-based demand forecasts for traditional vaccines[6] [4].

The analysis incorporates the prices of vaccines relevant to 18 individual antigens of three different types: (1) GAVI country prices; (2) PAHO country prices; (3) and non-GAVI, non-PAHO prices.

[2] The GAVI Alliance's co-financing support policy: low-income = GNI per capita <$1035. Intermediate = GNI per capita between $1035 and $1570. Graduating = GNI per capita >$1570.

[3] Shared transportation costs are defined as the costs of transportation when vehicles are utilized across multiple programs or activities in the health sector including immunization.

[4] Shared personnel costs are defined as the value of human resources providing immunization services as well as other curative and preventive services where a health workers' time may be shared across different programs or activities.

[5] GAVI-supported vaccines include pentavalent, rotavirus, pneumococcal, HPV, measles, measles–rubella, yellow fever, and meningococcal A, as well as vaccines that are under consideration to receive GAVI support within the decade—Japanese encephalitis, typhoid, IPV (inactivated polio vaccine), and cholera (stockpiles only).

[6] Traditional vaccines are defined as BCG, DTP, HepB birth dose, measles–mumps–rubella, and OPV (oral polio vaccine).

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Table 1
Vaccine prices by country groupings.

Vaccine *(n)*	Low-high vaccine price per dose (US$2010) between 2011 and 2020		
	GAVI eligible	Non-GAVI eligible	
	GAVI[a] [8] *(73 Countries)*	PAHO [12–15] *(4 Countries)*	Non-PAHO [16] *(17 Countries)*
Tuberculosis (BCG)	0.09–0.10	0.10–0.16	0.10–0.16
Diphtheria–tetanus–pertussis (DTP)	0.15–0.22	0.15–0.23	0.15–0.22
Pentavalent (DTP–HepB–Hib combination)	1.63–2.43	2.13–2.98	2.16–4.06
Hepatitis B birth dose (HepB birth)	0.21–0.27	0.27–0.36	0.27–0.36
Human papillomavirus (HPV)	3.50–4.41	11.64–13.57	11.64–13.57
Japanese encephalitis (JE)	0.34–0.39	0.44–0.50	0.45–0.51
Malaria	4.26–4.85	5.44–6.30	5.62–6.40
Measles	0.24–0.30	0.31–0.39	0.31–0.39
Measles–rubella (MR)	0.47–0.54	0.62–1.08	0.63–1.08
Measles–mumps–rubella (MMR)	1.29–1.75	1.56–2.36	1.56–2.36
Meningitis A conjugate (MenA)	0.41–0.52	0.53–0.67	0.54–0.69
Pneumococcal conjugate (PCV)	2.60–6.79	12.77–14.52	12.77–14.52
Inactivated polio vaccine (IPV)	0.85–0.97	2.58–5.68	2.58–5.68
Oral polio vaccine (OPV)	0.12–0.13	0.12–0.21	0.12–0.21
Rotavirus (2-dose)	1.92–2.25	2.49–7.27	2.53–7.27
Rotavirus (3-dose)	2.81–4.85	3.65–5.09	3.70–5.09
Typhoid	2.21–2.91	2.88–3.78	2.92–3.84
Yellow fever	0.65–0.80	0.85–1.04	0.86–1.06

[a] See the online supplement for a full list of countries and groupings.

Input prices for injection equipment and safety boxes including freight were obtained from GAVI price forecasts and consistently applied across countries. Prices of freight were not included for India and Indonesia, which locally produce vaccines for their national immunization programs [8,16].

For the 73 GAVI countries, we relied on ADF v9 2011–2020 vaccine price per dose projections provided by the GAVI Secretariat for GAVI-supported vaccines [8]. UNICEF price projections were utilized for traditional vaccines for GAVI countries and non-GAVI, non-PAHO countries [16]. For PAHO countries, we relied on price listings from the PAHO Revolving Fund for relevant PAHO-supported vaccines for available years [12–15]. For projections in additional years, we assumed that vaccine prices were 30% higher than GAVI prices based on the historical difference between PAHO and GAVI prices. For non-GAVI, non-PAHO countries, we relied on the higher price between the PAHO Revolving Fund price listings and 2011–2015 price projections from UNICEF Supplies and Logistics. Where prices were not available for non-GAVI, non-PAHO countries, vaccine prices were assumed to be 32% higher than GAVI prices based on the historical difference between UNICEF and GAVI prices [16].

While price inputs were available for the majority of the vaccines in the analysis, the one unlicensed vaccine–malaria–required separate price assumptions. The malaria vaccine price was assumed to be $5.00 based on expert discussions and review of the available literature [28–31]. Table 1 presents vaccine costs used in this analysis.

2.3.2. Routine supply chain costs

In order to address the complex interactions of transportation, storage, and labor costs in the vaccine supply chain, cost estimation for this component proceeded in three phases (see Fig. 1).

Phase 1: First, we relied on the HERMES simulation models of four reference countries [Benin, Niger, Mozambique (Gaza province), and India (Bihar state)] to estimate supply chain costs with current vaccine regimens and scenarios in which additional vaccines were introduced. HERMES is a decision-support software tool that can generate discrete event simulation models of supply chains, representing various components and processes of the supply chain and the movement of vaccines from the central store to vaccine administration locations. HERMES-generated simulation models include virtual representations of each vaccine vial (including the antigen type, presentation, and packaged volume) that enters the system, vaccine storage device (e.g., refrigerators and freezers), building, transport vehicle, and personnel. As a simulation run proceeds, millions of these virtual vaccine vials flow down through the system from the central storage location through a series of storage locations to where the vaccines are finally administered. At each location, the vaccines remain in storage devices until they are transported via vehicles to the next location in the supply chain, based on shipping frequencies and policies. Previous publications have described HERMES-generated models and data inputs in detail [17,18,32–40].

As a simulation run proceeds, three general categories of costs accrue: transport, storage and labor. Transportation costs accrue with each kilometer traveled by each transport vehicle. The cost per kilometer includes an amortization of the original purchase price of the vehicle over its anticipated lifetime mileage and the cost per kilometer of fuel and maintenance. A storage device's cost accrues by the day, which includes an amortization of the original purchase price of the device over its anticipated lifetime (10 years) and the daily cost of energy and maintenance. Daily labor costs are calculated by multiplying a person's salary by the percentage of time dedicated to the immunization program. By running the simulation models, Phase 1 estimated supply chain costs for current vaccine regimens for four reference countries and a limited number of new regimens including new vaccines.

Phase 2: Phase 2 examined how costs from Phase 1 would vary for a range of per capita vaccine regimen volumes. Phase 2 entailed developing a simplified spreadsheet version of each HERMES model in order to extrapolate the Phase 1 HERMES-generated costs to other countries that have different vaccine regimens, and thus volumes of vaccines, flowing through their systems. This spreadsheet model established a linear relationship (i.e., the slope and intercept) between per capita vaccine regimen volume and costs of transportation and storage. The resulting slopes and intercepts from this analysis are listed in Table 2.

Phase 3: The last phase extrapolated results from the four reference countries to the remaining 90 countries in the analysis. The analysis also projected costs from 2011 to the remaining years of the decade using specific anticipated per capita vaccine regimen volumes for each year according to the ADF [4]. Each target country

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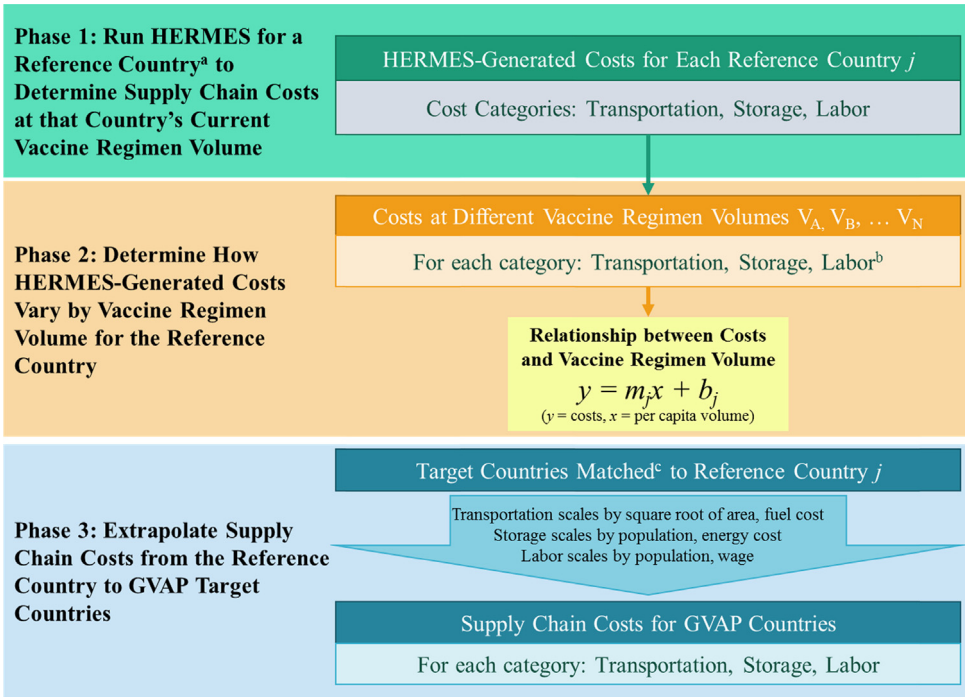

Fig. 1. *DOVE/HERMES supply chain cost estimation methods flowchart.*[a] Reference countries include Benin, Niger, Mozambique (Gaza province), and India (Bihar state). [b] Because labor costs do not scale according to vaccine regimen volume, no linear equation was developed; instead, base labor costs are scaled directly by population and wage. Vaccine regimen volume is the volume of doses required to fully vaccinate a person (for vaccines in our study scope) according to national immunization schedules. [c] Each target country was matched with one of the four reference countries with the most similar supply chain structure, based on the number of tiers in the supply chain (3, 4, or 5) and by the relative distribution of storage locations (top heavy, middle heavy, or bottom heavy clusters, among countries with 4-tier supply chains), as detailed in the online supplement.

was matched with one of the four reference countries with the most similar supply chain structure, based on the number of tiers in the supply chain (3, 4, or 5) and by the relative distribution of storage locations (top heavy, middle heavy, or bottom heavy clusters, among countries with 4-tier supply chains), as detailed in the online supplement. Our team separated the 4-level supply chains into three clusters based on the morphology of the supply chain and the average "branching ratios" for each level. Branching ratio for any level (e.g. district) is defined as the number of locations in the next lower level (e.g. sub-district), divided by the number of locations at the initial level (e.g. district). "Top-heavy" supply chains tend to have higher branching ratios for the upper levels compared to "middle heavy" and "bottom-heavy" ones. "Middle-heavy" supply chains tend to have higher branching ratios for the middle levels compared to top heavy and bottom heavy ones. Next, we extrapolated the costs for the assigned reference country to each target country separately for transportation, storage, and labor:

1. *Transportation costs:* Estimated using the ratio of the square root of the target country's geographic area over the square root of the reference country's area (since transportation costs increase with increasing distance traveled), which were adjusted by the ratio of the target country's fuel costs over the reference country's fuel costs;
2. *Storage costs:* Estimated using the ratio of the population of the target country over the population of the reference country (because population is proportional to the number of vaccines delivered, which in turn is proportional to the number of storage devices required), which were adjusted by the ratio of the target country's energy costs over the reference country's energy costs (because storage facility expenses depend on energy costs—in this case electricity prices served as a proxy scalar); and
3. *Labor costs:* Estimated using the ratio of the target country's population to the reference country's population (because total personnel required varies with population served) and the ratio of wages (because personnel costs vary based on per capita wages)—see the online supplement for country-specific scalar values.

The estimated supply chain costs for transportation, storage, and labor were subsequently disaggregated by vaccine, relying on the proportion of the volume contributed by each vaccine as a function of the packed volume per dose and the number of doses delivered relative to the total volume of vaccines delivered.

2.3.3. Routine service delivery costs

Service delivery costs consist of the following components and respective data sources:

1. *Immunization-specific personnel costs:* cMYP-specified line item for routine recurrent personnel costs, minus supply chain relevant personnel costs.
2. *Shared personnel costs:* cMYP-specified line item for costs of personnel who provide immunization services as well as other curative and preventive services.
3. *Non-personnel costs:* aggregate of cMYP-specified line items for training, social mobilization, disease surveillance, program management, and other recurrent costs.

All component costs associated with service delivery were obtained directly from respective line items from baseline years of country cMYPs. It was assumed that cMYP line-item costs are mutually exclusive and therefore no overlap exists between costing categories. This analysis abstracted country-specific service

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Table 2
Supply chain cost estimation process by component: mechanistic model equations and inputs.

Equation used to extrapolate costs from reference country to target country											
Transportation	$(((m_t \times \text{Vaccine regimen volume}) + b_t) \times \text{SQRT}(\text{target country area/reference country } j \text{ area}) \times (\text{target country gas price/reference country } j \text{ gas price}))$										
Storage	$(((m_s \times \text{Vaccine regimen volume}) + b_s) \times (\text{target country population/reference country } j \text{ population}) \times (\text{target country electricity price/reference country } j \text{ electricity price}))$										
Labor	$(\text{Reference country } j \text{ labor costs} \times (\text{target country population/reference country } j \text{ population}) \times (\text{target country hourly wage/reference country } j \text{ hourly wage}))$										
No. of tiers in supply chain	Morphology of supply chain	Reference country *j* match for supply chain category	m_t*	b_t	m_s*	b_s	HERMES 2011 labor cost	2011 Population	Area (sq km)	2011 Gas price (per liter)	2011 Electricity price (per kWh)	2011 Hourly wage rate
3 Levels	N/A	Benin	692	56,633	737	732,867	156,479	9,779,795	110,622	$1.14	$15.10	$0.40
4 Levels	Bottom heavy	Niger	7426	129,243	3851	416,363	374,116	16,511,462	1,266,700	$1.10	$13.20	$0.40
4 Levels	Middle heavy	*Average of bottom heavy & top heavy*	5638	184,941	2076	237,156	225,311	8,916,400	671,017	$1.22	$10.60	$0.40
4 Levels	Top heavy	Mozambique (Gaza only)	3849	240,639	300	57,949	76,505	1,321,338	75,334	$1.35	$8.00	$0.40
5 Levels	N/A	India (Bihar only)	3783	836,794	2131	53,495	131,128	103,804,639	94,163	$1.20	$16.60	$0.47

* The slope is the increase in cost for a one unit increase in the volume of the vaccine regimen per child that is handled by the supply chain, measured in cubic centimeters (cm^3).

delivery cost data from 63 cMYP costing tools, with baseline years ranging from 2004 to 2011. The majority (80%) of cMYP data was extracted from baseline years 2009 and later.

For the remaining 31 countries, service delivery cost data was modeled based on a regression analysis of the cMYP data. Since the cMYP-derived cost data were not normally distributed, a natural log transformation was performed. The three service delivery cost components were examined against variables that were considered potential drivers of routine immunization program costs. Analyzed variables included economic indicators, demographic/population data, child health indictors, health financing data, health systems capacity indicators, healthcare seeking variables, geography, and routine immunization schedule/coverage. The initial list of 42 variables was narrowed down based on the number of observations available across countries, correlations among variables, principle of parsimony and statistical significance in univariate and multivariate regression analyses. Accounting for collinearity, significance of variable effect size, and overall model fit, the following variables were selected to estimate total baseline costs for countries without cMYP data (see online supplement for details):

- Immunization-specific personnel costs were scaled by birth cohort size and land area.
- Shared personnel costs were related to birth cohort and DTP3 coverage.
- Non-personnel costs were modeled based on birth cohort, land area and the proportion of the population living in rural areas.

For validation, predicted costs were estimated from the regressions noted above for the 63 countries with cMYP data. Compared to actual service delivery costs for these countries, model-predicted values differed only by 2.45%.

For the baseline year, the average service delivery costs per dose were multiplied by GAVI's ADF v9 total doses to obtain baseline service delivery costs for each country. Beyond the baseline year, additional service delivery costs were modeled by applying a marginal cost per dose value for all additional doses. Marginal service delivery costs were obtained from a regression of cMYP-extracted service delivery cost components against total routine vaccine doses from respective baseline cMYP years. Thus, marginal costs in the model reflect the service delivery requirements necessary to deliver one additional dose beyond baseline year levels. Marginal cost per dose was considered to be modified by the national immunization schedule, represented by coverage of three doses of DTP. Separate marginal costs were obtained for two levels of DTP3 coverage under or above 80%, which was the median coverage level among countries in the analysis. The average and marginal service delivery costs per dose estimated across 94 countries are provided in Table 3.

2.3.4. Supplemental operational costs

Operational costs of supplemental immunization activities (SIAs) consist of non-vaccine costs necessary to deliver vaccines and manage campaign efforts. All costs associated with SIA operational costs were obtained directly from vaccine-specific line items from the baseline year of cMYPs. SIA operational costs per dose were calculated separately for small and large countries (population less than or greater than 10 million).

For the 63 countries with cMYP data, a population-weighted average operational cost per dose was calculated specific to measles ($0.65–$0.87), OPV ($0.65), and yellow fever vaccines ($0.71–$1.10). For other SIA vaccines, average operational cost per dose ($0.65–$0.68) was estimated across all injectable vaccines (measles, yellow fever, and tetanus). Higher costs per dose were estimated for larger countries, likely signaling the relatively greater operational support to reach target populations in these

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Table 3
Summary measures of estimated routine baseline service delivery costs per dose for 94 countries (US$2010).

	Immunization-specific personnel costs per dose	Shared personnel costs per dose	Non-personnel costs per dose	Total routine service delivery costs per dose
Average (non-weighted)[a]	0.69	1.75	0.53	2.97
Average (population weighted)[b]	0.32	0.74	0.21	1.27
Median	0.31	0.71	0.23	1.28
Minimum	0.05	0.16	0.05	0.28
Maximum	2.03	8.24	2.33	9.73
Marginal (all coverage levels)[c]	0.43	0.64	0.13	1.20
<80% DTP3 coverage	0.44	0.56	0.13	1.13
> = 80% DTP3 coverage	0.46	1.52	0.15	2.13

[a] Analysis based on 63 cMYPs with baseline years ranging from 2004 to 2011.
[b] Population weighted average costs are lower than non-weighted average costs due to countries with large populations having lower costs.
[c] Analysis based on 49 cMYPs with baseline years 2009 or later.

countries. Variations in vaccine-specific operational costs reflect: (1) the relatively larger investment in eradication and elimination campaigns (e.g., measles); and (2) lower costs of delivering oral vaccines (e.g., OPV).

2.4. Sensitivity and scenario analysis

Sensitivity analysis was carried out by varying seven key inputs in model simulations to construct the 95% uncertainty ranges around baseline estimates. Specifically, we performed a probabilistic sensitivity analysis using the Monte Carlo method, building distributions around key model parameters including total doses, vaccine prices, slopes and extrapolations of supply chain costs from reference countries, average and marginal cost per dose for service delivery, and operational cost per dose for SIA. For each parameter, random draws were taken from specified distributions 10,000 times. Non-cost values were given a beta distribution, while cost values used gamma distributions in order to represent the skew of observed costing data. Values were ranged between half and double the base estimate to examine the effect of each variable. This analysis was implemented using the latest version of the @RISK software.

In addition to the baseline scenario for costing immunization programs, we also estimated the costs of two different scenarios: (1) a scenario in which all 94 countries reach 90% routine vaccine coverage by 2020; and (2) a scenario in which the GAVI vaccine prices were applied to non-GAVI countries. The first scenario examines the costs to reach the GVAP goal of 90% routine vaccine coverage, where a linear scale-up was assumed from current coverage to 90% for vaccines introduced prior to 2017. The second scenario projects costs if 21 non-GAVI countries in our analysis were to access GAVI vaccine prices.

3. Results

The total cost of the full vaccination program across 94 low- and middle-income countries is projected to be US$61.9 billion (95% uncertainty range: $42.7–$87.4 billion) from 2011 to 2020. More than half (55%) of this expected cost is for service delivery, including costs for program management, training, social mobilization, and surveillance. An additional 38% relates to vaccine and injection supplies and the remainder (7%) represents supply chain costs. Fig. 2 presents the routine and supplemental immunization costs by component across the years. Examining the program costs per dose and per surviving infant, service delivery costs remain the greatest component of costs across all country income groupings (Table 4).

Thirty-two percent of the estimated total cost, equivalent to US$19.8 billion, supports the full immunization programs for Ethiopia, India, Nigeria, and Pakistan alone—four countries with large immunization target populations and substantial vaccine-preventable disease burden, including polio, measles, and rubella.

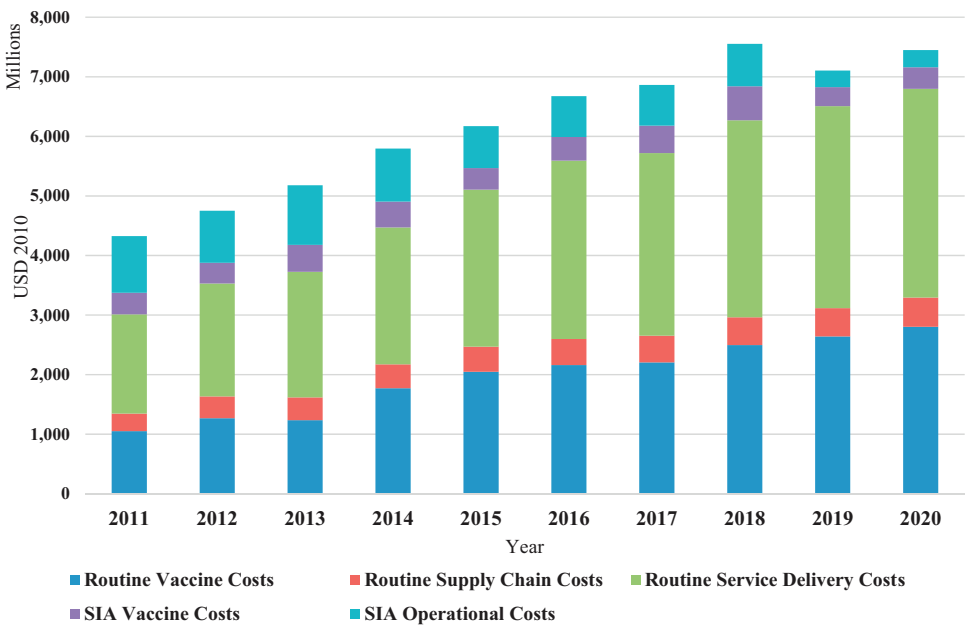

Fig. 2. Total immunization program costs by component and by routine vs. SIA, 2011–2020.

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Table 4
Costs per program dose and costs per surviving infant[a] by income level[b] across 2011–2020.

	Low-income (LIC)	Lower middle-income (LMIC)	Upper middle-income (UMIC)
Costs per program dose[c]			
Vaccine	$0.99	$0.78	$1.61
Supply chain	$0.32	$0.23	$0.52
Service delivery	$1.43	$1.26	$1.51
Total	$2.63	$2.18	$3.53
Costs per surviving infant			
Vaccine	$30.20	$22.94	$46.00
Supply chain	$6.30	$3.96	$11.70
Service delivery	$43.74	$37.13	$43.11
Total	$80.23	$64.03	$100.82

[a] Costs per program dose and costs per surviving infant are population-weighted by income level.
[b] LIC = GNI per capita <$1045. LMIC = GNI per capita between $1045 and $4125. UMIC = GNI per capita >$4125.
[c] Program doses include administered doses, wastage doses, and buffer stock doses.

3.1. Cost estimates for routine immunization

Routine immunization programs for the decade are estimated to amount to 82% of the total costs of immunization—approximately $50.7 billion ($34.2–$73.2 billion). The majority of routine immunization costs is due to service delivery at $26.9 billion ($15.8–$43.2 billion; 53% of routine immunization), with $10.6 billion ($6.2–$16.8 billion) for immunization-specific personnel costs and $16.2 billion ($9.6–$26.5 billion) for shared personnel costs. Vaccine and injection supplies amount to 39% of routine immunization costs at $19.7 billion ($10.6–$34.1 billion), whereas supply chain costs amount to $4.2 billion ($3.3–$5.2 billion), including $0.5 billion ($0.3–$0.6 billion) for shared transport. The total routine vaccine costs by vaccine and by GAVI eligibility status across the decade are shown in Fig. 3.

The 73 GAVI countries make up a majority of the total routine immunization costs at $43.2 billion ($29.2–$62.1 billion; 85% of routine immunization costs for 94 GVAP countries). Routine immunization costs are estimated to increase by more than half (56%) from $16.9 billion during the period 2011–2015 to $26.3 billion during 2016–2020 for GAVI countries. Similarly, the 21 non-GAVI countries may face a 55% increase in costs between the same time periods. Among GAVI countries, routine vaccine costs present the greatest increase of 66% – from $5.9 billion to $9.9 billion – comparing the first half of the decade to the second half. Among the non-GAVI countries, routine vaccine costs are projected to grow at 69%, from $1.4 billion to $2.4 billion.

Routine immunization costs are driven in large part due to seven vaccines—pentavalent, measles-containing (measles, MR, and MMR), pneumococcal conjugate (PCV), oral polio (OPV), and rotavirus vaccines—totaling $41.6 billion (82% of routine costs). Large program costs associated with these vaccines resulted from a combination of vaccine unit prices, service delivery costs and, in particular, increasing coverage levels across the decade. Increasing costs across the decade are partly due to an expanding number of vaccine introductions particularly of new and more expensive vaccines such as human papillomavirus (HPV) vaccine and inactivated polio vaccine (IPV). The greatest numbers of these vaccine introductions are currently planned for the year 2015, where 26% of vaccine introductions for GAVI 73 countries and 34% of vaccine introductions for 21 non-GAVI countries are projected to occur in 2015. The largest vaccine roll-out is for IPV, as all 94 countries in this analysis

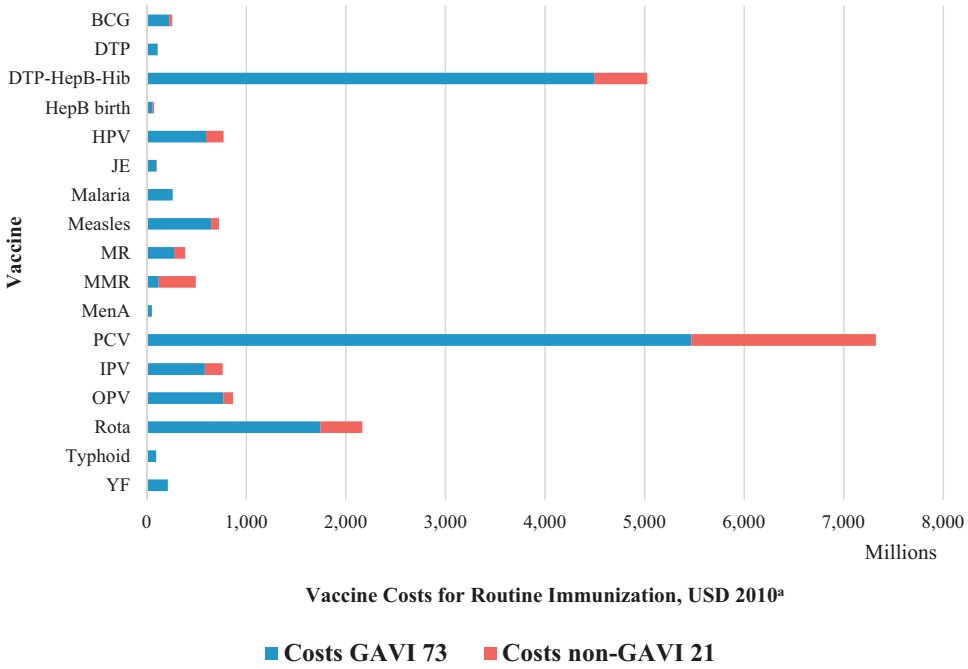

Fig. 3. *Routine vaccine costs by vaccine type and by GAVI eligibility status, total over 2011–2020.* [a] These represent full vaccine costs, not the incremental costs of introducing new vaccines.

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Table 5
Costing scenario analyses comparison by full results, difference, and percentage change.

Category[a]	Total costs, routine + SIA (US$2010 billions)			Difference from baseline (US$2010 billions)		Percentage change from baseline (%)	
	Base	90% Coverage	Price reduction	90% Coverage	Price reduction	90% Coverage (%)	Price reduction (%)
LIC	21.13	21.28	21.13	0.16	0.00	0.73	0.00
LMIC	36.44	37.10	34.62	0.66	−1.82	1.80	−5.00
UMIC	2.38	2.39	2.03	0.02	−0.34	0.68	−14.48
GAVI	53.98	54.72	53.98	0.74	0.00	1.38	0.00
Non-GAVI	7.89	7.97	5.72	0.08	−2.17	1.05	−27.47
Total	61.87	62.69	59.70	0.83	−2.17	1.34	−3.50

[a] Low-income country (LIC); lower middle-income country (LMIC); upper middle-income country (UMIC).

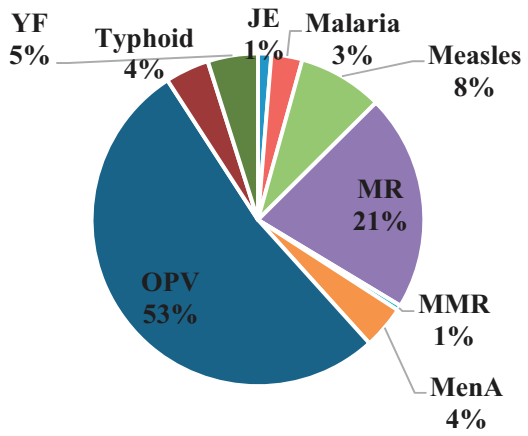

Fig. 4. Percentage of total SIA costs by vaccine for 94 GVAP countries, 2011–2020.

are projected to add a dose of IPV to their polio vaccine schedule between 2014 and 2016 in preparation for the eradication of polio, planned for 2018 [6,41].

3.2. Cost estimates for supplemental immunization activities

The total costs of SIAs against vaccine-preventable diseases including Japanese encephalitis (JE), malaria, measles-containing vaccines, meningococcal conjugate A (MenA), OPV, typhoid, and yellow fever, are estimated at $11.1 billion ($6.6–$17.2 billion; 18% of total immunization costs) across 2011 to 2020. Of this total, 79% of the costs are for campaigns against polio and measles (including vaccines for MR and MMR). In addition, 97% of the total SIA costs ($10.8 billion; $6.4–$16.7 billion) are projected for the 73 GAVI countries, while the remaining $0.3 billion ($0.2–$0.5 billion) in campaigns are projected to occur in 21 non-GAVI countries. The breakdown of total SIA costs by vaccine across the decade is shown in Fig. 4. The majority (64%) of total SIA costs are projected to be for operational costs ($7.0 billion; $3.7–$12.5 billion), with the remainder for costs of vaccines and injection supplies ($4.1 billion; $2.2–$7.1 billion).

3.3. Sensitivity and scenario analyses results

Sensitivity analysis revealed that vaccine prices are the biggest driver of baseline estimates (total costs may be 15% lower to 28% higher), followed by total doses (18% lower to 22% higher), service delivery marginal cost per dose (11% lower to 24% higher), service delivery average cost per dose (6% lower to 16% higher), and SIA operational cost per dose (4% lower to 10% higher). Assumptions around supply chain cost extrapolations were less influential on the total costs (see online supplement for a tornado diagram).

Based on a scenario analysis, if all countries were to reach the GVAP goal of 90% routine immunization coverage, the baseline costs of $61.9 billion is expected to increase to $62.7 billion (see Table 5). While we might have anticipated a larger increase in costs for the 90% coverage scenario, the relatively small (1.3%) increase is due to the large number of countries that are already projected to reach at least 90% coverage by 2020 in GAVI's ADF v9 [4]. In the second scenario, if non-GAVI countries are to obtain GAVI vaccine prices, total costs are projected to decrease to $59.7 billion. As the price reduction scenario only applies to 21 countries in the analysis, a $2.2 billion difference in projected costs is within expectations.

4. Discussion

This costing analysis adds to the international knowledge base by estimating the global costs to reach the GVAP goals across the Decade of Vaccines. By projecting the full costs of immunization programs, our findings may aid to garner greater country and donor commitments toward preventing millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities. Beyond the aggregate cost estimates, costs associated with vaccines, supply chain, and service delivery for both routine immunization and SIAs lend an additional level of insight necessary for mobilizing and effectively allocating resources for vaccine programs.

One of the key findings is that that more than half (53%) of total routine immunization costs are incurred for service delivery. As service delivery costs have increasingly become the main driver of costs of vaccine programs, additional consideration must be paid to financing operations and health systems beyond the costs of vaccines. This shift can be explained by decreasing vaccine prices of newer vaccines achieved through the collaboration of global partners such as the GAVI Alliance, combined with an increasing need for health systems investment to reach higher coverage of vaccine programs [4, 8].

Compared to the previous costing analysis conducted by Gandhi et al. projected routine immunization costs have increased marginally by $4.4 billion based on a combination of greater immunization coverage scale-up and decreasing vaccine price assumptions [24]. While the current analysis relied on the latest GAVI demand forecast [4], the previous work relied on an earlier version with different years in which countries are projected to introduce new vaccines and varying coverage levels countries are estimated to reach [42]. A comparison to the previous costing analysis by Gandhi et al. [24] can be found in Table 6. Our analysis overcomes key limitations of the previous work by providing a more detailed landscape of vaccination program cost drivers and additional sensitivity and scenario analyses.

Our findings suggest that costs per program dose and costs per surviving infant are lowest for lower middle-income countries (LMICs) rather than low-income countries (LICs). This can be explained by the larger disease burden in LICs resulting in these countries introducing relatively more vaccines during the decade compared to LMICs. In addition, LMICs may start to experience economies of scale with increasing coverage, resulting in lower cost per program dose for supply chain and service delivery. Costs are

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Table 6
Comparison to Gandhi et al. [24] findings (US$2010 billions).

	Gandhi et al.[a]	Our analysis
Total costs	57.5	61.9
Routine	49.4	50.7
Vaccine	24.0	19.7
Delivery[b]	25.4	31.0
SIA	8.1	11.1
Vaccine	2.5	4.1
Operational	5.6	7.0

[a] Key methodological differences with the Gandhi et al. analysis include the following. Gandhi et al. uses: (1) the GAVI Adjusted Demand Forecast version 4 (2011) for dose projections rather than the ADF v9 (2014); (2) constant prices across the decades rather than prices that are projected to decrease; (3) a global deflator for conversion to US$2010 rather than local inflation based on consumer price indices (CPI); (4) cMYPs for supply chain costs compared to HERMES-based analysis; and (5) different cMYP data and methods used to derive service delivery costs per dose.
[b] Routine delivery costs include both supply chain and service delivery.

expected to be highest for UMICs with greater GNI per capita and high levels of vaccination coverage. Moreover, we found cost per surviving infant to be relatively high for LICs due to higher infant mortality, large number of SIAs, and high marginal costs for service delivery to reach DTP3 coverage levels above 80%, which half of the LICs reach.

Our estimates can be validated against cost per dose benchmarks from the literature. The supply chain cost per dose was compared against a benchmark of $0.40 per dose according to region, tier, and percentage of urban population, where our results were reasonably aligned [43,44]. Service delivery cost per dose was examined against the previous analysis, which used an incremental cost per dose of $0.23 for childhood vaccines and $1.30 for HPV vaccine. Our marginal costs per dose used in the current analysis range from $1.13 to $2.13 according to DTP3 coverage level, where we observe greater costs to reach higher coverage levels. The previous analysis also relied on an operational cost per dose of $0.86 for SIAs, which are comparable to the SIA costs per dose in this analysis.

The greatest limitation of this analysis is the availability and quality of existing data. Since vaccine prices for middle-income countries are not available outside of the GAVI price forecasts and PAHO Revolving Fund price lists, our vaccine price projections for the 17 non-GAVI, non-PAHO countries are a conservative estimate. Complete cMYP data were only available from 63 countries receiving support for immunization from the GAVI Alliance. Country-level inconsistencies in cost definitions, calculations, and validation methods in cMYPs may yield data quality constraints. In particular, the estimate of marginal service delivery costs from cMYPs for countries above 80% DTP3 coverage may still not fully encompass consideration for increasing costs of covering the hardest to reach children. However, existing evidence supports the use of constant returns to scale when estimating marginal service delivery costs for public health interventions [45,46]. In addition, utilizing cMYP data to estimate costs for 21 higher-income countries has potentially underestimated service delivery costs in those countries, producing a conservative estimate.

Despite these limitations, the results inform the costs necessary to support the Decade of Vaccines across 94 countries to meet GVAP goals. This model was built to be updatable, where improved data quality can only help to further inform resource mobilization efforts for vaccination programs. As the model platform is built to also include financing projections, the analysis can further contribute to estimations of the funding gap for vaccines to be used by global decision-makers.

Authorship

AP, SO, and SG designed the study, developed the methodology, collected the data, performed the analysis, and wrote the manuscript. For the supply chain component, BAN, JR, KMG, LAH, STB, and BYL developed the methodology, collected the data, and performed the analysis. All authors contributed to critical revision of the manuscript and have approved the final article.

Sources of support

This study was performed with financial support from the Bill & Melinda Gates Foundation (Contract # 23120). The views expressed herein are those of the authors and do not necessarily reflect the official policy or position of the Bill & Melinda Gates Foundation.

Conflicts of interest

None.

Acknowledgements

We thank the GVAP Costing and Financing Steering Committee (Logan Brenzel, Thomas Cherian, Santiago Cornejo, Gian Gandhi, Hope Johnson, Thomas O'Connell, Claudio Politi, and Damian Walker) for guidance of this research. We also thank Jason Roffenbender for support in service delivery cost analysis and Anushua Sinha, Meghan Stack, and Richard Arilotta for their valuable comments.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.037.

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Vaccine 33S (2015) A109–A118

Contents lists available at ScienceDirect

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Cost-effectiveness of rotavirus vaccination in Kenya and Uganda

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ARTICLE INFO

Keywords:
Cost-effectiveness analysis
Rotavirus
Vaccination
DALYs
TRIVAC
Kenya
Uganda

ABSTRACT

Introduction: Rotavirus vaccines have the potential to prevent a substantial amount of life-threatening gastroenteritis in young African children. This paper presents the results of prospective cost-effectiveness analyses for rotavirus vaccine introduction for Kenya and Uganda.

Methodology: In each country, a national consultant worked with a national technical working group to identify appropriate data and validate study results. Secondary data on demographics, disease burden, health utilization, and costs were used to populate the TRIVAC cost-effectiveness model. The baseline analysis assumed an initial vaccine price of $0.20 per dose, corresponding to Gavi, the Vaccine Alliance stipulated copay for low-income countries. The incremental cost-effectiveness of a 2-dose rotavirus vaccination schedule was evaluated for 20 successive birth cohorts from the government perspective in both countries, and from the societal perspective in Uganda.

Results: Between 2014 and 2033, rotavirus vaccination can avert approximately 60,935 and 216,454 undiscounted deaths and hospital admissions respectively in children under 5 years in Kenya. In Uganda, the respective number of undiscounted deaths and hospital admission averted is 70,236 and 329,779 between 2016 and 2035. Over the 20-year period, the discounted vaccine program costs are around US$ 80 million in Kenya and US$ 60 million in Uganda. Discounted government health service costs avoided are US$ 30 million in Kenya and US$ 10 million in Uganda (or US$ 18 million including household costs). The cost per disability-adjusted life-year (DALY) averted from a government perspective is US$ 38 in Kenya and US$ 34 in Uganda (US$ 29 from a societal perspective).

Conclusions: Rotavirus vaccine introduction is highly cost-effective in both countries in a range of plausible 'what-if' scenarios. The involvement of national experts improves the quality of data used, is likely to increase acceptability of the results in decision-making, and can contribute to strengthened national capacity to undertake economic evaluations.

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http://dx.doi.org/10.1016/j.vaccine.2014.12.079
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1. Background

Diarrhea is the second leading cause of death worldwide among children aged 1–59 months [1]. Rotavirus is the main cause of severe childhood diarrhea [2,3] accounting for about 192,700 deaths each year (range 133,100–284,400), with about 50% of the deaths occurring in the World Health Organization (WHO) Africa Region [4]. WHO also estimates that 7.3% of deaths among children under 5 in Uganda and 6.4% in Kenya are attributable to rotavirus [5].

Rotavirus vaccines offer an opportunity to avert a substantial amount of childhood morbidity and mortality [6,7]. Currently, there are two rotavirus vaccines that are prequalified by WHO and supported by Gavi, the Vaccine Alliance (Gavi): the pentavalent Merck RotaTeq® (RV5), and GlaxoSmithKline Biologicals' monovalent Rotarix® (RV1). Both are orally administered vaccines given to young infants via a 2-dose (Rotarix®) or 3-dose (RotaTeq®) schedule. Post-introduction studies in the USA and elsewhere have shown that vaccine introduction has led to a reduction in the disease burden, and especially a reduction in the number of hospitalizations due to rotavirus [8].

Several African countries have introduced rotavirus vaccines into their national immunization programs. The vaccine was introduced in July 2014 in Kenya, while introduction in Uganda is planned for 2016. Both countries have shown a preference for the monovalent (RV1) vaccine which has fewer recommended doses than the pentavalent vaccine (RV5). In Kenya, another important practical consideration was the vaccine vial monitor which comes with RV1 but not RV5.

The cost-effectiveness of a new health intervention is one of the several important factors considered by decision-makers before an intervention is introduced. Therefore, a key objective of this analysis was to evaluate the cost-effectiveness of introducing RV1 into the routine immunization programs of Kenya and Uganda. The study used a decision support model and country-led process first developed under the ProVac Initiative of the Pan American Health Organization (PAHO) [9]. This study also aimed to strengthen national capacity to collect, use, and interpret epidemiological and economic evidence.

2. Methods

2.1. The process of conducting the country studies

In both countries, a national consultant was hired who then convened a national team of experts (the technical working group [TWG]), which had expertise in rotavirus, surveillance, immunization, and health system costs. Each team worked together to identify possible data sources for the model inputs and to determine the best choice of data to be used in the model. A comprehensive review of all published literature with special focus on local studies was supplemented by other local unpublished data, where relevant. The consultants also worked with the TWG to identify appropriate national sources of evidence, including government reports and national epidemiological studies. The TWG also reviewed the model results and helped develop a set of plausible 'what-if' scenarios. The study results were presented to national stakeholders by the national consultant on behalf of the national team.

2.2. TRIVAC model overview

The TRIVAC cost-effectiveness model (version 2.0) was used. This model was developed by PAHO's ProVac Initiative in collaboration with researchers from the London School of Hygiene and Tropical Medicine. The TRIVAC model is an Excel-based model (Microsoft Corporation, Redmond, Washington, US) used to evaluate the cost-effectiveness of three childhood vaccines (*Haemophilus influenzae* type b, pneumococcal conjugate vaccine, and rotavirus vaccine) [10]. The model has been designed for use at country level, and it has been used to train national teams and carry out cost-effectiveness evaluations in over 20 countries around the world.

The model input parameters are demographics, burden of disease, vaccine schedule, vaccine efficacy, vaccine coverage, vaccine costs, health service utilization, and health service costs. Mid estimates are entered for all parameters and used in the base-case scenario. Low and high values are entered for the most uncertain parameters and used in 'what-if' scenario analysis.

2.3. Comparator and key outcomes

In this study, a *status quo* of no vaccine introduction was compared to RV1 introduction in the routine immunization program. The model estimates the number of deaths, hospital admissions, and outpatient visits, as well as disability-adjusted life-years (DALYs) that can be averted by vaccine introduction. It also estimates vaccination program costs and healthcare costs that could be averted. Cost-effectiveness was estimated in terms of the cost per DALY averted. Based on WHO CHOICE guidelines, our criteria for cost-effectiveness was: if the incremental cost per DALY averted is less the gross domestic product (GDP) per capita then the vaccine was considered to be very cost-effective, if between one and three times the GDP per capita it was cost-effective, and if greater than three times the GDP per capita, then it was not cost-effective [11].

2.4. Conceptual framework for the analyses

In both Kenya and Uganda we evaluated the impact of RV1 introduction on rotavirus gastroenteritis (RVGE) outpatient visits, inpatient admissions, and deaths. In addition, the TRIVAC model allows the user to select whether or not they wish to consider the morbidity associated with RVGE cases, irrespective of whether or not they use health care services. RVGE cases were not included in the Kenya analysis, but in Uganda we evaluated the impact of the vaccine on non-severe and severe RVGE cases. The choice of the type of analysis was driven by the local context, i.e., the type and quality of disease burden data available and the type of evidence considered to be most relevant for national decision-makers.

2.5. Model set-up parameters

Based on country introduction plans, 2014 was selected as the year of vaccine introduction for Kenya; 2016 was selected for Uganda. Cost-effectiveness was evaluated for 20 birth cohorts because this is the maximum number of birth cohorts included in the TRIVAC model and it allows for trends in influential parameters such as RVGE mortality and vaccine price. It was assumed that rotavirus vaccine would be given with no age restriction, i.e., that vaccination can be initiated for children older than 15 weeks. This assumption was based on a recent WHO recommendation to lift the age restriction in countries with high rotavirus mortality [7]. Costs and benefits were discounted at 3% [12].

For Kenya, the analysis was done only from the government perspective due to insufficient data on lost wages and indirect medical costs incurred by households. For Uganda, both government and societal perspectives were evaluated.

2.6. Demographic data

Projections of live births, child mortality rates, and life expectancy over the 20-year period evaluated were obtained from

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the United Nations population data (the 2012 Revision) [13]. Both countries had approximately 1.5 million live births in 2012. Birth cohort data obtained from WHO/UNICEF Joint Reporting Forms (DTP denominator, 2012 data) [14] was used as an input for the low population estimate: 1.3 million live births for Kenya and 1.45 million for Uganda.

2.7. Disease burden

Disease burden estimates are shown in Table 1. For Kenya, the mid-value incidence of outpatient visits and inpatient admissions due to rotavirus was obtained from a study conducted in Eastern Kenya [15], as were the estimates used in the high/low-scenario analysis [16]. The mid-value estimates were 3019 rotavirus outpatient visits and 279 admissions per 100,000 children in Kenya. The estimated mortality due to rotavirus was 102 deaths per 100,000 children.

In Uganda, incidence of rotavirus gastroenteritis was estimated using a prevalence of acute diarrhea in children less than 5 years old of 24,000 per 100,000 [17]. This data was estimated based on a survey that established the proportion of children under five with acute watery diarrhea. Using this data yields an estimate of 3.2 episodes of diarrhea per child year [18], an estimate of 15% of acute rotavirus cases in the community attributable to rotavirus [18], and an estimate of 5% of rotavirus cases as severe [19]. The results: 10,944 per 100,000 cases of non-severe rotavirus, and 576 per 100,000 cases of severe rotavirus. The estimated mortality due to rotavirus was 121 per 100,000 children.

The model also accounts for a realistic age distribution of cases and deaths [20,21]. A disability weight of 0.119 for episodes of rotavirus diarrhea was used for the DALY calculations [22].

2.8. Vaccine timeliness, schedule, and coverage

Table 2 shows the input parameters for estimating rotavirus vaccine coverage and timeliness [23]. It was assumed that RV1 would be co-administered with the pentavalent vaccine, and would therefore share the same coverage. These coverage rates were 89% and 84% for the first and second doses, respectively, in Uganda [24], and 89% and 86%, respectively, in Kenya [25]. We assumed that during the first year of introduction, coverage rates would be only half of the desired target rates, but that in the second and subsequent years, the desired coverage rates would be attained.

2.9. Vaccine efficacy, relative coverage of deaths, waning, serotype coverage and herd immunity

Vaccine efficacy data were obtained from the published literature, as shown in Table 3 [26–29]. The relative coverage of deaths parameter adjusts for a concentration of deaths in the unvaccinated population to account for the possibility that there is an unequal

Table 1
Input parameters for estimating disease burden.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Kenya				
Annual incidence per 100,000 aged 1–59 m:				
Rotavirus outpatient visits	3019	1987	21,800	[15]; low [15]; high [16]
Rotavirus admissions	279	132	306	[15]; low [16]; high [15]
Rotavirus deaths	102	30	156	Calculated
Disability weight for DALY calculations				
Rotavirus outpatient visits	0.12	–	–	[22]
Rotavirus admissions	0.12	–	–	[22]
Mean duration of illness (in days)				
Rotavirus outpatient visits	5	–	–	[15,16]
Rotavirus admissions	6	–	–	[15,16]
Age distribution of outpatient visits and admissions				
<3 m	3.2%	–	–	[20]
3–5 m	11.3%	–	–	[20]
6–8 m	24.0%	–	–	[20]
9–11 m	20.1%	–	–	[20]
12–23 m	38.3%	–	–	[20]
24–35 m	3.0%	–	–	[20]
36–47 m	0.2%	–	–	[20]
48–59 m	0.0%	–	–	[20]
Uganda				
Annual incidence per 100,000 aged 1–59 m				
Rotavirus (non-severe) cases	10,944	8755	13,133	Calculated from [17,18,19]
Rotavirus (severe) cases	576	461	691	Calculated from [17,18,19]
Rotavirus deaths	121	81	182	Calculated
Disability weight for DALY calculations				
Rotavirus (non-severe) cases	0.12	–	–	[22]
Rotavirus (severe) cases	0.12	–	–	[22]
Mean duration of illness (in days)				
Rotavirus (non-severe) cases	5	–	–	[15,16]
Rotavirus (severe) cases	6	–	–	[15,16]
Age distribution of disease cases and deaths				
<3 m	4.0%	–	–	[21]
3–5 m	14.0%	–	–	[21]
6–8 m	24.0%	–	–	[21]
9–11 m	21.0%	–	–	[21]
12–23 m	31.0%	–	–	[21]
24–35 m	4.0%	–	–	[21]
36–47 m	2.0%	–	–	[21]
48–59 m	1.0%	–	–	[21]

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Table 2
Input parameters for estimating rotavirus vaccine (RV) coverage and timeliness.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Kenya				
Coverage of DTP1 by age in year 2014 (proxy for RV doses given with DTP1)				
3 m	73.7%	–	–	[23]
6 m	84.7%	–	–	[23]
9 m	85.7%	–	–	[23]
12 m	86.4%	–	–	[23]
24 m	88.3%	–	–	[23]
Coverage of DTP2 by age in year 2014 (proxy for RV doses given with DTP2)				
3 m	47.0%	–	–	[23]
6 m	79.6%	–	–	[23]
9 m	82.5%	–	–	[23]
12 m	83.4%	–	–	[23]
24 m	86.0%	–	–	[23]
Uganda				
Coverage of DTP1 by age in year 2016 (proxy for RV doses given with DTP1)				
3 m	52.9%	–	–	[23]
6 m	80.7%	–	–	[23]
9 m	82.4%	–	–	[23]
12 m	85.3%	–	–	[23]
24 m	87.5%	–	–	[23]
Coverage of DTP2 by age in year 2016 (proxy for RV doses given with DTP2)				
3 m	3.3%	–	–	[23]
6 m	66.9%	–	–	[23]
9 m	72.5%	–	–	[23]
12 m	79.0%	–	–	[23]
24 m	81.6%	–	–	[23]

Coverage projections over the period 2014–2033 for Kenya and 2016–2035 for Uganda were estimated by assuming RV will achieve the same coverage and timeliness as DTP, and by assuming a 5% annual decrease in the gap between final coverage in the cohort (coverage by age 24 m) and a ceiling of 100% (DTP1) and 100% (DTP2).

distribution of deaths across population groups. Relative coverage of deaths (adjustment factor to reduce effectiveness on the basis that higher risk children may not be reached by the program) was assumed to be 95.1%. The annual percentage decrease in dose efficacy is used to simulate waning protection, and we used a value of 28.8% per year [29]. The model assumes similar efficacy for all doses. No decline in vaccine serotype coverage per year was assumed for the base case, and a herd effect adjustment in children under 5 was applied by multiplying the direct effectiveness in children under 5 by 110% (i.e., including indirect benefits to unvaccinated children).

Table 3
Input parameters for estimating the health impact of RV1.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Vaccine efficacy vs rotavirus outpatient visits and non-severe RVGE				
Dose 1	13.3%	12.4%	13.9%	[26]
Dose 2	26.9%	25.1%	28.1%	[26]
Vaccine efficacy vs rotavirus admissions and severe RVGE				
Dose 1	30.4%	28.3%	31.8%	[28]
Dose 2	67.0%	37.0%	84.0%	[27]
Kenya				
Other vaccination impact assumptions				
% Relative coverage[a]	95%	80%	100%	Assumption. See note [a] below
% Decrease in dose efficacy per year[b]	28.8%	21.6%	50.0%	[29] and see note [b] below
% Contribution of herd effect in <5 years[c]	110%	100%	120%	Assumption. See note [c] below
Uganda				
Other vaccination impact assumptions				
% Relative coverage[a]	100%	80%	100%	Assumption. See note [a] below
% Decrease in dose efficacy per year[b]	47.5%	35.7%	59.4%	[27] and see note [b] below
% Contribution of herd effect in <5 years[c]	110%	100%	120%	Assumption. See note [c] below

[a] Relative coverage is the coverage of those at risk of getting the disease (i.e., effective coverage) relative to coverage in the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage. The Kenya and Uganda models used different estimates for the baseline.

[b] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 m, 4–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.

[c] Rather than endogenous modeling of transmission dynamics, the % of direct protection for <5 years is multiplied by a herd effect factor (e.g., 120%) to give the % of total protection in the cohort of interest before age 5 years. This excludes any herd effect in individuals 5 years+ and is therefore very conservative.

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2.10. Vaccine price and incremental costs

Both countries are eligible for Gavi support, and for rotavirus vaccine they would be responsible for only a co-pay during the first few years of introduction. In the base case, it was assumed that the governments would be initially responsible for the copay of $0.20 per dose for the first five years after vaccine introduction. This would increase by 15% per year for the next three years, and by 25% per year for the three years after that. Then, from the twelfth year after the vaccine was introduced, governments would pay the full price. We also explored the impact on the estimates of assuming that the governments do not receive any GAVI support and had to pay the full vaccine price of $2.50 over the 20-year period. Vaccine pricing assumptions are shown in Table 4. We assumed an incremental cost per dose of $0.38 [30]; this is the additional cost the government would bear to add this vaccine into the immunization system.

2.11. Health service utilization and costs

We also obtained data on the places where children receive care for rotavirus-related illness and the costs of care [19,31–34]. For Kenya, we inflated the non-disease-specific average costs for outpatient care [31] by 24% [16] to account for rotavirus-specific costs. We adjusted the costs for non-disease-specific average inpatient costs by 5% [16] to estimate the average costs for rotavirus inpatient care. For Uganda, data were extracted from the electronic health information system of the Ministry of Health (District Health Information Software version 2) [19]. Provider costs data were extracted from cost analysis studies carried out between 2003 and 2007 in 13 health facilities in Uganda, covering health center level 3 to the national referral hospital and including both government and private-not-for-profit health facilities, as well as private practitioners [33]. Costs were adjusted to 2016 value using a 5% inflation rate. These costs relate to general outpatient or inpatient cases rather than to rotavirus diarrhea specifically. Table 5 shows the weighted healthcare costs for outpatient and inpatient visits for each country.

2.12. Household costs (Uganda)

We also obtained country-specific information on household costs attributable to rotavirus outpatient care and admissions. These data were obtained from surveys conducted in 2003 and 2007 in three regions of Uganda, covering seven districts. These costs are for inpatient and outpatient services at private, private not-for-profit, and government-owned facilities, as well as for non-healthcare costs (e.g., transportation, meals, and other incidentals) [34]. Costs were extrapolated to 2016 US dollars as described above (Table 5).

2.13. Scenario and sensitivity analyses

We conducted one-way sensitivity analyses where we varied the value of each input by 10% in order to ascertain the impact of uncertainty in input values on the cost-effectiveness ratio. We also performed univariate and multivariate scenario analyses, where the cost-effectiveness ratios was estimated using the low or the high values of selected parameters, and compared with the baseline estimates.

3. Results

In Kenya, between the years of 2014 and 2033, introduction of the vaccine could avert approximately 1.2 million cases of rotavirus diarrhea and 61,000 deaths (undiscounted). In Uganda, for the period 2016–2035, the (undiscounted) estimates are 4 million and 70,236 respectively. The vaccine could also avert 3.9 million and 4.4 million DALYs in Kenya and Uganda, respectively. Tables 6 and 7 show the discounted health and economic benefits of the rotavirus immunization program.

Table 8 shows the discounted net costs and DALYs averted. We estimated that the immunization program would cost approximately $79 million for the 20 birth cohorts for Kenya and would avert about $30 million in healthcare costs for rotavirus-related illness. Thus the net program costs were estimated at about $50 million. In Uganda, the immunization program would cost approximately $62 million and would avert $10 million in healthcare costs; the net program costs would be $52 million for the 20 birth cohorts. If we considered the societal perspective for Uganda, immunization would avert an additional $8 million in indirect costs. In both countries, the vaccination program was found to be very cost-effective, with an estimated cost per DALY averted of $38 in Kenya and $34 in Uganda from the government perspective.

For the univariate sensitivity analysis, both country analyses showed that the two most important variables were the relative coverage of deaths and the percentage contribution to herd effects. Changing the values of the 10 variables within a range of 10% points of the mid (baseline) values resulted in not more than 15% variation in the estimated cost per DALY averted.

Figs. 1 and 2 show the results from the scenario analyses. For Uganda, even when we included all the parameter values that would make introducing the vaccine unfavorable, introduction was still very cost-effective. For Kenya, the estimated cost per DALY averted moved from the very cost-effective range to the cost-effective range. Also, when we assumed that the governments would pay the full price of the vaccine ($2.50) from the first year of introduction, we found that the vaccination program was still highly cost-effective in both countries.

4. Discussion

These studies evaluated the cost-effectiveness of introducing rotavirus vaccines into Kenya and Uganda's national immunization programs. Other researchers have previously evaluated rotavirus vaccine introduction [36–43], including studies done for Kenya and Uganda [15,16,35], and they also concluded that rotavirus vaccine introduction is cost-effective. However, our studies have updated some of the inputs from these studies and have used a consistent model which includes some additional features, e.g., stacked birth cohorts, timeliness of vaccination, waning vaccine-induced protection, and relative coverage.

Another objective was to provide countries with tools and processes that can be used to generate economic information to inform evidence-based policymaking on introducing new vaccine. Conducting these studies resulted in capacity-building, as both studies were country-led and involved local experts. The consultants who led this work and some of the technical working group members attended a three-day workshop prior to undertaking in the studies. The workshop provided an overview of rotavirus epidemiology, background on cost-effectiveness analysis, and workshop participants also had hands-on training on using the TRIVAC model. Twenty participants from six African countries participated in the workshop, including the two consultants who led the countries' studies reported here, and four other participants who were on the TWGs. The consultants were also provided with technical support by the modelers who developed the TRIVAC model and by PATH health economists.

Kenya and Uganda have approximately the same size birth cohorts and similar coverage of infant vaccines but there are several observations we can note about the input data and results for the two countries. A critical input is the annual RVGE mortality rate

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Table 4
Input parameters for estimating RV1 program costs.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Kenya				
Vaccine dose price projection[a]				
2014	$0.20	$0.20	$2.50	Assumed. See note [a] below
2015	$0.20	$0.20	$2.50	
2016	$0.20	$0.20	$2.50	
2017	$0.20	$0.20	$2.50	
2018	$0.20	$0.20	$2.50	
2019	$0.23	$0.20	$2.50	
2020	$0.26	$0.20	$2.50	
2021	$0.30	$0.20	$2.50	
2022	$0.79	$0.20	$2.50	
2023	$1.27	$0.20	$2.50	
2024	$1.75	$0.23	$2.50	
2025	$2.24	$0.26	$2.50	
2026	$2.22	$0.30	$2.50	
2027	$2.19	$0.50	$2.50	
2028	$2.17	$0.70	$2.50	
2029	$2.15	$0.90	$2.50	
2030	$2.13	$1.10	$2.50	
2031	$2.11	$1.05	$2.50	
2032	$2.09	$0.99	$2.50	
2033	$2.07	$0.94	$2.50	
Uganda				
Vaccine dose price projection[b]				
2016	$0.20	$0.20	$2.56	Assumed. See note [b] below
2017	$0.20	$0.20	$2.56	
2018	$0.20	$0.20	$2.56	
2019	$0.20	$0.20	$2.56	
2020	$0.20	$0.20	$2.56	
2021	$0.23	$0.20	$2.56	
2022	$0.26	$0.20	$2.56	
2023	$0.30	$0.20	$2.56	
2024	$0.30	$0.20	$2.56	
2025	$0.60	$0.20	$2.56	
2026	$0.90	$0.23	$2.56	
2027	$1.20	$0.26	$2.56	
2028	$1.25	$0.30	$2.56	
2029	$1.25	$0.35	$2.56	
2030	$1.15	$0.40	$2.56	
2031	$1.15	$0.40	$2.56	
2032	$1.15	$0.46	$2.56	
2033	$1.00	$0.69	$2.56	
2034	$1.00	$0.92	$2.56	
2035	$1.00	$1.00	$2.56	
Both countries				
Other vaccine dose costs				
International handling (% of vaccine price)	3.00%	3.00%	3.00%	[45]
International delivery (% of vaccine price)	2.00%	2.00%	2.00%	[45]
Wastage (% of doses discarded, etc.)[c]	5.00%	5.00%	5.00%	[45]
Incremental system costs of introduction[d]				
Incremental system cost per dose	$0.38	$0.38	$1.00	[30]

[a] The *base-case estimate* assumes that the Gavi price is available to Kenya through 2033. It assumes that the price per dose would decline to $1.00 by 2033. The government would be responsible for the copay of $0.20 per dose for the first five years after vaccine introduction. The copay would increase by 15% per year for the next three years, and by 25% per year for the three years after that. Then, from the 12th year after the vaccine introduction, the government would pay the full price. The *low-price estimate* assumes that the copay would remain at $0.20 for the first 10 years of vaccine introduction, that it would increase by 15% annually in the 11th to 13th year, and then increase by 67%, but it is assumed that the full vaccine price would decrease with time. The *high-price estimate* assumes that the government pays the full vaccine price from 2014 and that there is no decrease in the vaccine price per dose.

[b] Similar to Kenya, the base-case estimate for Uganda assumes that the Gavi price is available through 2035. It also assumes that this price per dose decreases from $2.56 in 2016 to $1.00 in 2035. The government's copay is $0.20 per dose for the first five years after vaccine introduction. The copay would then increase by 15% annually for the next three years. Subsequently, for the next four years, the government would pay 20%, 40%, 60%, and 80% of the vaccine price. From 2018, the government would pay the full price. The *low-price estimate* assumes that the GAVI/UNICEF price is available to Uganda through 2035. It also assumes that the price per dose decreases from $2.56 in 2016 to $1.00 in 2035. The government's copay is $0.20 through 2025. This would increase by 15% per year for the following three years. Subsequently, for the next four years, the government would pay 20%, 40%, 60%, and 80% of the vaccine price. In 2035, the government pays the full price. The *high-price estimate* assumes that the government pays $2.56 throughout.

[c] The % wastage is converted into a factor [1/(1 − % wastage)] which is multiplied by the expected number of doses required to meet the anticipated level of coverage.

[d] Estimated incremental system costs include cold chain storage (77% of cost), transport (18% of cost), training (3% of cost), and public communication (1% of cost). These costs are assumed to only occur only in the first year.

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Table 5
Input parameters for estimating health service costs (all costs are presented in 2013 US$).

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Kenya				
Outpatient visits				
Government cost per outpatient visit[a]				
Rotavirus outpatient visits	$5.00	$4.00	$6.00	Calculated from [31,32]. See note [a] below
Inpatient admissions				
Government cost per inpatient admission[b]				
Rotavirus admissions	$163.62	$163.62	$163.62	Calculated from [31,32]. See note [b] below
Uganda				
Outpatient visits				
Outpatient visits per disease episode				
Rotavirus (non-severe) cases	0.72	0.30	0.78	[17]; low [19]; high [44]
Rotavirus (severe) cases	0.72	0.30	0.78	[17]; low [19]; high [44]
Government cost per outpatient visit[c]				
Rotavirus (non-severe) cases	$1.78	$1.43	$2.12	[33]
Rotavirus (severe) cases	$1.78	$1.43	$2.12	[33]
Household cost per outpatient visit[d]				
Rotavirus (non-severe) cases	$1.83	$0.84	$4.12	[34]
Rotavirus (severe) cases	$1.83	$0.84	$4.12	[34]
Inpatient admissions				
Inpatient admissions per disease episode				
Rotavirus (severe) cases	0.72	0.30	0.78	[17]; low [19]; high [44]
Government cost per inpatient admission[e]				
Rotavirus (severe) cases	$25.63	$27.20	$41.42	[33]
Household cost per inpatient admission[f]				
Rotavirus (severe) cases	$15.60	$12.50	$18.80	[34]

[a] Government costs per outpatient visit include medications/drugs, diagnostic tests, and facilities. Outpatient visits are distributed as follows: 28% at the dispensary/clinic, 27% at health centers, 45% at country hospitals. The cost presented is the weighted average of the provider-specific costs.
[b] Government costs per inpatient admission include medications/drugs, diagnostic tests, and bed-day costs [the cost per bed-day multiplied by the expected length of stay]. Inpatient admissions are distributed as follows: 9% at health centers, 88% at county hospitals, and 3% at referral/tertiary hospitals. The cost presented is the weighted average of the provider-specific costs.
[c] Government costs per outpatient visit includes medications/drugs, diagnostic tests, and facilities. Because public funds also support public, not-for-profit (PNFP) entities providing healthcare in Uganda, these costs are also included in government costs. Outpatient visits are distributed as follows: 21% private (these are for-profit facilities; the costs not included in government costs), 34% PNFP, and 45% government facilities (all levels). The cost presented is the weighted average of the provider-specific costs.
[d] Household costs per outpatient visit include all costs associated with services, medications, and diagnostic testing at private (for-profit), PNFP, and government facilities, as well as non-healthcare costs such as travel and meals. Outpatient visits are distributed as follows: 21% private (for-profit), 34% PNFP, and 45% government facilities (all levels). The cost presented is the weighted average of the provider-specific costs.
[e] Government costs per inpatient admission includes medications, diagnostic tests, and bed-day costs [the cost per bed-day multiplied by the expected length of stay]. Inpatient admissions are distributed as follows: 25%PNFP, 45% government center (level III/IV), 23% government district hospital, 7% referral hospital. The cost presented is the weighted average of the provider-specific costs.
[f] Household costs per inpatient admission include all costs associated with services, medication, and diagnostic testing at PNFP and government facilities, as well as non-healthcare costs such as travel and meals. Inpatient admissions are distributed as follows: 25% PNFP, 45% government center (level III/IV), 23% government district hospital, 7% referral hospital. The cost presented is the weighted average of the provider-specific costs.

Table 6
Discounted health benefits (20 cohorts vaccinated between 2014 and 2033 for Kenya and between 2016 and 2035 for Uganda).

	No vaccine (Status quo)	With vaccine (RV1)	Averted
Kenya			
Total outpatient visits <5 years	3,678,244	2,980,795	697,449
Total inpatient admissions <5 years	339,741	179,682	160,059
Total deaths <5 years	99,202	52,994	46,208
DALYs lost	2,819,642	1,506,724	1,312,918
YLDs – DALYS due to morbidity	6549	5151	1398
YLLs – DALYs due to mortality	2,813,093	1,501,573	1,311,520
Uganda			
Total cases <5 years	16,710,401	13,787,302	2,923,099
Rotavirus (non-severe) cases	15,874,880	13,289,149	2,585,732
Rotavirus (severe) cases	835,520	498,153	337,367
Total outpatient visits	12,031,488	9,926,857	2,104,631
Rotavirus (non-severe) cases	11,429,914	9,568,187	1,861,727
Rotavirus (severe) cases	601,574	358,670	242,904
Total inpatient admissions	601,574	358,670	242,904
Rotavirus (severe) cases	601,574	358,670	242,904
Total deaths <5 years	133,884	80,567	53,317
Rotavirus (severe) cases	133,884	80,567	53,317
DALYs lost	3,798,404	2,289,373	1,509,031
YLDs – DALYS due to morbidity	27,235	22,471	4764
YLLs – DALYs due to mortality	3,771,170	2,266,903	1,504,267

Health benefits are discounted at 3% per year.

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Table 7
Discounted economic benefits (20 cohorts vaccinated between 2014 and 2033 for Kenya and between 2016 and 2035 for Uganda).

	No vaccine Status quo	RV1 With vaccine	Averted
Kenya			
Total Gov. Health Service Costs[a]	$73,986,688	$44,309,686	$29,677,002
Total outpatient visit costs	$18,399,755	$14,910,893	$3,488,862
Total inpatient admission costs	$55,586,933	$29,398,793	$26,188,140
Uganda			
Total Gov. health service costs[a,b]	$36,794,242	$26,829,626	$9,964,616
Total outpatient visit costs	$21,376,947	$17,637,544	$3,739,403
Rotavirus (non-severe) cases	$20,308,100	$17,000,277	$3,307,823
Rotavirus (severe) cases	$1,068,847	$637,267	$431,580
Total inpatient admission costs	$15,417,295	$9,192,082	$6,225,213
Rotavirus (severe) cases	$15,417,295	$9,192,082	$6,225,213
Total societal health service costs[c]	$68,203,190	$50,596,607	$17,606,583
Total outpatient visit costs	$43,401,334	$35,809,272	$7,592,061
Rotavirus (non-severe) cases	$41,231,267	$34,515,437	$6,715,830
Rotavirus (severe) cases	$2,170,067	$1,293,835	$876,232
Total inpatient admission costs	$24,801,856	$14,787,335	$10,014,521
Rotavirus (severe) cases	$24,801,856	$14,787,335	$10,014,521

Costs are discounted at 3% per year.
Gov. = Government.
[a] Government perspective includes the costs for medications/drugs, diagnostic tests, and facility or bed-day costs that are borne by the government/health system.
[b] Government perspective also includes private, not-for-profit (PNFP) facilities in Uganda.
[c] Societal perspective includes all costs included in the government perspective. In addition, it includes all household costs incurred when visiting government and private health providers.

per 100,000 for children under 5, which was assumed to be 121 in Uganda and 102 in Kenya. Thus, more deaths were prevented in Uganda than in Kenya. Similarly, the discounted vaccination program cost over 20 years was US$ 60 million in Uganda compared to US$ 80 million in Kenya, but this difference was attributable largely to the lower price projection assumed by the national team in Uganda. Discounted government health service costs avoided were US$ 30 million in Kenya and US$ 10 million in Uganda, despite a higher burden of disease estimated in Uganda. This was driven by the much lower estimate of the average cost per rotavirus admission assumed ($26 in Uganda compared to $164 in Kenya).

While undertaking these studies using a standardized model, we encountered some challenges and limitations with local data. Some data were not available in the format required by the model. For example, we could not find population data that was extrapolated to the same time frame for the analysis, and hence had to rely on UN population data. Also, for some parameters, we found some country-specific studies, but assumptions were required to use them in the analysis. In Uganda, although cost data were available for all levels of care and provider types, they did not specifically relate to rotavirus illness. Rather, unit cost data are related to general outpatient or inpatient cases.

Table 8
Discounted cost-effectiveness of RV (20 cohorts vaccinated between 2014 and 2033 for Kenya and between 2016 and 2035 for Uganda).

	RV1 Government perspective	
Kenya		
Cost-effectiveness compared to no vaccine		
Net cost of vaccine introduction	$49,604,533	
Costs of vaccine introduction	$79,281,535	
Health service costs avoided	$29,677,002	
DALYs averted	1,312,918	
YLDs averted – DALYS due to morbidity	1398	
YLLs averted – DALYs due to mortality	1,311,520	
US$ per DALY averted	$38	
Cost-effectiveness threshold for Kenya		
1 × GDP per capita (2012) – WHO threshold for 'highly cost-effective'	$942	
3 × GDP per capita (2012) – WHO threshold for 'cost-effective'	$2826	
	Government perspective	Societal perspective
Uganda		
Cost-effectiveness compared to no vaccine		
Net cost of vaccine introduction	$51,674,410	$44,032,443
Costs of vaccine introduction	$61,639,026	$61,639,026
Health service costs avoided	$9,964,616	$17,606,583
DALYs averted	1,509,031	1,509,031
YLDs averted – DALYS due to morbidity	4764	4764
YLLs averted – DALYs due to mortality	1,504,267	1,504,267
US$ per DALY averted	$34	$29
Cost-effectiveness threshold for Uganda		
1 × GDP per capita (2012) – WHO threshold for 'highly cost-effective'	$572	$572
3 × GDP per capita (2012) – WHO threshold for 'cost-effective'	$1716	$1716

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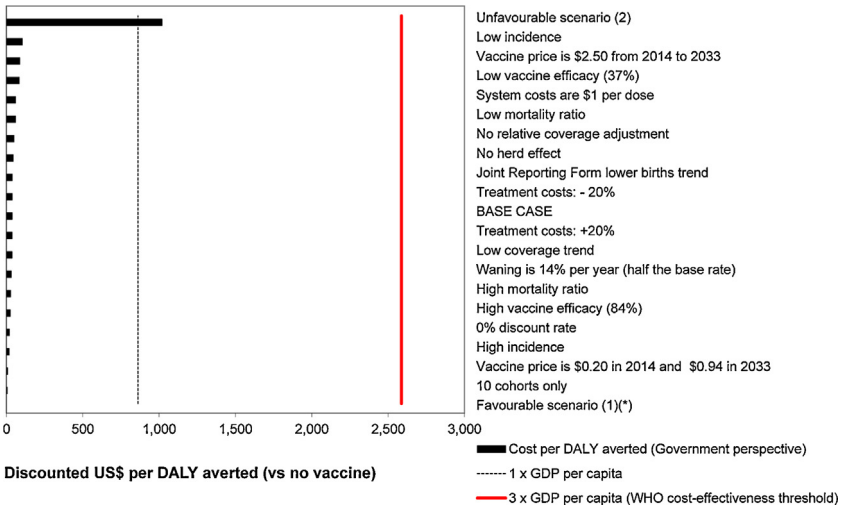

Fig. 1. US$ per DALY averted for base-case RV1 scenario and alternative 'what-if' scenarios: Government perspective for Kenya. (1) Favorable scenario = high values for annual incidence per 100,000, efficacy, and outpatient costs; low values for vaccine price; % change in dose efficacy is assumed to be 14% (half of the baseline value); all parameters held at the baseline values. (2) Unfavorable scenario = low values for demographics, annual incidence per 100,000, efficacy, % contribution in herd effect, % relative coverage of deaths, and outpatient costs; high values for vaccine price and incremental system costs per dose; all parameters held at the baseline values. (*) Scenario is cost-saving from a government perspective, i.e., the health service costs avoided exceed the cost of introducing the vaccine.

Another challenge was the lack of local data to inform some of the analyses. For example, in Kenya we found that there was large variability in the estimates from different studies on the incidence of outpatient and inpatient visits due to rotavirus. In Uganda, there was no population-based data on the incidence of rotavirus diarrhea; neither was there data at the community level on the percent of acute diarrhea attributable to rotavirus. Incidence of rotavirus diarrhea in the community was approximated from the prevalence of rotavirus diarrhea in Kenya using data on the proportion of diarrhea there which is due to rotavirus. We also could not find any local data on the case fatality rate (CFR), a key parameter driving the estimates. Instead, to derive reasonable RVGE mortality estimates, we used a proportional mortality approach (% of deaths among children under five due to rotavirus). These analyses highlight areas where local data are lacking. However, scenario analysis using a wide range of parameter values shows that, despite these uncertainties, rotavirus vaccines remain extremely cost-effective from both government and societal perspectives.

There are several limitations with the TRIVAC model but it serves as a reasonable decision-support tool in this context, where a variety of different scenarios and assumptions have been used and still indicate that the vaccine would be cost-effective. The main limitation of the TRIVAC model is that it is static and therefore does not capture realistic transmission and herd-immunity effects. However, there is very little evidence to support including these parameters in low-income settings and the vaccine is estimated to be cost-effective even without their inclusion. The TRIVAC model includes the option to run probabilistic sensitivity analysis but a transparent 'what-if' scenario analysis was preferable in this context. A more detailed discussion of the model's limitations is found in the TRIVAC methodology paper [10].

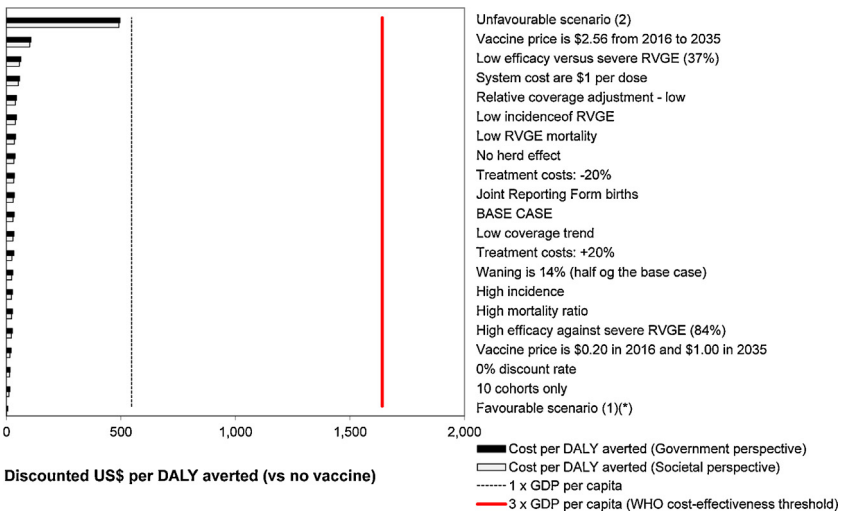

Fig. 2. US$ per DALY averted for base-case RV1 scenario and alternative 'what-if' scenarios: Government and societal perspectives for Uganda. (1) Favorable scenario = high values for demographics, annual incidence per 100,000, case fatality rate, efficacy, inpatient and outpatient costs; low values for vaccine price; % change in dose efficacy is assumed to be half of the baseline value (23.8%); all other parameters held at the baseline values. (2) Unfavorable scenario = low values for demographics, annual incidence per 100,000, case fatality rate, efficacy, % contribution in herd effect, inpatient and outpatient costs; high values for vaccine price and incremental system costs. (*) Scenario is cost-saving from a societal perspective, i.e., the health service costs avoided exceed the cost of introducing the vaccine.

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In conclusion, rotavirus vaccines would be very cost-effective for both countries compared to no vaccine. The engagement of local experts in the process of evidence-generation is likely to increase the acceptability of the results in decision-making and may also highlight the importance of strengthening national data collection efforts which provide key inputs for studies such as this.

Conflict of interest

All authors have read this statement and declare that they have no conflicts of interest.

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Vaccine 33S (2015) A119–A125

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Estimated impact and cost-effectiveness of rotavirus vaccination in Senegal: A country-led analysis

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ARTICLE INFO

Keywords:
Senegal
Cost-effectiveness
Rotavirus
Vaccination
DALY

ABSTRACT

Introduction: Rotavirus is the leading cause of acute severe diarrhea among children under 5 globally and one of the leading causes of death attributable to diarrhea. Among African children hospitalized with diarrhea, 38% of the cases are due to rotavirus. In Senegal, rotavirus deaths are estimated to represent 5.4% of all deaths among children under 5. Along with the substantial disease burden, there is a growing awareness of the economic burden created by diarrheal disease. This analysis aims to provide policy-makers with more consistent and reliable economic evidence to support the decision-making process about the introduction and maintenance of a rotavirus vaccine program.

Methods: The study was conducted using the processes and tools first established by the Pan American Health Organization's ProVac Initiative in the Latin American region. TRIVAC version 2.0, an Excel-based model, was used to perform the analysis. The costs and health outcomes were calculated for 20 successive birth cohorts (2014–2033). Model inputs were gathered from local, national, and international sources with the guidance of a Senegalese group of experts including local pediatricians, personnel from the Ministry of Health and the World Health Organization, as well as disease-surveillance and laboratory specialists.

Results: The cost per disability-adjusted life-year (DALY) averted, discounted at 3%, is US$ 92 from the health care provider perspective and US$ 73 from the societal perspective. For the 20 cohorts, the vaccine is projected to prevent more than 2 million cases of rotavirus and to avert more than 8500 deaths. The proportion of rotavirus deaths averted is estimated to be 42%. For 20 cohorts, the discounted net costs of the program were estimated to be US$ 17.6 million from the healthcare provider perspective and US$ 13.8 million from the societal perspective.

Conclusion: From both perspectives, introducing the rotavirus vaccine is highly cost-effective compared to no vaccination. The results are consistent with those found in many African countries. The ProVac process and tools contributed to a collaborative, country-led process in Senegal that provides a platform for gathering and reporting evidence for vaccine decision-making.

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1. Introduction

Recent case-control studies conducted in Africa have confirmed that rotavirus is the leading cause of acute, moderate to severe diarrhea among children under 5 years of age presenting at health-care facilities [1]. This supports the regional rotavirus surveillance coordinated by the African Regional Office of the World Health Organization (WHO), which reports that approximately 38% of cases reporting to hospital with acute diarrhea were rotavirus-positive [2]. Rotavirus is estimated to be responsible for about 5% of all deaths in young African children [3,4].

In the area of child health, many life-saving interventions, such as oral rehydration therapy and micro-nutrient supplementation,

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http://dx.doi.org/10.1016/j.vaccine.2014.12.065
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that prevent and manage diarrhea are available and have been proven to be effective [5]. Unfortunately, utilization and coverage of these inexpensive and effective interventions are low in most countries in Africa [6,7], although efforts are underway to improve uptake. Furthermore, strategies such as improving water quality and sanitation, food quality, and hygiene are generally long-term and linked to socio-economic empowerment and development of communities. In addition, these strategies have not had a great impact in reducing the incidence of rotavirus diarrhea [3]. Rotavirus immunization, on the other hand, is available and has been shown to have a dramatic effect on reducing diarrheal hospitalizations [8], diarrheal deaths [9,10], and to be cost-effective [11–16]. Thus, since 2009, WHO has recommended the introduction of rotavirus vaccination into the national expanded program on immunization (EPI), particularly in countries with high diarrheal mortality [17]. In addition, Gavi, the Vaccine Alliance, (GAVI) has prioritized support for rotavirus vaccine to low-income countries, and many countries in the African region are introducing rotavirus vaccine [18].

Currently, two rotavirus vaccines are available commercially and are pre-qualified by WHO for procurement by UNICEF [3]. A pentavalent, reassortant vaccine containing the common human rotavirus antigens, RotaTeq™ (Merck Research, Whitehouse, Pennsylvania, USA) is available as an oral, 3-dose, live attenuated vaccine. The monovalent rotavirus vaccine, Rotarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium) based on a human rotavirus strain, is licensed as an oral, 2-dose, live attenuated vaccine. Both vaccines are expected to provide similar benefits at similar cost for low-income countries. So, for simplicity, just one product—the monovalent vaccine, was evaluated.

In addition to the substantial morbidity, there is growing evidence of the economic burden created by diarrheal disease [19–24]. In particular, where resources are limited, such as in sub-Saharan Africa, it is critical for national authorities to be informed of the economic implications for their strategic choices. Consequently, cost-effectiveness analysis (CEA) has become an increasingly necessary criterion among other policy issues in new vaccine introduction strategy. This has been addressed by the Pan American Health Organization's (PAHO's) ProVac Initiative in Latin American countries and is now being disseminated under its auspices to other WHO regions [25]. The current initiative was launched in Senegal; the ProVac International Working Group (IWG) is helping to pave the way for better child health (saving lives and preventing diseases) by enabling national decisions-makers to identify and use more consistent and reliable evidence to support the decision-making process regarding vaccines.

2. Materials and methods

2.1. Model

The TRIVAC model, developed by researchers from the London School of Hygiene and Tropical Medicine (LSHTM), is built in Microsoft Excel with support from PAHO's ProVac Initiative and GAVI's *Haemophilus influenzae* type b (Hib) Initiative. TRIVAC is purposefully designed for use at country level, and allows national teams to perform cost-effectiveness analyses of vaccines for three diseases: pneumococcal, rotavirus, and Hib. Version 2.0 of the model was used for this analysis. The model includes the following categories of input parameters: demographics, burden of disease, vaccine schedule, vaccine efficacy, vaccine costs, health services utilization, and health services costs. Model inputs and their values are shown in Tables 1–5. Detailed model structure and methodology have been published previously [26].

Annual birth cohorts were followed for a five-year period, and the costs and health outcomes incurred by these populations were estimated under scenarios with and without rotavirus vaccine. Results are reported for one single cohort for the year 2019, when the vaccination program is expected to be fully scaled up, and for 20 cohorts from 2014 to 2033.

The analysis was conducted from both healthcare system and societal perspectives. Household out-of-pocket costs for direct medical expenses were included in the societal perspective, but non-medical and indirect costs were not included. All costs and health outcomes were discounted at 3% per year.

2.2. Demographic data

Data on number of live births per year, infant mortality rate, mortality rates for children under 5, and life expectancy at birth were gathered from local sources where available. National data on mortality rates were drawn from Demographic and Health Surveys and Situation Economique du Senegal (Economic Situation of Senegal) reports [27–29], whereas United Nations Population Division (UNPOP) data were used for births and life expectancy.

2.3. Disease burden

There are no Senegal-specific estimates for incidence of rotavirus gastroenteritis (RVGE), so we assumed a rate of 10,000 per 100,000 in children under 5, based on the pooled estimate from a global meta-analysis [30]. To estimate RVGE hospitalizations, we assumed an incidence rate of 500 per 100,000 in children under 5 globally, which is consistent with estimates from Kenya [31] and several countries in Latin America [32]. To estimate overall severe RVGE incidence, we divided RVGE hospital incidence (500 per 100,000 per year in children under 5) by the percentage of those with access to care in Senegal. The non-severe RVGE incidence was calculated by subtracting the severe RVGE incidence from the overall incidence of RVGE (10,000 per 100,000 in children under 5).

The proportion of diarrheal deaths due to rotavirus was estimated from Senegal-specific and regional surveillance data [33–37]. Estimates from these studies ranged from 26% to 41%; 34% was used as the base-case estimate, and the range was explored in the scenario analysis. Using this proportion, the number of deaths due to rotavirus in children under 5 was calculated by multiplying the diarrheal disease deaths in Senegal for the year 2010 by the proportion attributable to rotavirus. It is estimated that there were nearly 1000 deaths due to rotavirus in 2010, equivalent to 45 per 100,000 per year [38]. This was adjusted to the year of anticipated vaccine introduction (2014) by assuming the same percentage of mortality in children under 5 would be due to rotavirus over the period from 2010 to 2014.

2.4. Vaccine schedule and coverage

Senegal is expected to initially introduce the monovalent rotavirus vaccine. The vaccine requires two doses and will be administered within the current EPI infant vaccination schedule. Therefore, DTP1 and DTP2 coverage levels were used as proxies for rotavirus vaccine coverage projections, and were provided by the latest vaccine coverage survey conducted in February 2013 by the Directorate of Preventive Medicine within the Ministry of Health [39].

An adjustment factor (relative coverage), was applied to the coverage estimates to account for the likelihood that children at the highest risk of dying from rotavirus disease are less likely to be vaccinated. The relative coverage was determined by dividing the

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Table 1
Input parameters for estimating disease burden.

Parameter	Estimate	Scenarios		Sources
		Low	High	
Annual incidence per 100,000 aged 1–59 m:				
Rotavirus (non-severe) cases	7523	6816	8330	Assumption, derived from [30–32]
Rotavirus (severe) cases	2427	2184	2670	Assumption, derived from [30–32]
Rotavirus deaths[a]	45	40	50	[38]
Disability weight for DALY calculations				
Rotavirus (non-severe) cases	0.12	–	–	[54]
Rotavirus (severe) cases	0.12	–	–	[54]
Mean duration of illness (in days)				
Rotavirus (non-severe) cases	6	–	–	Assumption
Rotavirus (severe) cases	6	–	–	Assumption
Age distribution of disease cases and deaths				
<3 m	6.6%	–	–	[55,56]
3–5 m	19.4%	–	–	[55,56]
6–8 m	31.9%	–	–	[55,56]
9–11 m	19.8%	–	–	[55,56]
12–23 m	21.8%	–	–	[55,56]
24–35 m	0.5%	–	–	[55,56]
36–47 m	0.0%	–	–	[55,56]
48–59 m	0.0%	–	–	[55,56]

[a] Derived from diarrheal disease mortality estimates for Senegal. In the absence of vaccination, this ratio is assumed to decline in each successive birth cohort in line with the general trend in mortality among children under age 5. This is done by assuming that the fraction of deaths under age 5 caused by the disease remains fixed over time.

Table 2
Input parameters for estimating health service costs (all costs are presented in 2013 US$).

Parameter	Estimate	Scenarios		Sources
		Low	High	
Outpatient visits				
Government cost per outpatient visit[a]				
Rotavirus outpatient visits	$3.50	$1.75	$5.25	[57]
Household cost per outpatient visit[b]				
Rotavirus outpatient visits	$1.36	$0.68	$2.04	Assumption, derived from [57]
Inpatient admissions				
Government cost per inpatient admission[c]				
Rotavirus admissions	$64.50	$32.25	$96.75	[57]
Household cost per inpatient admission[d]				
Rotavirus admissions	$33.23	$16.61	$49.84	Assumption, derived from [57]

[a] Government costs per outpatient visit include all cost components including drugs and diagnostics.
[b] Household costs per outpatient visit include all direct medical out-of-pocket payments. Productivity losses and travel expenses are not included.
[c] Government costs per inpatient admission include the cost per bed-day multiplied by the expected length of stay (6 days), and the cost of drugs and diagnostics.
[d] Household costs per inpatient admission include all direct medical out-of-pocket payments. Productivity losses and travel expenses are not included.

DTP coverage in the lowest wealth quintile by the DTP coverage in the entire population.

2.5. Vaccine efficacy

Many pivotal studies of rotavirus vaccines conducted worldwide have demonstrated good efficacy against severe rotavirus cases. Data for this analysis in Senegal were based on the large, randomized, controlled trial of the monovalent rotavirus vaccine (Rotarix™) carried out in South Africa and Malawi [40] using 2 and 3 doses of the vaccine. The overall vaccine efficacy in preventing severe RVGE was 61.2% (95% confidence interval [CI]): 44% to 73.2%). In preventing severe RVGE among infants who received two doses of vaccine, the overall efficacy of the vaccine was 58.7% (95% CI: 35.7% to 74.0%); in those who received three doses, the overall vaccine efficacy was 63.7% (95% CI: 42.4% to 77.8%). In Senegal, the efficacy rate used was the pooled data from both countries at two doses, which corresponds to 58.7% efficacy (95% CI: 35.7% to 74.0%).

The protective effect of rotavirus vaccines has been shown to decline over time. For most efficacy and effectiveness studies a reduction is reported after one year, and again after two years [41]. Waning vaccine protection was determined in this analysis by comparing second-season efficacy (42%) against first-season efficacy (59%) from the pooled Malawi/South Africa clinical trial data. This gives 29% waning protection per year, calculated as follows: ([59–42%]/59%).

2.6. Vaccine and systems costs

Vaccine cost per dose includes the vaccine price, handling, and delivery fees. As a GAVI-eligible country in the intermediate

Table 3
Input parameters for estimating rotavirus vaccine (RV) coverage and timeliness.

Dose	Parameter (months)	Coverage (%)	Sources
First			
	3	73.4	[39,55]
	6	88.1	[39,55]
	9	91.8	[39,55]
	12	94.7	[39,55]
	24	96.7	[39,55]
Second			
	3	34.7	[39,55]
	6	78.5	[39,55]
	9	85.9	[39,55]
	12	89.9	[39,55]
	24	94.7	[39,55]

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Table 4
Input parameters for estimating RV1 program costs.

Parameter	Estimate	Alternate scenario	Sources
Vaccine dose price projection			
2014	$0.20	$2.50	GAVI [42]
2015	$0.23	$2.38	GAVI [42]
2016	$0.26	$2.26	GAVI [42]
2017	$0.30	$2.14	GAVI [42]
2018	$0.35	$2.04	GAVI [42]
2019	$0.40	$1.93	GAVI [42]
2020	$0.46	$1.84	GAVI [42]
2021	$0.53	$1.75	GAVI [42]
2022	$0.61	$1.66	GAVI [42]
2023	$0.70	$1.58	GAVI [42]
2024	$1.50	$1.50	Assumption
2025	$1.50	$1.42	Assumption
2026	$1.50	$1.35	Assumption
2027	$1.50	$1.28	Assumption
2028	$1.50	$1.22	Assumption
2029	$1.50	$1.16	Assumption
2030	$1.50	$1.10	Assumption
2031	$1.50	$1.05	Assumption
2032	$1.50	$0.99	Assumption
2033	$1.50	$0.94	Assumption
Other vaccine dose costs			
International handling (% of vaccine price)	3%	–	Assumption
International delivery (% of vaccine price)	2%	–	Assumption
Wastage (% of doses discarded etc)[a]	5%	–	Assumption
Incremental system costs of introduction[b]			
Incremental system cost per dose	$0.50	$0.35–$1.00	[43,44]

co-financing group, Senegal will benefit from support for vaccine; its co-pay agreement starts at $0.20 per dose and increases by 15% annually [42]. Handling and delivery fees obtained from GAVI applications are 3% and 2%, respectively. A wastage rate of 5% was included in the calculation of vaccine price.

Estimates for the incremental systems cost to deliver each dose of rotavirus vaccine were derived from the Senegal Project Optimize study conducted in 2013 for cold-chain costs per dose, in addition to detailed costing work conducted in Ethiopia [43,44]. The incremental cost estimate was $0.50 per dose, including start-up costs such as training and communication as well as ongoing costs for supervision, cold chain, transportation and supplies. The cost assumes that the existing immunization program staff in the health facilities were used for the introduction.

2.7. Health services utilization

The health delivery system is divided into three major levels of care. The first line of care is provided by facilities called health posts. Services are oriented toward promotional and preventive activities and serve a large proportion of the rural population.

The second line of care consists of health centers and district hospitals. These intermediate-level healthcare facilities provide basic curative healthcare services, including maternal and dental care.

The third line of care is comprised of regional and national hospitals, including teaching facilities. Many medical and surgical specialties such as cardiology, internal medicine, pediatrics, gynecology, neurology, and neurosurgery can be found at these facilities.

In order to determine the distribution of visits and admissions for diarrheal disease across health facility levels, we used local reports [45] and WHO-CHOICE estimates [46], then conducted phone interviews with five district public health doctors working in four different regions of Senegal (Fatick, Thies, Diourbel, and Kaolack). (WHO-CHOICE is an initiative that, among other things, identifies healthcare interventions that are most cost-effective.)

District and regional hospitals are estimated to provide services to approximately 70% of severe rotavirus cases, while 20% are seen in national hospitals, and the remaining cases in lower levels of care. Non-severe cases, by contrast, were seen primarily in health posts and health centers (75%), while the remainder were seen in district, regional, and national hospitals.

Table 5
Input parameters for estimating the health impact of RV1.

Parameter	Estimate (%)	Scenarios		Source/s
		Low (%)	High (%)	
Vaccine efficacy vs rotavirus (non-severe) cases	47.0	30.0	60.0	[11]
Vaccine efficacy vs rotavirus (severe) cases	59.0	36.0	74.0	[40]
Other vaccination impact assumptions				
% Relative coverage[a]	94.0	80.0	100	Assumption
% Decrease in dose efficacy per yr[b]	28.8	21.6	50.0	Assumption
% Contribution of herd effect in <5 yr[c]	110	100	120	Assumption

[a] Relative coverage is the coverage in those at risk of getting the disease (i.e., effective coverage) relative to coverage in the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.

[b] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 m, 4–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.

[c] Rather than endogenous modeling of transmission dynamics, the % of direct protection for children under 5 yr is multiplied by a herd effect factor (e.g., 120%) to give the % of total protection in the cohort of interest before age 5 yr. This excludes any herd effect in individuals aged 5 yr+ and is therefore very conservative.

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Table 6
Health benefits (20 cohorts vaccinated over the period 2014–2033).

	No vaccine (Status quo)	RV1With vaccine	Averted
Total non-severe cases <5 yr	3,280,936	2,194,481	1,086,455
Total severe cases <5 yr	1,051,476	614,092	437,384
Total deaths <5 yr	15,772	9192	6580
Total deaths<5 yr (undiscounted)	20,456	11,952	8503
DALYs	457,460	267,180	190,280
YLDs—DALYs due to morbidity	8470	5490	2980
YLLs—DALYs due to mortality	448,990	261,680	187,300

Health benefits are discounted at 3% per year unless otherwise indicated.

Table 7
Economic benefits (20 cohorts vaccinated over the period 2014–2033).

	No vaccine (status quo)	RV_1 With vaccine	Averted
Total gov. health service costs	$18,849,182	$11,208,602	$7,640,580
Total outpatient visit costs	$3,831,449	$2,437,821	$1,393,628
Total inpatient admission costs	$15,017,733	$8,770,781	$6,246,952
Total societal health service costs	$28,064,115	$16,668,266	$11,395,849
Total outpatient visit costs	$5,309,974	$3,379,203	$1,930,772
Total inpatient admission costs	$22,754,141	$13,289,063	$9,465,078

Costs are discounted at 3% per year.

2.8. Health services costs

Government costs per inpatient bed-day and the cost per outpatient visit are available from WHO-CHOICE [46]. Since the additional disease-specific costs are not included in these estimates, for all diseases we inflated CHOICE estimates by 25% to account for the cost of disease-specific drugs, diagnostics, and procedures. This fraction is based on the fraction reported in a recent South African pneumonia costing study [47]. Household costs were assumed to be equivalent to the percentage of total health expenditure which is out-of-pocket, based on estimates from the WHO Global Health Expenditure Database [48]. In Senegal, 34% of healthcare expenditures are borne by households. The formula used to estimate the household cost per visit or admission was: [Government cost per case/(1 − % of total cost borne by households)] − Government cost per case. Household costs included direct medical expenses, but not direct non-medical or losses in productivity.

2.9. Sensitivity analysis

Scenario analysis was performed to assess the impact of changes in specific model input values on the cost-effectiveness – cost/DALY (disability-adjusted life year) averted of rotavirus vaccination. Variables included incidence of disease, mortality, vaccine efficacy, waning protection, vaccine coverage, relative coverage, vaccine systems costs, vaccine prices, cost of healthcare services and percentage discounting.

3. Results

3.1. Health impact of vaccination

The outcomes presented in Table 6 reflect the projected health outcomes under scenarios with and without a rotavirus vaccination program. Introduction of rotavirus vaccine in Senegal could result in a reduction of more than 2 million cases of rotavirus and nearly 190,000 DALYs and avert more than 8500 deaths from 2014 to 2033. Once the program is fully implemented, vaccination is estimated to avert over 80,000 cases and prevent more than 450 deaths per year, equivalent to 42% of all rotavirus deaths.

3.2. Cost and cost-effectiveness of vaccination

The healthcare costs with and without vaccination are shown in Table 7. The costs averted due to vaccination are higher from the societal perspective due to the inclusion of household out-of-pocket costs. The cost-effectiveness of rotavirus vaccination is $92 and $73 per DALY averted from the health provider and societal perspectives, respectively (Table 8).

Table 8
Discounted cost-effectiveness of RV (20 cohorts vaccinated over the period 2014–2033).

	RV1	
	Government perspective	Societal perspective
Cost-effectiveness compared to no vaccine		
Net cost of vaccine introduction	$17,570,000	$13,810,000
Costs of vaccine introduction	$25,210,000	$25,210,000
Health service costs avoided	$7,640,000	$11,400,000
DALYs averted	190,280	190,280
YLDs averted—DALYS due to morbidity	2980	2980
YLLs averted—DALYs due to mortality	187,300	187,300
US$ per DALY averted	$92	$73
Cost-effectiveness threshold		
1× GDP per capita (2012)—WHO threshold for 'highly cost-effective'	$1032	$1032
3× GDP per capita (2012)—WHO threshold for 'cost-effective'	$3095	$3095

Costs and DALYs are discounted at 3% per year.

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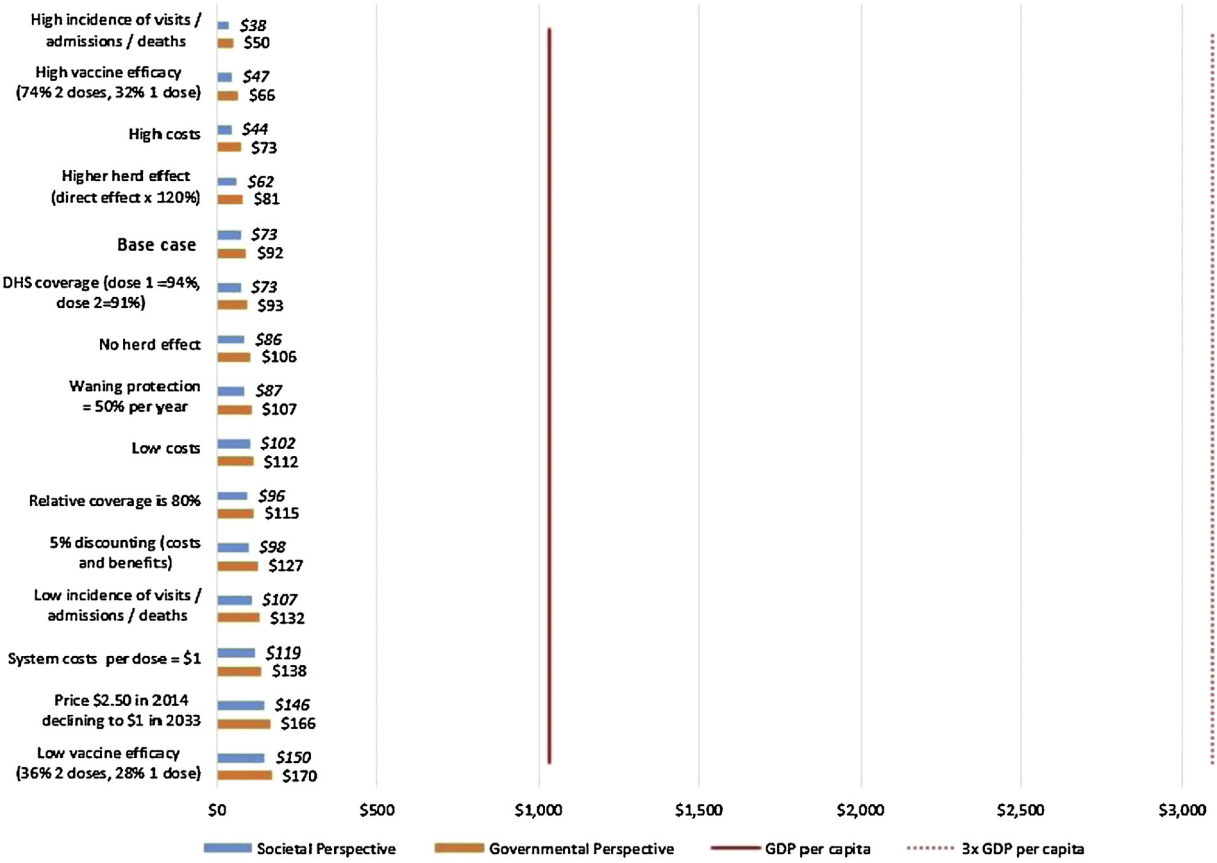

Fig. 1. US$ per DALY averted for base-case scenario and alternative scenarios: Government perspective and societal perspective.

3.3. Scenario analysis

Fig. 1 presents the results of varying select model input values on the cost-effectiveness of vaccination. The base case from a provider perspective is $92 per DALY averted. Under all scenarios involving the most influential factors, results vary from $50 to $170 per DALY averted—all well below the cost-effectiveness threshold of $1040, the GDP per capita for Senegal [49]. This suggests that the model results are robust to changes in the value of all major variables.

4. Discussion

The results of this evaluation suggest that rotavirus vaccination would be highly cost-effective and would substantially reduce child illness and deaths due to rotavirus in Senegal. The analysis was performed using local data where possible, and relied on regional and global estimates when national data were not available or practical to collect. Limited data on the burden of rotavirus in Senegal were available, but those data were assessed together with national and regional data from other African countries to broaden and strengthen the body of evidence.

Although analyses that project costs and benefits into the future aim to use the best available data to achieve highly valid results, limitations will always be present. Healthcare costs were estimated from WHO-CHOICE; although this is a good source of data in the absence of costs collected directly at the national or sub-national level, future evaluations should seek to incorporate these local costs as they become available. A small sample of local costs gathered from a survey of physicians and facilities were explored within the scenario analysis and the changes observed had little effect on the cost-effectiveness of vaccination. Local data were available on cold-chain systems costs from a recent project in Saint Louis, Senegal. Since cold-chain and related transportation costs are the most significant portion of vaccine systems costs, the local data were valuable in assessing these costs. However, the data were modeled for one region and extrapolated nationally for this analysis. Variations in systems costs were also explored in sensitivity analysis and cost-effectiveness results were robust to a doubling of the base case estimate.

Results obtained in this study are consistent with the cost-effectiveness of rotavirus vaccine from previous studies done in many developing country settings worldwide [14,16,50–53], and in particular, consistent with a cost-effectiveness study conducted in Malawi [14]. Vaccine program cost-effectiveness for both perspectives in Senegal would be similarly favorable to results from Malawi, which demonstrated $74.73 per DALY averted.

The study was performed by local researchers, with input data and results reviewed and approved by a local group of experts, which contributes to the relevance and validity of the analysis. Engaging local experts in the collection and validation of model inputs and results is very likely to increase the acceptability of the evidence for local policy-makers. This in turn may improve the likelihood that the evidence will be incorporated into decision-making about the adoption and ongoing support of vaccination programs in Senegal.

Senegal recently made the decision to introduce rotavirus vaccines with GAVI support. Over time, the country is expected to contribute a greater share of the vaccine price. Eventually, Senegal may graduate from GAVI eligibility and incur the full price of vaccine. As Senegal and other countries take on an increasing share of costs, analyses that elucidate the benefits and costs of new vaccines are likely to become even more relevant to the decision-making process.

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Conflict of interest statement

The authors have no conflicts to declare.

Acknowledgements

We would like acknowledge the financial support provided by the Bill and Melinda Gates Foundation (OPP1032888) through PAHO's Provac International Working Group. We also want to thank Erin Kester and Nathaniel Hendrix for their editorial contributions.

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Vaccine 33S (2015) A126–A134

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness analysis of rotavirus vaccination in Argentina

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ARTICLE INFO

Keywords:
Rotavirus vaccination
Cost-effectiveness
Argentina

ABSTRACT

Background: Rotavirus is a leading cause of severe diarrhea in children under 5. In Argentina, the most affected regions are the Northeast and Northwest, where hospitalizations and deaths are more frequent. This study estimated the cost-effectiveness of adding either of the two licensed rotavirus vaccines to the routine immunization schedule.

Methods: The integrated TRIVAC vaccine cost-effectiveness model from the Pan American Health Organization's ProVac Initiative (Version 2.0) was used to assess health benefits, costs savings, life-years gained (LYGs), DALYs averted, and cost/DALY averted of vaccinating 10 successive cohorts, from the health care system and societal perspectives. Two doses of monovalent (RV1) rotavirus vaccine and three doses of pentavalent (RV5) rotavirus vaccine were each compared to a scenario assuming no vaccination. The price/dose was US$ 7.50 and US$ 5.15 for RV1 and RV5, respectively. We ran both a national and subnational analysis, discounting all costs and benefits 3% annually. Our base case results were compared to a range of alternative univariate and multivariate scenarios.

Results: The number of LYGs was 5962 and 6440 for RV1 and RV5, respectively. The cost/DALY averted when compared to no vaccination from the health care system and societal perspective was: US$ 3870 and US$ 1802 for RV1, and US$ 2414 and US$ 358 for RV5, respectively. Equivalent figures for the Northeast were US$ 1470 and US$ 636 for RV1, and US$ 913 and US$ 80 for RV5. Therefore, rotavirus vaccination was more cost-effective in the Northeast compared to the whole country; and, in the Northwest, health service's costs saved outweighed the cost of introducing the vaccine. Vaccination with either vaccine compared to no vaccination was highly cost-effective based on WHO guidelines and Argentina's 2011 per capita GDP of US$ 9090. Key variables influencing results were vaccine efficacy, annual loss of efficacy, relative coverage of deaths, vaccine price, and discount rate.

Conclusion: Compared to no vaccination, routine vaccination against rotavirus in Argentina would be highly cost-effective with either vaccine. Health and economic benefits would be higher in the Northeast and Northwest regions, where the intervention would even be cost-saving.

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1. Background

Rotavirus (RV) is a leading cause of severe diarrhea in children aged less than 5 years, with the WHO estimating 453,000 deaths globally in 2008. RV is also associated with high morbidity due to severe dehydrating diarrhea and vomiting, and high costs to the health care system and families [1].

In Argentina in 1991, the probability that a child under 2 years old would need, because of RV-associated gastroenteritis (RVGE), an outpatient visit (OV) or hospital admission was estimated to be 1 in 8 and 1 in 31, respectively [2]. This risk is quite similar to that in other Latin American and Caribbean countries [3]. In the Northeast and Northwest of Argentina a higher frequency of hospitalizations and deaths due to diarrhea have been reported [4,5]. These regions have also lower per capita incomes and higher infant and under-5 mortality rates than the national averages [6,7].

Monovalent (Rotarix®, Glaxo Smith Kline) (RV1) and pentavalent RotaTeq®, Merck Sharp & Dohme) (RV5) RV vaccines have

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http://dx.doi.org/10.1016/j.vaccine.2014.12.074
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demonstrated safety and efficacy against severe RVAGE in clinical trials [8,9]. Moreover, cost-effectiveness analyses in various countries have suggested that RV vaccination would be a cost-effective intervention [3,10–12].

The Argentine government prioritizes vaccination as a state policy, emphasizing this strategy as a sign of social equity. However, decisions regarding new vaccine introduction should be grounded on a broad evidence base that reflects the conditions in each country. In Argentina, the National Technical Advisory Group on Immunizations is represented by the National Immunization Commission (CoNaIn), which consists of a group of immunization experts, representatives of scientific societies, the immunization program, and the Ministry of Health. This commission makes recommendations on the introduction of vaccines into the immunization program based on technical, programmatic, and social criteria. The main objective of these recommendations is to strengthen the Ministry of Health's decision-making process [13].

Moreover, in recent years, the Pan American Health Organization (PAHO) ProVac Initiative has supported the National Program for the Control of Immune-preventable Diseases (ProNaCEI), developing tools for economic analyses and providing training to a national multidisciplinary team, to help with the evidence-based decision-making [14]. For example, a cost-effectiveness analysis of two pneumococcal conjugate vaccines (PCVs) in Argentina supported the introduction of the 13-valent PCV into the immunization program in 2012 [15].

In the research described in this article, the National Ministry of Health, in collaboration with the PAHO ProVac Initiative, conducted a cost-effectiveness analysis in order to assess the costs and health benefits of adding either of the two licensed RV vaccines into the routine child immunization program in Argentina. The study considered the country as a whole, and also assessed the Northeast and Northwest regions of the nation, in order to better understand subnational variations and equity issues. The results of this analysis aim to contribute to an evidence-based recommendation regarding the introduction of RV vaccine in Argentina.

2. Methods

2.1. Model general overview

The analysis considered the status quo (no RV vaccination) versus introduction of RV1 or RV5 into the routine child immunization schedule, from the health care system perspective (base scenario) and from the societal perspective.

The RV component of the integrated TRIVAC vaccine cost-effectiveness model (Version 2.0) was used for the analysis. This model has been extensively described elsewhere [16]. Briefly, the TRIVAC model is a spreadsheet software program that calculates incremental cost-effectiveness ratios (ICERs) and other indicators for three childhood vaccines (*Haemophilus influenzae* type b, PCV, and RV), utilizing parameters such as demography, disease burden, vaccine costs, vaccine coverage, vaccine efficacy, and health service utilization and costs. It has been developed in Microsoft Excel by investigators from the London School of Hygiene & Tropical Medicine (LSHTM) for PAHO's ProVac Initiative. The program was adapted to comply with the requirements of the study designed in Argentina.

For the purpose of this study, data parameters related to RV burden of disease, vaccination, and treatment in children <5 years of age were entered. During the first five years of life, the model estimates the number of outpatient visits (OVs), hospitalizations, and deaths due to RVGE, and the costs to manage the disease borne by the health care system and the society. Life expectancy for each cohort and standard methods were used to calculate disability-adjusted life years (DALYs) [17]. Age weighting was not assumed for the base case evaluation. Ten successive birth cohorts were assessed, from the years 2012 to 2021, in order to evaluate the impact of time-dependent parameters (e.g., mortality trends, vaccine price) and to provide an annual forecast of costs and health benefits. Finally, the model provides an incremental cost-effectiveness ratio (ICER) of introducing a vaccine versus no vaccination, which indicates the cost per DALY averted expressed in 2011 United States dollars (US$).

2.2. Disease burden

Epidemiological parameters included the annual incidence of OVs and hospitalizations associated with RV per 100,000 children less than 5 years of age, for the whole country and for the Argentine Northeast (NEA), which covers the provinces of Misiones, Corrientes, Chaco, and Formosa; and Northwest (NWA), that includes Salta, Jujuy, Tucumán, Santiago del Estero, and Catamarca provinces. For data collection regarding disease burden in the country, databases from different areas of the Ministry of Health were consulted, and some estimations and adjustments were made. Table 1 summarizes the estimates for disease burden data used for this analysis.

OVs and hospitalizations due to diarrhea and acute gastroenteritis of presumed infectious origin (ICD10 A09X) in children less than 5 years old were collected for the 2007–2008 period. The OVs data were obtained from the National Health Surveillance System (SNVS), and the hospitalizations data were obtained from the Statistics and Health Information Directory (DEIS) [18,19]. Data regarding OVs and hospitalizations were collected for the entire country, the NWA and the NEA.

In Argentina there are three main health care providers: the public system, social security, and the private sector. In general, people with no health insurance at all are assisted in the public sector, the ones who have health insurance provided by trade unions receive care in the social security health care sector, and the ones who have prepaid health insurance use the private sector. As SNVS and DEIS databases collect information from the public health care sector, the incidence rates were adjusted to include OVs and hospitalizations occurring within social security and the private sector as well. For this purpose, information about the proportions of the population who have health insurance provided by trade unions, prepaid health insurance, or no health insurance at all was obtained from the 2010 National Census, for the entire country, the NEA, and the NWA [20]. We assumed that the probability of having an OV or of being hospitalized is the same regardless of the health insurance category.

The incidence rate of OVs and hospitalizations due specifically to RVGE for the entire country, the NWA and the NEA, was estimated by applying the respective proportion of RV isolation reported by sentinel surveillance units for acute diarrhea in ambulatory care and in admission care [21]. These sentinel units conduct intensified active surveillance in five different provinces; over the 2006–2007 period, they processed more than 2500 samples. Finally, the age distribution of disease cases and deaths was estimated to be 6.6% in less than 3 month and in 3 to 5 month-age groups; 19.9% in 6 to 8 month and in 9 to 11 month-age groups; 38.5% in 12 to 23 month-age group; 4.5% in 24 to 36 month-age group; and 2% in 36 to 47 month and in 48 to 59 month-age children. These estimations were based on national reports and on information provided by the sentinel surveillance units for acute diarrhea and were considered to be similar for the entire country and the two northern regions [21,22].

Data on mortality due to diarrhea and acute gastroenteritis of presumed infectious origin was collected by the DEIS for the same periods for the entire country, the NWA and the NEA [23]. As

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Table 1
Input parameters for estimating disease burden, for Argentina as a whole and for the Argentine Northwest (NWA) and the Argentine Northeast (NEA).

Parameter	Country-wide	NWA	NEA	Source/s
Population <5 years old	3,329,198	457,602	382,409	[20]
% of population assisted in the public health care sector	38%	47%	54%	[20]
Public health care sector OVs due to diarrhea and acute gastroenteritis [a]	486,415	145,360	55,000	[18]
Total health care system estimated OVs due to diarrhea and acute gastroenteritis [a]	1,280,038	309,277	101,852	Estimated
RV outpatient isolation [b]	21.8%	19.6%	21.8%	[21]
Annual incidence per 100,000 aged 1-59 mo RV (non-severe) OVs [a]	8382	13,247	5806	Estimated
Public health care sector hospitalizations due to diarrhea and acute gastroenteritis[a]	24,837	5958	4462	[19]
Total health care system estimated hospitalizations due to diarrhea and acute gastroenteritis[a]	65,359	12,676	8262	Estimated
RV inpatient isolation [b]	33.6%	34.4%	33.6%	[21]
Annual incidence per 100,000 aged 1-59 mo RV (severe) hospitalizations [a]	660	953	726	Estimated
Death cases due to diarrhea and acute gastroenteritis [a]	91	26	26	[23]
RVGE CFR[a]	0.14%	0.21%	0.31%	[22,23,38]

OVs: outpatient visits; RV: rotavirus; RVGE: rotavirus-associated gastroenteritis; CFR: case fatality ratio.
[a] (Mean) 2007–2008.
[b] (Mean) 2006–2007 reported by sentinel surveillance units for acute diarrhea.

deaths are reported for all health care sectors, no adjustments were required in this sense, but we applied the proportion of RV isolation for hospitalized patients to estimate RVGE-related deaths. Case fatality ratio (CFR) was estimated based on RVGE-associated deaths and RVGE hospitalizations for the entire country, NWA, and NEA. Finally, we assumed that all non-severe cases survived.

We considered an average duration of illness of six days based on data reported by Rheinghans et al. [3]. This figure was used to estimate health resource utilization and years lived with a disability (YLD), which is the disability component of DALYs. For YLD estimation we also considered a disability weight of 0.105, based on WHO estimations [24]. For years of life lost (YLL) estimation, which is the other component of DALYs, we assumed an increasing life expectancy for the birth cohorts between 2012 and 2021 (from 75.9 to 77.4 years) based on data reported by the National Institute of Statistics and Census (INDEC) [6].

2.3. Selected schedule and vaccine coverage

A 2- and 3-dose schedule (2–4 and 2–4–6 months as Diphtheria, Tetanus and Pertussis (DPT) vaccination) was used for RV1 and RV5, respectively. DPT 1, 2, and 3 coverage in 2011 was 94.4%, 92.9%, and 92.5%, respectively. However, these coverages include those children who receive their vaccines late. To avoid the peak age of intussusception (a rare bowel disorder), we assumed that all children arriving for initial vaccination who were over 15 weeks of age would not be eligible for inclusion in the RV vaccine program, as per the recommendations on the manufacturers' labels and other guidance. [25–27]. Therefore, our model assumed a lower vaccination coverage of 88%, 87.2%, and 79.2% for 1, 2, and 3 doses, respectively, thus accounting for children who are likely to receive their vaccines late and therefore be excluded from RV vaccination [28].

We also assumed a 90% relative coverage of deaths, which represents the extent to which overall program coverage reaches those children at highest risk of death. As there is no local data regarding this parameter, this was an authors' estimation.

2.4. Vaccine efficacy

Vaccine efficacy against hospitalizations and OVs due to RVGE reported by pivotal studies was considered [8,9,29]. In order to assess the efficacy of a schedule using fewer doses than recommended, we referred to work by De Palma et al. [30] and Patel et al. [31], who described the experiences in El Salvador and Nicaragua, respectively, where data on reduced immunization schedules were reported. In these studies, vaccine efficacy for RV1 was 51% for 1 dose and efficacy for RV5 was 51% for 2 doses and 52% for 1 dose.

2.5. Serotype coverage and Indirect effects of vaccination

In the base scenario, 100% vaccine type coverage was considered, assuming cross protection between serotypes not considered in the vaccine. Neither herd immunity nor serotype replacement was included. However, herd immunity was taken into account in the scenario analysis.

2.6. Immunization program costs

Argentina procures most vaccines through the PAHO Revolving Fund. A price of US$ 7.50 and US$ 5.15 was assumed for each dose of RV1 and RV5, respectively. An annual decrease in the price of 2% was applied, according to ProNaCEI projections based on experiences with other vaccines.

The price of the vaccine was adjusted for the capitalization of the PAHO Revolving Fund (3% of dose price), delivery, freight and insurance (5% of dose price), and 10% wastage. Additional non-vaccine costs incurred by the health care system due to RV vaccine introduction included expansion of the cold chain, transportation, materials, training, supervision, and monitoring. These additional non-vaccine costs were estimated at US$ 1.78 and US$ 1.23 per dose for RV1 and RV5, respectively, by the ProNaCEI, based on other vaccines' expenditures. Table 2 shows the model inputs regarding vaccination effectiveness and costs.

2.7. Health service utilization and costs

Data regarding utilization of health resources and societal costs were obtained from children's hospitals in three different provinces: "Hospital Nacional Ricardo Gutiérrez" in the city of Buenos Aires, "Hospital Materno Infantil" in Salta (NWA), and "Hospital de Niños del Niño Jesús" in Tucumán (NWA).

Health resource utilization in the ambulatory setting was estimated by using questionnaires administered to 25 pediatricians to inquire about usual treatment of watery acute diarrhea in children less than 5 years old (Appendix 1). These questionnaires were also used to estimate the proportion of patients with good recovery at home and those who need rehydration therapy.

Data regarding utilization of health resources for admitted patients were obtained by reviewing 36 medical charts. Data recorded included number of visits to the emergency room on average, blood tests, stool and urine samples, and treatment provided. The mean length of admission stay was estimated to be three days, based on information from DEIS databases [19]. Although a mean length of stay of 4.4 days (range 2–9 days) was recorded by charts review, we considered DEIS database a better indicator as it is a bigger sample and also more conservative for this study.

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Table 2
Input parameters for estimating RV1 and RV5 program costs.

Parameter	RV1	RV5	Source/s
Vaccine efficacy of a complete schedule			
vs non-severe RVGE	70%	86%	[9,29]
vs severe RVGE	85%	95.8%	[8,9]
Efficacy of a reduced vaccination schedule			
Dose 1	51%	52%	[30,31]
Dose 2	–	51%	[30,31]
Other vaccination impact assumptions			
% vaccine serotype coverage	100%	100%	Assumption
% relative coverage	90%	90%	Assumption
Vaccine coverage under a restricted vaccination schedule			
DPT1	88%	88%	[28]
DPT2	87.6%	87.6%	[28]
DPT3	–	79.20%	[28]
Vaccine price per dose	$ 7.50	$ 5.15	PAHO Revolving Fund [a]
Other vaccine costs per dose			
International handling (% of vaccine price)	3.00%	3.00%	ProNaCEI estimations
International delivery (% of vaccine price)	5.00%	5.00%	ProNaCEI estimations
Wastage (% of doses discarded)	10.00%	10.00%	ProNaCEI estimations
Incremental system costs of introduction [b]	$ 1.78	$ 1.23	ProNaCEI estimations

[a] 2011 Vaccine prices.
[b] Estimated incremental system costs include expansion of cold chain, transportation, materials, training, supervision, and monitoring.

We estimated the average outpatient and inpatient health resource utilization and assumed it to be similar for all regions and health care providers. Finally, modules were developed for outpatient or inpatient RVGE, combining health resource utilization data with specific unit cost information from each health care provider.

A micro-costing methodology was used, and all costs were estimated in Argentine pesos (AR$) at 2011 values and then converted to U.S. dollars, using the average official exchange rate of that year of AR$ 4.13 = US$ 1.00[1]

Unit costs for medications, services, and diagnostic tests were estimated based on the costs of regulated lists, agreements with self-administered hospitals, data provided by public hospitals, the REMEDIAR program (which provides health care attention and medication for free in public primary care centers), and the *Vademecum* price list. All these costs were updated to the year 2011 according to variations in the health care section of the consumer price index[2].

Societal costs considered out-of-pocket expenses and parental productivity loss due to non-attendance at their jobs during a child's hospitalization. Out-of-pocket expenses included transportation, telephone calls, food and drinks, diapers, medications, and care of siblings during a child's hospitalization. To gather data, a survey was administered to 16 parents of children admitted to hospital with acute diarrhea (Appendix 2).

Parental productivity loss was estimated based on the average monthly take-home pay of employed persons in 2011, adjusted by the unemployment rate for 2011, using data from INDEC [32,33]

No differences in costs were considered between the regions and the country overall because of the small sample size. We only considered differences in demography and disease burden.

Table 3 shows the health care system and societal costs included in the model.

2.8. Cost-effectiveness analysis

In order to interpret the cost-effectiveness results (cost per DALY averted), WHO guidelines were used. In Argentina there is no established threshold of cost-effectiveness to determine whether an intervention is economically acceptable or viable. So, for this analysis, the 2011 national per capita gross domestic product (GDP) was used as a criterion for comparison with ICER outcomes, as recommended by the Commission on Macroeconomics and Health (CMH) and adopted by the WHO [34]. This approach considers an intervention "highly cost-effective" when the cost of averting one DALY is less than the per capita GDP, and it is not cost-effective if the cost per DALY averted is greater than three times the GDP per capita. A discount rate of 3% was applied to health benefits and future costs based on regional and international guidelines [35–37].

2.9. Additional scenarios

We assessed the robustness of our results when different assumptions were used.

Scenarios were run for the entire country and included different incidence rate of OVs, hospitalizations, and deaths. For OVs and hospitalizations we considered a 25% lower burden assuming that some people with health insurance provided by trade unions may obtain care in the public sector, thus these OVs and admissions would be already included in the public sector's surveillance; and the possibility of a lower burden in people with private insurance. Regarding deaths, we included a higher case fatality ratio (0.17%), assuming a higher proportion of RV isolation for RVGE-related deaths (40.0%) as reported in local studies for hospitalized patients [22,38]. We also inflated the health benefits by 110% to crudely account for herd effects in children <5 years of age as was suggested by some studies following the introduction of rotavirus vaccination [39–41].

Conservative vaccine impact scenarios were evaluated for both vaccines assuming a lower vaccine efficacy. For this purpose, 69.6% and 90.5% efficacy was used for RV1 and RV5, respectively; which is the min 95% CI reported in pivotal trials [8,9]. We also reduced overall vaccination coverage and relative coverage of deaths (20% less), and assumed a waning vaccine efficacy over time (10–20%/year). However, we also assessed the impact of RV1 vaccination, considering an efficacy of 96.0% and 83.8% for hospital admissions and OVs, respectively, as it was reported for European children [42].

We also evaluated lower treatment costs and vaccine price (20%) and varied the discount rate from 0% to 5% [36].

Finally, we did a multivariate pessimistic scenario combining lower burden, lower vaccine efficacy, and lower overall and relative vaccination coverage.

[1] Average official exchange rate was estimated based on data from the Argentine Central Bank (BCRA) http://www.bcra.gov.ar/index.asp
[2] Consumer price index is produced by the National Institute of Statistics and Census (INDEC)

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Table 3
Input parameters for estimating health service utilization and costs (all costs are presented in 2011 US$).

Parameter	Estimate	Scenarios Low	High	Source/s
Health care system cost per outpatient visit [a]				
Public sector	$ 9.21	$ 8.28	$ 10.12	Estimation [b]
Social security sector	$ 9.14	$ 8.19	$ 10.01	Estimation [b]
Private sector	$ 9.20	$ 8.28	$ 10.12	Estimation [b]
Health care system cost per inpatient admission [a]				
Public sector	$ 480.1	$ 432.1	$ 528.11	Estimation [b]
Social security sector	$ 486.5	$ 437.85	$ 535.15	Estimation [b]
Private sector	$ 619.2	$ 495.20	$ 681.12	Estimation [b]
Household cost per inpatient admission [c]				
Public sector	$ 64.3	$ 57.87	$ 70.73	
Social security/private sector	$ 115.2	$ 103.68	$ 126.72	Estimation [d]

[a] Health care system costs include medications, services, and diagnostic tests.
[b] Estimation was based on the costs of regulated lists, agreements with self-administered hospitals, data provided by public hospitals, the REMEDIAR program (which provides health care attention and medication for free at public primary care centers), and the *vademecum* price list. The cost presented is the weighted average of the provider-specific costs.
[c] Household costs per inpatient admission include out of pocket expenses and parental productivity loss due to non-attendance at their jobs during the hospitalization. Out of pocket expenses included transportation, telephone calls, food and drinks, diapers, medications, and care of siblings' costs during hospitalization.
[d] Out-of-pocket expenses were estimated based on surveys answered by children's parents. Parental productivity loss was estimated based on the average monthly take-home pay of employed persons in 2011, adjusted by the unemployment rate for 2011, with data coming from INDEC [32,33]. The cost presented is the weighted average of the provider-specific costs.

3. Results

Table 4 shows the discounted health and economic accumulated outcomes of the 10 evaluated cohorts (2012–2021) following the hypothetical introduction of RV1 into the routine child immunization schedule for the entire country, the NWA, and the NEA. Table 5 shows those outcomes for the introduction of RV5. Both tables also present results for one year (Median: 2017).

From the health care system and societal perspective, the cost per DALY averted compared to no vaccination was US$ 3870 and US$ 1802 for the RV1 and US$ 2414 and US$ 358 for the RV5, respectively, in the entire country. ICERs were lower in the NEA and NWA for both vaccines.

Based on previously described assumptions, routine vaccination using RV1 would result in more children with a complete RV vaccination schedule compared to RV5. On the other hand, using RV5 would prevent more DALYs, OVs, hospitalizations, and deaths. Although the burden of disease is higher in the NWA than in the NEA, both vaccines would avert more DALYs in the NEA, due to higher mortality in this region.

In terms of economic assessment, and based on WHO guidelines, which would consider all interventions in Argentina with a cost per DALY averted<US$ 9090[3] to be highly cost-effective, either vaccine is a highly cost-effective alternative compared to no vaccination in the entire country and in the NEA. Moreover, vaccination with either vaccine is a cost-saving alternative in the NWA, as treatment cost savings outweigh incremental vaccination costs in this region.

3.1. Analysis of additional scenarios

To assess the robustness of our results, additional scenarios were analyzed for both vaccines compared to the base scenario (Fig. 1).

Variables having highest impact in the cost per DALY averted when compared to the base case were: vaccine efficacy, the relative coverage the vaccines provided against deaths, a lower burden of disease and treatment costs, and the discount rate. When RV1 efficacy was increased, the cost per DALY averted for this vaccine became lower than for RV5.

The robustness of the study findings was supported by the analysis of additional scenarios. Only when all the pessimistic assumptions were combined under an unfavorable scenario, which is unlikely to occur, was RV vaccination not cost-effective. On the other hand, when the variables selected were modified using univariate analysis, both vaccines remained highly cost-effective, according to WHO standards, in all the scenarios.

4. Discussion

Various economic studies on rotavirus have been carried out in Latin America, the Caribbean, and the United States [3,10–12]. So far, and consistent with the findings in our analysis, all of these studies have shown that vaccination against RV in those countries is cost-effective. Further, the studies indicated that RV vaccination programs would represent a high-impact intervention for public health in those nations due to the high disease burden related to this pathogen, and the health care system costs associated with treatment.

In our analysis both vaccines proved to be a highly cost-effective alternative to no vaccination. The higher impact in the Northeast and Northwest regions (with vaccination even being cost-saving in the Northwest region) is related to the high burden of disease in those areas. The high admission rates and CFRs in the Northeast and the Northwest may also reflect a lower educational level, limited access to primary care, or scarce economic resources of people living in these regions.

This study has some limitations. Estimates regarding the RVGE burden were made based on OVs and hospitalizations from the public health care sector, and assumed that people with social security or private insurance would have a similar behavior. However, this population, generally with a higher educational level and greater access to care, may tend to visit the doctor more often [43]. Nevertheless, with close follow-up and fewer dehydration cases, the patients may not need to be admitted so frequently and death would not be expected.

Another limitation is that an incremental cost-effectiveness ratio was not generated comparing RV1 and RV5 head to head. We considered that such a comparison might not be appropriate, particularly when there is insufficient evidence to suggest a clear difference in their cost or effectiveness. In this analysis, RV5 showed a greater impact than RV1 in preventing visits, hospitalizations, and deaths associated with RVGE. This resulted in a greater

[3] Corresponds to the GDP per capita of Argentina, in United States dollars, for the year 2011. Source: *Secretaría de Política Económica del Ministerio de Economía de la Nación.*

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Table 4
RV1 outcomes summary for the entire country, Northwest region, and Northeast region (10 cohorts and annual forecast 2017).

Monovalent vaccine (RV1)	Country-wide		NWA		NEA	
	Health care system perspective	Societal perspective	Health care system perspective	Societal perspective	Health care system perspective	Societal perspective
Outcomes summary (10 cohorts)						
Cost per DALY averted (US$)	$ 3870	$ 1802	Cost-saving	Cost-saving	$ 1470	$ 636
DALYs averted	6440	6440	1777	1777	1804	1804
Life years gained (LYGs)	5962	5962	1678	1678	1765	1765
Total net costs (US$) [a]	$ 24,923,806	$ 11,604,538	−$ 1,680,532	−$ 4,089,935	$ 2,652,080	$ 1,146,537
Incremental vaccination costs (US$) [a]	$ 108,344,565	$ 108,344,565	$ 14,260,134	$ 14,260,134	$ 12,175,681	$ 12,175,681
Number of fully immunized children	5,993,212	5,993,212	789,684	789,684	673,868	673,868
Treatment costs savings (US$) [a]	$ 83,420,759	$ 96,740,027	$ 15,940,666	$ 18,350,069	$ 9,523,600	$ 11,029,144
Annual costs forecast (2017) [a]						
Vaccination cost (US$)	$ 10,499,200	$ 10,499,200	$ 1,380,637	$ 1,380,637	$ 1,179,074	$ 1,179,074
Treatment costs savings (US$)	$ 8,358,813	$ 9,693,412	$ 1,594,271	$ 1,835,243	$ 952,545	$ 1,103,128
Total net costs (US$)	$ 2,140,387	$ 805,788	−$ 213,634	−$ 454,606	$ 226,529	$ 75,946

Burden of disease	No vaccine	Vaccine	Averted	No vaccine	Vaccine	Averted	No vaccine	Vaccine	Averted
Outcomes (10 cohorts) [b]									
Outpatient visits	2,427,893	974,620	1,453,273	506,899	204,359	302,540	189,635	76,260	113,375
Hospitalizations	191,072	52,193	138,879	36,462	10,039	26,423	23,709	6499	17,210
Deaths	243	66	177	69	19	50	72	20	52
Annual forecast (2017) [b]									
Outpatient visits	262,144	102,609	159,535	54,297	21,396	32,901	21,319	8258	13,061
Hospitalizations	19,125	5209	13,916	3644	1001	2643	2369	648	1721
Deaths	24	7	17	7	2	5	7	2	5

[a] Costs are discounted at 3% per year.
[b] Health benefits are discounted at 3% per year.

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Table 5
RV5 outcomes summary for the entire country, Northwest region, and Northeast region (10 cohorts and annual forecast 2017).

Pentavalent vaccine (RV5)	Country-wide		NWA		NEA	
	Health care system perspective	Societal perspective	Health care system perspective	Societal perspective	Health care system perspective	Societal perspective
Outcomes summary (10 cohorts)						
Cost per DALY averted (US$)	$ 2414	$ 358	Cost-saving	Cost-saving	$ 913	$ 80
DALYs averted	7000	7000	1929	1929	1952	1952
Life years gained (LYGs)	6440	6440	1813	1813	1906	1906
Total net costs (US$) [a]	$ 16,894,756	$ 2,504,625	-$ 3,236,431	-$ 5,840,436	$ 1,782,142	$ 155,908
Incremental vaccination costs (US$) [a]	$ 108,316,989	$ 108,316,989	$ 14,261,450	$ 14,261,450	$ 12,170,248	$ 12,170,248
Number of fully immunized children	5,462,377	5,462,377	720,268	720,268	613,879	613,879
Treatment costs savings (US$) [a]	$ 91,422,233	$ 105,812,364	$ 17,497,880	$ 20,101,885	$ 10,388,106	$ 12,014,339
Annual costs forecast (2017) [a]						
Vaccination cost (US$)	$ 10,501,986	$ 10,501,986	$ 1,381,577	$ 1,381,577	$ 1,179,097	$ 1,179,097
Treatment costs savings (US$)	$ 9,162,049	$ 10,604,183	$ 1,750,300	$ 2.010.776	$ 1,039,156	$ 1,201,834
Total net costs (US$)	$ 1,339,937	−$ 102,197	−$ 368,722	−$ 629,199	$ 139,940	−$ 22,737

Burden of disease	No vaccine	Vaccine	Averted	No vaccine	Vaccine	Averted	No vaccine	Vaccine	Averted
Outcomes (10 cohorts) [b]									
Outpatient visits	2,427,893	716,359	1,711,534	506,899	150,473	356,426	189,635	56,141	133,494
Hospitalizations	191,072	41,028	150,044	36,462	7905	28,557	23,709	5119	18,590
Deaths	243	52	191	69	15	54	72	16	56
Annual forecast (2017) [b]									
Outpatient visits	262,144	75,582	186,562	54,297	15,787	38,510	21,319	6105	15,214
Hospitalizations	19,125	4088	15,037	3644	787	2857	2369	509	1860
Deaths	24	5	19	7	1	6	7	1	6

[a] Costs are discounted at 3% per year.
[b] Health benefits are discounted at 3% per year.

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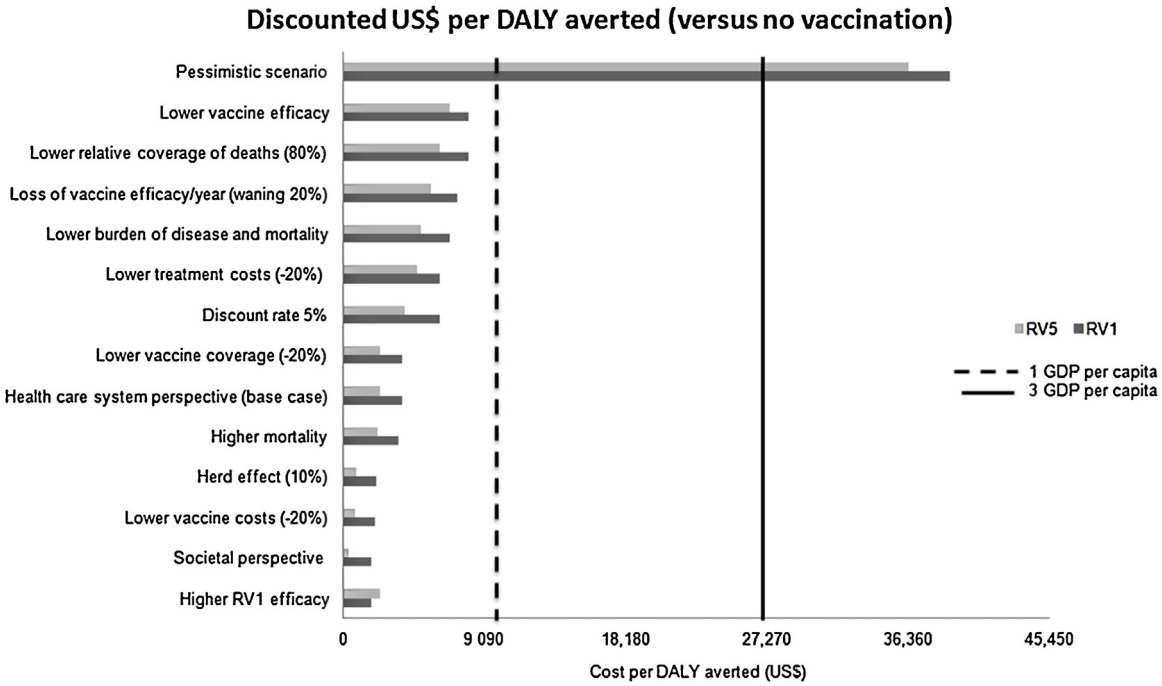

Fig. 1. US$ per DALY averted for RV1 and RV5 base case scenarios and alternative "what-if" scenarios.

number of LYGs and DALYs averted. These outcomes agree with those of Fernando de la Hoz et al., who also reported a positive difference for RV5 when compared with RV1 in children less than 2 years in Colombia [12]. This superiority of RV5 over RV1 was due to differences in efficacy inputs, which were based on the outcomes of the first, pivotal trials [8,9]. However, differences in methods (e.g., severity scales, primary endpoint) and settings of these studies may have influenced efficacy outcomes, so they are not fully comparable. Actually, when considering a 96% RV1 efficacy as reported for the European cohort of children, which is closest to the population of the RV5 pivotal trial, differences in health benefits and cost per DALY averted favored RV1. Furthermore, the RV1 vaccine has a shorter vaccination schedule and thus lower risk of dropout, so it would result in about 500,000 more children being fully vaccinated. This explains the difference in costs of the vaccination program, and it is important to be considered because the effectiveness of an incomplete vaccination schedule is still unclear.

An incremental analysis comparing nationwide vaccination with sub-national vaccination (e.g., vaccinating in only the two northern regions) was not done. Although this assessment is feasible, it would not be even considered by the Ministry of Health as this strategy applies only when the disease is confined to a particular region. As examples, yellow fever vaccination and Argentine hemorrhagic fever vaccination have been targeted to specific populations in Argentina. This would not be the case for RV vaccination, which, despite being more prevalent in the two northern regions, affects people all over the country. However, the fact that RV vaccination would be more cost-effective in the NWA and NEA is relevant for policy makers as its implementation would contribute to reduce social inequities in these regions.

Finally, no elevated risk of intussusceptions was reported with RV1 and RV5 in clinical trials, but a low level risk has been described in some post-licensure studies [44,45]. However, this issue was outside the scope of this study and would be very unlikely to influence the overall cost-effectiveness conclusions due to the rare nature of the adverse event.

In conclusion, rotavirus vaccination would be a highly cost-effective intervention in Argentina, with a larger impact in the two northern regions. The results of this analysis seek to contribute to an evidence-based recommendation about the implementation of rotavirus vaccination. We also recommend strengthening surveillance before the vaccine is introduced, so that its potential impact can be measured with greater certainty.

Authors' contributions

Analía Urueña, Tomás Pippo, María Sol Betelu, Federico Virgilio, Máximo Disoque, and Carla Vizzotti contributed to the conception and design of the study and acquisition, analysis, and interpretation of data. Analía Urueña, María Sol Betelu, and Federico Virgilio drafted the article. Tomás Pippo, Máximo Disoque, and Carla Vizzotti reviewed it critically for important intellectual content. Laura Hernández, Norberto Giglio, and Angela Gentile contributed to the study by acquiring, analyzing, and interpreting data and by reviewing the article critically. All authors approved the final version.

Conflict of interest statement

All authors declare that there are no conflicts of interest.

Acknowledgments

The authors are grateful to Juan Stupka (Instituto INEI-ANLIS "Dr. Carlos G. Malbrán"), who kindly shared his information and participated in discussions, and to Cara Janusz (Pan American Health Organization) and Andrew Clark (London School of Hygiene & Tropical Medicine) for revising the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.074.

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Vaccine 33S (2015) A135–A142

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Cost-effectiveness analysis of introducing universal human papillomavirus vaccination of girls aged 11 years into the National Immunization Program in Brazil

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ARTICLE INFO

Keywords:
Papillomavirus vaccines
HPV vaccines
Cost-benefit analysis
Cost effectiveness
Uterine cervical neoplasms
Uterine cancer

ABSTRACT

Objectives: To evaluate the impact and cost-effectiveness of introducing universal human papillomavirus (HPV) vaccination into the National Immunization Program (NIP) in Brazil.
Methods: The Excel-based CERVIVAC decision support model was used to compare two strategies: (1) status quo (with current screening program) and (2) vaccination of a cohort of 11-year-old girls. National parameters for the epidemiology and costs of cervical cancer were estimated in depth. The estimates were based on data from the health information systems of the public health system, the PNAD 2008 national household survey, and relevant scientific literature on Brazil. Costs are expressed in 2008 United States dollars (US$), and a 5% discount rate is applied to both future costs and future health benefits.
Results: Introducing the HPV vaccine would reduce the burden of disease. The model estimated there would be 229 deaths avoided and 6677 disability-adjusted life years (DALYs) averted in the vaccinated cohort. The incremental cost-effectiveness ratios (ICERs) per DALY averted from the perspectives of the government (US$ 7663), health system (US$ 7412), and society (US$ 7298) would be considered cost-effective, according to the parameters adopted by the World Health Organization. In the sensitivity analysis, the ICERs were most sensitive to variations in discount rate, disease burden, vaccine efficacy, and proportion of cervical cancer caused by types 16 and 18. However, universal HPV vaccination remained a cost-effective strategy in most variations of the key estimates.
Conclusions: Vaccine introduction could contribute additional benefits in controlling cervical cancer, but it requires large investments by the NIP. Among the essential conditions for attaining the expected favorable results are immunization program sustainability, equity in a population perspective, improvement of the screening program, and development of a surveillance system.

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1. Introduction

Human papillomavirus (HPV) vaccines were first licensed in 2006, with the approval of Gardasil (Merck, quadrivalent, including HPV types 6, 11, 16, and 18) and of Cervarix (GlaxoSmithKline, bivalent, including HPV types 16 and 18). After that step, recommendations for vaccine introduction were developed by health authorities in European Community high-income countries, North America, and Australia. By the end of 2011, at least 37 countries had introduced an HPV vaccine into their National Immunization Program (NIPs) [1]. In the Americas, by the end of 2011, six countries (United States, Canada, Mexico, Panama, Peru, and Argentina) had introduced the vaccine, and other nations

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http://dx.doi.org/10.1016/j.vaccine.2014.12.031
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had approved their incorporation into their NIPs (Guyana and Suriname) [2,3].

In Brazil, Gardasil was registered with the National Agency for Sanitary Surveillance (*Agência Nacional de Vigilância Sanitária – ANVISA*) in 2006, and Cervarix in 2008. After their licensure, the vaccines became available in private immunization clinics. At the same time, medical associations intensified their pressure on the Ministry of Health (MoH) to incorporate the vaccine into the country's NIP. However, reports produced by public health institutions slowed vaccine introduction into the NIP, due to issues regarding the long-term vaccine effectiveness and population impact, prioritization of cervical cancer screening and treatment, the high cost and budget impact of the vaccine, and the need to develop special strategies for its delivery [4].

In 2008, the MoH launched a call for proposals for HPV cost-effectiveness studies. In 2012, preliminary findings from the research described in this article were presented to the Brazilian government [5], and the decision to introduce HPV vaccine into the NIP was announced by the MoH.

In March 2014, the quadrivalent HPV vaccine was introduced into the NIP in a school-based program. In 2014, the program targeted girls aged 11–13; in 2015, girls aged 9–11 years will be vaccinated, and from 2016, the vaccine will be administered to 9-year-old girls. An extended schedule (0, 6, and 60 months) was adopted.

This study evaluates the impact and cost-effectiveness of introducing universal HPV vaccination into the NIP in Brazil. Epidemiological, health resource utilization, and cost estimates were based predominantly on national health information systems data. The CERVIVAC decision-support model was used to estimate health impact and cost-effectiveness. This tool was developed by the ProVac Initiative of the Pan American Health Organization (PAHO). This PAHO initiative has worked to strengthen countries' decision-making regarding the introduction of new vaccines, particularly rotavirus, pneumococcal conjugate, HPV, and *H. influenzae* type b (Hib) in the Latin American and Caribbean region [6]. Cost-effectiveness is calculated by comparing HPV vaccination at age 11 years with the status quo (no HPV vaccination), and with both scenarios assuming no changes in current or future cervical cancer program screening and treatment practices. The study uses freely accessible recent national data and a transparent model that provides a consistent basis for international comparisons with other countries of Latin America and the Caribbean.

2. Methods

2.1. The CERVIVAC model

CERVIVAC is an Excel-based decision support model that tracks a single cohort of pre-adolescent girls over their lifetime. Numbers of cervical cancer cases and deaths are estimated by multiplying the number of women alive at each age with national estimates of disease incidence and mortality. Cervical cancer cases are divided into local and regional categories, with different disability weights assigned to each. The model estimates the number of cases, deaths, and disability-adjusted life years (DALYs) expected to occur over a lifetime for one cohort of girls. Total cancer treatment costs are estimated by multiplying the total number of cervical cancer cases in each age group by the average costs of receiving treatment in the public and private sector. We did not assume any preferential age weighting for the working age range. The impact of vaccination (number of cases, deaths, and DALYs averted) is calculated by multiplying the number of cervical cancer cases and deaths by: (a) the expected coverage of the vaccination program; (b) the proportion of cervical cancers that are likely to be prevented by the types (types 16 and 18) included in the vaccine; and (c) the anticipated long-term efficacy of the vaccine.

The model does not take into account the effect of the HPV vaccine on the male population, unvaccinated individuals, genital warts, or other cancers.

2.2. Strategies compared

This model compared two strategies: (1) no vaccination and (2) vaccination of a cohort of 11-year-old girls, using a three-dose vaccination schedule. In both scenarios, the model assumes no changes in current or future cervical cancer program screening practices. The cervical cancer screening strategy adopted in Brazil currently offers free Pap smear testing for the female population aged 25–64 years. The recommendation for the screening interval is every 3 years after two consecutive negative annual exams [7]. Diagnosis and treatment of precancerous lesions are provided freely by the public health sector.

The base case analysis did not consider catch-up of various cohorts of girls or boys, or any additional vaccine booster doses. The average cost-effectiveness of HPV vaccination is calculated in terms of the cost per DALY averted, cost per case averted, and cost per death averted.

In the cost-effectiveness analyses of introducing HPV vaccine 16 and 18 (without differentiation between Gardasil or Cervarix) against cervical cancer, the government, health system, and society perspectives were adopted. The government perspective included only direct medical costs of the public health system (*Sistema Único de Saúde, SUS*). The health system perspective included direct medical costs of both the public (SUS) and the private health systems. The society perspective included the direct medical costs, direct non-medical costs (transportation expenses), and indirect costs of lost productivity. The time horizon used in the analysis was 100 years. The costs are expressed in 2008 United States dollars (US$) at the exchange rate of US$ 1.00 = R$1.83 [8]. A 5% discount rate is applied to both future costs and future health benefits [9].

2.3. Epidemiological and disease burden estimates

The incidence and mortality rates for cervical cancer were based on national studies with adjusted data from the Mortality Information System (*Sistema de Informações de Mortalidade, SIM*) and population-based cancer registries [10–12] (Table 1).

The estimated percentage of cases of cervical cancer diagnosed in stages I, II, III, and IV and the 5-year survival rate of each stage were based on data from the Hospital Cancer Registry of the State of São Paulo, the largest good quality available database [13].

The disabilities weights for stages I, II, III, and IV used to calculate disability-adjusted life years (DALYs) were based on disease burden estimates of the WHO [14,15].

2.4. Health service utilization and costs for the treatment of cervical cancer estimates

Estimates of access to medical treatment were based on information provided by the MoH and estimates of a Brazilian population survey, the National Survey of Household Samples (*Pesquisa Nacional por Amostra de Domicílios – PNAD Saúde 2008*) [16] (Table 2).

Estimates were grouped into sets of procedures performed in cervical cancer treatment care, according to specialized publications and clinical guidelines [17]. Costs were estimated for both the public and private health systems (Table 2).

Costing was performed using "gross costing" or "top-down" methodology, where costs represent national averages actually

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Table 1
Input parameters for estimating cervical cancer disease burden.

Parameter	Estimate	Scenarios		Source
		Low	High	
Annual incidence of cervical cancer: deaths per 100,000 by age				
10–14 yr	0	0	0	[5]
15–19 yr	0	0	0	[5]
20–24 yr	0	0	0	[5]
25–29 yr	1	1	2	[5]
30–34 yr	4	3	6	[5]
35–39 yr	6	5	14	[5]
40–44 yr	10	8	22	[5]
45–49 yr	14	11	31	[5]
50–54 yr	17	14	32	[5]
55–59 yr	21	17	39	[5]
60–64 yr	25	20	47	[5]
65–69 yr	31	25	59	[5]
70–74 yr	38	30	77	[5]
75–79 yr	47	38	96	[5]
80–84 yr	63	51	128	[5]
85–89 yr	63	51	128	[5]
90–94 yr	63	51	128	[5]
95–99 yr	63	51	128	[5]
Annual incidence of cervical cancer: cases per 100,000 by age				
10–14 yr	0	0	0	[5]
15–19 yr	0	0	0	[5]
20–24 yr	1	1	2	[5]
25–29 yr	6	4	9	[5]
30–34 yr	15	11	23	[5]
35–39 yr	25	19	53	[5]
40–44 yr	40	31	85	[5]
45–49 yr	56	44	119	[5]
50–54 yr	66	54	125	[5]
55–59 yr	80	66	153	[5]
60–64 yr	96	79	184	[5]
65–69 yr	120	98	228	[5]
70–74 yr	147	118	298	[5]
75–79 yr	184	148	372	[5]
80–84 yr	245	197	496	[5]
85–89 yr	245	197	496	[5]
90–94 yr	245	197	496	[5]
95–99 yr	245	197	496	[5]
% distribution of cervical cancer by severity				
% local cancer[a]	55%	–	–	[13]
% regional cancer[b]	45%	–	–	[13]
Disability weights for DALY calculations				
% of healthy time lost (local cancer)	8%	–	29%	[14,15]
% of healthy time lost (regional cancer)	75%	48%	–	[14,15]
Average 5-year survival rate (% alive after 5 years)				
Local cancer	80%	–	–	[13]
Regional cancer	40%	–	–	[13]

[a] Local cancer refers to FIGO stages 1a–2a.
[b] Regional cancer refers to FIGO stages 2b–4b.

Table 2
Input parameters for estimating health service utilization and costs (all costs are presented in 2008 US$).

Parameter	Estimate	Scenarios		Source
		Low	High	
Local cancer				
% receiving treatment	75%	70%	100%	[5]
Government cost per woman treated[a]	$1811	$845	$3261	[5]
Household cost per woman treated[b]	$1472	$852	$1162	[5]
Regional cancer				
% receiving treatment	80%	75%	100%	[5]
Government cost per woman treated[c]	$2646	$1235	$4762	[5]
Household cost per woman treated[d]	$2110	$1207	$1795	[5]

[a] Local cancer costs borne by the government per woman treated include hospitalizations, procedures, and outpatient visits, distributed as follows: 75% public hospital and clinic, 0% social security hospital and clinic, and 75% private hospital and clinic. The cost presented is the weighted average of the provider-specific costs.
[b] Local cancer costs borne by the household per woman treated include productivity losses to families due to lost wages and travel expenses, distributed as follows: 75% public hospital and clinic, 0% social security hospital and clinic, and 25% private hospital and clinic. The cost presented is the weighted average of the provider-specific costs.
[c] Regional cancer costs borne by the Government per woman treated include hospitalizations, procedures, and outpatient visits, distributed as follows: 75% public hospital and clinic, 0% social security hospital and clinic, and 0% private hospital and clinic. The cost presented is the weighted average of the provider-specific costs.
[d] Regional cancer costs borne by the household per woman treated include productivity losses to families due to lost wages and travel expenses, distributed as follows: 75% public hospital and clinic, 0% social security hospital and clinic, and 25% private hospital and clinic. The cost presented is the weighted average of the provider-specific costs.

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paid by the public health system. Cost estimates are expressed in 2008 US$, the reference year for epidemiological estimates in the context of a technology assessment of HPV vaccine in Brazil [5].

2.4.1. Direct medical costs in the public health system (SUS)

In order to estimate health service utilization and costs in the public health system (SUS) we used data from: Primary Care Information System (*Sistema de Informação da Atenção Básica, SIAB*) [18]; Outpatient Information System (*Sistema de Informações Ambulatoriais do SUS, SIA/SUS*) [19]; the Authorizations for High Complexity Procedures (*Autorizações de Procedimentos de Alta Complexidade, APAC*), which is part of the SIA/SUS; the Cervical Cancer Information System (*Sistema de Informação do Câncer do Colo do Útero, SISCOLO*) [20]; the Hospitalization Information System (*Sistema de Informações Hospitalares do SUS, SIH/SUS*) [21]; and the 2008 Health Supplement of the National Survey of Household Samples (*Pesquisa Nacional por Amostra de Domicílios, PNAD*) [16].

Hospitalizations, procedures, and visits were identified using the International Classification of Diseases (ICD-10) codes related to cervical cancer (C53.0, C53.1, C53.8, and C53.9). The codes of procedures and their individual costs were retrieved from the Table of Procedures, Drugs, Orthotics, Prosthetics, and Special Materials (*Tabela de Procedimentos, Medicamentos e Órteses, Próteses e Materiais especiais do SUS*) [22]. The MoH's Health Prices Database (*Banco de Preços em Saúde*) [23] was also consulted.

Estimates for surgical treatment of cervical cancer considered all inpatient abdominal hysterectomies (Wertheim-Meigs, radical, extended radical, and total) due to tumors. Leiomyomas are the most frequent cause of hysterectomy and, based on literature and expert opinion, we assumed that cervical cancer was the cause of 20% of abdominal hysterectomies [24]. Clinical treatment of cervical cancer included hospitalizations, chemotherapy, radiotherapy, and additional complementary complex procedures.

2.4.2. Direct medical costs in the private health system

The participation of the private system in the country's health care was estimated based on data from the 2008 Health Supplement of the National Survey of Household Samples (*Pesquisa Nacional por Amostra de Domicílios, PNAD*) [25].

The frequencies of procedures in the private health system were estimated based on the pattern of care provided by the SUS. To estimate the costs in the private system, the procedures were valued based on the National Table of Equivalence of Procedures (*Tabela Única Nacional de Equivalência de Procedimentos, TUNEP*). This table was chosen as representative of costs in the private system.

2.4.3. Direct non-medical costs

Direct non-medical costs were costs of patient transportation for procedures and visits, included when the analysis was conducted from the society perspective.

Transportation costs were estimated based on the average fare of public transportation in the Brazilian state capitals (US$ 1.03), obtained from the National Association of Urban Transport (*Associação Nacional das Empresas de Transportes Urbanos – NTU*). The cost of transportation for outpatient treatment took into account the average number of visits. A round trip (US$ 2) was considered for each outpatient or hospital procedure, and multiplied by the estimated frequencies of procedures and visits in the public and private systems.

2.4.4. Indirect costs

Indirect costs represent the working days lost by the patient and the caregiver in the diagnosis and treatment of the cervical cancer. We adopted the human capital method. We considered the average monthly income of women over 15 years old weighted by their participation in the labor market [26]. The monthly income was converted into daily income by dividing the average monthly income by 22 (working days). The estimated average daily income for women over 15 years old was US$ 13.

One working day lost was assumed for outpatient procedures. Indirect costs of outpatient procedures were obtained by multiplying the average daily income (US$ 13) by the frequencies of the respective procedures.

The average length of stay in hospital according to age group, retrieved from SIH/SUS, was used to estimate the indirect costs of hospital treatment in both the public and private systems. The number of working days lost for each age group was multiplied by the daily income (US$ 13).

2.4.5. HPV vaccination program cost estimates

The base case immunization schedule requires three vaccine doses. Using the value quoted by the PAHO Revolving Fund, US$ 13.10, the amount spent per vaccinated girl would be US$ 39.30. To that figure we added an estimate produced by the NIP for infrastructure coordination and logistics investments needed to introduce this new vaccine (US$ 15 million). Administration costs provided were estimated at US$ 10 per vaccinated girl, based on previous studies relating to Brazil [27] (Table 3).

The input parameters for estimating the health impact of HPV vaccination are listed in Table 4. The discounted lifetime health benefits of HPV vaccination are described in Table 5, and the lifetime economic benefits of vaccination are given in Table 6. For 2008 we estimated the population of girls aged 11 at 1,680,678 using data from *Instituto Brasileiro de Geografia e Estatística* and United Nations Population Division.

With the above values, the estimated costs of vaccinating one cohort of 11-year-old girls, without catch-up, plus initial infrastructure and logistics investment, would be US$ 54,187,058 (Table 7).

2.5. Sensitivity analyses

Univariate sensitivity analyses were performed on the following parameters: cervical cancer incidence and mortality rates, access to cervical cancer treatment, vaccine efficacy, waning vaccine efficacy, one booster dose at age 26 years, only two vaccine doses, percentage of coverage of types 16 and 18, vaccination program costs, Global Burden of Disease 2010 disability weights, and discount rates.

A favorable and unfavorable scenario analysis was also performed. In the favorable scenario, we used the higher estimates of incidence of cervical cancer cases and deaths, cancer treatment utilization, vaccine efficacy, and coverage of types 16 and 18. In the unfavorable scenario, the lower estimates of the same parameters were used.

3. Results

3.1. Base case analysis

The CERVIVAC model estimated that with the current strategy (screening and no vaccination) 4476 cases of cervical cancer, 528 deaths, and 15,429 DALYs would occur in this cohort in a lifetime horizon. With the vaccination program, there would be 2539 cases of cervical cancer (a 43% reduction), 300 deaths (a 43% reduction), and 8752 DALYs (a 43% reduction).

Table 5 provides a detailed analysis of the total number of cases, deaths, and DALYs that would occur with the universal vaccination program versus with the continuation of the current strategy. Table 6 makes a similar comparison for the economic benefits for these two alternatives, in the three perspectives adopted (government, health system, and society). With the implementation of the vaccination program, the direct medical costs related to cancer

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Table 3
Input parameters for estimating HPV vaccine program costs (all costs are presented in 2008 US$).

Parameter	Estimate	Scenarios		Source
		Low	High	
Costs of vaccine doses				
Price per dose	$13.19	$11.87	$14.51	[5]
Percentage international handling	3.5%	3.5%	3.5%	PAHO Revolving Fund
Percentage international delivery	5.0%	5.0%	5.0%	Assumption, ProVac team
Percentage wastage[a]	5.0%	5.0%	5.0%	Assumption, ProVac team
Costs of syringes				
Price per dose	$0.17	$0.17	$0.17	[5]
Percentage international handling	3.5%	3.5%	3.5%	PAHO Revolving Fund
Percentage international delivery	5.0%	5.0%	5.0%	Assumption, ProVac team
Percentage wastage[a]	5.0%	5.0%	5.0%	Assumption, ProVac team
Costs of safety box				
Price per box	$1.96	$1.96	$1.96	[5]
Percentage international handling	3.5%	3.5%	3.5%	PAHO Revolving Fund
Percentage international delivery	5.0%	5.0%	5.0%	Assumption, ProVac team
Percentage wastage[a]	5.0%	5.0%	5.0%	Assumption, ProVac team
Total number of syringes per safety box	100	50	150	Assumption, ProVac team
Incremental health system costs[b]				
% of vaccine delivered at schools	10%	–	–	Assumption, expert opinion
% of vaccine delivered at facilities	90%	–	–	Assumption, expert opinion
Extra system costs per dose (school-based)	$4.55	$2.28	$6.83	National Immunization Program
Extra system costs per dose (facility-based)	$4.55	$2.28	$6.83	National Immunization Program

[a] The % wastage is converted into a factor [1/(1 − % wastage)] that is multiplied by the expected number of doses required to meet the anticipated level of coverage.
[b] Estimated incremental health system costs include infrastructure and logistics investments necessary for the introduction of this new vaccine. They are assumed to only occur in the first year.

Table 4
Input parameters for estimating the health impact of HPV vaccination.

	Estimate	Scenarios		Source
		Low	High	
Coverage in year of introduction				
1 dose	80.0%	70.0%	90.0%	National Immunization Program
2 doses	60.0%	50.0%	70.0%	National Immunization Program
3 doses	50.0%	40.0%	60.0%	National Immunization Program
Booster	60.0%	50.0%	70.0%	National Immunization Program
Vaccine efficacy[a]				
Vaccine efficacy after primary dose 1 (p1)	48.4%	0.0%	96.8%	[37]
Vaccine efficacy after primary dose 2 (p2)	48.4%	0.0%	96.8%	[37]
Vaccine efficacy after primary dose 3 (p3)	94.3%	91.7%	96.8%	[37]
Duration of protection from one dose[b]				
Mean duration of protection (years)	100	20	100	Assumption, ProVac team
Standard deviation	1	1	1	Assumption, ProVac team
Duration of protection from two doses[b]				
Mean duration of protection (years)	100	20	100	Assumption, ProVac team
Standard deviation	1	1	1	Assumption, ProVac team
Duration of protection from three doses[b]				
Mean duration of protection (years)	100	20	100	Assumption, ProVac team
Standard deviation	1	1	1	Assumption, ProVac team
% of cervical cancer caused by types 16/18				
% of types due to 16 and 18	70.0%	52.0%	85.0%	[38]

[a] Reflects vaccine efficacy values among girls who are completely naïve to HPV16/18 infection. As the age of vaccination increases, vaccine efficacy is expected to decrease. We have assumed 94.5% efficacy for girls aged 11 and 93.6% vaccine efficacy for girls aged 12.
[b] We assumed lifelong protection from vaccination.

Table 5
Discounted lifetime health benefits of HPV vaccination in girls aged 11 years.[a]

	No vaccine (status quo)	HPV vaccine		
		With vaccine	Averted	% reduction
Total cervical cancer cases	4476	2539	1937	43
Local cancer	3292	1867	1425	–
Regional cancer	1183	671	512	–
Deaths	528	300	229	43
DALYs	15,429	8752	6677	43
Due to local cervical cancer (YLDs)	3000	1702	1298	–
Due to regional cervical cancer (YLDs)	3962	2248	1715	–
Due to cervical cancer deaths (YLLs)	8467	4803	3664	–

[a] Health benefits are discounted at 5% per year.

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Table 6
Discounted lifetime economic benefits of HPV vaccination in girls aged 11 years (all costs are presented in 2008 US$).[a]

	No vaccine (status quo)	HPV vaccine		
		With vaccine	Averted	% reduction
Total gov. health service costs[b]	$6,977,497	$3,957,836	$3,019,661	43
Local cancer	$4,472,687	$2,537,036	$1,935,651	–
Regional cancer	$2,504,810	$1,420,800	$1,084,010	–
Total health system service costs[c]	$10,855,935	$6,157,798	$4,698,137	43
Local cancer	$7,017,499	$3,980,527	$3,036,972	–
Regional cancer	$3,838,436	$2,177,271	$1,661,165	–
Total societal health service costs[d]	$12,609,382	$7,152,403	$5,456,979	43
Local cancer	$8,106,699	$4,598,352	$3,508,347	–
Regional cancer	$4,502,683	$2,554,051	$1,948,632	–

[a] Costs are discounted at 5% per year.
[b] Government perspective includes direct medical costs: all bed day and disease-specific drug/diagnostic costs borne by the government at the following health providers: health centers and public primary/secondary/tertiary hospitals.
[c] Health system perspective includes direct medical costs: all bed day and disease-specific drug/diagnostic costs borne by the government and private health system at the following health providers: health centers and public and private primary/secondary/tertiary hospitals.
[d] Societal perspective includes as direct medical costs all costs included in the government and health system perspectives. In addition, it includes all household costs incurred when visiting both government and private health providers, and indirect costs of lost productivity.

Table 7
Discounted lifetime incremental cost-effectiveness ratios of HPV vaccination in girls aged 11 years (all costs are presented in 2008 US$).

	Government perspective	Health system perspective	Societal perspective
Cost-effectiveness compared to no vaccine			
Net cost of vaccine introduction	$51,167,398	$49,488,921	$48,730,079
Costs of vaccine introduction	$54,187,058	54,187,058	$54,187,058
Health service costs avoided	$3,019,661	$4,698,137	$5,456,979
DALYs averted	6677	6677	6677
DALYS due to morbidity (YLDs)	3013	3013	3013
DALYs due to mortality (YLLs)	3664	3664	3664
US$ per DALY averted	$7663	$7412	$7298
US$ per case averted	$26,417	$25,556	$25,159
US$ per death averted	$223,800	$216,506	$213,139
Cost-effectiveness threshold			
1 × GDP per capita (2012) – WHO threshold for 'highly cost-effective'		$8121	$8121
3 × GDP per capita (2012) – WHO threshold for 'cost-effective'		$24,364	$24,364

treatment would be reduced by 43% (from US$ 6,977,497 to US$ 3,957,836) in the government perspective (public health system), by 43% (from US$ 10,855,935 to US$ 6,157,798) in the health system perspective (public and private health system), and by 43% in the society perspective (including cancer treatment costs, family costs from transportation, and indirect costs of lost productivity of women) (from US$ 12,609,382 to US$ 7,152,403).

The CERVIVAC model predicted that, over a lifetime, the ICERs would be US$ 7663, US$ 7412, and US$ 7298 per DALY averted, respectively, from the government, health system, and society perspectives (Table 7). The HPV vaccination would be considered a very cost-effective strategy, with ICERs below 1 GDP per capita (US$ 8121) [28].

3.2. Deterministic sensitivity analysis

A series of one-way sensitivity analyses on parameter values were undertaken to test the robustness of the model results. Eleven key parameters were varied one at time while the remaining assumptions were held constant. The horizontal bar graph in Fig. 1 shows the estimated ICER if one model parameter is varied while the other parameter values remain at base case values. Universal HPV vaccination remained a very cost-effective strategy in most variations of the key parameter values. The ICERs were most sensitive to variations in discount rate, disease burden (incidence and mortality rates of local and regional cancers), vaccine efficacy, number of vaccine doses, and vaccine coverage of serotypes 16 and 18.

In the multivariate sensitivity analysis, the ICER varied from US$ 1601 per DALY averted for the favorable scenario to US$ 18,917 for the unfavorable scenario. Even in the unfavorable scenario, the HPV vaccination would be considered a cost-effective strategy, with ICERs below 3 GDP per capita (US$ 24,364).

4. Discussion

Although most published cost-effectiveness studies of HPV vaccination are from high-income countries, an increasing number of studies have been conducted in less developed nations. A systematic review of cost-effectiveness studies of HPV vaccination in low- and middle-income countries [29] identified, as of April 2012, 25 articles, with 9 of the 25 being multi-country studies. For the Latin American and Caribbean region, eight studies were identified; in 3, Brazil was the object of analysis, in either a single-country study or a multi-country analysis.

To these three studies, published in 2007, 2009, and 2012 [27,30,31], we added another study, also published in 2012 [32]. The studies have substantial methodological differences, in terms of sources and values for epidemiological, vaccine, health resource utilization, and cost estimates as well as the models used (three static and one dynamic). This makes direct comparisons with our results very challenging. All the studies indicated that HPV vaccine introduction would be from cost-saving to very cost-effective in almost all scenarios. The most important driver for variation was vaccine cost. However, in recent years that cost has declined noticeably and become more stable with the incorporation of the vaccine in many countries and the participation of PAHO, GAVI Alliance, and the Bill and Melinda Gates Foundation in financing efforts.

Our study was based on a simple Excel one-cohort model that considers only impact on cervical cancer morbidity and mortality. The model is conservative but consistent and useful,

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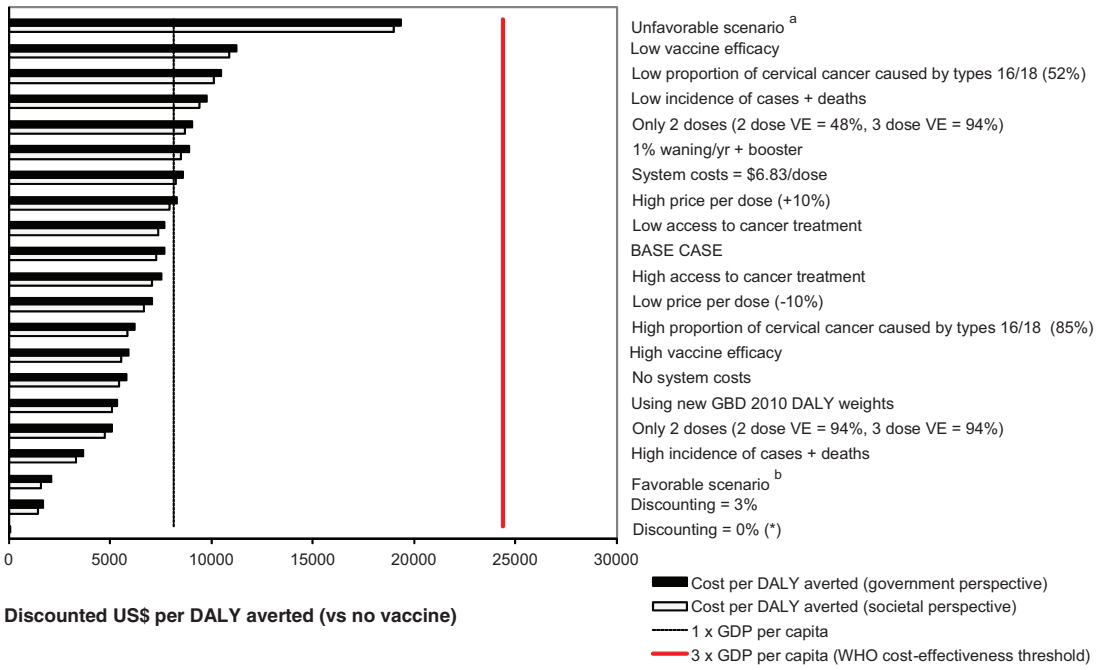

Fig. 1. US$ per DALY averted for base case HPV vaccine scenario and alternative "what-if" scenarios: government perspective and societal perspective (all costs are presented in 2008 US$). (*) Scenario is cost-saving from the societal perspective, i.e., health service costs avoided exceed the cost of introducing the vaccine. [a]Unfavorable scenario uses low incidence of cases, low incidence of deaths, low access to cancer treatment, low vaccine efficacy and low percentage of cervical cancer caused by types 16 and 18. [b]Favorable scenario uses high incidence of cases, high incidence of deaths, high access to cancer treatment, high vaccine efficacy and high percentage of cervical cancer caused by types 16 and 18.

and it has been considered adequate for initial studies of routine vaccination of young girls [33]. This simple model does not fully simulate the natural history of HPV infection and cervical cancer. As it assumes no changes in current or future cervical cancer program screening and treatment practices, it may underestimate future costs, contributing to higher ICERs. As a static model, our cohort model has some limitations. The probability of new infections is age-specific and constant over time, and interactions between individuals are not modeled. Therefore, this model only estimates the direct effects of vaccination on vaccinated groups and does not capture the herd immunity, that is, the indirect effect of vaccination reducing the probability of HPV exposure in unvaccinated groups. This model underestimates the overall effectiveness of HPV vaccination, contributing to higher ICERs. On the other hand, it may overestimate vaccine efficacy, because it does not take into account serotype replacement and waning over time.

While most studies adopted a 3% annual discount rate, we followed Brazilian guidelines [9] and adopted a 5% rate.

Our epidemiological and direct medical cost estimates were based on good quality national data, but vaccination program costs are more subject to uncertainty. Vaccine administration costs are not known in Brazil. In the case of HPV vaccination, a school-based program was implemented for the first time in the country, increasing uncertainty regarding administration costs. More knowledge of these costs is needed for future analyses. Cervical cancer incidence and mortality data were based on studies dedicated to improving the Mortality Information System data, population-based cancer registries, and hospital cancer registries as well as more accurately identifying national temporal tendencies. Since the year 2000 a clear tendency toward lower cervical cancer incidence and mortality rates has been seen in all geographical regions. This has been considered the result of improvements in the national cervical cancer screening program [10,12]. This tendency of declining age-standardized incidence rates has been seen in most countries where effective screening has been in place for a long time, including Brazil, as observed in a study of worldwide trends based on the International Agency for Research on Cancer data [34]. This effect has not been considered in the model.

To develop the estimates of health services utilization and costs of treatment of cervical cancer, this study sought to optimize the use of available data in health information systems and secondary databases. The cost methodology adopted – "gross costing", based on the average reimbursement of procedures is a recommended alternative of costing health services, particularly when from a national perspective. Cost estimates tend to be more conservative, contributing to higher ICERs, but have the advantage of national representativeness, reproducibility and comparability with other studies.

There were discrete differences in the ICERs observed in the three analyses, of the government, health system, and society perspectives. These differences are not very surprising given that the public health system is the most important system in Brazil. Most cervical cancer cases are treated in the public system. The non-medical direct costs and indirect costs are lower than in developed countries, where they tend to impact the results in a society-perspective analysis. But when annual national costs were estimated for Brazil, these costs (private system and indirect costs) were important from an economic point of view [5].

In our sensitivity analysis, the most important variations were with the discount rate, epidemiological and vaccine efficacy estimates. A 2-dose schedule with similar efficacy as the 3-dose schedule showed an important effect, as vaccine cost is still an important cost driver. The cost of HPV vaccine is still a challenge for middle- and low-income countries, so a reduction in the number of doses in the schedule decreases costs of the vaccination program and increases accessibility.

Recent studies showed non-inferiority of antibody levels after two doses of both HPV vaccines administered 6 months apart to girls (9–13 years) in comparison to three doses in young women (16–26 years) [35,36]. For the bivalent vaccine, non-inferiority of antibody levels persisted 21 months after vaccination [36]. The preliminary data are encouraging, but duration of protection after a

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2-dose schedule is still a question. Results of longer follow-up with clinical outcomes are necessary. There is also evidence that immune response may be boosted by revaccination (one dose) administered 5 years after the primary vaccination schedule [37]. These data allowed the use of extended vaccination schedules, such as the one adopted by the Brazilian MoH (0, 6, and 60 months). Although there are no data available on vaccine efficacy/effectiveness with these alternative schedules, the range of efficacy considered in our study is likely to encompass the uncertainty in this variable.

Brazil has just introduced HPV vaccination into its NIP. This study should be reproduced in the future, as part of a vaccination impact analysis. The first results of the effectiveness and population impact of HPV vaccination introduction are being published for developed countries. These results are mostly favorable, as is its safety. Sustainable and good quality surveillance systems are expensive but very important, and should be a priority, as the results of these vaccination programs are still subject to many gaps in scientific knowledge and to social and political factors [2,38].

Conflict of interest statement: No potential conflicts of interest were disclosed.

Funding source: This study is part of a health technology assessment project of introducing new vaccines into the Brazilian National Immunization Program and was supported by the Ministry of Health of Brazil, the National Council of Technological and Scientific Development (CNPq) (576616/2008-7) and National Institute of Science and Technology for Health Technology Assessment (IATS).

Authors' contributions: All authors have reviewed and approved the final version of the article. Hillegonda Maria Dutilh Novaes was responsible for the conception and design of the study. Patrícia Coelho de Soárez, Gulnar Azevedo e Silva, Andreia Ayres, Alex Itria, Cristina Helena Rama, Ana Marli Christovam Sartori, Andrew Clark, and Stephen Resch were responsible for acquisition of data, analysis and interpretation of data; Hillegonda Maria Dutilh Novaes and Patrícia Coelho de Soárez were responsible for drafting the article and revising it critically for important intellectual content. Hillegonda Maria Dutilh Novaes coordinated the study.

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Vaccine 33S (2015) A143–A153

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness analysis of pneumococcal conjugate vaccine introduction in Paraguay

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ARTICLE INFO

Keywords:
Pneumococcal conjugate vaccine
Cost effectiveness
Paraguay

ABSTRACT

Objective: To describe a cost-effectiveness analysis of 10- or 13-valent pneumococcal conjugate vaccine (PCV10 or 13) introduction in Paraguay compared to no vaccination.
Methods: The integrated TRIVAC vaccine cost-effectiveness model (version 2.0) jointly developed by the Pan American Health Organization's ProVac Initiative and the London School of Hygiene & Tropical Medicine was applied from the government and societal perspectives to estimate the cost-effectiveness (CE) of PCV introduction during 2010 and 2011. The cost-effectiveness ratios of PCV10 and PCV13 were separately compared to non-vaccination. The model calculated health and economic benefits of vaccination for 10 birth cohorts of children <5 years of age. A base case scenario with two primary doses at 2 and 4 months and a booster dose at 12 months (2 + 1 schedule) and alternate scenarios with varying parameters were considered.
Results: With PCV10 introduction, the incremental costs of the vaccination program would be approximately US$ 67 million to vaccinate all 10 cohorts of children; with PCV13, US$ 87 million. Health services costs avoided by the government with PCV10 would be US$ 19.5 million; with PCV 13, US$ 17.7 million. From the societal perspective, savings were much greater: with PCV10, US$ 43 million; with PCV13, US$ 35 million. For the higher priced PCV13, the average cost-effectiveness ratio was better than for PCV10 when compared to no vaccination, but regardless both were cost effective for government and society based on a threshold of 3× GDP per capita in Paraguay (2009 US$ 2516). The number of averted meningitis and all-cause pneumonia cases and deaths was greater with PCV13 than with PCV10 when compared to no vaccination.
Conclusion: The introduction of either PCV10 or PCV13 would be cost effective when compared to no vaccination, and in some scenarios, highly cost effective in Paraguay. The outcomes of these analyses demonstrate that a pneumococcal vaccine could substantially reduce morbidity and mortality in children <5 years in Paraguay.

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1. Introduction

Pneumococcus is responsible for meningitis, pneumonia, sinusitis, acute otitis media (AOM), and bacteremia. These diseases are a leading cause of vaccine-preventable deaths and disability in children <5 years of age worldwide. According to the World Health Organization (WHO), in 2008 this pathogen was responsible for 476,000 deaths in children <5 years, with the burden borne mostly by developing countries [1]. In Latin America, an estimated 12,000–28,000 deaths from invasive pneumococcal diseases (IPD) occur annually [2].

Until recently, the only available pneumococcal vaccine was the polysaccharide vaccine which covered 23 disease serotypes,

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http://dx.doi.org/10.1016/j.vaccine.2014.12.078
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but was not effective in children under 2 years of age. Given that the burden of IPD is greatest in children, subsequent research and development focused on a childhood vaccine candidate. The first in a series of three products successfully developed and launched with this goal in mind was the pneumococcal conjugate 7-valent vaccine (PCV7), which protected against serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. It was followed by the 10- (PCV10) and 13-valent vaccines (PCV13), both covering a greater number of serotypes, and therefore, potentially increasing IPD serotype coverage worldwide. PCV10 includes the same seven serotypes as the PCV7, plus 1, 5 and 7F; and PCV13 includes the same 10 as the PCV10, plus 3, 6A and 19A. These two new vaccines are WHO prequalified [1].

In Paraguay, the Expanded Program on Immunization (EPI) was established under the National Health Code as a preventative public health activity in 1980 and it is one of the Ministry of Public Health and Social Welfare (MSPyBS) priority programs [3,4]. In the late 1980s, the EPI routine schedule included only four traditional vaccines: Bacille Calmette-Guérin (BCG) for protection against tuberculosis (TB); Oral Poliomyelitis Vaccine (OPV); Diphtheria–Pertussis–Tetanus (DPT); and Measles–Rubella (MR). Since then, research and innovation have resulted in new vaccines being added to Paraguay's National Immunization Schedule. Currently, the EPI procures vaccines through the PAHO Revolving Fund for Vaccine Procurement to provide protection against 13 diseases, free of charge: BCG, OPV, Rotavirus, Pentavalent (DPT + Hepatitis B and *Haemophilus influenzae* type b [Hib]), MMR (measles, mumps and rubella), YF (yellow fever) and seasonal influenza.

The EPI in Paraguay conducts periodic evaluations, including assessment of surveillance indicators to track disease burden and epidemiological trends, as well as vaccination coverage in target populations. Within this framework, and considering the potential of introducing a PCV, the MSPyBS set out to conduct a cost-effectiveness study to assist national decision makers. The specific objectives were to review, document and evaluate any epidemiological evidence regarding the need to introduce PCV; to assess the potential impact of PCV introduction, incremental program costs, potential savings for the healthcare system and health benefits (cases, sequelae and deaths averted); and to compare the cost-effectiveness of PCV10 to the status quo (no vaccination) and that of PCV13 to the status quo (no vaccination).

2. Methods

2.1. General model description

This study employed the ProVac Initiative's TRIVAC tool, which was developed jointly by PAHO and the London School of Hygiene & Tropical Medicine for the ProVac Initiative as a tool for estimating the cost-effectiveness (CE) of Hib, rotavirus and PCV introduction [5]. The tool evaluates vaccine impact and incremental cost-effectiveness ratios (ICER), providing a coherent and transparent framework for each vaccine, with comparable and standardized outcomes. For this analysis, TRIVAC model version 2.0 was applied [6], utilizing parameters, such as demography, disease burden, vaccine costs, vaccine coverage, vaccine efficacy, vaccine serotype coverage, health service utilization and costs. The TRIVAC model estimates the number of cases, inpatient admissions and deaths, with and without vaccination, for up to 20 birth cohorts. Life-years gained (LYG) are estimated by comparing years of life lost (YLL) and disability adjusted life-years lost (DALYs) with and without vaccination. Average life expectancies and standard methods are used to calculate DALYs. Finally, the model provides an ICER that indicates the cost per DALY averted expressed in United States dollars (US$).

The primary perspective of the study was that of the government, including *the Ministry of Health and Social Security System*, i.e. costs borne by the government. A secondary lens of analysis was from the societal perspective (government, social security and private sector (including family and household)), and included costs borne by the household, such as, out-of-pocket expenses, transportation costs, and food and medicines not otherwise covered. Productivity losses were not considered. Both perspectives captured direct medical costs associated with inpatient and outpatient treatment.

The costs and benefits attributed to each birth cohort were aggregated to provide results for a 10-year vaccination program, thus allowing the model to capture trends in vaccine price and pneumococcal mortality over time. The model provides outcomes for a base case scenario, plus alternate scenarios, so that the impact of uncertainty and changes in key variables can be evaluated.

This study evaluated the cost-effectiveness of both PCV10 and PCV13 versus the status quo (no vaccination) in Paraguay. The model compared health benefits of the vaccine to incremental costs of vaccine introduction and healthcare cost savings from reduced medical visits, inpatient admissions and disease-related sequelae [7–9]. In the base case scenario, a vaccination schedule with two primary doses administered at 2 and 4 months and a booster dose at 12 months (2 + 1 schedule) [2] was considered. Alternate scenarios considered different possible vaccination schedules.

Following the WHO recommendations and MERCOSUR guidelines for the economic evaluation of health technologies, a discount rate of 3% was applied for both health benefits and costs MERCOSUR [10]. An assumption was made that there would not be substantial changes in inflation, health worker salaries, or the cost of supplies and drugs over time, so these were not considered. Alternate scenarios considered the indirect effects of herd protection and serotype replacement; however, the cost of treating adverse events following vaccination was not considered.

2.2. Demographics

The study's target population was children <5 years of age. The analysis evaluated costs and health benefits accrued by 10 birth cohorts beginning in 2010, the year that Paraguayan Ministry of Health determined was a potential year for PCV introduction. Population projections were provided by the *General Directorate of Statistics, Surveys, and Census* (DGEEC) [11]. According to the DGEEC national projections for 1950–2050, in 2010 there were an estimated 151,351 births and 739,448 children <5 years of age. An estimated 58% of children were living in urban areas in 2010, but this is projected to rise to 61% by 2020. Life expectancy at birth is expected to increase as well, by an estimated 3 years for both sexes, to 71 years for males and 76 for females by 2020.

2.3. Disease burden

Epidemiological indicators, including incidence, case-fatality ratio and disease-specific disability weights, were considered in the model to estimate total DALYs with and without the vaccine [12]. Since there are no specific studies or information about IPD incidence in Paraguay, the National Immunization Technical Advisory Group (NITAG), MSPyBS, Asunción, Paraguay was consulted, and it was agreed that incidence data from Latin America would be used [13]. Moreover, data provided by the MSPyBS Department of Biostatistics was used to validate the data obtained from the literature [14–28]. These data systematize the public health network's information on medical visits, inpatient admissions, disabilities and deaths, by disease and *International Classification of Diseases*, 10th edition (ICD-10) codes.

The distribution of IPD cases and deaths, by age, was estimated using medical records of patients with pneumonia and meningitis from the *Instituto de Medicina Tropical* (Institute of

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Tropical Medicine; Asunción, Paraguay; IMT). In children <5 years in Paraguay, the greatest risk of contracting pneumococcal disease is among those <2 years (75.4% of cases), with 35.8% of cases occurring in those 3–8 months of age, and 28.3% in those 12–23 months of age.

Table 1 shows the annual incidence of disease per 100,000 children <5 years for all-cause acute otitis media (AOM), all-cause pneumonia, pneumococcal meningitis and invasive pneumococcal non-pneumonia non-meningitis disease (NPNM). Mortality rates for the latter three syndromes and related sequelae for meningitis are included too [14–23]. Disability weight for DALY was obtained from the literature [24–28], while mean duration of illness and age distribution of disease cases were obtained by review of clinical histories in the *IMT* hospital.

2.4. Vaccination schedule and coverage

In the base case scenario, a PVC vaccination program with two dose primary schedule followed by one booster (2 + 1) was evaluated. In order to estimate coverage per dose in the year of introduction, EPI information on Pentavalent and MMR1 dose coverage over the last 5 years was used. During that period, administrative coverage for the third pentavalent dose showed a decreasing trend, declining from 88% in 2005 to 72% in 2009 [29]. However, other sources, such as surveys by the *Paraguayan Center for Population Studies* (CEPEP) and the DGEEC, report Pentavalent above 90% for the same period, a discrepancy that suggests the denominator could be over-estimated. Therefore, a lower coverage in the first few years of introduction was assumed, with a steady increase towards the universal target for childhood vaccination coverage (>95%) in Latin America and the Caribbean (Table 2). Based on the coverage survey data and considering administrative data for Pentavalent first and second doses and the MMR first dose (coinciding with the PCV booster), a 20% annual decrease was assumed in the gap between final cohort coverage and the ceiling maximum of 95% coverage (the target for all vaccines in the National Immunization Schedule).

2.5. Vaccine efficacy and serotype coverage

The two available pneumococcal vaccines have good safety profiles. In addition, both vaccines have been shown to have immunogenicity greater than or equal to the 7-valent. However, trials to demonstrate clinical efficacy of PCV10 and 13 have not been conducted; therefore, data for 7- and 11-valent efficacy were considered for this cost-effectiveness study [30,31].

The composition of the 10-valent has been show to provide better protection against AOM than the 7-valent. Its composition is similar to that of the 11-valent, which yielded a 33% efficacy in prevention of AOM cases in a clinical trial in the Czech Republic [32]. Therefore, the 11-valent AOM efficacy was used to evaluate the 10-valent in protection against AOM. Table 3 shows a summary of the per-protocol efficacy of the vaccine against pneumonia and IPD as used in the model.

Data on pneumococcal serotypes circulating in the country were obtained from the *Central Public Health Laboratory* (LCSP), MSPyBS, Asunción, Paraguay, for the 2000–2005 and 2006–2009 periods. Samples were obtained from the *Network of Sentinel Surveillance Units of Meningitis and Bacterial Pneumonia* (VIMENE), MSPyBS, Asunción, Paraguay, as well as, from other units participating in routine surveillance. The serotypes with the highest level of circulation in the country were 14, 5 and 6B. The frequency of the serotypes varied in both periods, with a differential increase in the set of serotypes covered by the two vaccines. For the 2006–2009 period, vaccine-specific serotype coverage for PCV10 and PCV13 was 80% and 85%, respectively.

2.6. Healthcare services utilization

The distribution of healthcare service utilization by health sector was estimated based on the DGEEC *2008 Continuous Household Survey* [33], which considered the following questions: If you have been sick or injured in the last 90 days, did you seek treatment? If so, at which facility? According to this source, 54.7% of the respondents received outpatient treatment from the public sector; 13.8% from the *Instituto de Previsión Social* (Social Security Institute, Asunción, Paraguay; IPS); and 31.5% from the private sector, which includes pharmacies and others.

Because data on private sector inpatient admissions is not available, the proportion of these visits was based on interviews with experts. For estimating the distribution of public sector inpatient admissions (the MSPyBS and the IPS), hospital discharge data was used. According to expert opinion, 10% of visits related to pneumonia, meningitis or NPNM were to private hospitals; 20% to IPS, the social security system; and the remaining 70% to public hospitals. The distribution of admissions by treatment level was made based on MSPyBS data on hospital services by facility.

2.7. Costs

2.7.1. Inpatient and outpatient treatment costs [34]

The costs per ambulatory visit and per hospitalization were derived from data for 2009 [35,36], and only recurrent costs of the different services were considered. Neither the cost of infrastructure nor of equipment was considered [37].

Cost data for visits and inpatient admissions were specific to all-cause AOM, all-cause pneumonia, meningitis and bacteremia. Costs for outpatient visits and hospitalizations were estimated at four healthcare facilities: IMT, the General Pediatric Hospital (HGP), IPS and a private sector facility. In each case, the cost of drugs, supplies, laboratory services and radiology was considered. Treatment cost per patient is reported in Table 4 by syndrome, severity of disease and visit type.

Total number of outpatient visits and inpatient admissions per disease episode were obtained from IMT expert opinion. Even if estimations were done for complicated and uncomplicated cases, in the model only the cost of uncomplicated cases was used.

2.7.2. Meningitis sequelae costs

The costs of sequelae were calculated with information provided by the IMT, based on the average cost per year to manage meningitis sequelae cases, including both hearing and neurological disability outcomes.

The cost of hearing sequelae included: outpatient visits, audiometric studies, computed tomography (CT-scan) of the ears, hearing aids, and speech and language therapy. The number of services was averaged for different degrees of severity. The costs of neurological sequelae include: visits, CT-scan and magnetic resonance imaging (MRI) of the brain, speech and language therapy, and education for children with different abilities.

The costs associated with treatment for sequelae were imputed entirely as costs to society, since there are no data on coverage for this type of care in the public sector.

2.7.3. Societal costs

Costs borne by those households accessing care in the private sector were calculated based on payments made by families for visits, diagnosis, hospitalization and treatment, according to the fees charged for these services. In the case of drugs, market value was considered.

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Table 1
Input parameters for estimating disease burden.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Annual incidence per 100,000 aged 1–59 m				
All-cause acute otitis media	90,000	81,000	99,000	Teele et al. [14]
All-cause pneumonia cases	22,000	10,000	29,900	UNICEF/WHO [15]
Pneumococcal meningitis	10.0	5.7	19.9	Duarte et al. [16]
Pneumococcal NPNM	86.0	34.0	116.5	Peter Klemets [17].
% case fatality ratios (CFRs) in ages 1–59 m[a]				
All-cause pneumonia cases	0.04%	0.01%	1.10%	Cálculo en base al anuario estadístico del Paraguay 2008. DGEEC [18]
Pneumococcal meningitis	38.3%	37.17%	45.43%	Lovera, Arbo, [19] & Lovera et al. [20]
Pneumococcal NPNM	12.5%	11.25%	13.75%	Bakir et al. [21]
% Major sequelae (single)	30.0%	–	–	Lovera, Gamarra, & Arbo [22]
% Major sequelae (multiple)	18.0%	–	–	Edmonet al. [23].
Disability weight for DALY calculations				
All-cause acute otitis media	0.02	–	–	Unites States Centers for Disease Control and Prevention [24]
All-cause pneumonia cases	0.28	–	–	Gupta et al. [25]
Pneumococcal meningitis	0.62	–	–	Rudan et al. [26]
Pneumococcal NPNM	0.45	–	–	Rudan, O'Brien, Nair, & Liu et al. [27]
% Major sequelae (single)	0.23	–	–	Russell et al. [28]
% Major sequelae (multiple)	0.47	–	–	Teele et al. [14]
Mean duration of illness (in days)				
All-cause acute otitis media	6	–	–	Instituto de Medicina Tropical (Institute of Tropical Medicine; Asunción, Paraguay; IMT) patient clinical history sheet
All-cause pneumonia cases	6	–	–	IMT, patient clinical history sheet
Pneumococcal meningitis	10	–	–	IMT, patient clinical history sheet
Pneumococcal NPNM	6	–	–	IMT, patient clinical history sheet
Age distribution of disease cases and deaths				
<3 m	3.8%	–	–	IMT, patient clinical history sheet
3–5 m	13.2%	–	–	IMT, patient clinical history sheet
6–8 m	22.6%	–	–	IMT, patient clinical history sheet
9–11 m	7.5%	–	–	IMT, patient clinical history sheet
12–23 m	28.3%	–	–	IMT, patient clinical history sheet
24–35 m	5.7%	–	–	IMT, patient clinical history sheet
36–47 m	9.4%	–	–	IMT, patient clinical history sheet
48–59 m	9.4%	–	–	IMT, patient clinical history sheet

[a] In the absence of vaccination, CFRs are assumed to decline in each successive birth cohort in line with the general trend in under-five mortality. This is done by assuming the fraction of under five deaths caused by the disease remains fixed over time.

Table 2
Input parameters for estimating PCV vaccine coverage and timeliness.

Parameter (m)	Estimate (%)	Scenarios		Source(s)
		Low	High	
Coverage of DTP1 by age in year 2011 (proxy for PCV doses given with DTP1)				
3	64.0	–	–	EPI, Paraguay
6	80.0	–	–	EPI, Paraguay
9	80.0	–	–	EPI, Paraguay
12	80.0	–	–	EPI, Paraguay
24	80.0	–	–	EPI, Paraguay
Coverage of DTP2 by age in year 2011 (proxy for PCV doses given with DTP2)				
3	0.0	–	–	EPI, Paraguay
6	63.2	–	–	EPI, Paraguay
9	79.0	–	–	EPI, Paraguay
12	79.0	–	–	EPI, Paraguay
24	79.0	–	–	EPI, Paraguay
Coverage of DTP3 by age in year 2011 (proxy for PCV doses given with DTP3)				
3	0.0	–	–	EPI, Paraguay
6	54.6	–	–	EPI, Paraguay
9	78.0	–	–	EPI, Paraguay
12	78.0	–	–	EPI, Paraguay
24	78.0	–	–	EPI, Paraguay
Coverage of Measles dose 1 by age in year 2011 (proxy for PCV booster doses given with Measles dose 1)				
3	0.0	–	–	EPI, Paraguay
6	0.0	–	–	EPI, Paraguay
9	0.0	–	–	EPI, Paraguay
12	78.0	–	–	EPI, Paraguay
24	78.0	–	–	EPI, Paraguay

Coverage projections over the period 2011–2020 were estimated by assuming PCV will achieve the same coverage and timeliness as DTP, and by assuming a 20% annual decrease in the gap between final coverage in the cohort (coverage by age 24 m) and a ceiling of 95% (DTP1), 95% (DTP2) and 95% (Measles dose 1).

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Table 3
Input parameters for estimating PCV health benefits.

Parameter	PCV10			PCV13			Source(s)
	Estimate (%)	Scenarios		Estimate (%)	Scenarios		
		Low (%)	High (%)		Low (%)	High (%)	
Vaccine efficacy vs all-cause acute otitis media							
Dose 1	17.0	10.5	34.0	3.0	2.0	6.9	
Dose 2	30.9	19.1	44.3	5.5	3.7	9.0	
Dose 3	33.6	20.8	44.3	6.0	4.0	9.0	Pavia et al. [30], Prymula et al. [32]
Vaccine efficacy vs all-cause pneumonia cases							
Dose 1	1.6	0.5	2.4	1.6	0.5	2.4	
Dose 2	5.3	1.8	7.9	5.3	1.8	7.9	
Dose 3	6.0	2.0	9.0	6.0	2.0	9.0	Lucero et al. [31]
Vaccine efficacy vs vaccine type pneumococcal meningitis/NPNM							
Dose 1	20.9	15.2	23.6	20.9	15.2	23.6	
Dose 2	70.4	51.0	79.2	70.4	51.0	79.2	
Dose 3	80.0	58.0	90.0	80.0	58.0	90.0	Lucero et al. [31]
vaccine serotype coverage							
Pneumococcal meningitis	80.0	74.0	86.0	85.0	80.0	86.0	Central Public Health Laboratory (LCSP); MSPyBS, Asunción, Paraguay.
Pneumococcal NPNM	80.0	74.0	86.0	85.0	80.0	86.0	LCSP)
Other vaccination impact assumptions							
coverage[a]	95	90	100	95	90	100	EPI Paraguay
Decrease in dose efficacy per yr[b]	0.0	0.0	2.0	0.0	0.0	2.0	EPI Paraguay
Contribution of herd effect in <5 yrs[c]	110	100	120	110	100	120	EPI Paraguay
Decline in vaccine type coverage (yr)[d]	2.5	0.0	5.0	2.5	0.0	5.0	EPI Paraguay

[a] Relative coverage is the coverage in those at risk of getting the disease (i.e. effective coverage) relative to coverage in the entire birth cohort (i.e. overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.

[b] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 m, 4–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.

[c] Rather than endogenous modeling of transmission dynamics, the % direct protection <5 yrs is multiplied by a herd effect multiplier (e.g. 120%) to give the % total protection in the cohort of interest before age 5.0 yrs. This excludes any herd effect in individuals aged 5 yrs+ and is therefore very conservative.

[d] Vaccine type disease replacement is handled by reducing the expected vaccine type coverage in successive vaccinated cohorts by a fixed % each year, thus reducing overall expected impact of the program in each successive vaccinated cohort by a similar amount. Thus, for a given vaccinated cohort, the % vaccine type coverage is equal to: $[T \times (1-R)\hat{}N]$ where, T = % of disease caused by vaccine types in the year of vaccine introduction, R = % reduction in vaccine type coverage per year following vaccine introduction, N = number in the sequence of vaccinated birth cohorts.

Additionally, a survey was conducted in the public sector among relatives of IMT inpatients to identify and estimate costs borne by families above and beyond the coverage provided by the government. These family-borne expenses include patient and caregiver transportation, food, and any additional expenses for drugs, laboratory work or radiology. Productivity losses were not considered in this analysis.

2.7.4. Program costs

Program costs were calculated based on the vaccine price per dose adjusted for wastage and estimates of freight, customs, as shown in Table 5. Additionally, costs per dose associated with incremental needs for transportation, training and communication for new vaccine introduction were estimated.

3. Results

The primary outcomes of the analysis summarize the cumulative costs and health benefits among 10 cohorts following the vaccine introductions, based on demographics, disease burden, vaccination coverage, vaccine efficacy, incremental program cost, and healthcare services costs.

WHO defines an intervention as: "highly cost effective" if the ICER is less than the Gross Domestic Product (GDP) per capita of a country in a given year; "cost effective" if the ICER is 1–3 times the GDP per capita; and "not cost effective" if the ICER is more than the 3 times the GDP per capita. Paraguay's GDP per capita for 2009 [38] was US$ 2516. Therefore, using this value as a reference threshold, a health intervention would be considered highly cost effective if the cost per DALY averted were ≤US$ 2516; cost effective, if US$ 2516–7549; and not cost effective, if >US$ 7549.

3.1. Base case

Table 6 shows the primary outcomes for both vaccines in terms of IPD cases and deaths averted, incremental costs to the immunization program and reduction of treatment costs for a cumulative 10 cohorts, from both the government and societal perspectives. Table 6 also summarizes costs per DALY averted. Table 7 shows health benefits of introducing both vaccines compared to no vaccination, in addition to DALYs due to morbidity and mortality. Discounted economic benefits from government health services and societal perspective were calculated, both outpatient and inpatient costs are presented in Table 8.

When comparing the introduction of PCV10 or PCV13 to a scenario of non-vaccination, both vaccines would be considered cost-effective. PCV10 would likely be cost-effective from the government perspective, i.e. considering only costs borne by the government; and highly cost effective from the societal perspective, i.e. considering both costs borne by the government as well as by households. With PCV13, the price per dose is higher than PCV10; therefore, the average cost-effectiveness ratio is higher as well. Still, when compared to a scenario of no vaccination, PCV13 would be cost-effective from both the government and societal perspectives. In terms of impact, PCV13 would likely reduce more

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Table 4
Input parameters for estimating health service utilization and costs (all costs are presented in 2009 US$).

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Outpatient visits				
Outpatient visits per disease episode				
All-cause acute otitis media	0.40	0.36	0.44	Instituto de Medicina Tropical (Institute of Tropical Medicine; Asunción, Paraguay; IMT) expert opinión
All-cause pneumonia cases	0.70	0.63	0.77	IMT expert opinion
Pneumococcal meningitis	1.00	0.90	1.00	IMT expert opinion
Pneumococcal NPNM	1.00	0.90	1.00	IMT expert opinion
Government cost per outpatient visit[a]				
All-cause acute otitis media	$9	$8	$10	IMT, Pedriatric General Hospital (HGP), Lambaré Hospital, Instituto de Previsión Social (Social Security Institute,IPS), Private Sector, Asunción, Paraguay
All-cause pneumonia cases	$19	$17	$21	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Pneumococcal meningitis	$17	$16	$19	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Pneumococcal NPNM	$17	$15	$18	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Household cost per outpatient visit[b]				
All-cause acute otitis media	$20	$18	$22	IMT, HGP, Lambaré Hospital, IPS, Private Sector
All-cause pneumonia cases	$25	$23	$28	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Pneumococcal meningitis	$36	$33	$40	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Pneumococcal NPNM	$42	$38	$46	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Inpatient admissions				
Inpatient admissions per disease episode				
All-cause pneumonia cases	0.50	0.40	0.72	Instituto de Medicina Tropical (Institute of Tropical Medicine; Asunción, Paraguay; IMT) Expert opinión
Pneumococcal meningitis	1.00	0.90	1.10	IMT Expert opinion
Pneumococcal NPNM	0.35	0.32	0.39	IMT Expert opinion
Government cost per inpatient admission[c]				
All-cause pneumonia cases	$498	$395	$482	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Pneumococcal meningitis	$964	$868	$1061	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Pneumococcal NPNM	$731	$658	$804	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Household cost per inpatient admission[d]				
All-cause pneumonia cases	$238	$181	$221	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Pneumococcal meningitis	$412	$371	$453	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Pneumococcal NPNM	$206	$185	$226	IMT, HGP, Lambaré Hospital, IPS, Private Sector
Meningitis sequelae				
Government cost of meningitis sequelae per year[e]				
Major sequelae (single)	$0	$0	$0	
Major sequelae (multiple)	$0	$0	$0	
Household cost of meningitis sequelae per year[f]				
Major sequelae (single)	$1362	$1226	$1498	Private Sector, Asunción, Paraguay
Major sequelae (multiple)	$3865	$3479	$4252	Private Sector, Asunción, Paraguay

[a] Government costs per outpatient visit include physician's wages, administrative costs, drugs and diagnostics costs. The cost presented is the weighted average of the provider-specific costs.

[b] Household costs per outpatient visit include out-of-pocket payments for consultations, drugs, diagnostics and travel expenses. The cost presented is the weighted average of the provider-specific costs. Outpatient visits are distributed as follows: Public Sector 47.1%, 12.4% Social Security hospital, 40.5% Private Sector.

[c] Government costs per inpatient admission include the cost per bed day multiplied by the expected length of stay (6 days for pneumonia, 7 days for pneumococcal meningitis and NPNM) and the cost of any disease-specific drugs and diagnostics. The cost presented is the weighted average of the provider-specific costs.

[d] Household costs per inpatient admission include out-of-pocket payments for hospitalization, diagnostics, drugs and travel expenses. Productivity losses to families due to lost wages are not included. The cost presented is the weighted average of the provider-specific costs. Inpatient admissions are distributed as follows: 70% Public Sector, 20% Social Security hospital, and 10% Private Sector.

[e] Sequelae costs borne by the Government is excluded because all sequelae costs are paid by households.

[f] Sequelae costs borne by households include travel expenses, out-of-pocket payments for consultations and drugs and are applied annually from the age of meningitis onset until full life expectancy. These costs are included and discounted over time in the base case (best estimate) scenario.

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Table 5
Input parameters for estimating PCV10 and PCV13 program costs.

Parameter	PCV10			PCV13			Source(s)
	Estimate	Scenarios		Estimate	Scenarios		
		Low	High		Low	High	
Vaccine dose price projection							
2011	$14.85	$14.85	$14.85	$20.00	$20.00	$20.00	OPS. Boletín de Inmunización. Volumen 23 No. 1 Febrero del 2011. http://www.paho.org/immunization
2012	$14.85	$14.55	$14.85	$20.00	$19.60	$20.00	Assumption
2013	$14.85	$14.26	$14.85	$20.00	$19.21	$20.00	Assumption
2014	$14.85	$13.98	$14.85	$20.00	$18.82	$20.00	Assumption
2015	$14.85	$13.70	$14.85	$20.00	$18.45	$20.00	Assumption
2016	$14.85	$13.42	$14.85	$20.00	$18.08	$20.00	Assumption
2017	$14.85	$13.15	$14.85	$20.00	$17.72	$20.00	Assumption
2018	$14.85	$12.89	$14.85	$20.00	$17.36	$20.00	Assumption
2019	$14.85	$12.63	$14.85	$20.00	$17.02	$20.00	Assumption
2020	$14.85	$12.38	$14.85	$20.00	$16.67	$20.00	Assumption
2021	$14.85	$12.13	$14.85	$20.00	$16.34	$20.00	Assumption
2022	$14.85	$11.89	$14.85	$20.00	$16.01	$20.00	Assumption
2023	$14.85	$11.65	$14.85	$20.00	$15.69	$20.00	Assumption
2024	$14.85	$11.42	$14.85	$20.00	$15.38	$20.00	Assumption
2025	$14.85	$11.19	$14.85	$20.00	$15.07	$20.00	Assumption
2026	$14.85	$10.97	$14.85	$20.00	$14.77	$20.00	Assumption
2027	$14.85	$10.75	$14.85	$20.00	$14.48	$20.00	Assumption
2028	$14.85	$10.53	$14.85	$20.00	$14.19	$20.00	Assumption
2029	$14.85	$10.32	$14.85	$20.00	$13.90	$20.00	Assumption
2030	$14.85	$10.12	$14.85	$20.00	$13.62	$20.00	Assumption
Other vaccine dose costs							
International handling (% of vaccine price):	17.00%	15.00%	20.00%	17.00%	15.00%	20.00%	EPI, Paraguay Purchase Order
International delivery (% of vaccine price):	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	EPI Paraguay Purchase Order
Wastage (% of doses discarded etc)[a]	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	EPI Paraguay Purchase Order
Safety box cost (100 syringes per box)							
Price of each safety box	$1.24	–	–	$1.24	–	–	EPI Paraguay Purchase Order
International handling (% of vaccine price):	17.00%	–	–	17.00%	–	–	EPI Paraguay Purchase Order
International delivery (% of vaccine price):	0.00%	–	–	0.00%	–	–	EPI Paraguay Purchase Order
Wastage (% of doses discarded etc)[a]	5.00%	–	–	5.00%	–	–	EPI Paraguay Purchase Order
Incremental system costs of introduction[b]							
Incremental system cost per dose	$2.90	$2.90	$2.90	$2.90	$2.90	$2.90	EPI Paraguay Data

[a] The % wastage is converted into a factor [1/(1 – % wastage)] which is multiplied by the expected number of doses required to meet the anticipated level of coverage.
[b] Estimated incremental system costs include publicity (72% of cost), additional salaries (21% of cost),and others (additional distribution, capacitation) (7% of cost). They are assumed to only occur in the first year only/they are assumed to be recurrent costs each year.

deaths and cases of meningitis and pneumonia in children <5 years than PCV10.

With PCV10 introduction, the incremental costs of the vaccination program would be approximately US$ 67 million to vaccinate all 10 cohorts of children; with PCV13, it would be US$ 87 million, which reflects the differential price per dose available in Paraguay at the time of analysis. Health services costs avoided to the government would be US$ 19.5 million with PCV10 and US$ 17.7

Table 6
Discounted cost-effectiveness of PCV (10 cohorts vaccinated over the period 2011–2020).

	PCV10		PCV13	
	Government perspective	Societal perspective	Government perspective	Societal perspective
Cost-effectiveness compared to no vaccine				
Net cost of vaccine introduction	$47,474,013	$23,675,660	$69,126,188	$51,577,532
Costs of vaccine introduction	$67,051,958	$67,051,958	$86,905,789	$86,905,789
Health service costs avoided	$19,577,945	$43,376,298	$17,779,601	$35,328,257
DALYs averted	12,328	12,328	14,106	14,106
YLDs averted—DALYS due to morbidity	1537	1537	1334	1334
YLLs averted—DALYs due to mortality	10,791	10,791	12,772	12,772
US$ per DALY averted	$3851	$1920	$4901	$3657
Cost-effectiveness of PCV13 compared to PCV10				
Net cost of vaccine introduction	–	–	$21,652,175	$27,901,872
Costs of vaccine introduction	–	–	$19,853,831	$19,853,831
Health service costs avoided	–	–	–$1798,345	–$8048,041
DALYs averted	–	–	1778	1778
YLDs averted - DALYS due to morbidity	–	–	(203)	(203)
YLLs averted - DALYs due to mortality	–	–	1981	1981
US$ per DALY averted	–	–	$12,181	$15,696
Cost-effectiveness threshold				
1× GDP per capita (2009)—WHO threshold for 'highly cost-effective'	$2516	$2516	$2516	$2516
3× GDP per capita (2009)—WHO threshold for 'cost-effective'	$7549	$7549	$7549	$7549

Costs and DALYs are discounted at 3% per year.

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Table 7
Discounted health benefits (10 cohorts vaccinated over the period 2011–2020).

	No vaccine (status quo)	PCV10		PCV13	
		With vaccine	Averted	With vaccine	Averted
Total cases <5 yrs	6958,169	5612,609	1345,560	6636,663	321,506
All-cause acute otitis media	5586,597	4297,297	1289,300	5328,371	258,226
All-cause pneumonia admissions	1365,613	1311,855	53,758	1305,315	60,298
Pneumococcal meningitis	621	360	261	310	311
Pneumococcal NPNM	5338	3097	2242	2667	2671
Total outpatient visits	1901,933	1571,201	330,732	1813,587	88,346
All-cause acute otitis media	1329,610	1022,757	306,854	1268,152	61,458
All-cause pneumonia admissions	568,778	546,388	22,390	543,664	25,114
Pneumococcal meningitis	369	214	155	185	185
Pneumococcal NPNM	3176	1843	1334	1587	1589
Total inpatient admissions	616,766	591,634	25,132	588,511	28,255
All-cause pneumonia admissions	614,526	590,335	24,191	587,392	27,134
Pneumococcal meningitis	559	324	235	279	280
Pneumococcal NPNM	1682	975	706	840	841
Total deaths <5 yrs	1324	959	365	893	432
All-cause pneumonia admissions	498	479	20	477	22
Pneumococcal meningitis	217	126	91	109	108
Pneumococcal NPNM	609	354	255	307	302
Total children with permanent disability	194	112	82	96	98
Sequelae group A	121	70	51	60	61
Sequelae group B	73	42	31	36	37
DALYs Lost	49,443	37,115	12,328	35,337	14,106
YLDs—DALYS due to morbidity	10,271	8734	1537	8937	1334
YLLs—DALYs due to mortality	39,172	28,381	10,791	26,400	12,772

Health benefits are discounted at 3% per year.

million with PCV 13. When the societal perspective is considered, the treatment cost savings are much greater: US$ 43 million with PCV10 and US$ 35 million with PCV13. The latter perspective yields more favorable cost-effectiveness results for the vaccines because additional costs incurred by families are included in the averted treatment costs.

3.2. Scenario analysis

Alternative scenarios were also modeled by changing some parameters in the base case scenario, making it possible to evaluate the model's robustness and the impact of these changes on primary outcomes (Figs. 1 and 2). The disease incidence, vaccine

Table 8
Discounted economic benefits (10 cohorts vaccinated over the period 2011–2020).

	No vaccine (status quo)	PCV10		PCV13	
		With vaccine	Averted	With vaccine	Averted
Total government health service costs[a]	$380,408,354	$360,830,409	$19,577,945	$362,628,753	$17,779,601
Total outpatient visit costs	$38,224,959	$32,864,841	$5360,118	$36,450,727	$1774,232
All-cause acute otitis media	$19,944,152	$15,341,349	$4602,803	$19,022,284	$921,868
All-cause pneumonia admissions	$18,181,767	$17,466,038	$715,729	$17,378,964	$802,803
Pneumococcal meningitis	$10,831	$6283	$4548	$5411	$5420
Pneumococcal NPNM	$88,210	$51,171	$37,039	$44,068	$44,142
Total inpatient admission costs	$342,183,395	$327,965,568	$14,217,827	$326,178,026	$16,005,369
All-cause pneumonia admissions	$340,218,489	$326,825,717	$13,392,772	$325,196,389	$15,022,100
Pneumococcal meningitis	$598,573	$347,235	$251,338	$299,038	$299,535
Pneumococcal NPNM	$1,366,333	$792,616	$573,717	$682,599	$683,734
Total sequelae costs*	$0	$0	$0	$0	$0
Major sequelae (single)	$0	$0	$0	$0	$0
Major sequelae (multiple)	$0	$0	$0	$0	$0
Total societal health service costs[b]	$626,338,266	$582,961,968	$43,376,298	$591,010,009	$35,328,257
Total outpatient visit costs	$107,933,204	$91,104,384	$16,828,819	$102,875,280	$5,057,924
All-cause acute otitis media	$65,032,460	$50,023,971	$15,008,489	$62,026,498	$3,005,961
All-cause pneumonia admissions	$42,555,084	$40,879,895	$1,675,190	$40,676,095	$1,878,989
Pneumococcal meningitis	$33,262	$19,295	$13,967	$16,617	$16,645
Pneumococcal NPNM	$312,398	$181,223	$131,174	$156,069	$156,328
Total inpatient admission costs	$504,990,342	$484,119,876	$20,870,466	$481,504,140	$23,486,202
All-cause pneumonia admissions	$502,384,989	$482,608,499	$19,776,490	$480,202,545	$22,182,444
Pneumococcal meningitis	$854,315	$495,592	$358,723	$426,803	$427,512
Pneumococcal NPNM	$1751,038	$1015,785	$735,253	$874,792	$876,246
Total sequelae costs*	$13,414,720	$7737,707	$5677,013	$6630,588	$6784,132
Major sequelae (single)	$4962,943	$2862,662	$2100,282	$2453,069	$2509,874
Major sequelae (multiple)	$8451,777	$4875,046	$3576,731	$4177,519	$4274,257

Costs are discounted at 3% per year.

[a] Government perspective includes direct medical costs related to the treatment—all bed day and disease-specific drug/diagnostic, hospital supplies, costs borne by the government at the following health providers: Health Centre, Public 1ary/2ary/3ary hospital.

[b] Societal perspective includes household expenditures, such as, out-of-pocket expenses, transportation costs, food and medicines not otherwise covered and all costs included in the Government perspective. In addition it includes all household costs incurred when visiting both Government and Private health providers. Productivity losses were not considered in this analysis.

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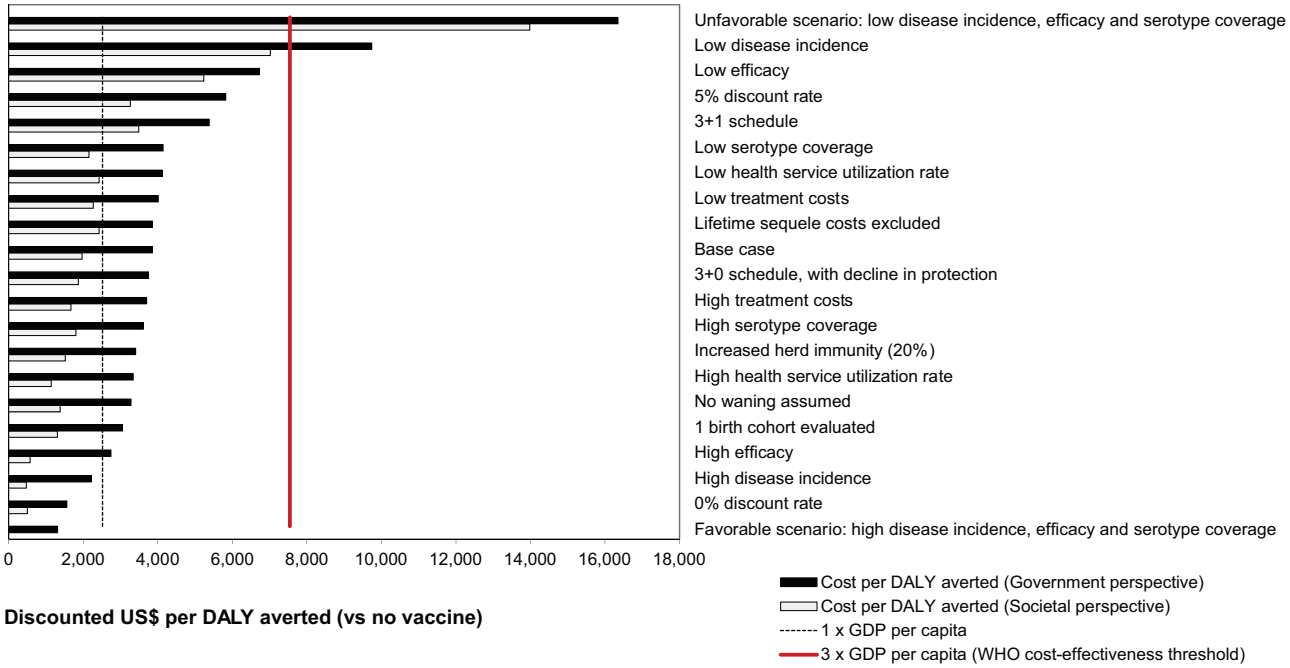

Fig. 1. US$ per DALY averted for PCV10 base case scenario and alternative 'what-if' scenarios: government perspective and societal perspective.

efficacy and vaccine serotype coverage were the variables with the greatest impact on the outcomes of the model and the CE ratio. The sensitivity of the following variables was also evaluated: treatment cost estimates (±10%), hospitalization rate assumptions (±10%), and assumptions about the presence and absence of herd effects (0 and 20%).

With regard to disease burden inputs, scenario analysis was performed on all incidence data. For AOM, an alternative scenario assumed 10% lower and 10% higher incidence. For pneumonia, incidence due to all causes, the minimum scenario was estimated with data from the MSPyBS Department of Biostatistics and the maximum scenario used WHO Global Burden of Disease project estimates. For cases of meningitis and pneumococcal NPNM, the minimum scenario considered the possibility that half of the cases occur; the maximum scenario doubled the number. Mortality and permanent sequelae in the minimum and maximum scenarios were estimated applying approximately 10% to the base scenario.

The use of the on-label vaccination schedule (3 + 1) and the exclusion of sequelae costs were also taken into account in separate scenarios. The former because of the difficulty to estimate all sequelea cost (Figs. 1 and 2). Although the values of the cost-effectiveness ratio are higher, all scenario results that consider the PCV 13 introduction are similar to those of PCV10. In the 3 + 1 schedule, despite it being more costly, the outcome continues to be cost effective for

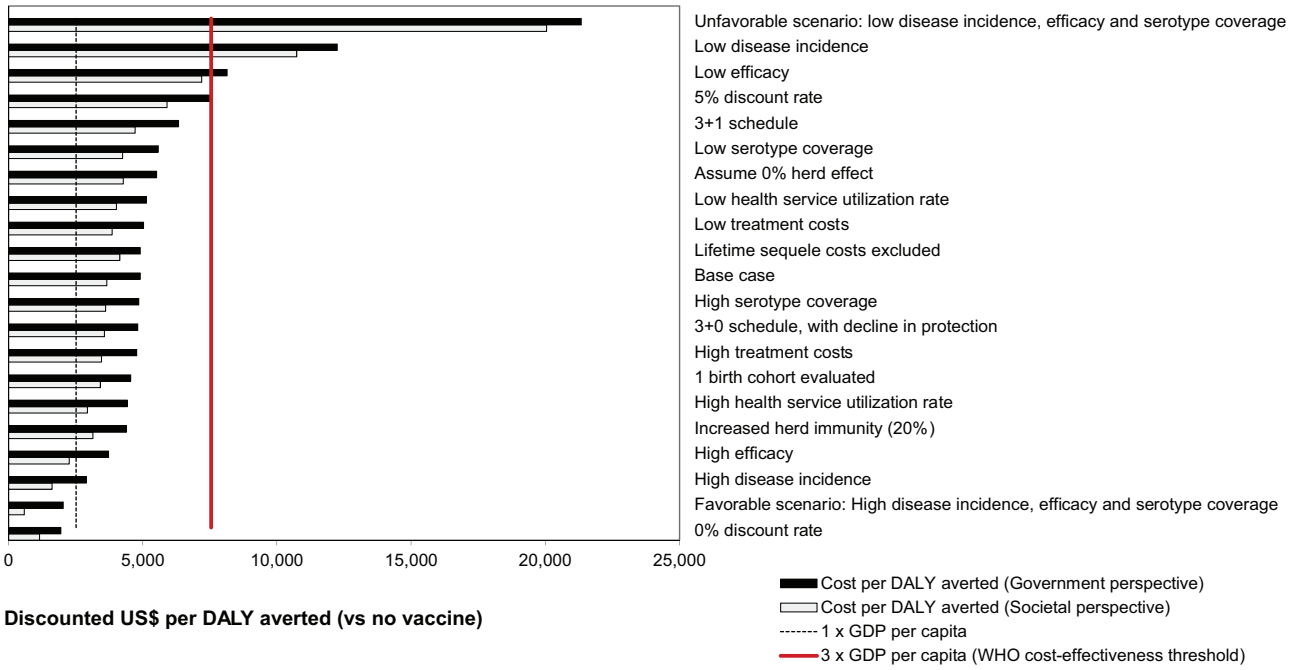

Fig. 2. US$ per DALY averted for PCV13 base case scenario and alternative 'what-if' scenarios: government perspective and societal perspective.

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both vaccines considering both perspectives, government as well as societal.

According to these scenarios, it was noted that at lower than estimated incidence rates, introduction of either vaccine would not be cost effective, neither from the government nor the societal perspective. The same was true when combining low incidence, low efficacy and reduced serotype coverage. However, these scenarios are considered pessimistic and very unlikely.

4. Discussion

This is one of many PCV cost-effectiveness analyses conducted with support from the PAHO ProVac Initiative in Latin America and the Caribbean [39]. Most of these national analyses show PCV introduction to be cost-effective or highly cost-effective at PAHO Revolving Fund prices [40,41]. The TRIVAC tool and its outcomes allowed national authorities in Paraguay to consider projected numbers of averted IPD cases and deaths, vaccine introduction costs, and the savings gained from reduced treatments costs, for both the government, as well as society.

The results of this study were presented to the Paraguayan Technical Advisory Committee on Immunization. Based on its results and other technical criteria, the committee recommended to include PCV10 in the childhood National Immunization Schedule, stating in 2012, utilizing three doses for children <1 year of age and one single dose for those 12–23 months.

Although both PCV10 and PCV13 were both shown to be cost effective when compared to no vaccination in Paraguay, the decision regarding which vaccine to introduce was based on a number of factors. Of the many factors, the important drivers in the decision making process were the evaluation of impact on IPD cases and deaths, as well as, serotype circulation in the country. Importantly, the national decision makers substantially valued the potential disease reduction in AOM and associated health services costs that PCV10 demonstrated in this analysis.

Another factor considered was the vaccine unit cost and the aggregate impact on the EPI budget. For PCV10 introduction, a price of US$ 14.85 per dose for each of the three doses per child was taken into account. Under these circumstances, the EPI budget would have increased approximately 43%. With PCV13 introduction, a price of US$ 20.00 for each of the same number of doses would have increased EPI budget by approximately 57%. Introduction of either vaccine would account for approximately 4% and 6% of the MSPyBS total budget, respectively, returning to 2005–2007 budgetary levels.

At the time of this analysis, the PAHO Revolving Fund offered only PCV10. The fact that the fund uses a transparent procurement method with significant benefits for the country was taken into account when the Paraguayan Technical Advisory Committee on Immunization recommended to use the 10-valent and the Ministry of Health opted for this vaccine in their final decision.

4.1. Limitations

This analysis had some limitations primarily due to the scarcity of epidemiological and disease burden data in Paraguay. The data used were obtained from the public sector and international literature. In addition, the distribution of outpatient visits was estimated based on data from a household survey and on expert opinion for inpatient admissions; the same distribution was used for all of the diseases taken into consideration.

Also, cost estimates for some diseases, such as AOM, may be overestimated since figures were based on referral hospitals. Outside of the capital city, however, costs may be lower. Costs for meningitis and NPNM were more likely to be accurate since these diseases are usually treated at the referral facilities.

Societal costs could also have been underestimated since loss of productivity was not included. In addition, the estimated cost of sequelae was made only at the household level, not at the government level, since this information is not available.

These limitations should not, however, significantly affect interpretation of the model outcomes. The different scenarios proposed sought to mitigate the limitations found, and although the cost per DALY varied, the outcomes clearly show that PCV vaccine introduction is cost effective.

4.2. Conclusions

This study shows that PCV vaccination in Paraguay would reduce morbidity and mortality in children <5 years. Additionally, the findings show that both vaccines would be cost-effective in a range of scenarios when compared to no vaccination, and even highly cost effective in some scenarios. The findings of this study aided national health authorities with decision making, allowing for a more transparent and explicit process, and preventing potential conflicts of interest.

In addition to the outcomes of a CE analysis, the decision regarding which of the PCVs to introduce should take into account their impact on prevention of IPD cases and related deaths, serotypes circulating at the local level, and cost savings related to avoided treatment, especially AOM treatment, among other important criteria. Another critical consideration is affordability. In the case of Paraguay, despite the financial impact PCV introduction demonstrated to have on the EPI budget, perhaps even doubling it, finding a fiscal space for vaccine introduction was possible considering the substantial cost savings—generated by reduced medical visits, inpatient admissions, laboratory work, radiology and drugs. In Paraguay, the cost effectiveness of adding PCV10 to the National Immunization Schedule was made clear by the outcomes of the cost analysis performed with the TRIVAC model.

Conflict of interest statement

The authors declare that they have no conflict of interests.

Acknowledgements

The authors gratefully acknowledge discussions with Dra. Esperanza Martinez, Minister of Public Health; the Paraguayan Technical Advisory Committee on Immunization; and the important help received from the Instituto de Medicina Tropical to estimate costs: Dr. Oscar Merlo, General Director; Lic. Ana Sosa, Head of Nurses; and Lic. Julia Guirlán, Head of the Administrative Department.

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Vaccine 33S (2015) A154–A166

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Cost-effectiveness analysis of 10- and 13-valent pneumococcal conjugate vaccines in Peru

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ARTICLE INFO

Keywords:
Pneumococcal conjugate vaccine
Cost effectiveness
Disability adjusted life years
Children
Peru

ABSTRACT

Objective: To evaluate the cost-effectiveness of introducing the 10-valent pneumococcal conjugate vaccine (PCV10) versus the 13-valent PCV (PCV13) to the National Immunization Schedule in Peru for prevention of pneumococcal disease (PD) in children <5 years of age.
Methods: The integrated TRIVAC vaccine cost-effectiveness model from the Pan American Health Organization's ProVac Initiative (version 2.0) was applied from the perspective of the Government of Peru. Twenty successive cohorts of children from birth to 5 years were evaluated. Clinical outcomes were pneumococcal pneumonia (PP), pneumococcal meningitis (PM), pneumococcal sepsis (PS) and acute otitis media from any causes (AOM). Measures included prevention of cases, neurological sequelae (NS), auditory sequelae (AS), deaths and disability adjusted life years (DALYs). A sensitivity analyses was also performed.
Findings: For the 20 cohorts, net costs with PCV10 and PCV13 were US$ 363.26 million and US$ 408.26 million, respectively. PCV10 prevented 570,273 AOM; 79,937 PP; 2217 PM; 3049 PS; 282 NS; 173 AS; and 7512 deaths. PCV13 prevented 419,815 AOM; 112,331 PN; 3116 PM; 4285 PS; 404 NS; 248 AS; and 10,386 deaths. Avoided DALYs were 226,370 with PCV10 and 313,119 with PCV13. Saved treatment costs were US$ 37.39 million with PCV10 and US$ 47.22 million with PCV13. Costs per DALY averted were US$ 1605 for PCV10, and US$ 1304 for PCV13. Sensitivity analyses showed similar results. PCV13 has an extended dominance over PCV10.
Conclusion: Both pneumococcal vaccines are cost effective in the Peruvian context. Although the net cost of vaccination with PCV10 is lower, PCV13 prevented more deaths, pneumococcal complications and sequelae. Costs per each prevented DALY were lower with PCV13. Thus, PCV13 would be the preferred policy; PCV10 would also be reasonable (and cost-saving relative to the status quo) if for some reason 13-valent were not feasible.

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1. Introduction

Streptococcus pneumoniae (SP) is an important cause of pneumonia, meningitis and other invasive pneumococcal diseases (IPD) in children <5 years of age, especially in developing countries [1–3]. Each year, IPD is the cause of over half a million deaths in children <5 years worldwide [4], with more than 10,000 of those deaths in Latin America and the Caribbean (LAC) [5]. It is estimated to be the most common cause of vaccine-preventable deaths in children <5 years in the region of the Americas [5] and IPD treatment is responsible for a significant economic burden [6].

Although there are more than 90 serotypes of SP [7], not all cause disease. The new pneumococcal conjugate vaccines (PCV) protect against the serotypes most commonly associated with invasive disease [4,8]. In Peru, the 7-valent PCV (PCV7) was added to the

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http://dx.doi.org/10.1016/j.vaccine.2014.12.039
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National Immunization Schedule in 2009 by the *National Immunization Program of the Ministry of Health (MINSA)* [9]. PCV7 had been proven effective in preventing IPD [8] and providing modest protection against all-cause acute otitis media (AOM) [10].

In 2011, however, PCV7 was withdrawn from the global market and replaced by higher valence vaccines: the 10-valent (PCV10) (Synflorix®, GlaxoSmithKline) and the 13-valent (PCV13) (Prevenar 13®, Wyeth/Pfizer). PCV10 added three additional serotypes—1, 5 and 7F—plus a Non-Typeable *Haemophilus influenzae* (NTHi) protein carrier that could protect against AOM [11]. PCV13 covers an additional three—3, 6A and 19A (i.e., six more than PCV7) [12]. Evidence shows that their safety and immunogenicity profiles of these higher valences vaccines are similar to that of PCV7 and they do not interference with other vaccines in young children [11,12]. Since these two higher valence vaccines differ in serotypes covered, NTHi protein carrier, and unit price per dose, their impact as a public health intervention could differ. Economic evaluations (EE) should play an important role in decision-making regarding their adoption [13].

In this context, the *National Institute of Health* of Peru (Instituto Nacional de Salud, INS), the MINSA scientific research branch that provides evidence for public health decision-making, with support from the ProVac Initiative of the Pan American Health Organization (Washington, DC, USA; PAHO) [14,15], carried out this EE. The study objective was to evaluate the cost-effectiveness of introducing the PCV10 versus the PCV13 to the National Immunization Schedule for prevention of IPD in children <5 years of age in Peru.

2. Methods

2.1. General modeling approach and comparators

This study employed the TRIVAC cost-effectiveness model, developed by the London School of Hygiene and Tropical Medicine in collaboration with the PAHO ProVac Initiative [14,15]. The pneumococcal component of TRIVAC (version 2.0) [16] was adapted for Peru to conduct the cost-effectiveness analysis (CEA) from the perspective of the Government of Peru, including direct costs borne by its public health system—MINSA and the *EsSalud* Social Security System [17].

Since PCV7 had been withdrawn from the market, PCV10 and PCV13 were compared to having no PCV vaccination program. The incremental cost-effectiveness of the less costly vaccine was compared to that of the more costly to estimate whether the additional benefits would be worth the additional cost.

The TRIVAC model was populated with data on demographics, disease burden, local vaccine serotype distribution, vaccine efficacy, health services utilization, health service costs and vaccination program costs.

It followed 20 stacked cohorts of children from birth to death. IPD cases and deaths were only considered for the first 5 years of life, but permanent meningitis sequelae, life-years gained (LYG) and Disability Adjusted Life-Years (DALY) were calculated over the life-time of each birth cohort. The model estimated the number of cases, deaths and sequelae due to *S. pneumonia*, as well as associated costs in scenarios with and without vaccination. These outputs were then used to calculate health impact (e.g., DALYs averted), economic impact (e.g., net costs, incremental program costs and treatment costs averted), cost-effectiveness (e.g., cost-per-death averted) and cost-utility (e.g., cost-per-DALY averted). The results from each cohort were combined and used to report both the cumulative and annual health benefits and costs associated with each scenario [16].

DALYs were estimated using the disability weights defined for each disease syndrome by the World Health Organization (WHO) [18] and the life-expectancy-at-birth estimated for each cohort by the *National Institute of Statistics and Informatics* of Peru (INEI), using validated international methods [19]. A 3% discount rate for both costs and benefits was used and did not include age weighting (preference for life-years gained during productive years of life) [20,21]. A Gross Domestic Product Per Capita (GDP-PC) for the year 2011 of US$ 6009 (1 US$ = 2.80 PEN [Peruvian Nuevos Soles]) was used as the cost-effectiveness threshold.

The model calculated the number of cases of all-cause AOM, pneumococcal pneumonia, pneumococcal meningitis and pneumococcal sepsis by multiplying the incidence rate by the estimated life-years at risk between birth and 5 years of age. Life-years at risk were calculated for each birth cohort using projections for the number of births and the infant and child mortality rate. Fig. 1 shows the general model structure. In the scenario with vaccination, the total number of averted cases was estimated by multiplying the number of cases in each age group (<3 months, 3–5 months, 6–8 months, 9–11 months, 12–23 months, 24–35 months, 36–47 months, 48–59 months) by the dose- and age-specific program coverage (using DTP1/2/3 timing of vaccination as a proxy), the dose-specific vaccine efficacy and the vaccine-type coverage. Other factors were varied in "what-if" scenario analysis (e.g., waning protection, herd effects <5 years, serotype replacement, low efficacy, low program coverage). Deaths were estimated by applying the reported case-fatality ratio (CFR) to estimates of the number of cases post-vaccination. Pneumococcal meningitis sequelae were obtained by multiplying meningitis survivors (total estimated cases minus deaths) by the estimated proportion of those children that would develop neurological and auditory sequelae [16].

Costs were estimated based on the number of children vaccinated according to vaccine coverage per dose and adjusted for wastage, freight, handling and extra system costs, which included all other incremental costs, in addition to the vaccine and supply procurement. An average number of ambulatory visits and hospitalizations were estimated for disease type and multiplied by the weighted average cost per case. The cost per case was derived from the proportion receiving care by provider type and the associated treatment cost per provider. To estimate the life-time costs associated with meningitis sequelae, an average estimated annual cost until death was assigned [16].

2.2. Demographics

INEI provided data on the number of live births per year, infant mortality rate and life expectancy at birth for each of the 20 cohorts. Mortality rate in children <5 years of age was obtained from United Nations Department of Economic and Social Affairs' Population Division [22]. This demographic information was included for each of the 20 birth cohorts (2012–2031) and four previous cohorts (2008–2011). The latter was needed to calculate more accurate 'annual' events and the cost of the first 5 years of the vaccination program.

2.3. Disease burden

Pneumococcal pneumonia, pneumococcal meningitis, pneumococcal sepsis and all-cause acute otitis media were evaluated. AOM was included due to the etiologic role of NTHi in this disease [23,24]. Disease burden data on pneumococcal syndromes in Peru is sparse, and there are concerns about how representative the available data is and whether the full extent of disease is being detected in laboratories. Consequently, we have included a description of how disease incidence and CFRs were derived for each syndrome studied; Table 1 shows the estimates. Low and high range estimates were defined to explore the "what if" scenario analysis.

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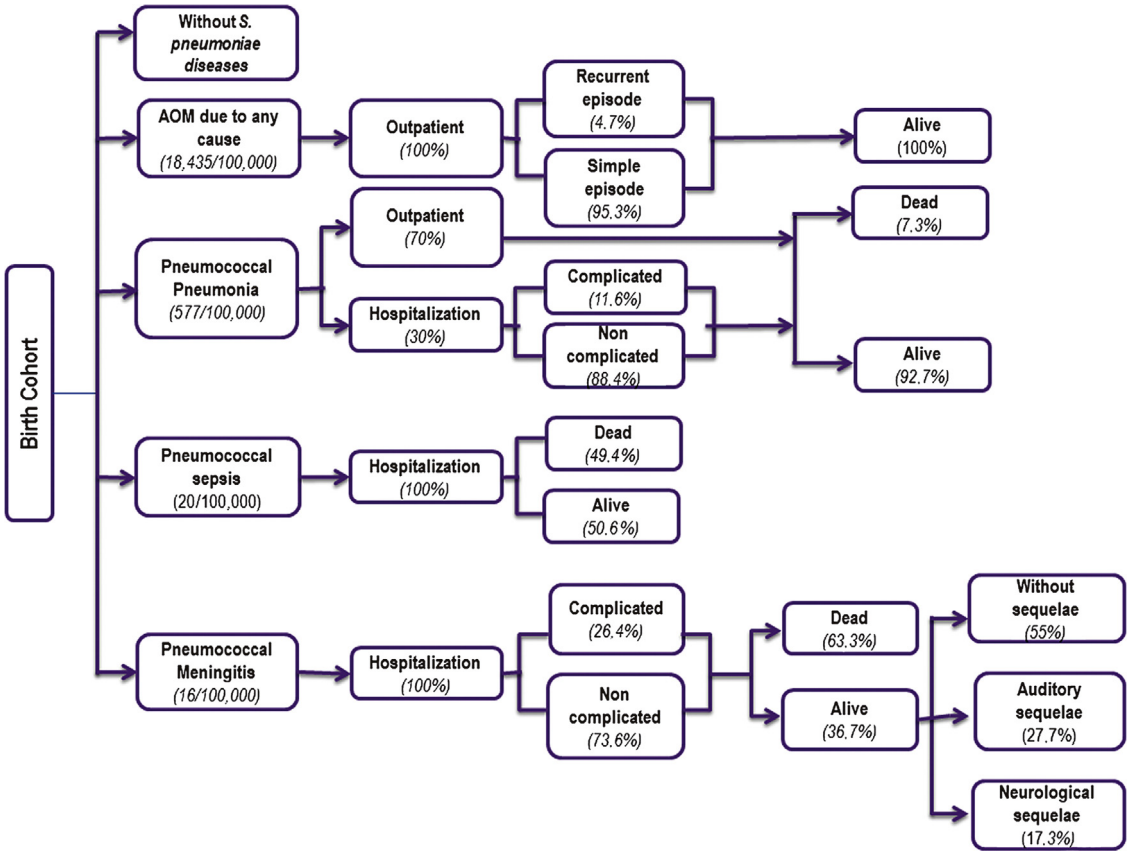

Fig. 1. Conceptual framework for the model and invasive pneumococcal disease burden in Peru.

2.3.1. Pneumococcal pneumonia

For the base case, estimates of cumulative incidence and case fatality rates for pneumococcal pneumonia in Peru were taken from a systematic review by O'Brien and colleagues [3]. For the scenario analysis, the cumulative incidence of pneumococcal pneumonia estimates were derived from primary data: cases of clinical pneumonia reported by MINSA and EsSalud, the percentage of radiologically confirmed pneumonia cases projected in a systematic review of LAC data [5], and the proportion of molecular confirmations of *S. pneumoniae* from radiological pneumonia reported in a primary study of a Peruvian population [25].

2.3.2. Pneumococcal meningitis

Cumulative incidence and case fatality rates for pneumococcal meningitis came from O'Brien's and colleagues estimations [3]. Also, the proportions of auditory and neurological sequelae were based on a systematic review by Baraff and colleagues [26].

2.3.3. Non-pneumonia non-meningitis is pneumococcal diseases (NPNM): pneumococcal sepsis

No reliable data on cumulative incidence of pneumococcal sepsis in Peru was found. Thus, estimates reported by O'Brien [3] were used: a ratio of 1.27 cases of NPNM for each case of Pneumococcal meningitis in countries with <75 deaths per 100,000 live births (Peru). Also, pneumococcal-specific sepsis case fatality was assumed to be 78% of the case fatality rate for pneumococcal meningitis, based on the same systematic review [3].

2.3.4. Acute otitis media

The base case cumulative incidence of AOM used came from data reported by Rudan and colleagues [27]. However, two other estimates were assessed in the "what if" scenario analysis, one based on outpatient reports from the Peruvian ambulatory care health system, and the other, on data published by Teele and colleagues [28]. The TRIVAC model assumes that there are no AOM cases severe enough to lead to hospitalization or to be a cause of death [16].

2.3.5. Disability weights, distribution of disease cases and deaths by age

The disability weights due to pneumococcal cases, as well as auditory and neurological sequelae, came from the Global Burden of Disease: 2004 Update [18]. The distribution of cases and deaths by age were taken from Hortal and colleagues [29] who evaluated the incidence of pneumococcal serotypes in pediatric inpatients <5 years of age in Uruguay. This report was used because the baseline distribution of pneumococcal serotypes (pre-vaccination period) in Uruguay was similar to the distribution reported in Peru [30].

2.4. Vaccine impact

2.4.1. Vaccination schedule and coverage

The approved National Immunization Schedule for PCV7 in Peru included two primary doses at 2 and 4 months of age, plus a booster at 12–18 months (PCV2 + 1) [4,31,32]. Vaccination coverage was assumed based on coverage levels achieved with PCV7 for 2011, which were 99.2% for the first dose, 95.8% for the second and 92.5% for the booster. The model also assumed that vaccination coverage could have an annual increase of 5%, up to a possible maximum of 99%. Moreover, coverage and timing estimates were based on Diphtheria, Pertussis and Tetanus (DPT) vaccine coverage as showed in Table 2 [33]. On the other hand, the coverage reported by the Peruvian Demographic and Family Health Survey (ENDES) [34] was considered for the "what-if" scenario analysis as low coverage,

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Table 1
Input parameters for estimating disease burden of all causes acute otitis media, pneumococcal pneumonia, pneumococcal meningitis and pneumococcal sepsis in Peru (2011).

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Annual incidence per 100,000 children 1–59 months of age				
All causes acute otitis media	18,435	2552	90,000	Rudan I, and colleagues [27] (estimate), Teele and colleages [28]. (High), Peruvian statistics (Low)
Pneumococcal pneumonia	577	63	718	O'Brien, and colleagues [3] (estimate and high), Modified Peruvian statistics[c] (low) [5,25]
Pneumococcal meningitis	16.0	12.0	19.0	O'Brien, and colleagues [3] (estimate, high and low)
Pneumococcal NPNM (sepsis)[a]	22.0	21.9	68.0	O'Brien, and colleagues [3] (estimate, High and low)
% case fatality ratios in ages 1–59 m[b]				
All causes pneumonia cases	7.3%	6.3%	9.9%	O'Brien, and colleagues [3] (estimate, high and low)
Pneumococcal meningitis	63.3%	54.9%	72.6%	O'Brien, and colleagues [3] (estimate, high and low)
Pneumococcal NPNM (sepsis)[a]	49.4%	49.4%	49.4%	O'Brien, and colleagues [3] (estimate, high and low)
% sequelae in pneumococcal meningitis survivors				
% Auditory sequelae	27.7%	–	–	Baraff and colleagues [26]
% Neurological sequelae	17.3%	–	–	Baraff and colleagues [26]
Disability weight for DALY calculations				
All causes acute otitis media	0.02	–	–	WHO[d] Global Burden of Disease (GBD) 2004 [18]
Pneumococcal pneumonia cases	0.26	–	–	WHO GBD 2004 [18]
Pneumococcal meningitis	0.62	–	–	WHO GBD 2004 [18]
Pneumococcal NPNM (sepsis)[a]	0.26	–	–	PROVAC Model assumption
% Auditory sequelae	0.12	–	–	WHO GBD 2004 [18]
% Neurological sequelae	0.38	–	–	WHO GBD 2004 [18]
Mean duration of illness (in days)				
All causes acute otitis media	7	–	–	Delphi whit Peruvian physicians
Pneumococcal pneumonia cases	6	–	–	Delphi whit Peruvian physicians
Pneumococcal meningitis	10	–	–	Delphi whit Peruvian physicians
Pneumococcal NPNM (sepsis)[a]	6	–	–	Delphi whit Peruvian physicians
Age distribution of disease cases and deaths (in months)				
<3 m	9.4%	–	–	Hortal and colleagues [29]
3–5 m	9.4%	–	–	Hortal and colleagues [29]
6–8 m	9.8%	–	–	Hortal and colleagues [29]
9–11 m	9.8%	–	–	Hortal and colleagues [29]
12–23 m	28.6%	–	–	Hortal and colleagues [29]
24–35 m	15.3%	–	–	Hortal and colleagues [29]
36–47 m	8.9%	–	–	Hortal and colleagues [29]
48–59 m	8.9%	–	–	Hortal and colleagues [29]

[a] All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).
[b] In the absence of vaccination, Case Fatality Ratios are assumed to decline in each successive birth cohort in line with the general trend in under-five mortality. This is done by assuming the fraction of under five deaths caused by the disease remains fixed over time.
[c] Peruvian statistics provided clinical pneumonia cases, Which was modified for obtaining pneumococcal pneumonia estimations.
[d] WHO = World Health Organization.

which assumes 69.0% for the first dose, 65.6% for the second and 62.3% for the booster.

2.4.2. *Vaccine effectiveness estimations*

Both PCV10 and PCV13 were licensed based on WHO' immunological non-inferiority criteria for correlation of protection in efficacy trials of PCV7 [4]. The efficacy of both of the newer pneumococcal vaccines was based on a meta-analysis of PCV7 clinical data that estimated 81% efficacy (PCV3 + 1 schedule) [8]. Efficacy was multiplied by the serotype coverage of each vaccine. Serotype distribution was obtained from sentinel surveillance in Peru [30].

The efficacy of PCV10 to prevent AOM was extrapolated from a study carried out in Czech Republic and Slovakia that assessed a PCV11 prototype [35] and reported a 33.6% efficacy in preventing all-cause AOM. PCV10 includes Haemophilus Influenzae Type b (Hib) surface protein D as a carrier—possibly providing additional protection against NTHi, an important cause of AOM—and is similar in composition to the PCV11 prototype [24,36]. Efficacy for PCV13 in preventing AOM cases was directly extrapolated from the meta-analysis of PCV7 clinical data [37]. However, given that the frequency distribution of etiologic agents for AOM may vary by country, the effectiveness of each vaccine was weighted according to Eq. (1), which takes into account the proportional distribution of Hib and *S. pneumoniae* in Peru, together with the country-specific pneumococcal serotype coverage. The proportion of cases of AOM caused by *S. pneumoniae* and NTHi was 32.4% and 18.3%, respectively, based on the meta-analysis published by Bardach and colleagues [36]. The proportional vaccine coverage of pneumococcal AOM (excluding cross-protection serotypes) was 58% for PCV10 and 70% for PCV13 [38]. Therefore, the weighted effectiveness to prevent AOM cases was 12.3% for PCV10 and 7% for PCV13 (Table 3).

Estimation of PCV efficacy against AOM:

$$\text{Efficacy} = \%\text{Spc} \times \text{ESpc} + \%\text{Spnc} \times \text{ESpnc} + \%\text{NTHi} \times \text{ENTHi} \quad (1)$$

where:

%Spc: Proportion of AOM cases due to *S. pneumoniae* serotypes included in PCV.
%ESpc: Efficacy against serotypes *S. pneumoniae* serotypes included in PCV.
%Spnc: Proportion of AOM cases due to *S. pneumoniae* serotypes not included in PCV.
%Espnc: Efficacy against serotypes *S. pneumoniae* serotypes not included in PCV.
%NTHi: Proportion of AOM cases due to NTHi.
ENTHi: Efficacy against NTHi (relative negative effect for PCV13 and positive effect for PCV10).

The estimated efficacy of 2 + 1 schedule against vaccine-type IPD was assumed to be similar to the 3 + 1 efficacy per the WHO Strategic Advisory Group of Experts (SAGE) on Immunization [4]. For a two-doses and one dose were estimated based on the report by

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Table 2
Input parameters for estimating coverage and timing of pneumococcal conjugate vaccine (PCV) in Peru, 2012–2031[a]

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Coverage of DTP1 by age in year 2012 (proxy for PCV doses given with DTP1)				
3 m	85.9%	59.8%	86.6%	
6 m	95.9%	66.7%	96.7%	Clark and
9 m	96.7%	67.3%	97.5%	Sanderson
12 m	98.0%	68.2%	98.8%	[33]
24 m	98.3%	68.4%	99.1%	
Coverage of DTP2 by age in year 2012 (proxy for PCV doses given with DTP2)				
3 m	16.8%	11.5%	17.6%	
6 m	89.0%	60.9%	92.9%	Clark and
9 m	92.7%	63.5%	96.8%	Sanderson
12 m	94.0%	64.4%	98.1%	[33]
24 m	95.5%	65.4%	99.7%	
Coverage of DTP3 by age in year 2012 (proxy for PCV doses given with DTP3)				
3 m	0.0%	0.0%	0.0%	
6 m	75.6%	50.9%	81.8%	Clark and
9 m	84.2%	56.7%	91.0%	Sanderson
12 m	86.9%	58.5%	94.0%	[33]
24 m	91.5%	61.6%	98.9%	
Coverage of Measles dose 1 by age in year 2012 (proxy for PCV booster doses given with Measles dose 1)				
3 m	0.5%	0.5%	0.5%	
6 m	0.6%	0.6%	0.6%	Clark and
9 m	1.0%	1.0%	1.0%	Sanderson
12 m	13.4%	13.6%	13.6%	[33]
24 m	89.4%	90.8%	90.8%	

[a] Coverage projections over the period 2012–2031 were estimated by assuming PCV will achieve the same coverage and timeliness as DTP, and by assuming a 0% annual decrease in the gap between final coverage in the cohort (coverage by age 24 m) and a ceiling of 100% (DTP1), 99% (DTP2) and 99% (DTP3) and 100% (Measles dose 1).

Mahon and colleagues [39] and Urueña and colleagues, respectively [40].

2.4.3. Vaccine serotype coverage

Based on sentinel surveillance reports of bacterial pneumonia and meningitis among children <5 years in Peru for the period 2000–2008 (before introduction of PCV7) [30], we estimated a 70.8% coverage from serotypes included in PCV10 and 81.3% for those in PCV13. The estimated distributions were concordant to the findings of a report from several hospitals in Lima [41]. Table 3 shows the estimated impact of each of the vaccination alternatives by clinical syndrome, relative efficacy and serotype coverage for the base case.

2.4.4. Relative coverage of deaths

This parameter adjusts vaccine coverage to account for the effective coverage of children who would have contracted IPD or, more importantly, would have died if the population had not been vaccinated, as a percent of overall national coverage. A 90% relative coverage of deaths was assumed [16].

2.4.5. Indirect effects of vaccination

Serotype replacement is a phenomenon characterized by an increase in IPD cases caused by serotypes not included in the vaccines, such as previously reported for serotype 19A [42]. Because 19A is not included in PCV10, we estimated an overall 1.3% reduction in disease protection with each successive vaccinated cohort; whereas for PCV13, the reduction assumed was 1.25%. The base case scenario did not consider herd effect; however, the "what if" scenario analysis did consider it for unvaccinated children <5 years of age, for both vaccines, with an assumed 10% effect [43].

Table 3
Input parameters for estimating PCV10 and PCV13 impact in Peru, 2012–2031.

Parameter	PCV10			PCV13			Source/s
	Estimate	Scenarios		Estimate	Scenarios		
		Low	High		Low	High	
Vaccine efficacy versus all-cause acute otitis media							
Dose 1	6.5%	6.5%	25.8%	3.9%	3.0%	6.9%	Urueña and colleagues [40]
Dose 2	11.8%	11.8%	33.6%	7.1%	5.5%	9.0%	Mahon and colleagues [39]
Dose 3	12.8%	12.8%	33.6%	7.7%	6.0%	9.0%	Prymula and colleagues(PCV10) [35], Pavia and colleagues(PCV13) [37]
Vaccine efficacy versus vaccine type pneumococcal pneumonia/pneumococcal meningitis/pneumococcal NPNM (sepsis)[e]							
Dose 1	41.0%	31.9%	74.8%	41.0%	31.9%	74.8%	Urueña and colleagues [40]
Dose 2	74.5%	58.0%	97.4%	74.5%	58.0%	97.4%	Mahon and colleagues [39]
Dose 3	81.0%	63.0%	97.4%	81.0%	63.0%	97.4%	Lucero and colleagues [8]
% vaccine serotype coverage							
Pneumococcal pneumonia cases	70.8%	70.8%	70.8%	81.3%	81.3%	81.3%	SIREVA-Peruvian Surveillance [30]
Pneumococcal meningitis	70.8%	70.8%	70.8%	81.3%	81.3%	81.3%	SIREVA-Peruvian Surveillance [30]
Pneumococcal NPNM (sepsis)[a]	70.8%	70.8%	70.8%	81.3%	81.3%	81.3%	SIREVA-Peruvian Surveillance [30]
Other vaccination impact assumptions							
% relative coverage[b]	90%	90%	100%	90%	90%	100%	TRIVAC assumption [16]
% decrease in dose efficacy per year[c]	1.3%	0.0%	5.0%	1.3%	0.0%	5.0%	TRIVAC assumption [16]
Decline in vaccine type coverage/year [d,e]	2.5%	0.0%	5.0%	0.0%	0.0%	5.0%	TRIVAC assumption [16]

[a] All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).
[b] Relative coverage is the coverage in those at risk of getting the disease (i.e., effective coverage) relative to coverage in the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.
[c] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 months, 4–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.
[d] We did not include a herd effect multiplier according to Peruvian physicians' expert opinion (Delphi) for case base. However, we use herd effect multiplier in scenario analyses.
[e] Vaccine type disease replacement is handled by reducing the expected vaccine type coverage in successive vaccinated cohorts by a fixed % each year, thus reducing overall expected impact of the program in each successive vaccinated cohort by a similar amount. Thus, for a given vaccinated cohort, the % vaccine type coverage is equal to: $[T^*(1-R)N]$ where, T = % of disease caused by vaccine types in the year of vaccine introduction, R = % reduction in vaccine type coverage per year following vaccine introduction, N = number in the sequence of vaccinated birth cohorts.

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Table 4
Input parameters for estimating health service utilization and costs (in 2012 US$) in Peru.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Outpatient visits				
Outpatient visits per disease episode				
All causes acute otitis media	0.79	0.79	0.79	Delphi whit Peruvian physicians
Pneumococcal pneumonia cases	0.68	0.68	0.68	Delphi whit Peruvian physicians
Government cost per outpatient visit				
All causes acute otitis media[a]	$18	$18	$134	Average Peruvian cost (estimate and low), Peruvian private sector cost (High)
Pneumococcal pneumonia cases[b]	$41	$41	$171	Average Peruvian cost (estimate and low), Peruvian private sector cost (High)
Inpatient admissions				
Inpatient admissions per disease episode				
Pneumococcal pneumonia cases	0.30	0.30	0.30	DGE-Ministry of Health
Pneumococcal meningitis	0.75	0.75	0.75	Delphi whit Peruvian physicians
Pneumococcal NPNM (sepsis)	1.00	1.00	1.00	Delphi whit Peruvian physicians
Government cost per inpatient admission				
Pneumococcal pneumonia cases[c]	$643	$643	$1585	Average Peruvian cost (estimate and low), Peruvian private sector cost (High)
Pneumococcal meningitis[d]	$1148	$1148	$3225	Average Peruvian cost (estimate and low), Peruvian private sector cost (High)
Pneumococcal NPNM (sepsis)[e]	$2806	$2806	$5241	Average Peruvian cost (estimate and low), Peruvian private sector cost (High)
Meningitis sequelae				
Government cost of meningitis sequelae per year[f]				
Auditory sequelae	$80	$50	$150	Average Peruvian cost (estimate and low), Peruvian private sector cost (High)
Neurological sequelae	$113	$50	$150	Average Peruvian cost (estimate and low), Peruvian private sector cost (High)

[a] Government costs per outpatient visit (all cause acute otitis media) include Ministry of Health and Social Security. Outpatients visits are distributed as follows: 88.8% Ministry of Health, 11.1% Social security. The cost presented is the weighted average of the provider-specific costs.
[b] Government costs per outpatient visit (pneumococcal pneumonia) include Ministry of Health and Social Security. Outpatients visits are distributed as follows: 78.4% Ministry of Health, 21.6% Social security. The cost presented is the weighted average of the provider-specific costs.
[c] Government costs per inpatient admission (pneumococcal pneumoniae) include Ministry of Health and Social Security [the cost per bed day multiplied by the expected length of stay and the cost of any disease-specific drugs and diagnostics]. Inpatient admissions are distributed as follows: 77% Ministry of Health, 23% Social security. The cost presented is the weighted average of the provider-specific costs.
[d] Government costs per inpatient admission (pneumococcal meningitis) include Ministry of Health and Social Security [the cost per bed day multiplied by the expected length of stay and the cost of any disease-specific drugs and diagnostics]. Inpatient admissions are distributed as follows: 97.2% Ministry of Health, 2.8% Social security. The cost presented is the weighted average of the provider-specific costs.
[e] Government costs per inpatient admission (pneumococcal sepsis) include Ministry of Health and Social Security [the cost per bed day multiplied by the expected length of stay and the cost of any disease-specific drugs and diagnostics]. Inpatient admissions are distributed as follows: 83.1% Ministry of Health, 16.9% Social security. The cost presented is the weighted average of the provider-specific costs. All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).
[f] Sequelae costs borne by the Government include Ministry of Health and Social Security and are applied annually from the age of meningitis onset until full life expectancy. These costs are included and discounted over time in the base case (best estimate) scenario.

2.4.6. Health services utilization and costs

The ENDES estimations show that 51.9% and 22.6% of children <5 years are covered by the SIS (Seguro Integral de Salud) of MINSA and EsSalud as public insurance modalities [34]. Treatment for childhood pneumococcal disease in the Police and Armed Forces Health Service Sector or by the Private Sector was excluded from this analysis. Data on health services utilization was provided by MINSA and EsSalud.

To define routine treatment protocols for each of the clinical syndromes analyzed, a cross-sectional survey of pediatricians was conducted. These were chosen by a stratified random sample with proportional distribution to the number of physicians in each region of the country. Of the 100 pediatricians invited to participate nationwide, 76 accepted. Participants completed an AOM questionnaire developed with the support of the Peruvian Society of Pediatrics and ad hoc questionnaires developed by PAHO for invasive disease, pneumonia, and meningitis [16]. Disease management of auditory and neurological sequelae was obtained directly from experienced physicians from the National Rehabilitation Institute. The proportion of pneumonia cases requiring inpatient treatment was provided by the MINSA and EsSalud.

Cost savings to the health system due to the prevention of pneumococcal clinical syndromes were estimated according to the type of health provider, complexity of care level and the type of management (outpatient or inpatient).

Unit costs for health care services were based on the cost of public sector care, using official documents delineating standard pricing methodology used by MINSA [44]. Medication costs were based on the Peruvian Observatory of Pharmaceutical Products, mandatory for MINSA and EsSalud [45].

A survey on health care utilization was completed by the 76 Peruvian physicians to estimate the number of medical procedures and medication quantities prescribed for each condition. Table 4 summarizes the input parameters for estimating health care services utilization and costs from the perspective of the Government of Peru.

2.4.7. Vaccination program costs

Vaccine unit prices were obtained from the PAHO Revolving Fund. In the year of analysis (2012), the price per dose of PCV10 was US$ 14.24 and of PCV13 was US$ 16.34. These prices were adjusted for capitalization of the PAHO Revolving Fund (3.5% of dose price), delivery, freight and insurance (15% of dose price).

All additional costs incurred by the health system were estimated at US$ 1.40 per dose, which included expansion of cold chain, transportation, materials, training, supervision and monitoring. An annual decrease rate of 2% over the vaccine price was assumed. The price of the safety box was valued at US$ 0.64 per unit, with each box holding a maximum of 150 syringes. In addition, safety boxes were subject to a delivery expense of 7.5% over price, plus an estimated 20% wastage; no extra cost was assumed for capitalization. Also additional was the cost per syringe: US$ 0.16, plus an 8% adjustment factor for freight/handling and 1% for wastage. This information was provided by the MINSA National Department of Supplies and Strategic Resources in Health (DARES). Table 5 shows the input parameters for PCV10 and PCV13 program costs, including estimations for all predicted birth cohorts.

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Table 5
Input parameters for estimating PCV10 and PCV13 program costs in Peru, 2012–2031.

Parameter	PCV10			PCV13			Source/s
	Estimate	Scenarios(US$)		Estimate	Scenarios(US$)		
	(US$)	Low	High	(US$)	Low	High	
Vaccine dose price projection							
2012	$14.24	$14.24	$14.24	$16.34	$16.34	$16.34	PAHO Revolving Fund
2013	$13.96	$12.82	$14.24	$16.01	$14.71	$16.34	National Team estimations
2014	$13.68	$11.53	$14.24	$15.69	$13.24	$16.34	National Team estimations
2015	$13.40	$10.38	$14.24	$15.38	$11.91	$16.34	National Team estimations
2016	$13.13	$9.34	$14.24	$15.07	$10.72	$16.34	National Team estimations
2017	$12.87	$8.41	$14.24	$14.77	$9.65	$16.34	National Team estimations
2018	$12.61	$7.57	$14.24	$14.47	$8.68	$16.34	National Team estimations
2019	$12.36	$6.81	$14.24	$14.19	$7.82	$16.34	National Team estimations
2020	$12.11	$6.13	$14.24	$13.90	$7.03	$16.34	National Team estimations
2021	$11.87	$5.52	$14.24	$13.62	$6.33	$16.34	National Team estimations
2022	$11.64	$4.97	$14.24	$13.35	$5.70	$16.34	National Team estimations
2023	$11.40	$4.47	$14.24	$13.08	$5.13	$16.34	National Team estimations
2024	$11.17	$4.02	$14.24	$12.82	$4.61	$16.34	National Team estimations
2025	$10.95	$3.62	$14.24	$12.57	$4.15	$16.34	National Team estimations
2026	$10.73	$3.26	$14.24	$12.31	$3.74	$16.34	National Team estimations
2027	$10.52	$2.93	$14.24	$12.07	$3.36	$16.34	National Team estimations
2028	$10.31	$2.64	$14.24	$11.83	$3.03	$16.34	National Team estimations
2029	$10.10	$2.37	$14.24	$11.59	$2.73	$16.34	National Team estimations
2030	$9.90	$2.14	$14.24	$11.36	$2.45	$16.34	National Team estimations
2031	$9.70	$1.92	$14.24	$11.13	$2.21	$16.34	National Team estimations
Other vaccine dose costs							
International handling (% of vaccine price)	3.50%	1.22%	1.22%	3.50%	1.22%	1.22%	PAHO Revolving Fund
International delivery (% of vaccine price)	22.00%	1.22%	1.22%	22.00%	1.22%	1.22%	PAHO Revolving Fund
Wastage (% of doses discarded etc.)[a]	1.00%	0.00%	0.00%	1.00%	0.00%	0.00%	Ministry of Health-Ministry of Health
Safety box cost (150 syringes per box)							
Price of each safety box	0.64	–	–	0.64	–	–	DARES-Ministry of Health
International handling (% of vaccine price)	0.00%	–	–	0.00%	–	–	DARES-Ministry of Health
International delivery (% of vaccine price)	7.52%	–	–	7.52%	–	–	DARES-Ministry of Health
Wastage (% of doses discarded etc.)[a]	20.00%	–	–	20.00%	–	–	PROVAC estimations
Incremental system costs of introduction							
Incremental system cost per dose	1.00	1.00	1.00	1.00	1.00	1.00	National Estrategy of Inmunizations-Ministry of Health

[a] The % wastage is converted into a factor [1/(1 – % wastage)] that is multiplied by the expected number of doses required to meet the anticipated level of coverage.

2.5. Sensitivity analysis and "what if" scenarios

A one-way sensitivity analysis was conducted, varying each input systematically by ±10% and recording the % change in the discounted US$ per DALY averted. Since an important aspect of an EE is analysis of results under different assumptions [20,46], this study modified the base case assumptions and parameters to create and analyze different scenarios.

We generated a scenario of low pneumococcal disease incidence based on statistics that were lower than the expected incidence projected for Peru by the WHO pneumococcal burden report [18]; meningitis and invasive NPNM disease were below the lower limit of the 95% CI of the incidence for each disease reported in the systematic review [3]. Additionally, a scenario of high AOM incidence was estimated based on data from the study by Teele and colleagues [28]. Moreover, we created a scenario of low and high case fatality rates based on the lower and upper confidence interval limits from the meta-analysis by O'Brien and colleagues [3].

We assumed a scenario of low efficacy of PCV13 in preventing AOM cases taking the point estimate of 6% from the meta-analysis of Pavia and colleagues and one high efficacy of 9% from the same study [37]. The high efficacy scenario for the effect of PCV10 on AOM cases was 33.6% based on Prymula and colleagues [35]. For other syndromes, we considered a high efficacy of 97.4% against vaccine serotypes for both PCVs based on the study of Black and colleagues [47] and a low efficacy of 85% against vaccine serotypes from the meta-analysis by Lucero and colleagues [8]. Additionally, we proposed a scenario without reduced efficacy over time and another that incorporated a herd effect of 10% for both PCVs.

We also incorporated a scenario with low immunization coverage based on data from the ENDES survey. Its coverage proportions were lower than those provide by the NIS and used in the base case analysis. Additionally, a scenario with a reduction (80%) and another with an increase (100%) of the relative coverage of deaths for both PCVs were included.

We used estimated costs of private sector health care services to build a scenario of higher ambulatory and inward costs in the public sector. We proposed a scenario with a discount rate of 5% [20,21] and one analyzing only 10 birth cohorts. Regarding the price of the vaccine, we evaluated the effect of a fixed price versus an annual decrease of 10%.

We generated a scenario favorable to vaccination that included a high incidence and high case fatality ratio, high efficacy, a decrease of 10% in the price of annual vaccination, a herd effect (direct effect × 110%), no adjustment for relative coverage, higher outpatient and hospital costs and lower serotype replacement (i.e., 1% per PCV10). We also ran a scenario that was unfavorable to the vaccine, with lower incidence, mortality efficacy, coverage, in/outpatient costs, and a relative coverage adjustment of 80%, with no change in the vaccine price over time.

3. Results

3.1. Vaccine impact

All results reported are discounted by 3%. Among the 20 cohorts of children evaluated from 2012 to 2031, the scenario without vaccination would result in 7,327,014 AOM cases; 229,238

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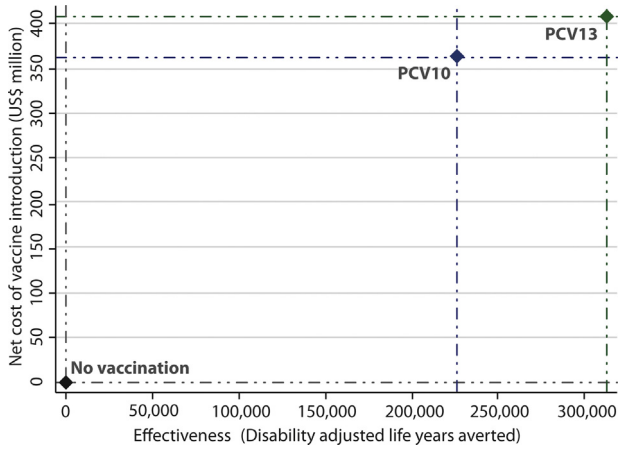

Fig. 2. Incremental cost effectiveness analysis between 10- and 13- valent pneumococcal conjugate vaccines in Peru, 2012.

pneumococcal pneumonia (PP); 6359 pneumococcal meningitis (PM); 8744 pneumococcal sepsis (PS); 1323 neurologic and auditory sequelae (NAS); and 21,194 deaths. With PCV13 or PCV10 vaccination, the number of cases of PP, PM and PS and associated deaths would be reduced by 49% and 35%, respectively. Also, PVC13 would reduce neurological and auditory sequelae by 49%; PCV10, by 34%. The total number of DALYs averted and LYG would be 38.3% higher with PCV13 than with PCV10.

Table 6 details the results for each of the three strategies analyzed: no vaccination, PCV10 vaccination and PCV13 vaccination. In summary, we found that PCV10 prevents more AOM cases and PCV13 avoids more cases of PP PM, PS, NAS and deaths.

3.2. Costs

The study results demonstrated that, in Peru, a vaccination program that uses PCV13 is more costly than one using PCV10, with cumulative net costs amounting to US$ 54.8 million more for PCV13 over the 20 cohorts studied. However, discounted cost savings to health system are greater for PCV13, which saves US$ 9.8 million more than PCV10. Therefore, the net cost difference of PCV13 minus PCV10 for the 20 cohorts is US$ 44.9 million. Table 7 conveys the discounted economic benefits in the three case-base scenarios, and Table 8 presents the discounted net cost for the two vaccination options.

3.3. Cost-effectiveness and incremental cost-effectiveness ratio

The intervention was considered cost-effective if the cost per DALY averted was $\leq 3\times$ the GNI-PC, and highly cost-effective if $<1\times$ the GNI-PC [48]. The discounted cost per avoided DALY was US$ 1605 with PCV10 and US$ 1304 with PCV13; both ratios fall below the 2011 GDP-PC of Peru (US$ 6009). The more costly ratio was PCV13—when its base case results were compared directly to those of PCV10, its additional benefits would be worth the additional investment (incremental cost-effectiveness ratio [ICER] = US$ 519 per DALY averted). Moreover, the cost per LYG, avoided hospitalization and avoided death were lower with PCV13 than with PCV10. These results show that PCV13 has extended dominance over PCV10 in the Peruvian context (Fig. 2).

3.4. Sensitivity analyses

The scenario analyses for PCV10 and PCV13 are shown in Figs. 3 and 4, respectively. In nearly all scenarios, both PCV vaccines were highly cost-effective, and even, cost-saving when compared to no vaccination. A scenario with several unfavorable scenarios was still cost-effective, suggesting the recommendation to introduce PCV is robust. In all scenarios, PCV13 was slightly more cost-effective than PCV10. This was driven by the assumption that PCV13 would cover a larger number of pneumococcal-related diseases, and therefore, would prevent a greater number of deaths. PCV10 was shown to prevent a greater number of AOM cases, but the reduction in AOM treatment costs did not shift enough to make PCV10 a more favorable option. PCV10 was assumed to have an effectiveness reduction for each successive cohort (simulating a scenario of serotype replacement). However, even when this assumption was removed, PCV13 was still the more cost-effective option.

4. Discussion

Our findings indicate that introducing PCV10 or PCV13 to the National Immunization Schedule in Peru is a cost-effective measure when compared to no vaccination. PCV10 introduction would have lower program costs than PCV13. PCV13 would reduce more cases of PP, PM, PS, sequelae and deaths than PCV10. However, PCV10 would prevent more AOM cases. Also, the cost per prevented hospitalization, death and DALY would be lower with PCV13. These results are a clear example of extended dominance in economic evaluation areas. Despite the fact that the PCV13 program is more costly than the PCV10, the cost-per-unit effectiveness is lower for PCV13 [49,50]. Observed differences between the two currently available PCV options are driven by the greater assumed serotype protection of PCV13, which implies a greater impact on IPD prevention; and the NTHi coverage by PCV10 and its effect on AOM. Therefore, IPD prevention with PCV13—and its subsequent impact on deaths, hospitalizations and disabilities—makes this vaccine an intervention with a higher value at the public health level, particularly for effect on LYG and avoided DALYs. Even though the cost of introducing PCV10 is lower, PCV13 is projected to provide a greater overall health benefit; it may therefore, be useful to perform a budget impact analysis to determine the fiscal impact of introducing one vaccine rather than the other [51]. Thus, these findings that PCV13 would be the most favorable option for the Government of Peru as it endeavors to meet its commitment to bring health to all Peruvians [52,53], in a fiscally responsible manner.

EEs concur [54,55]. In Argentina [56], Uruguay [57], and Brazil [58,59] PCV was shown to be more cost-effective than the non-vaccination scenario.

In a report from Sweden and Denmark [60], a study from Greece, Germany and the Netherlands [61], and another from Gambia [62], PCV13 prevented more cases of IPD and deaths and gained more quality adjusted Life Years (QALYs) than PCV10. The same results were observed in Canada, which had a 2 + 1 PCV schedule like that of Peru [63]. A study in Mexico showed PCV13 to have better health outcomes and cost savings than PCV7 and PCV10 [64]. Also, a CEA in Colombia found that PCV13 prevents more disease and deaths with a higher LYG than PCV10, although PCV10 has more cost savings [42]. In Argentina, Urueña and colleagues, using the TRIVAC model, showed that PCV13 prevented more cases of pneumonia, IPD, sequelae with a higher number of LYG and averted more DALYs than PCV10 [40].

Nevertheless, there are some EEs whose findings differ. In Turkey [65] and Norway [66], PCV10 was found to be more cost-effective than PCV13. These differing conclusions underscore that EEs are context-dependent (country or region) and may be affected by the assumptions and models used [13,67].

In Peru, a prior EE showed PCV13 to be more cost-effective, and it prevented more pneumonia cases than PCV10 and PCV7

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Table 6
Discounted health benefits (20 cohorts vaccinated over the period 2012–2031)[a]

	No vaccine	PCV10		PCV13	
	(status quo)	With vaccine	Averted	With vaccine	Averted
Total cases <5 years	7,571,354	6,915,878	655,477	7,031,807	539,547
All causes acute otitis media	7,327,014	6,756,741	570,273	6,907,199	419,815
Pneumococcal pneumonia cases	229,238	149,300	79,937	116,906	112,331
Pneumococcal meningitis	6359	4142	2217	3243	3116
Pneumococcal NPNM (sepsis)[b]	8744	5695	3049	4459	4285
Total outpatient visits	5,924,759	5,421,711	503,047	5,518,331	406,428
All causes acute otitis media	5,770,023	5,320,934	449,090	5,439,419	330,604
Pneumococcal pneumonia cases	154,735	100,778	53,958	78,912	75,824
Total inpatient admissions	82,284	53,591	28,693	41,963	40,321
Pneumococcal pneumonia cases	68,771	44,790	23,981	35,072	33,699
Pneumococcal meningitis	4769	3106	1663	2432	2337
Pneumococcal NPNM (sepsis)	8744	5695	3049	4459	4285
Total deaths <5 years	21,194	13,682	7512	10,808	10,386
Pneumococcal pneumonia cases	14,148	9134	5015	7215	6933
Pneumococcal meningitis	3399	2194	1205	1733	1666
Pneumococcal NPNM (sepsis)	3647	2354	1292	1860	1787
Total children with permanent disability	1323	868	455	672	651
Auditory sequelae	820	538	282	416	404
Neurological sequelae	503	330	173	256	248
Disability Adjusted Life Years (DALYs)	642,147	415,778	226,370	329,028	313,119
DALYS due to morbidity	13,173	9500	3673	8098	5075
DALYs due to mortality	628,974	406,278	222,696	320,931	308,044

[a] Health benefits are discounted at 3% per year.
[b] All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).

[31]. Also contrasting our findings, GlaxoSmithKline® (GSK) performed a cost-utility analysis on PCV introduction in Peru whose results suggested that PCV10 was more cost-effective than PCV13 [68]. Because the GSK analysis assumed a higher effectiveness of PCV10 on 6A and 19A serotypes, and our analysis was driven by an assumption of cross-protection, the findings differed. These serotypes have an important impact on invasive disease; these assumptions could foster better results for the PCV1. Serotype 19A is a key factor in the CEA on PCV [69]; its increasing frequency and its direct effects, producing more IPD cases, deaths and sequelae in LAC, have been previously recognized [42]. However, official reports suggest a minimal participation of NTHi etiologic agent in pneumonia [30]. Our study included an explicit, direct adjustment for serotype replacement over time, focused mainly on 19A [16,67].

Overall, in response to a request by MINSA, our study provides a comprehensive assessment of the cost-effectiveness introducing a new PCV to the National Immunization Schedule in Peru. The strengths of our study are several. First, we used the TRIVAC model, which has been previously used in several countries in LAC: Argentina, Bolivia, Ecuador, El Salvador, Guatemala, Nicaragua and Paraguay [15,16,40] and validated by an external expert panel [16,67]. Second, the development of this study was transparent, with various independent, public and private institutions participating; all participants were required to declare any potential conflicts of interest and none were reported; data was registered and based on official communications by organizations. Third, the scenario analyses considered variations based on other data sources and differences were found between the two PCVs that were consistent across the circumstances. Fourth, TRIVAC is a deterministic, static cohort model that follows more than one live cohort over time. It is better able to evaluate trends in key parameters, e.g., vaccine price, type replacement, mortality in the absence of vaccination, among others. This approach also provided had the added benefit of being useful for carrying out a Budget Impact Analysis [16,67]. Finally, costs were calculated based on official reports, and this included weighting by distribution of cases per health care level, region and specific syndrome management.

4.1. Limitations

This EE has some limitations as well. The TRIVAC model has been found to be consistent with the PneumoADIP cohort model and the

Table 7
Discounted economic benefits of pneumococcal conjugate vaccine-10 (PCV10) versus PCV13 in Peru (20 cohorts vaccinated over the period 2012–2031).

	No vaccine	PCV10		PCV13	
	(status quo)	With vaccine	Averted	With vaccine	Averted
Total government health service costs[a]	$187,084,198	$149,699,031	$37,385,167	$139,864,039	$47,220,160
Total outpatient visit costs	$109,119,066	$98,901,345	$10,217,721	$100,111,508	$9,007,558
All causes acute otitis media	$102,751,561	$94,754,250	$7,997,311	$96,864,221	$5,887,340
Pneumococcal pneumonia cases	$6,367,505	$4,147,095	$2,220,410	$3,247,288	$3,120,217
Total inpatient admission costs	$74,222,749	$48,340,565	$25,882,184	$37,851,971	$36,370,778
All causes pneumonia cases	$44,215,372	$28,797,048	$15,418,324	$22,548,868	$21,666,504
Pneumococcal meningitis	$5,476,527	$3,566,810	$1,909,718	$2,792,909	$2,683,619
Pneumococcal NPNM (sepsis)[b]	$24,530,849	$15,976,707	$8,554,142	$12,510,194	$12,020,655
Total sequelae costs*	$3,742,384	$2,457,121	$1,285,263	$1,900,560	$1,841,824
Auditory sequelae	$1,999,473	$1,312,767	$686,706	$1,015,427	$984,046
Neurological sequelae	$1,742,911	$1,144,355	$598,557	$885,133	$857,778

[a] Government perspective includes [all bed day and disease-specific drug/diaganostic costs borne by the Government of Peru at the following health providers: Ministry of Health and Social Security]. Costs are discounted at 3% per year
[b] All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).

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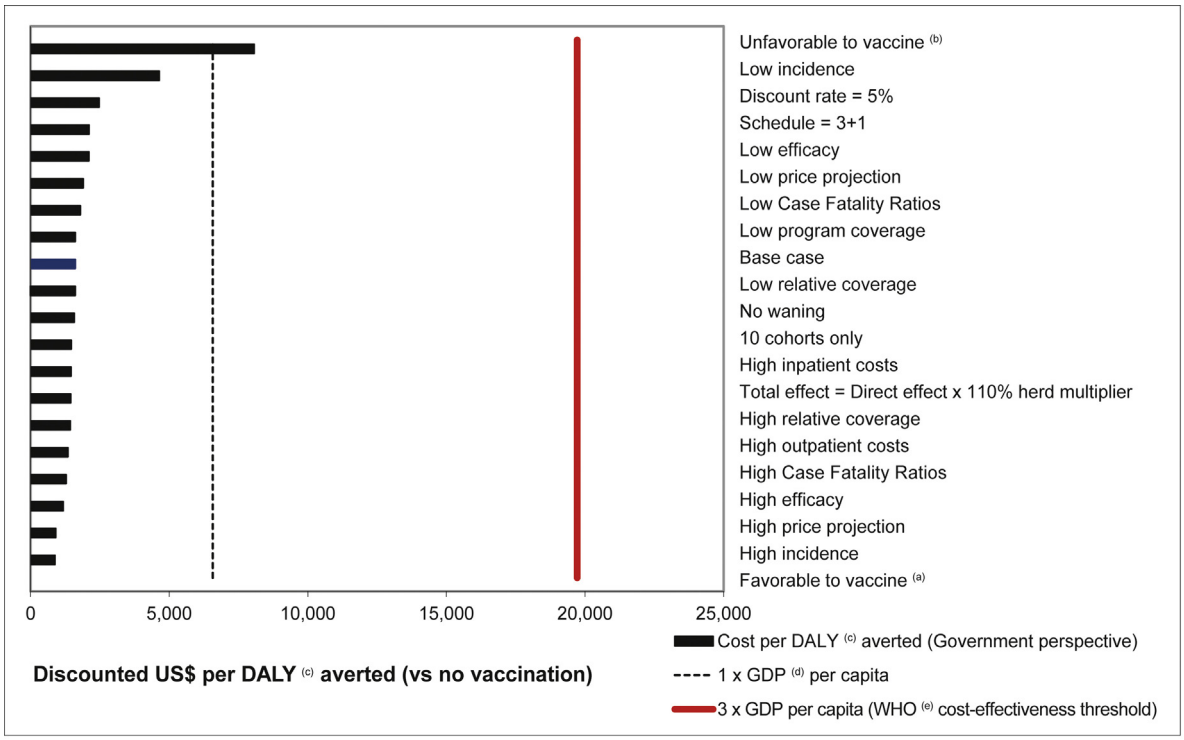

(a) Favorable scenario = High incidence and high case fatality ratio, high efficacy, a decrease in the price of annual vaccination of 10%, a herd effect (direct effect x 110%), no adjustment for relative coverage, higher outpatient and hospital costs, serotype replacement of 1% per year for PCV10. This would be a cost saving escenario i.e. the Pneumococcal disease health services costs averted exceed the cost of introducing PCV.
(b) Unfavorable scenario = Lower incidence, mortality and vaccine efficacy, lower vaccination coverage, a relative coverage adjustment of 80%, lower inpatient and outpatient costs and no change in the price of the vaccine over time.
(c) DALY = Disability adjusted life years.
(d) GDP= Gross Domestic Product
(e) WHO = World Health Organization.

Fig. 3. Cost per disability adjusted life year (DALY) averted for base case 10-valent Pneumoccocal Conjugate Vaccine scenario and alternative "what if" scenarios: Government of Peru perspective.

Table 8
Discounted cost-effectiveness of pneumococcal conjugate vaccine-10 (PCV10) versus PCV13 in Peru (20 cohorts vaccinated over the period 2012–2031)[a]

	PCV10 Government perspective	PCV13 Government perspective
Cost-effectiveness compared to no vaccine		
Net cost of vaccine introduction	$363,268,692	$408,264,249
Costs of vaccine introduction	$400,653,860	$455,484,409
Health service costs avoided	$37,385,167	$47,220,160
DALYs averted[b]	226,370	313,119
YLDs averted – DALYS due to morbidity	3673	5075
YLLs averted – DALYs due to mortality	222,696	308,044
US$ per DALY averted	$1605	$1304
Cost-effectiveness of PCV13 compared to PCV10		
Net cost of vaccine introduction	–	$44,995,556
Costs of vaccine introduction	–	$54,830,549
Health service costs avoided	–	$9,834,992
DALYs averted	–	86,749
YLDs averted – DALYS due to morbidity	–	1402
YLLs averted – DALYs due to mortality	–	85,347
US$ per DALY averted	–	$519
Cost-effectiveness threshold		
1× GDP per capita (2012) – WHO threshold for 'highly cost-effective'	$6573	$13,227
3× GDP per capita (2012) – WHO[c] threshold for 'cost-effective'	$19,719	$39,681

[a] Costs and DALYs are discounted at 3% per year.
[b] DALYs= Disability adjusted life years.
[c] WHO = World Health Organization.

cross-sectional SUPREMES model [67]. However, such static models do not account for realistic changes over time in positive (herd) and negative indirect effects (serotype replacement) [16]. TRIVAC does not currently include indirect effects and only considers a herd-effect scenario for children <5 years of age. There is evidence that older individuals could also benefit indirectly from the vaccination of infants, but the duration of this effect is unclear. The development of a dynamic model could provide a better approximation of the infectious disease pattern and a more accurate estimate of its prevention through vaccination [70]. Dynamic modeling, however, is complex and requires good quality, primary data, e.g., reproductive rates for *S. pneumoniae* colonization and age-specific burden of disease in older age groups [16,50,71]. Also, when a vaccine is cost-effective in a static model, usually a dynamic model would only make it appear more so. In the case of pneumococcal disease, however, there is concern that the negative indirect effects could outweigh the positive ones [16].

Second, we found deficiencies in primary epidemiological data without etiological reports from health service providers and lack of evidence about head-to-head clinical efficacy related to the syndromes studied. Thus, we have extrapolated data from meta-analyses and others primary studies, and this could lead to an inaccurate estimation of disease burden and efficacy. Third, we utilized a public health care system perspective and incorporated only direct cost. However, expenses and lost income incurred by households during hospitalization, plus the cost to society can affect CEA results. Estimating such costs is difficult at the national level. Fourth, TRIVAC generates a specific model

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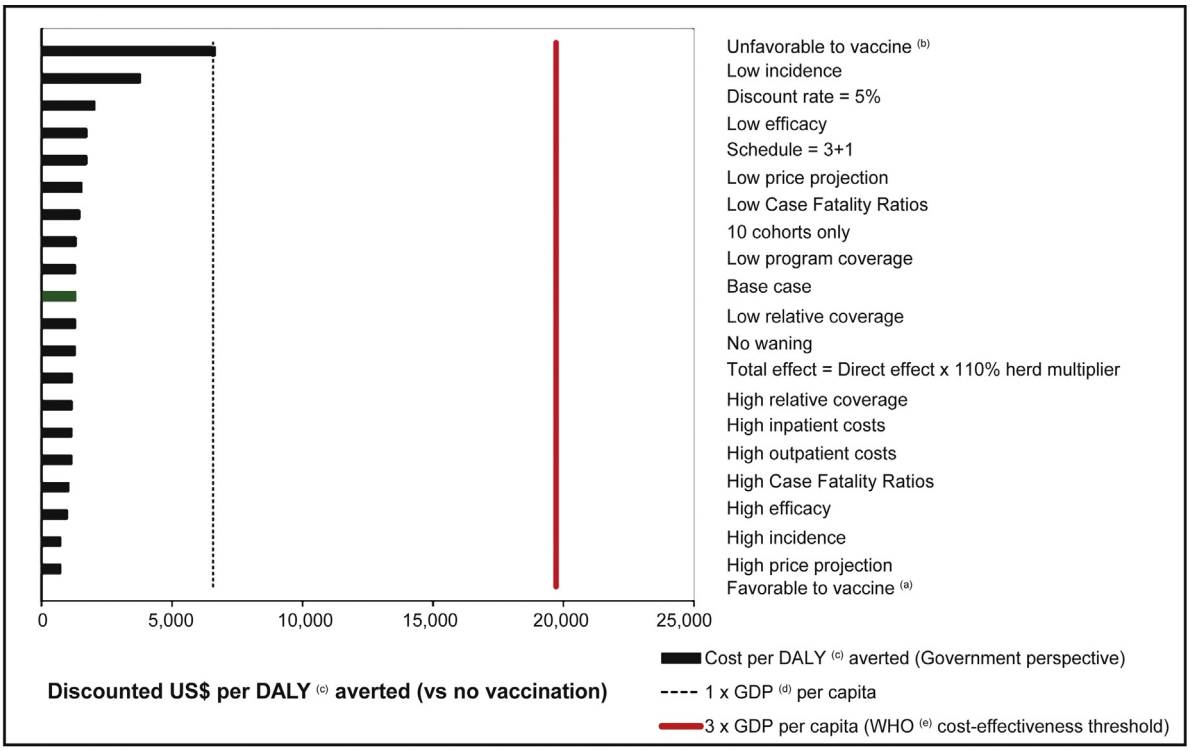

(a) Favorable scenario = High incidence and high case fatality ratio, high efficacy, a decrease in the price of annual vaccination of 10%, a herd effect (direct effect x 110%), no adjustment for relative coverage, higher outpatient and hospital costs, and the same case base serotype replacement for PCV13. This would be a cost saving scenario i.e. the pneumococcal disease health services costs averted exceed the cost of introducing PCV.
(b) Unfavorable scenario = Lower incidence, mortality and vaccine efficacy, lower vaccination coverage, a relative coverage adjustment of 80%, lower inpatient and outpatient costs and no change in the price of the vaccine over time.
(c) DALY = Disability adjusted life year.
(d) GDP= Gross Domestic Product.
(e) WHO= World Health Organization.

Fig. 4. Cost per disability adjusted life year (DALY) averted for base case 13-valent Pneumoccocal Conjugate Vaccine scenario and alternative "what if" scenarios: Government of Peru perspective.

for each vaccine, contrasting PCV impact versus no new vaccine state; so the model assumes that benefits from a new vaccine are not influenced by a preceding PCV any other additional health intervention [16]. However, this was probably not an issue in the current study since PCV7 had been taken off the market. Fifth, the analysis was restricted to children <5 years of age, though there is evidence that the vaccine could have effects later; however, the greatest pneumococcal disease burden occurs in this age group [5]. Finally, we did not include a probabilistic sensitivity analysis for evaluating the extended dominance, which was found in the case base scenario, nevertheless the "what if" scenario analysis is a relevant approach specially in making decision process.

5. Conclusions

In the Peruvian context, PCV13 has shown better health outcomes, but PCV10 would have lower introduction costs. Whit this results, PCV13 would be the preferred policy; and PCV10 would also be reasonable (and cost-saving relative to the status quo) if for some reason 13-valent were not feasible. MINSA must consider the Government priorities when deciding on the best option. Since this study constituted a national and inter-institutional effort to provide the best available evidence for vaccine decision-making in Peru, its results are an important scientific component for improving this process on the health of the population, especially among its youngest and most vulnerable, with actions that are fiscally responsible.

Conflict of interest statement

The authors declare that they have no conflict of interests.

Acknowledgements

This study was made possible through the financial support of the *Instituto Nacional de Salud* (National Institute of Health, Lima, Peru) and the PROVAC Initiative of the Pan American Health Organization (Washington, DC, USA).

This study was presented at 9th International Symposium of Pneumococci and Pneumococcal Diseases, Hyderabad, India, March 2014, and supported by the National Council of Science, Technology and Technological Innovation of Peru (CONCYTEC) and International Clinical Epidemiology Network (INCLEN Trust). The authors are grateful to the Ministry of Health of Peru, especially to the following departments: *Dirección General de Epidemiología* (DGE), *Dirección de Abastecimiento de Recursos Estratégicos* (DARES), *Dirección de Gestión Sanitaria* (DGS), Oficina General de Estadística e Informática (OGEI), *Instituto Nacional de Rehabilitación* (INR), and *Instituto Nacional de Enfermedades Neurológicas* (INCN). The authors also wish to acknowledge EsSalud, Sanidades de las Fuerzas Armadas y Policiales, Superintendencia Nacional de Aseguramiento en Salud (SUNASA), Sociedad Peruana de Pediatría (SPP) and the numerous pediatricians nationwide who generously shared their experience and knowledge by participating in the discussions. Finally, we thank Dr. Verónica Carrión and Dr. Julio M. Ruiz Olano for their support with primary data collection.

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Additional information

Official and comprehensive version (Spanish) of this study can be visited at: http://www.ins.gob.pe/repositorioaps/0/4/jer/evidencias/Nota%20T%C3%A9cnica%202012%20-%203_%20Estudio%20de%20costo%20efectividad%20de%20las%20vacunas%20deca-%20y%20trece-valente%20para%20la%20prevenci%C3%B3n%20de%20enfermedad%20asociada%20a%20Streptococcus%20pneumoniae%20en%20ni%C3%B1os.pdf

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Vaccine 33S (2015) A167–A173

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness analysis of the introduction of the human papillomavirus vaccine in Honduras

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ARTICLE INFO

Keywords:
HPV vaccine
Honduras
Cost-effectiveness

ABSTRACT

Background: Cervical cancer is the leading cause of cancer deaths in Honduras. With the availability of a vaccine to prevent human papillomavirus (HPV), the causative agent for cervical cancer, the Honduran Secretary of Health undertook a cost-effectiveness analysis of introducing the HPV vaccine to support their national decision-making process.

Methods: A national multidisciplinary team conducted this analysis with the CERVIVAC model, developed by the London School of Hygiene and Tropical Medicine in collaboration with the Pan American Health Organization's ProVac Initiative. The cumulative costs and health benefits of introducing the HPV vaccine were assessed over the lifetime of one single cohort of 11-year-old girls. We assumed a three-dose series with 95% vaccination coverage of the cohort using a mixture of school-based and facility-based delivery. To estimate national cervical cancer cases and deaths, we used United Nations demographic projections and GLOBOCAN estimates based on registry data from El Salvador, Guatemala, and Nicaragua. Based on estimates from the World Health Organization (WHO) and the Division of Intensified Cooperation with Countries (ICO), we assumed that 70% of cervical cancer would be due to vaccine types HPV16 and HPV18. We used a vaccine dose price of US$ 13.45 and evidence from the scientific literature to estimate vaccine effectiveness. National information was used to estimate health service utilization and costs of cervical cancer treatment. All costs and health benefits were discounted at 3%.

Results: Upon fully vaccinating 86,906 11-year old girls, 2250 (undiscounted) cervical cancer cases and 1336 (undiscounted) deaths would be prevented over the lifetime of the cohort. After discounting future health benefits at 3% per year, the equivalent cases and deaths prevented were 421 and 170. HPV vaccination is estimated to cost around US$ 5 million per vaccinated cohort, but this would be offset by around US$ 1 million in avoided costs borne by the government to treat cervical cancer. Furthermore, 4349 discounted disability adjusted life years (DALYs) could be avoided at a cost of US$ 926 per DALY avoided, making HPV vaccination in Honduras a highly cost-effective intervention.

Discussion: The net cost of HPV vaccination per DALY avoided is less than the WHO threshold for cost-effectiveness. However, at a cost of around US$ 5 million per vaccinated cohort, an important element to consider in this discussion is the budgetary implications that the introduction of the HPV vaccine would cause for the country.

Conclusions: When comparing the costs and benefits of HPV vaccine introduction in Honduras, it is clear that this intervention would be highly cost-effective and that the intervention would greatly reduce cervical cancer disease. For these reasons, it is in the country's best interest to explore financing opportunities that could support the vaccine's introduction.

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http://dx.doi.org/10.1016/j.vaccine.2014.12.067
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1. Introduction

Cervical cancer is the leading cause of cancer deaths in Honduras. In 2012, there were 991 new cases diagnosed among women [1]. The Papanicolaou (PAP) screening test is recommended every three years for women in Honduras between the ages of 30 to 59 who have had a negative PAP result in their previous exam [2]. However, this secondary prevention screening program only reaches 35% of the female target population. There are two newly available safe and efficacious vaccines to prevent human papillomavirus (HPV), the causative agent of cervical cancer, and many countries are considering introducing the vaccine into the routine immunization schedule. The World Health Organization (WHO) recommends the use of HPV vaccines for girls ages 9–13 where preventing cervical cancer is a national priority and where the vaccines are found to be cost-effective at the country level [3]. For these reasons, Honduras' Health Secretariat decided to assess the cost-effectiveness of introducing a HPV vaccine as one additional strategy to prevent and control cervical cancer in the country.

The expanded program on immunization (EPI) in Honduras currently covers the population with 14 vaccines to prevent important causes of childhood disease. In 2009 and 2011, the country introduced two new vaccines into the program. The Pan American Health Organization (PAHO) recommends that immunization programs consider technical, programmatic and social criteria in their decision-making process for adopting new vaccines [4,5]. The criteria include the political and public health priority; disease burden; vaccine efficacy; vaccine quality and safety; other competing or complementary interventions (including other vaccines); economic and financial criteria; and programmatic and logistical considerations such as vaccine presentation and cold chain capacity, vaccine availability, and program performance [4,6]. In Honduras, the National Immunization Advisory Commission (CNPI) (better known in the literature as a National Immunization Technical Advisory Group [NITAG]) plays an important role in assessing these criteria in order to make evidence-based recommendations to the Health Secretariat [7]. The early experiences with introducing rotavirus and pneumococcal conjugate vaccines demonstrated the importance of early preparation and assessment of available evidence. The Secretary of Health seeks to do the same with decisions regarding the potential introduction of a HPV vaccine into the routine program.

The National Immunization Program and the National Cancer Program of the Honduran Secretary of Health, with support from the Pan American Health Organization (PAHO) ProVac Initiative, conducted this study with the aim of developing evidence on the costs and health benefits of HPV vaccine to support decision making at the country-level. Another important aim was to train the national team and help strengthen their capacity to conduct economic evaluations in the future. The PAHO ProVac Initiative has been described elsewhere [8,9].

2. Methods

This analysis was carried out by a national multidisciplinary team using the PAHO ProVac Initiative's CERVIVAC Model. CERVIVAC is a user-friendly model based on Microsoft Excel® and intentionally designed for use at the national level. The model can be used to estimate the cost-effectiveness of HPV vaccination and/or the cost-effectiveness of alternative cervical cancer screening strategies. The focus of this analysis was HPV vaccination. This part of the model requires national teams to provide estimates of cervical cancer incidence and mortality by age, health service utilization and costs for cervical cancer treatment, and details about costs (vaccine price, wastage, schedule, and mode of delivery) and effectiveness (efficacy, duration of protection, vaccine type coverage, and vaccine program coverage) of the HPV vaccine program. The model tracks a single cohort of girls from pre-adolescence until death and compares lifetime costs and health benefits with and without HPV vaccination. Thus the comparator is no HPV vaccination.

2.1. Primary outcomes and other measures

The primary outcome measure is the incremental net cost per disability-adjusted life-year (DALY) averted. DALYs combine years of life lost due to premature mortality (YLLs), calculated using the average expectation of life at the age and year of cervical cancer death, and life-years lost due to disease morbidity (YLDs), calculated by multiplying the duration of cervical cancer illness by standard DALY weights. DALY weights indicate the proportion of healthy time which is lost due to living with cervical cancer. Future costs and health benefits can be discounted at an optional rate specified by the national team. CERVIVAC also includes the option to build alternative 'what-if' scenarios (either univariate or multivariate) in order to evaluate how sensitive the results are to plausible changes in key parameters.

Cervical cancer cases and deaths are calculated by multiplying age-specific estimates of cervical cancer incidence and mortality by United Nations projections of the number of women alive in each single year and age group as the cohort ages. Cervical cancer cases are then divided into local and regional cancer categories based on the classification system established by the Federation of International Gynecologists and Obstetricians (FIGO). Local cancer refers to FIGO stages IA–IIA and regional cancer refers to FIGO stages IIB–IVB [10]. The duration of illness for local and regional cervical cancer is derived from estimates of 5-year survival for each.

The costs of cervical cancer treatment are calculated by multiplying the number of cases in each year by the average lifetime cost per each woman treated; all costs are roughly assumed to occur within the first year of treatment. Average costs are calculated by estimating the percent of health care received from each type of provider and the cost associated with each. National teams can choose to present costs in terms of a government, health systems, or societal perspective; the latter includes costs borne by households. For the analysis of HPV vaccination, the health care costs and DALYs only consider cervical cancer and not the cost and morbidity associated with precancerous lesions.

The costs of the vaccine program include the price of the vaccine, syringes, and safety boxes, as well as the cost of international handling and delivery. The number of required doses is calculated based on the anticipated coverage of each dose and inflated to account for the anticipated vaccine wastage. National teams can also specify the coverage and target age of a booster dose. The expected percent reduction in cervical cancer cases and deaths in each future year and age group is calculated by multiplying the dose-specific program coverage by dose-specific vaccine efficacy and the proportion of cervical cancer caused by types included in the vaccine (namely types HPV16 and HPV18).

Version 1.2.23 of the model was used for the current analysis. We evaluated HPV vaccination beginning in 2016 in an 11-year-old girl cohort (86,906 girls) versus the status quo, which is no vaccination. We selected 2016 as the year of initiation for the HPV vaccination program because an introduction date any earlier would not be feasible given the current constraints of the program and health-sector budget. All costs and health benefits were discounted by 3%. Costs are reported in 2013 US dollars based on an official exchange rate of 20 lempiras per dollar [11].

2.2. Data sources

Data on demography, disease burden, health service utilization and costs, vaccine impact, and program costs were collected,

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Table 1
Input parameters for estimating cervical cancer disease burden.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Annual incidence of cervical cancer: DEATHS per 100,000 by age				
10–14 yrs	–	–	–	Ferlay et al. [1]
15–19 yrs	2	1	2	Smoothing assumption
20–24 yrs	3	2	4	Smoothing assumption
25–29 yrs	5	4	5	Ferlay et al. [1]
30–34 yrs	13	10	15	Smoothing assumption
35–39 yrs	21	17	25	Smoothing assumption
40–44 yrs	29	23	35	Ferlay et al. [1]
45–49 yrs	43	34	51	Ferlay et al. [1]
50–54 yrs	51	41	61	Ferlay et al. [1]
55–59 yrs	65	52	77	Ferlay et al. [1]
60–64 yrs	58	46	69	Ferlay et al. [1]
65–69 yrs	80	64	96	Ferlay et al. [1]
70–74 yrs	79	64	95	Ferlay et al. [1]
75–79 yrs	91	73	109	Smoothing assumption
80–84 yrs	103	82	124	Smoothing assumption
85–89 yrs	115	92	138	Ferlay et al. [1]
90–94 yrs	128	102	153	Smoothing assumption
95–99 yrs	142	114	171	Smoothing assumption
Annual incidence of cervical cancer: CASES per 100,000 by age				
10–14 yrs	–	–	–	Ferlay et al. [1]
15–19 yrs	7	5	8	Smoothing assumption
20–24 yrs	13	11	16	Smoothing assumption
25–29 yrs	20	16	24	Ferlay et al. [1]
30–34 yrs	37	29	44	Smoothing assumption
35–39 yrs	53	42	64	Smoothing assumption
40–44 yrs	70	56	84	Ferlay et al. [1]
45–49 yrs	96	77	116	Ferlay et al. [1]
50–54 yrs	92	73	110	Ferlay et al. [1]
55–59 yrs	107	85	128	Ferlay et al. [1]
60–64 yrs	91	73	109	Ferlay et al. [1]
65–69 yrs	119	95	142	Ferlay et al. [1]
70–74 yrs	105	84	126	Ferlay et al. [1]
75–79 yrs	107	86	129	Smoothing assumption
80–84 yrs	110	88	132	Smoothing assumption
85–89 yrs	112	90	134	Ferlay et al. [1]
90–94 yrs	114	91	137	Smoothing assumption
95–99 yrs	117	93	140	Smoothing assumption
% Distribution of cervical cancer by severity				
% Local cancer[a]	21%	–	–	Expert consensus
% Regional cancer[b]	79%	–	–	
Disability weights for DALY calculations				
% Of healthy time lost (Local cancer)	8%	–	29%	Expert consensus
% Of healthy time lost (Regional Cancer)	75%	48%	–	
Average 5-years survival rate (% alive after 5 years)				
Local cancer	81%	–	–	Expert consensus
Regional cancer	23%	–	–	

[a] Local cancer refers to FIGO stages IA-IIA.
[b] Regional cancer refers to FIGO stages IIB-IVB.

assessed, and adjusted to populate the CERVIVAC model. Data were identified from diverse sources, including the expanded program on immunization, the Honduran Foundation for the Fight Against Cancer, the National Cancer Control Program, the PAHO country office for Honduras, and national public and private hospitals. Additionally, the national team reviewed published and grey literature, different National Health Secretariat databases and other organizations and institutions. These data are summarized in Tables 1–4 and described in detail below.

National data on age-specific cervical cancer incidence and mortality was reviewed but due to a lack of registry information and local studies, the national team used international estimates for the burden of cervical cancer in Honduras. GLOBOCAN, the global database of the International Agency for Research on Cancer, provides estimates of the incidence and mortality of major cancer types for 184 countries, including Honduras. GLOBOCAN estimates 29.4 cervical cancer cases and 14.1 deaths per 100,000 Honduran women (age-standardized rate) [1]. GLOBOCAN cervical cancer mortality estimates were derived from registry data in neighboring countries (Nicaragua, Guatemala, and El Salvador) and incidence of the disease was derived from this same data and modeled survival [1,12]. The national team reviewed this data with the CNPI and agreed to use the GLOBOCAN data source for the base-case analysis [12][1]. With regards to the distribution of cervical cancer by severity, we assumed that the 21% of the disease in Honduras is diagnosed as local cancer and 79% is diagnosed at a more advanced stage (stages I and II are local cancer; Stages III and IV are regional/more advanced cancer). Honduras does not have national data based on

[1] At time of analysis, only GLOBOCAN 2008 estimates were available. We did not update the analysis with 2012 estimates because we did not have access to age-specific estimates at time of analysis. Despite this limitation, we can confirm that crude rates did not change.

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Table 2
Input parameters for estimating health service utilization and costs (all costs are presented in 2013 US$).

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Local cancer				Expert consensus ($n = 5$)
% Receiving treatment	80%	60%	90%	
Government cost per treated woman[a]	$1260	$1260	$1260	
Household cost per treated woman[b]	$292	$193	$292	
Regional cancer				Expert consensus ($n = 5$)
% Receiving treatment	80%	60%	90%	
Government cost per treated woman[c]	$3325	$3325	$3325	
Household cost per treated woman[d]	$1428	$1428	$1428	

[a] Local cancer costs borne by the government per treated woman include cervical conization and hysterectomy. Outpatient visits are distributed as follows: 80% public health hospital and 20% social security hospital and private sector. The cost presented is the weighted average of the provider-specific costs.
[b] Local cancer costs borne by the household per treated woman include productivity losses to families due to lost wages, travel expenses and feeding, out-of-pocket payments for consultations and drugs. The cost presented is the weighted average of the provider-specific costs. Lost wages constitute 65% of this cost.
[c] Regional cancer costs borne by the government per treated woman include radiotherapy, chemotherapy or/and both. Outpatient visits are distributed as follows: 80% public health hospital and 20% social security hospital and private sector. The cost presented is the weighted average of the provider-specific costs.
[d] Regional cancer costs borne by the household per treated woman include productivity losses to families due to lost wages, travel expenses and food, out-of-pocket payments for consultations and drugs. The cost presented is the weighted average of the provider-specific costs. Lost wages constitute 65% of this cost.

Table 3
Input parameters for estimating HPV vaccine program costs.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Costs of vaccine doses				
Price per dose	$13.45	$13.10	$13.79	PAHO Revolving Fund [14]
Percentage international handling	3.5%	3.5%	3.5%	
Percentage international delivery	15.0%	15.0%	15.0%	
Percentage wastage[a]	5.0%	5.0%	5.0%	Secretaria de Salud [18]
Costs of syringes				
Price per dose	$0.06	$0.06	$0.06	PAHO Revolving Fund [14]
Percentage international handling	3.5%	3.5%	3.5%	
Percentage international delivery	15.0%	15.0%	15.0%	
Percentage wastage[a]	5.0%	5.0%	5.0%	Secretaria de Salud [18]
Costs of safety box				
Price per box	$1.18	$1.18	$1.18	PAHO Revolving Fund [14]
Percentage international handling	3.5%	3.5%	3.5%	
Percentage international delivery	15.0%	15.0%	15.0%	
Percentage wastage[a]	0.0%	0.0%	0.0%	Secretaria de Salud [18]
Total number of syringes per safety box	75	50	150	
Incremental health system costs[b]				
% Of vaccine delivered at schools	90%	–	–	Expert consensus ($n = 4$)
% Of vaccine delivered at facilities	10%	–	–	
Extra system costs per dose (school-based)	$3.00	$2.60	$5.00	Secretaria de Salud [19]
Extra system costs per dose (facility-based)	$2.56	$2.00	$5.00	

[a] The % wastage is converted into a factor [1/(1 − % wastage)] which is multiplied by the expected number of doses required to meet the anticipated level of coverage.
[b] Estimated incremental system costs include promotion material (posters, trifolds), information system (Vac1, Vac2, vaccination surveillance lists) logistic and mobilization costs. They are assumed to only occur in the first year only/they are assumed to be recurrent costs each year.

Table 4
Input parameters for estimating the health impact of HPV vaccination.

Parameter	Estimate (%)	Scenarios		Source(s)
		Low (%)	High (%)	
Coverage in year of introduction				
1 Dose	100.0	95.0	100.0	Expert consensus ($n = 4$)
2 Doses	99.0	90.0	100.0	
3 Doses	95.0	85.0	100.0	
Booster	95.0	85.0	100.0	
Vaccine efficacy[a,b]				
Vaccine efficacy after primary dose 1 (p1)	48.4	0.0	96.8	Schiller et al. [15]
Vaccine efficacy after primary dose 2 (p2)	48.4	0.0	96.8	
Vaccine efficacy after primary dose 3 (p3)	94.3	91.7	96.8	
% Of cervical cancer caused by types 16/18				
% Of types due to 16 and 18	70.0	52	85	World Health Organization [20]

[a] Reflects vaccine efficacy values among girls who are completely naïve to HPV16/18 infection. As the age of vaccination increases, vaccine efficacy is expected to decrease. We have assumed 94.3% efficacy for girls 11 years old.
[b] Vaccine effectiveness in a given year is equal to the Excel equation: = vaccine efficacy × (1—NORMDIST[years since vaccination, average years protected, standard deviation years protected, 1]). We assumed lifelong protection in the base-case scenario.

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the FIGO classification that could detail the different stages of local or regional cancer [10]. Table 1 summarizes disease burden estimates considered for the base-case and alternative scenarios. For projections of the number women alive in each future year and age group, we used demographic data published in 2008 by the United Nations Population Division (UNPOP) [1,13].

Table 2 summarizes the treatment cost estimates considered for this analysis. The base-case analysis considered only costs borne by the government for treatment of cervical cancer disease in the public sector. Approximately 80% of women with cervical cancer are cared for in the public sector, with the remaining 20% relying on the private sector and/or social security services. An ingredients-based approach, following recommended protocols for cervical cancer treatment in Honduras, was used to calculate government costs. Cost items included fee scales detailing administrative expenses, medical supplies and materials. A secondary perspective considering societal costs is presented after accounting for direct medical and non-medical costs incurred by patients and their families. Household costs were based on informed assumptions by the national ProVac study team. These costs include loss of productivity; purchases of medical materials; payment for private medical services; transportation, accommodation, and food costs (Table 2).

Costs of the HPV vaccination program are described in Table 3 [14,16,18]. Costs account for vaccine and supply procurement, adjusted for wastage, and incremental system costs. We assumed a price of US$ 13.45 per dose, considering a simple mean of the two products available from the PAHO Revolving Fund in 2013 [14]. Unit price for the bivalent (US$ 13.10) and quadrivalent vaccines (US$ 13.79) were assessed in alternate scenarios. Both vaccines are packaged in single-dose vials and therefore wastage was assumed at 5%. International delivery and handling fees were estimated at 15% of the supply purchase. These are standard rates negotiated with the PAHO Revolving Fund [14]. The extra system costs due to HPV vaccine to the routine vaccination program considered the cost of all promotional material (posters, brochures, etc.), logistics, social mobilization, revised vaccination cards, and coverage-tracking tools for health facilities. This cost was estimated at US$ 3 per dose delivered in schools and US$ 2.56 per dose delivered at a health facility.

Data to estimate the impact of vaccination is summarized in Table 4 [14,18]. Vaccine effectiveness is modeled on the reported clinical efficacy of the three-dose HPV vaccine series in HPV-naïve women, the proportion of cervical cancers in Honduras that are caused by HPV16 and HPV18, the two high-risk genotypes that the vaccines prevent against, and the assumed coverage achieved. We assumed lifelong protection for both vaccines in the base-case scenario considering that clinical data to date has demonstrated durable protection in time [15]. No booster dose was considered for the base case.

3. Results

In this analysis, we evaluated the costs and health benefits of introducing the HPV vaccine into the routine immunization program in Honduras in different scenarios. The routine delivery of HPV vaccines in the immunization program has the potential to reduce cervical cancer deaths by as much as 62% (Table 5), in the lifetime of a single cohort of girls. With 95% coverage of the adolescent female cohort, HPV vaccine would be expected to prevent 421 new cervical cancer cases (2250 undiscounted) and as a result save 170 female lives (1336 undiscounted) over their lifetime (Table 5). It is expected that this prevention would lead to averting 4349 discounted disability-adjusted life-years (DALYs). We assumed high vaccine coverage based on the results of an HPV vaccination pilot carried out in two Regions of the country. During this pilot, HPV vaccination was provided to 11 year old girls through a combined school and facility based strategy. Third dose coverage reached 96% and 100%, and the vaccine was very well accepted by parents and girls thanks to social mobilization and communication efforts. We also considered a lower coverage of 85% in sensitivity analysis.

Table 5
Discounted lifetime health benefits of HPV vaccination in girls 11 years old.

	No vaccine (Status quo)	HPV vaccine With vaccine	Averted
Total cervical cancer cases	682	260	421
Local cancer	208	79	129
Regional cancer	474	181	293
Deaths	275	105	170
DALYs	7034	2685	4349
YLD due to local cervical cancer	221	85	137
YLD due to regional cervical cancer	1081	413	668
YLL due to cervical cancer deaths	5732	2188	3544

Health benefits are discounted at 3% per year.

Table 6
Discounted lifetime economic benefits of HPV vaccination in girls aged 11 years.

	No vaccine (Status quo)	HPV vaccine With vaccine	Averted
Total Gov. health service costs[a]	$1469,198	$560,789	$908,409
Local cancer	$209,566	$79,991	$129,575
Regional cancer	$1259,632	$480,798	$778,834
Total societal health service costs[b]	$2058,825	$785,848	$1272,977
Local cancer	$258,214	$98,560	$159,654
Regional cancer	$1800,611	$687,288	$1113,323

Costs are discounted at 3% per year.

[a] Government perspective includes all bed days and disease-specific drug/diagnostic costs borne by the government at the following health providers: health centers, public 1ary/2ary/3ary hospitals.

[b] Societal perspective includes all costs included in the government perspective. In addition, it includes productivity losses, all household costs incurred when visiting both government and private health providers, i.e., transportation and food costs, purchases of medical materials, and payment for private medical services.

A HPV vaccination program in Honduras would cost the government approximately US$ 4,937,997 for each girl cohort that completed a full series of HPV vaccinations (Table 7). This estimate includes the different elements needed for introducing the vaccine, including incremental costs for program operations, infrastructure, and mobilization. However, it is expected that the treatment cost savings due to the primary prevention of cervical cancer could amount to US$ 908,409 for the government and nearly US$ 1.3 million for society as a whole, including cost savings to both government and households (Table 6). Therefore, the net cost of HPV vaccination in a girl cohort is approximately US$ 4 million from the government perspective and approximately US$ 3.7 million from the societal perspective (Table 7).

The cost per DALY averted of introducing the HPV vaccines compared to status quo is US$ 926 and US$ 843 from the government and societal perspectives, respectively. Both incremental cost-effectiveness ratios (ICERs) fall below the 2012 gross domestic product (GDP) per capita in Honduras (US$ 2339) [16], which can be used as a threshold for determining the cost-effectiveness of an intervention [17]. Therefore, these results demonstrate the likely cost-effectiveness of a HPV vaccination program in Honduras (Table 7).

Notwithstanding the uncertainty inherent to these kinds of analyses, the national team evaluated multiple alternative scenarios. The majority of these scenarios reinforced the base case conclusion that the introduction would be highly cost-effective or at least cost-effective (less than three times GDP per capita), with

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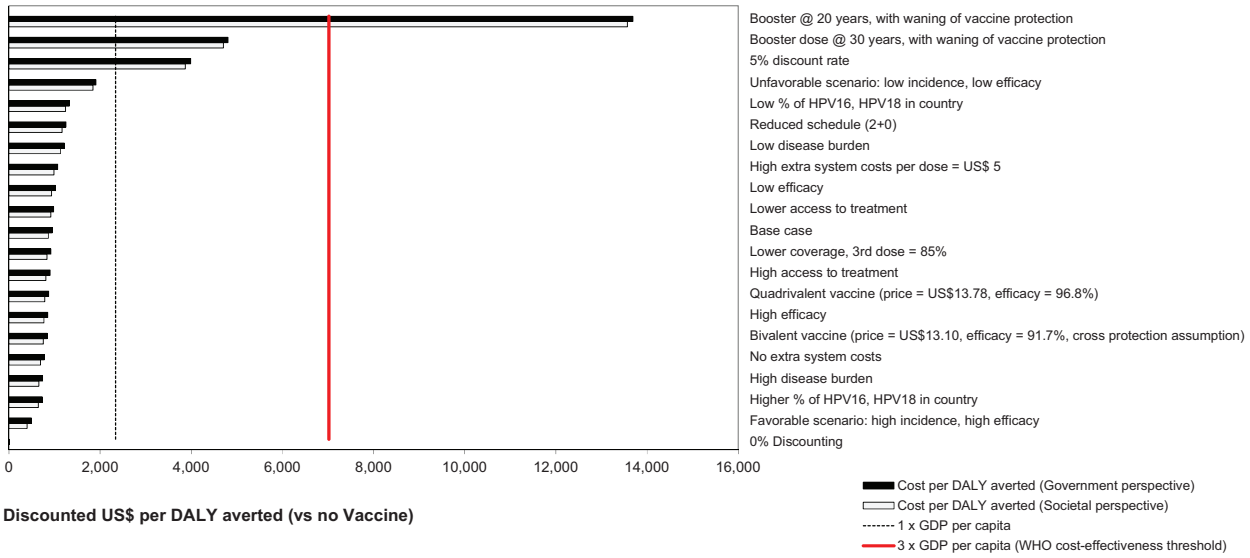

(1) Favorable scenario = All 20 scenarios are favorable, with only the scenario assuming a 5% discount rate failing the threshold of highly cost-effective and moving into cost-effective.

(2) Unfavorable scenario = No scenario was unfavorable to the vaccine.

Fig. 1. US$ per DALY averted for base-case HPV vaccine scenario and alternative 'what-if' scenarios: government perspective and societal perspective. (1) Favorable scenario = all 20 scenarios are favorable, with only the scenario assuming a 5% discount rate failing the threshold of highly cost-effective and moving into cost-effective. (2) Unfavorable scenario = no scenario was unfavorable to the vaccine.

the exception of one scenario in which the team assumed the need for a booster dose and only 20 years of protection (Fig. 1).

4. Discussion

Introduction of the HPV vaccine would be a highly cost-effective investment for the Honduran Health Secretariat and it would have significantly positive results for women's health in the country. Especially in the context of the challenges faced by the secondary screening prevention program in Honduras, adding a primary prevention strategy could accelerate the reduction of disease burden and prevent the acquisition of infection in the vulnerable adolescent female population. Nonetheless, there are other important considerations besides the cost-effectiveness of the vaccine.

In particular, the budgetary impact of adding a HPV vaccine to the routine immunization program would be significant. For a three-dose series, and based on the information currently available about the price per dose through the PAHO Revolving Fund, the government would need to secure approximately US$ 5 million for each vaccinated cohort. That additional sum represents 0.8% of the Health Secretariat's 2013 total budget of US$ 600 million. On the one hand, given the urgency with which the government would like to control this important public health problem, the immunization program might be able to secure the increased budget. On the other hand, the affordability of adopting this vaccine is contested at this time due to the serious economic crisis facing the country. Therefore, in spite of the vaccine being considered highly cost-effective in this analysis, lower prices for the vaccine must be pursued in order for the government to adequately finance the public program. Support should be sought from Gavi, the Vaccine Alliance through a new window of financing opening up for "graduating" countries. Support from international partners could provide an opportunity that would potentially accelerate the introduction of this lifesaving vaccine.

Although this analysis concludes that the vaccine would be highly cost-effective, it is important to mention some limitations related to the data and methods presented in this paper. The public health policymaking reality in Honduras is quite complex; the country lacks technological infrastructure, trained human resources, and adequate financial resources. Because it is possible that the Honduran context will change substantially by 2016, it is important to revise the available data so that they more accurately represent the current situation. However, an important aim of this analysis were to quantify the budget impact of introducing the vaccine in 2016 and to use this evidence to inform decision-makers about the importance of the vaccine's introduction. It should also be noted that some educated assumptions were necessary to inform inputs for which no data was available.

Table 7
Discounted lifetime cost-effectiveness of HPV vaccination in girls 11 years old.

	Government perspective	Societal perspective
Cost-effectiveness compared to no vaccine		
Net cost of vaccine introduction	$4029,588	$3665,020
Costs of vaccine introduction	$4937,997	$4937,997
Health service costs avoided	$908,409	$1272,977
DALYs averted	4349	4349
YLDs averted—DALYS due to morbidity	805	805
YLLs averted—DALYs due to mortality	3544	3544
US$ per DALY averted	$926	$843
Cost-effectiveness threshold		
1 × GDP per capita (2012)—WHO threshold for 'highly cost-effective'	$2339	$2339
3 × GDP per capita (2012)—WHO threshold for 'cost-effective'	$7018	$7018

Costs and DALYs are discounted at 3% per year.

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Another limitation is not including the national screening program in this analysis. Honduras' screening program has multiple issues. These include weak coverage (35%) due to weak infrastructure; limited human resources and human resources with limited capacity, especially in the interior of the country; untimely identification HPV and abnormal lesions; high concentration of service providers in large cities, leaving the rest of the country poorly covered; and a high burden on both the public and private sector to care for patients with advanced disease. While the vaccination of girls would have a positive impact on the target population, it should be considered as one of the national strategies for cervical cancer prevention. The national screening program should be seen as another, and appropriate measures to strengthen it should be considered as well as the introduction of the vaccine.

This study, based on a simple but accessible model, has helped to strengthen the national capacity to conduct economic evaluations. In addition, it has helped to highlight important gaps in national data, specifically the lack of good quality information on cervical cancer incidence and mortality.

5. Conclusion

Introduction of HPV vaccination in Honduras is estimated to be highly cost-effective and would offer substantial future benefits for girls vaccinated today. Other technical, programmatic, and social issues are considered in the process of making a decision on the introduction of a new vaccine. Cost-effectiveness data contributes to this process.

Acknowledgements

The authors would like to acknowledge the technical and financial support provided by PAHO and the BMGF (Grant OPP50788), with a special thanks to Andrew Clark at the London School of Hygiene and Tropical Medicine for his review of this article.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Vaccine 33S (2015) A174–A181

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of HPV vaccination in Belize

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ARTICLE INFO

Keywords:
HPV vaccines
Belize
Cervical cancer
Cost-effectiveness

ABSTRACT

Objective: Among women in Belize, cervical cancer is both the leading cancer and the leading cause of cancer deaths. Both the quadrivalent and bivalent human papillomavirus (HPV) vaccines are licensed in Belize. The Ministry of Health of Belize convened a multidisciplinary team to estimate the costs, health benefits, and cost-effectiveness of adding an HPV vaccine to the national immunization schedule.
Methodology: The CERVIVAC cost-effectiveness model (Version 1.123) was used to assess the lifetime health and economic outcomes of vaccinating one cohort of girls aged 10 years against HPV. The comparator was no HPV vaccination. The PAHO Revolving Fund negotiated price of US$ 13.79 per dose was used (for the quadrivalent vaccine) and national data sources were used to define demography, cervical cancer incidence and mortality, cervical cancer treatment costs, and vaccine delivery costs. Estimates from international agencies were used in scenario analysis.
Results: In a cohort of ~4000 Belizean girls tracked over a lifetime, HPV vaccination is estimated to prevent 69 new cases of cervical cancer (undiscounted), and 51 cervical cancer deaths (undiscounted). Considering the potential cervical cancer treatment costs and lost wages avoided by households (societal perspective), the cost per disability-adjusted life year (DALY) averted was estimated to be US$ 429. This increased to US$ 1320 when cervical cancer treatment costs and lost wages were excluded from the analysis. Both estimates are far below the gross domestic product (GDP) per capita of Belize (US$ 4795). The lifetime health care costs saved by the women and their families represent more than 60% of the investment cost needed by the Government for the vaccine.
Conclusion: Routine HPV vaccination would be highly cost-effective in Belize. If affordable, efforts should be made to expedite the introduction of this vaccine into the Belizean national immunization program.
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1. Background

Cervical cancer is both the leading cancer and the leading cause of cancer deaths among women in Belize [1,2]. The human papillomavirus (HPV) is an established carcinogen for cervical cancer [3]. The most prevalent HPV types known to cause cervical cancer are 16, 18, 52, 31, and 58, and the presence of both HPV genotypes 16 and 18 has been well established in Belize [4].

Since 2006 two HPV vaccines aimed at reducing the acquisition and spread of HPV types associated with cervical cancer through primary prevention have been available on the global market. One of the vaccines, Cervarix, is a three-dose bivalent vaccine produced by GlaxoSmithKline that provides protection against types 16 and 18 [5]. The other, Gardasil/Silgard, is a three-dose quadrivalent vaccine manufactured by Merck & Co. that protects against HPV types 16, 18, 6, and 11. HPV types 6 and 11 are known to cause genital warts [6].

The recommended target age group for the HPV vaccines is girls ranging from ages 9 to 13 years [5,6]. Since the launch of the bivalent and quadrivalent HPV vaccines in 2006, their safety has been studied by various surveillance agencies worldwide. Globally, over 60 million doses of the vaccines have been administered, and they have demonstrated a good safety, immunogenicity, and efficacy profile [7].

Belize, a developing Central American country, has been steadily increasing its wealth over the past two decades (Fig. 1). However, in this transition, inequities in access to adequate health care have remained [8]. Belize's cervical cancer screening program has an 80%

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http://dx.doi.org/10.1016/j.vaccine.2014.12.042
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Fig. 1. Map of Belize (See ref. [38]).

coverage goal. However, this target has not been met, with coverage of women between ages 21–55 years growing from 11% to 68% in the past decade and with many women still presenting with advanced disease [9]. Access to care for established cervical cancer is limited, so women often seek care abroad, but with no structured referral system.

With the new availability of vaccines to prevent HPV in adolescent girls, primary prevention of cervical cancer through immunization could be an important component of a successful prevention and control program, along with screening and adequate referral and treatment services. This cost-effectiveness analysis was conducted to inform the Belize Ministry of Health (MOH), about the potential impact and value of HPV vaccine introduction.

2. Objective

The aim of this analysis was to evaluate the anticipated health outcomes, incremental vaccination costs, averted health care system costs, and cost-effectiveness of introducing the HPV vaccine among adolescent girls in Belize at a national level. Two base case scenario perspectives were analyzed: (a) government and (b) societal. Costs for cervical cancer treatment are borne by households in Belize so the Government perspective included only the cost of the vaccine and its delivery. The societal perspective included out-of-pocket expenses related to cervical cancer treatment and care as well as associated lost wages.

3. Methods

3.1. Model general overview

CERVIVAC is a user-friendly Microsoft Excel-based model purposefully designed for the ProVac Initiative of the Pan American Health Organization (PAHO). The ProVac Initiative works to strengthen national capacity for developing and using economic evidence in the decision-making process for new vaccine

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adoption. This analysis was conducted using the CERVIVAC model version 1.1.23. The model tracks a single cohort of girls from pre-adolescence until death and compares lifetime costs and health effects with and without HPV vaccination [10]. The model requires national teams to populate the model with estimates of cervical cancer incidence and mortality by age; health service utilization and costs for cervical cancer treatment; vaccine program costs (vaccine price, wastage, schedule, mode of delivery, etc.); and vaccine effectiveness (efficacy, duration of protection, vaccine type coverage, etc.).

Cervical cancer cases and deaths are calculated by multiplying age-specific estimates of cervical cancer incidence and mortality by national projections of the number of women alive in each single year and in each age group as the cohort ages. Cervical cancer cases are then divided into local and regional cancer categories. Local cancer refers to International Federation of Gynecology and Obstetrics (FIGO) stages IA-IIA, and regional cancer refers to FIGO stages IIB-IVB [11,12]. The duration of illness for local and regional cervical cancer is derived from estimates of 5-year survival for each.

Baseline health services utilization and associated costs were identified, categorized, and quantified for both early (local) and advanced (regional) cervical cancer disease. Health services utilization was considered as either public or private, and the proportion of women seeking each service was enumerated. Incremental vaccination program costs included the cost of the vaccine, adjusted for wastage, and the other extra expenses needed to add the vaccine to the existing national vaccination program.

The primary outcome measure is the incremental net cost per disability-adjusted life year (DALY) averted. DALYs combine years of life lost due to premature mortality – YLLs (calculated using the average life expectancy at the age and year of cervical cancer death) and years of life lost due to disease morbidity – YLDs (calculated by multiplying the duration of cervical cancer illness by standard disability weights). Scenario analyses were conducted to evaluate the robustness of the results to plausible changes in influential parameters.

3.2. Demography

The numbers of women in specific age groups were provided by the Statistical Institute of Belize [13]. A reference year of 2012 was selected for data gathering as this was the year of the most recently conducted cancer survey [1]. The Educational digest of Abstract of Statistics 2012 for Belize provided the population estimate for the cohort of girls aged 10 attending school, which was 4033 [14]. This number guided the estimation for the school based immunization program coverage.

3.3. Disease burden

Data on disease burden due to cervical cancer were provided by the Epidemiology Unit of the Ministry of Health (MOH) of Belize (Table 1) [1]. These data were used in the base case scenario for incidence and mortality. However, national reporting systems are often prone to under-reporting and data quality issues, so we also ran a scenario using international (GLOBOCAN 2008) estimates of incidence and mortality [15]. In a third scenario we used PAHO cumulative mortality data for Belize from 2005 through 2009 [16].

Because limited national data on cervical cancer staging was available, an expert consultation was conducted at the Belize Cancer Centre Dangriga (BCCD), the sole referral center in Belize for cancer management. In 2012, 46% of all cervical cancer cases diagnosed in Belize were managed at the BCCD, of which 83% had at least stage IIB disease or greater. Based on this experience, experts estimated that in Belize at least 50% of women have regional disease at the time of diagnosis of cervical cancer [17].

Standard disability weights as recommended by the World Health Organization's Global Burden of Disease 2004 for the calculations of DALYs were used, without age-weighting [18]. For 5-year survival estimates we assumed 23% (low scenario = 20%) for local cancer and 81% (low scenario = 40%) for regional cancer based on estimates from the International Agency for Research on Cancer [19].

3.4. Costs

3.4.1. Health service utilization costs

Costing was performed from the societal perspective, (Table 2). Surgical care for the earliest stages of cervical cancer (I to IA1) can be obtained in the public health system, but gynecologic oncology services (indicated for stages IA2 to IIA) are only available privately [20,21]. The BCCD, a private non-profit organization, provides chemotherapy but has no established link with governmental services as a referral center. For its patients who require radiation treatment, the BCCD has an established partnership with the Hospital Universitario Esperanza's Centro de Radioterapia y Oncología in Guatemala. The BCCD receives donations of funds, equipment, and supplies to operate, including donations from MOH. Costs for chemotherapy were obtained from the BCCD fee schedule [22]. Costs for radiation in Guatemala and the associated travel expenses to be borne by the patient were obtained from standards provided by the BCCD [22]. Costs for radiation and other associated out-of-pocket expenses in Mexico and the United States were obtained from fee schedules and the Belize MOH [21,23]. All costs are presented in 2012 US dollars (US$).

The labor costs for providing health services were estimated using the basic salaries of physicians and nurses employed by the government, with data coming from the MOH [24]. To assess productivity and income losses in households where a woman was being treated, the minimum wage was used to make a conservative estimate. This was $3.30 Belizean dollars per hour in 2012 [25], equivalent to US$ 1.15.

Not all women requiring radiation can afford to travel abroad for care, and they eventually receive hospice care [26]. The main hospice in Belize is a non-profit foundation that uses volunteer skilled and unskilled staff. Medications and supplies for care are donated, but patients still bear some out-of-pocket costs. Costs for medication and medical supplies were provided by the Pharmaceutical Department of the Ministry of Health (MOH) and from the hospice's records [26,27]. To estimate the cost of care for a woman with terminal disease, a terminal care cost scenario was developed, based on the time spent by caregivers, medications for pain management, and other supplies expected to be used over a life expectancy of one month.

Based on a review of charts for patients managed at the BCCD, assumptions were developed on the percentages of women who received surgery, radiation, and chemotherapy. Women who had local disease were assumed to be absent from work for three months, and those with regional disease were assumed to be absent for six months.

3.4.2. Immunization program costs

At the time of this study the price of the quadrivalent vaccine was US$ 13.79 through the PAHO Revolving Fund [28] (Table 3). Syringe costs, shipping and handling costs, and estimates for wastage were all obtained from the Maternal and Child Health (MCH) of the MOH [9]. Syringes were estimated to cost US$ 0.10, no additional safety boxes were assumed to be required to introduce the new vaccine, shipping and handling costs were assumed to represent 25% of vaccine price, and 10% wastage of the vaccines and syringes was assumed [29]. Estimated programmatic costs for staff education, social marketing, and vaccine distribution

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Table 1
Input parameters for estimating cervical cancer disease burden.

Parameter	Estimate	Scenarios		
		"Low"	"High"	
Annual incidence of cervical cancer deaths per 100,000 by age				
10–14 years	–	–	–	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
15–19 years	0	0	2	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
20–24 years	0	0	3	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
25–29 years	14	3	5	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
30–34 years	25	5	7	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
35–39years	36	13	9	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
40–44 years	32	17	12	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
45–49 years	28	25	29	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
50–54 years	16	13	42	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
55–59 years	23	23	30	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
60–64 years	57	33	41	Mid = SIB [13], Low = PAHO[16], High = GLOBOCAN [15]
65–69 years	92	37	51	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
70–74 years	58	23	58	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
75–79 years	83	45	96	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
80–84 years	109	46	135	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
85–89 years	140	59	173	Mid = SIB [13], Low = PAHO 16], High = GLOBOCAN [15]
90–94 years	180	75	222	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
95–99 years	231	97	286	Mid = SIB [13], Low = PAHO [16], High = GLOBOCAN [15]
Annual incidence of cervical cancer cases per 100,000 by age				
10–14 years	–	–	–	Mid = SIB [13], Low, High = GLOBOCAN [15]
15–19 years	0	5	5	Mid = SIB [13], Low, High = GLOBOCAN [15]
20–24 years	0	11	11	Mid = SIB [13], Low, High = GLOBOCAN [15]
25–29 years	21	16	16	Mid = SIB [13], Low, High = GLOBOCAN [15]
30–34 years	24	30	30	Mid = SIB [13], Low, High = GLOBOCAN [15]
35–39 years	89	45	45	Mid = SIB [13], Low, High = GLOBOCAN [15]
40–44 years	65	59	59	Mid = SIB [13], Low, High = GLOBOCAN [15]
45–49 years	42	72	72	Mid = SIB [13], Low, High = GLOBOCAN [15]
50–54 years	49	84	84	Mid = SIB [13], Low, High = GLOBOCAN [15]
55–59 years	114	59	59	Mid = SIB [13], Low, High = GLOBOCAN [15]
60–64 years	80	82	82	Mid = SIB [13], Low, High = GLOBOCAN [15]
65–69 years	45	103	103	Mid = SIB [13], Low, High = GLOBOCAN [15]
70–74 years	115	115	115	Mid = SIB [13], Low, High = GLOBOCAN [15]
75–79 years	75	88	88	Mid = SIB [13], Low, High = GLOBOCAN [15]
80–84 years	52	62	62	Mid = SIB [13], Low, High = GLOBOCAN [15]
85–89 years	29	35	35	Mid = SIB [13], Low, High = GLOBOCAN [15]
90–94 years	16	19	19	Mid = SIB [13], Low, High = GLOBOCAN [15]
95–99 years	9	11	11	Mid = SIB [13], Low, High = GLOBOCAN [15]
% Distribution of cervical cancer by severity				
% Local cancer[a]	50%	–	–	Assumption, expert consensus
% Regional cancer[b]	50%	–	–	Assumption, expert consensus
Disability weights for DALY calculations				
% Of healthy time lost (local cancer)	8%	–	29%	GBD 2004 [18]
% Of healthy time lost (regional cancer)	75%	48%	–	GBD 2004 [18]
Average 5-year survival rate (% alive after 5 years)				
Local cancer	81%	40%	40%	SurvCan [19]
Regional cancer	23%	20%	20%	SurvCan [19]

"Low" and "High" estimates for cervical cancer incidence and mortality refer the alternative age-specific scenarios that were used. Therefore, for some age groups, the mid/low/high sequence may not appear in a logical order.

[a] Local cancer refers to FIGO stages IA-IIA.

[b] Regional cancer refers to FIGO stages IIB-IVB.

Table 2
Input parameters for estimating health service utilization and societal costs (all costs are presented in 2012 US$).

Parameter	Estimate	Scenarios		Sources
		Low	High	
Local cancer				
% Receiving treatment	100%	80%	100%	Assumption, ProVac national team
Household cost per treated woman[a]	$9423	–	–	Fees for surgical fees, chemotherapy, radiation, assumptions
Regional cancer				
% Receiving treatment	100%	80%	100%	Assumption, ProVac national team
Household cost per treated woman[a]	$8963	–	–	Fee for surgical fees, chemotherapy, radiation, assumptions

[a] Local and regional cancer costs borne by the household per treated woman include productivity losses to families due to lost wages, travel expenses within Belize and out of country, out-of-pocket payments for health care services, drugs, and supplies. The cost presented is the weighted average of the provider-specific costs. There are no government funding schemes for cervical cancer treatment in Belize.

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Table 3
Input parameters for estimating HPV vaccine program costs.

Parameter	Estimate	Scenarios		Sources
		Low	High	
Costs of vaccine doses				
Price per dose	$13.79	$13.08	$14.25	Mid = PAHO Revolving Fund, Low = bivalent price, High = assumption
Percentage international handling	3.5%	–	–	PAHO Revolving Fund
Percentage international delivery	25.0%	5.0%	5.0%	Assumption, EPI Manager,
Percentage wastage[a]	10.0%	5.0%	5.0%	Assumption, EPI Manager
Costs of syringes				
Price per dose:	$0.10	$0.17	$0.17	PAHO Revolving Fund
Percentage international handling	0.0%	3.5%	3.5%	Assumption, EPI Manager
Percentage international delivery	0.0%	5.0%	5.0%	Assumption, EPI Manager
Percentage wastage[a]	10.0%	5.0%	5.0%	Assumption, EPI Manager
Costs of safety box				
Price per box	$0.00	$2.00	$2.00	Assumption, EPI Manager
Percentage international handling	0.0%	3.5%	3.5%	Assumption, EPI Manager
Percentage international delivery	0.0%	5.0%	5.0%	Assumption, EPI Manager
Percentage wastage[a]	0.0%	5.0%	5.0%	Assumption, EPI Manager
Total number of syringes per safety box	100	50	150	Assumption, EPI Manager
Incremental health system costs[b]				
% Of vaccine delivered at schools	95%	–	–	Assumption, EPI Manager, expert consensus
% Of vaccine delivered at facilities	5%	–	–	Assumption, EPI Manager, expert consensus
Extra system costs per dose (school-based)	$2.00	$0.00	$10.00	Assumption, EPI Manager, expert consensus
Extra system costs per dose (facility-based)	$2.00	$0.00	$10.00	Assumption, EPI Manager, expert consensus

[a] The % wastage is converted into a factor [1/(1 – % wastage)] that is multiplied by the expected number of doses required to meet the anticipated level of coverage.
[b] Estimated incremental system costs include technical staff training (5% of cost), field staff outreach (31% of cost), communication and social marketing (31% of cost), sensitization workshop for teachers and key stakeholders(31% of cost), and fuel for distribution (2% of cost). They are assumed to only occur in the first year only.
With the exception of vaccine prices, assumptions for alternative values are not necessarily high or low.

were obtained from the MCH of the MOH, based on expenditures for previous staff education workshops and ministerial marketing campaigns.

3.5. Cost-effectiveness analysis

To determine whether the HPV vaccine is cost-effective in Belize, the national per capita gross domestic product (GDP) was used as a threshold for comparison with the incremental cost-effectiveness ratios, as recommended by WHO. WHO considers an intervention highly cost-effective if the cost per DALY averted is less than one per capita GDP, cost-effective if the cost per DALY lies between one and three times the per capita GDP, and not cost-effective if the cost per DALY is greater than three times the GDP per capita [30].

3.6. Vaccine efficacy and effectiveness

Schiller et al. [31] estimated efficacy at 94.5% for cervical intraepithelial neoplasia grade 3 or higher (CIN3+) that is associated with HPV-16/18 (Table 4). This end point was selected as a proxy for invasive cervical cancer. In the base case, three doses with no booster were assumed, with 95% coverage for the complete series of three doses, based on previous immunization programs conducted by the MCH department of the MOH in Belize [9]. The Ministry anticipated that the majority of vaccine distribution would be though schools (95%), with the remainder being through health clinics (5%). The proportion of cervical cancer caused by HPV types 16 and 18 was estimated to be 70%, with the remaining cervical cancers due to other HPV genotypes. [32].

For the base case analysis, we assumed lifelong protection for the vaccine. Since the vaccine is relatively new, it is unknown if a booster dose will be required to maintain immunity for the cohort. We also ran a scenario in which a booster dose at 20-years of age would be required to sustain this level of protection.

3.7. Scenario analysis

Ten alternative plausible scenarios of policy interest to the Ministry of Health were analyzed, from both a governmental and societal perspective. Mortality and incidence data from GLOBOCAN 2008 indicated cervical cancer to be the second leading cancer affecting women in Belize, providing a low estimate for comparison. Mortality data for 2005 through 2009 from PAHO were very similar to the data from Belizean sources and also covered a greater time span. Lower vaccine coverage of 95% for the first dose, 85% for the second dose, and 75% for the third dose were assumed in one scenario. In the event of dropout from the cohort, the MOH team wanted to be assured that the vaccine's introduction would still be cost-effective.

A two-dose scenario was also considered for the cohort. In some countries a two-dose schedule for the vaccine has been implemented despite the manufacturer's recommendations of three doses. Although data are not available on the duration of protection, studies have shown that for the initial four years following a two-dose schedule, immunogenicity is comparable to the three-dose schedule in both the bivalent and quadrivalent vaccines [33].

In addition, vaccine efficacy was varied, from a low of 91.7% to a high of 96.8% [33], as was the prevalence of serotypes 16 and 18, from 68% to 74% [32].

Finally, startup costs of US$ 13.50 per dose were considered. Since social marketing should be conducted to ensure the vaccine's acceptability to the general public, the government must provide funds for more than just the vaccine cost in order to have a successful program.

4. Results

The model estimated that if one cohort of 4100 girls 10 years old received the HPV vaccine, 69 cervical cancer cases and 51 deaths would be averted over a lifetime (undiscounted). After discounting at 3% per year, this is equivalent to 16 cases, seven deaths and

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Table 4
Input parameters for estimating the health impact of HPV vaccination.

Parameter	Estimate	Scenarios		Sources
		Low	High	
Coverage in year of introduction				
1 dose	95.0%	70.0%	90.0%	EPI Manager, expert consensus
2 doses	95.0%	70.0%	80.0%	EPI Manager, expert consensus
3 doses	95.0%	65.0%	75.0%	EPI Manager, expert consensus
Booster	70.0%	65.0%	75.0%	EPI Manager, expert consensus
Vaccine efficacy[a]				
Vaccine efficacy after primary dose 1 (p1)	48.4%	0.0%	96.8%	Low = 0%, High = same as 3 doses, mid = average of low+high
Vaccine efficacy after primary dose 2 (p2)	48.4%	0.0%	96.8%	Low = 0%, High = same as 3 doses, mid = average of low+high
Vaccine efficacy after primary dose 3 (p3)	94.3%	91.7%	96.8%	Low = 0%, High = same as 3 doses, mid = average of low+high
Duration of protection from 1 dose[b]				
Mean duration of protection (years)	100	20	100	Assumption CERVIVAC model version 1.1.23
Standard deviation	1	1	1	Assumption CERVIVAC model version 1.1.23
Duration of protection from 2 doses[b]				
Mean duration of protection (years)	100	20	100	Assumption CERVIVAC model version 1.1.23
Standard deviation	1	1	1	Assumption CERVIVAC model version 1.1.23
Duration of protection from 3 doses[b]				
Mean duration of protection (years)	100	20	100	Assumption CERVIVAC model version 1.1.23
Standard deviation	1	1	1	Assumption CERVIVAC model version 1.1.23
% of cervical cancer caused by types 16/18				
% of types due to 16 and 18	70.0%	–	–	Assumption CERVIVAC model version 1.1.23

[a] Reflects vaccine efficacy values among girls who are completely naïve to HPV16/18 infection. As the age of vaccination increases, vaccine efficacy is expected to decrease. We have assumed 92.8% efficacy for girls aged 10 years and 90.5% vaccine efficacy for girls aged 11 years, based on HPV prevalence assumed by CERVIVAC.
[b] Vaccine effectiveness in a given year is equal to the Excel equation: =VaccineEfficacy * (1 – NORMDIST (YearsSinceVaccination, AverageYearsProtected, StandardDeviationYearsProtected, 1)). This typically produces a sigmoid "reverse S shape" curve.

162 DALYs averted (Table 5). The program cost per fully immunized woman would be US$63.

The total discounted cost of introducing the HPV vaccine to one cohort of girls would be US$ 214,018 (Table 6). If they were not vaccinated, treatment costs would be US$233,888. If vaccinated, treatment costs would be reduced to US$89,876. This represents a saving of US$ 144,413. The net costs of vaccine introduction (vaccine program costs minus the potential treatment cost savings) would be US$ 69,605. Of the amount saved, if the vaccine were introduced, US$ 91,502 would be savings from local-cancer treatment, and US$ 52,911 would be savings from regional-cancer treatment.

With these costs and savings identified, the incremental cost-effectiveness ratio associated with the introduction of HPV vaccine in Belize is estimated to be US$ 429 per DALY averted, (Table 7). This increased to US$ 1320 when cervical cancer treatment costs and lost wages were excluded from the analysis. The per capita gross domestic product for Belize (2012) was US$ 4795 [34]. The ICER in either scenario is less than the GDP per capita and therefore introduction of the HPV vaccine would be considered a highly cost-effective health intervention.

Table 5
Discounted lifetime health benefits of HPV vaccination in girls aged 10 years[a].

	No vaccine (status quo)	HPV vaccine	
		(With vaccine)	Averted
Total cervical cancer cases	25	10	16
Local cancer	16	6	10
Regional cancer	10	4	6
Deaths	11	4	7
DALYs	262	100	162
Due to local cervical cancer (YLDs)	17	6	10
Due to regional cervical cancer (YLDs)	22	8	13
Due to cervical cancer deaths (YLLs)	224	86	138

[a] Health benefits are discounted at 3% per year.

Table 6
Discounted lifetime economic benefits of HPV vaccination in girls aged 10 years[a]

	No vaccine (status quo)	HPV vaccine	
		(With vaccine)	Averted
Total societal health service costs[b]	$233,888	$89,475	$144,413
Local cancer	$148,195	$56,693	$91,502
Regional cancer	$85,693	$32,782	$52,911

[a] Costs are discounted at 3% per year.
[b] Societal perspective includes costs of health care services, including surgery, imaging, chemotherapy, and radiation as well as travel, accommodations, and other out-of-pocket expenses related to care.

Table 7
Discounted lifetime cost-effectiveness of HPV vaccination in girls aged 10 years.

	Societal perspective
Cost-effectiveness compared to no vaccine	
Net cost of vaccine introduction	$69,605
Costs of vaccine introduction	$214,018
Health service costs avoided	$144,413
DALYs averted	162
Due to morbidity (YLDs)	23
Due to mortality (YLLs)	138
US$ per DALY averted	$429
Cost-effectiveness threshold	
1 x GDP per capita (2012) – WHO threshold for "highly cost-effective"	$4,795[a]
3 x GDP per capita (2012) – WHO threshold for "cost-effective"	$14,385[a]

[a] If government costs are considered separately, the ICER of $1320 is also highly cost-effective.

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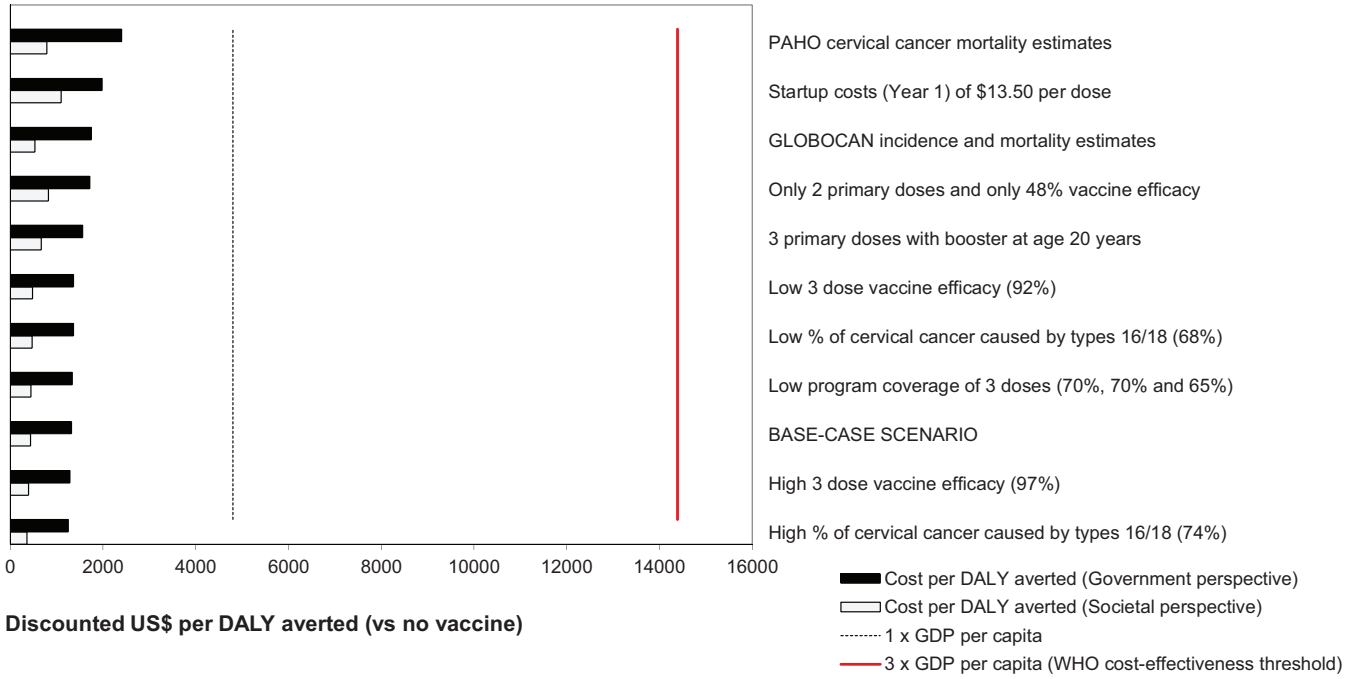

Fig. 2. ICER values for scenarios considered by the Belize government.

All ten of the scenarios considered were cost effective from both the governmental and societal perspectives, (Fig. 2).

5. Discussion

In Belize, primary prevention of cervical cancer through the successive vaccination of cohorts of 10-year-old girls would likely have a great impact on the burden and associated costs of the disease. Adding the HPV vaccine to the national EPI program is likely to be highly cost-effective even if the HPV 16/18 prevalence is lower than in other countries of Latin America and the Caribbean, and also even if only two doses are given instead of the three as recommended by the manufacturers. We assumed that the efficacy of only two doses is expected to be lower, (Table 4), so the ICER would be less cost-effective than if three doses were used, (Fig. 2). Further, even though the necessity of a booster dose is unknown, this analysis has shown that the vaccine would still be highly cost-effective. Newer vaccines are under production with greater genotype protection [35], and, if their costs are not prohibitive, their introduction might further drive down the burden of the disease.

The vaccine does not protect women who have already been exposed to the relevant HPV genotypes through sexual activity. Therefore, it would be prudent for the government to strengthen its screening program and thus improve the early detection of precancerous and cancerous lesions in adult females. Among the country's many ethnic groups, the Mayans suffer the highest mortality rate due to cervical cancer, despite comprising only 11% of the total population [13,36]. Additional affordable screening tools such as visual inspection with acetic acid would facilitate prompt identification of at risk women in vulnerable subgroups of the population. Of note, this analysis focused on the costs and benefits of providing HPV vaccine to school-age girls. Given resources to support further data acquisition and analysis, the analysis could be expanded to consider the costs and impact of alternative screening modalities for other female cohorts. Belize would also benefit from strengthening its referral system within the country and abroad for women with established disease in order to improve their access to adequate, prompt, appropriate services.

The CERVIVAC model is currently expanding its scope to allow evaluation of the impact and cost-effectiveness of enhanced screening options [10]. If an enhanced screening program were evaluated and shown to be cost-effective, then budget impact and other criteria would need to be carefully assessed, and a new comprehensive cervical cancer prevention program would need to be considered. While the country's small population may have limited the reliability of estimates for some aspects of disease burden and presumed costs, scenarios based on data from international sources still supports the base case outcome.

In Belize, both from health and political viewpoints, the prevention and control of cervical cancer is a high priority [23]. WHO recommends the introduction of the HPV vaccine to a country's national immunization program if cervical cancer prevention and control is a national priority and if the vaccination is cost-effective and sustainable [37]. This study suggests the HPV vaccine would be highly cost-effective. The next step for the government will be to determine a path for mobilizing resources to incorporate the HPV vaccine into the immunization schedule.

Contributors

LW Data collection and analysis, write up and manuscript approval

CJ Data collection and analysis, write up and manuscript approval

AC Data collection and analysis, write up and manuscript approval

EP Data collection and analysis, write up and manuscript approval

NL Data collection and analysis and manuscript approval

EW Data collection and analysis and manuscript approval

Conflict of interest

None of the authors of this manuscript have any conflicts of interest.

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Acknowledgments

The contribution, guidance and assistance from the members of staff of the Ministry of Health in Belize, the Belize Cancer Centre, Dangriga and the Belize Paliative Care Foundation and PAHO are greatly appreciated.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.042.

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Vaccine 33S (2015) A182–A191

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness analysis of the introduction of the pneumococcal conjugate vaccine (PCV-13) in the Egyptian national immunization program, 2013

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ARTICLE INFO

Keywords:
Pneumococcal conjugate vaccine
Cost-effectiveness
Egypt
Immunization program
vaccine

ABSTRACT

Introduction: Pneumonia is one of the most important causes of morbidity and mortality in children under 5 in Egypt, and the Ministry of Health of Egypt is considering introducing pneumococcal conjugate vaccine (PCV) in its national immunization program. We performed an economic analysis to evaluate the cost-effectiveness of this vaccine in Egypt and to provide the decision-makers with needed evidence.
Methods: The analysis was done using the TRIVAC model. Data included demographic characteristics, burden of disease, coverage and efficacy of the vaccine, health resource utilization, and costs of pneumococcal disease vaccination and treatment. Whenever possible, we used national or regional data. Two alternatives were compared: (1) general vaccination of children younger than 5 years with the 13-valent pneumococcal conjugate vaccine (PCV13), using a three-dose schedule without booster, and (2) no vaccination. Outcomes of 10 cohorts from birth to 5 years were analyzed. The study was performed from the governmental perspective and selected public health providers.
Results: In comparison to no vaccine, the introduction of PCV13 would be cost-effective, with an incremental cost-effectiveness ratio of US$ 3916 per disability-adjusted life-year (DALY) averted (government perspective). The total incremental cost of the PCV vaccination program (10 cohorts) would be approximately US$ 1.09 billion. Over the 10 cohorts, the program would avert 8583 pneumococcal deaths – 42% of all pneumococcal-related deaths.
Conclusion: The introduction of PCV13 would be a good value for money from the government perspective. It would represent a high-impact public health intervention for Egypt and respond to the National Immunization Technical Advisory Group (NITAG) resolution on reducing pneumonia burden and overall child mortality. Strengthening surveillance will be critical to generating high-quality national data, improving future economic analyses that support evidence-based decisions for introducing vaccines and public health interventions, and to monitoring their impact.

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1. Introduction

Pneumonia remains the leading cause of deaths in children aged 1–59 months worldwide, representing 14.1% of deaths, and *Streptococcus pneumoniae* is the most common cause of vaccine-preventable severe pneumonia and death [1,2]. Two new pneumococcal conjugate vaccines (PCVs) are currently available

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http://dx.doi.org/10.1016/j.vaccine.2014.12.044
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and are being introduced in several countries. They target either 10 (PCV-10) or 13 (PCV-13) of the most prevalent serotypes. Several clinical trials have proven their safety and efficacy in preventing invasive pneumococcal disease (IPD), pneumonia, and acute otitis media (AOM) [3–13], and they are currently used in more than 100 countries around the world, including many low- and middle-income countries. In addition, they can be easily integrated in the Expanded Program on Immunization (EPI) schedule, and were shown to be safely co-administered with other vaccines without interference. In its 2012 position paper, the World Health Organization (WHO) recommended the inclusion of PCVs in childhood immunization programs worldwide [14].

Pneumonia is considered one of the most important causes of morbidity and mortality in children under 5 years in Egypt; the incidence of pneumococcal pneumonia estimated at 529 per 100,000 in 2010, according to a recent systematic review [15]. In Egypt, local data on the incidence of pneumonia and prevalence of the various serotypes are limited. However, a national, laboratory-based sentinel-surveillance study of bacterial meningitis conducted between 1998 and 2004 showed that approximately 36% of isolates from patients with bacterial meningitis were due to *S. pneumoniae* among children under 5 [16]. A study looking at serotype distribution of these isolates revealed that only about a third of the serotypes were included in the PCV7 vaccine, but no data are available on distribution of serotypes that cause severe pneumonia or invasive pneumococcal disease other than meningitis [17].

In Egypt, the National Immunization Technical Advisory Group (NITAG) is the entity responsible for immunization policy and the decision-making process. The *Haemophilus influenzae* type B (Hib) vaccine was introduced in early 2014 and is combined with DTP and Hepatitis B in the form of a pentavalent vaccine. The Ministry of Health and Population (MOHP) is considering introducing PCV in its immunization program. The country chose to study PCV13 because this vaccine provides better coverage of pneumococcal strains circulating in Egypt as compared to PCV10. Consequently, the EPI conducted a cost-effectiveness analysis (CEA) in collaboration with the ProVac International Working Group (IWG) through the Agence de Médecine Préventive (AMP), and the WHO regional office for the Eastern Mediterranean. The aim was to help the EPI staff build cost-effectiveness analysis skills and provide decision-makers with needed evidence for introducing this vaccine into Egypt's routine vaccination schedule.

Objectives of this study were to assess health outcomes, incremental vaccination program costs, averted healthcare system costs, the cost-effectiveness of introducing PCV13 in the national immunization program, and to compare these measures against no vaccination.

2. Methods

2.1. General description of the model

The analysis was performed using the TRIVAC model (version 2.0) developed at the London School of Hygiene and Tropical Medicine (LSHTM) with support from the Pan American Health Organization's (PAHO's) ProVac Initiative and the Global Alliance for Vaccines and Immunization (GAVI) [18]. The TRIVAC model is a static cohort model, developed in EXCEL and designed for use in low- and middle-income countries. The model structure has been described in detail elsewhere [19]. Briefly, four diseases were included in the model: all-cause AOM, pneumococcal (*Spn*) pneumonia cases, *Spn* meningitis and *Spn* non-pneumonia non-meningitis (NPNM); these are other forms of invasive disease, primarily sepsis and bacteremia. The model uses data such as demographics, burden of disease, program coverage and efficacy of PCV13, serotype coverage, waning protection, health resource utilization, and costs of both pneumococcal disease vaccination and treatment of children under 5.

Whenever possible and available, local data from Egypt was used. If local data was not available, regional, or global data was reviewed by a panel of national and international experts and used for the study. Experts' opinions were obtained during professional EPI meetings in high committees, including members of the MOHP, professors of pediatrics, the head of the polio eradication certification committee, and senior medical epidemiologists. All of them had to reach a consensus.

The model provides outcomes about the number of pneumococcal disease cases averted, outpatient visits and admissions averted, deaths averted, the costs incurred to include the vaccine in the national schedule, and health services costs prevented due to cases of disease averted. The model also provides information on life-years saved, disability-adjusted life-years (DALYs) averted throughout the lifetime of that cohort, and an incremental cost-effectiveness ratio (ICER), with the cost expressed in US dollars per DALY averted [19]. To estimate DALYs averted, the model considered the WHO Global Burden of Disease (GBD) project disability weights for each disease (WHO GBD 1990).

The cost-effectiveness of PCV13 as opposed to the no-vaccination scenario was determined as follows: ICER = (cost of the vaccination program – health care costs saved through disease prevention)/DALYs averted. [20]

Using the WHO recommended threshold [21], if the ICER of the vaccine is less than the gross domestic product (GDP) per capita, it is considered highly cost-effective; if it is between 1 × and 3 × GDP per capita, it is considered cost-effective; and if it is more than three GDP per capita, it is not cost-effective.

Multivariate sensitivity analysis was used to determine how changes in values of one or several inputs simultaneously would affect the outcome under a given set of assumptions. Key drivers of the model results were tested, as were parameters that had uncertain values or came from multiple sources.

Two alternatives were compared: (1) introduction of PCV13 into the current national immunization program and (2) no introduction of PCV13. The total outcomes over 10 cohorts (2014–2023) from birth to 5 years were analyzed. The discount rate was defined at 3%, as recommended by WHO [20]. Age weighting was not considered in the analysis. The study was performed from the government perspective; public health providers were included (clinics, primary, secondary, and tertiary hospitals).

2.2. Demographic data

The in-country population in mid-2013 was estimated at 86 million, with the total population of children younger than 5 at 9 million (WHO, 2010). Demographic data used to populate the model was derived from the 2006 census done by the Central Authority for Public Mobilization and Statistics (CAPMAS). In 2012, live births were estimated at 2.6 million. The mortality rates for infants and children under 5 were 6.5 per 1000 and 20.4 per 1000, respectively. Life expectancy was estimated at 73 years in 2012 (United Nations Population Division [UNPOP], 2010 revision).

2.3. Disease burden

Data on incidence and deaths for each clinical syndrome was obtained from various sources (Table 1). For all-cause AOM, data was based on the incidence of acute respiratory infections reported in Rudan 2004 [22], and then was doubled to assume an AOM incidence of 29,300 per 100,000. Another study conducted in Boston [23], which showed an incidence of 90,000 per 100,000 cases of

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Table 1
Input parameters for estimating disease burden.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Annual incidence per 100,000 aged 1–59 m:				
All-cause acute otitis media	29,305	29,305	90,000	Rudan et al., 2004 [22]
Pneumococcal pneumonia cases	529	476	980	Rudan et al. 2013 [15]
Pneumococcal meningitis	14.0	0.4	14.3	Epidemiology surveillance unit, MoHP
Pneumococcal NPNM	84.1	63.8	106.2	GBD 2000
% Case fatality ratios (CFRs) in ages 1–59 m:[a]				
Pneumococcal pneumonia cases	2.50%	2.23%	3.00%	Maternal and child Health Department, MoHP 2012
Pneumococcal meningitis	7.9%	7.90%	15.00%	Teleb et al. 2013 [25]
Pneumococcal NPNM	4.6%	4.18%	5.02%	GBD 2000
% Sequelae in pneumococcal meningitis survivors				
% Major sequelae (single)	20.2%	–	–	Edmond et al. 2010 [27]
% Major sequelae (multiple)	4.5%	–	–	Edmond et al. 2010 [27]
Disability weight for DALY calculations				
All-cause acute otitis media	0.02	–	–	WHO GBD 1990
Pneumococcal pneumonia cases	0.28	–	–	WHO GBD 1990
Pneumococcal meningitis	0.62	–	–	WHO GBD 1990
Pneumococcal NPNM	0.28	–	–	Assumption (Griffiths PhD)
% Major sequelae (single)	0.24	–	–	Assumption (Griffiths PhD)
% Major sequelae (multiple)	0.63	–	–	Assumption (Griffiths PhD)
Mean duration of illness (in days)				
All-cause acute otitis media	6	–	–	Assumption
Pneumococcal pneumonia cases	6	–	–	Assumption
Pneumococcal meningitis	10	–	–	Assumption
Pneumococcal NPNM	6	–	–	Assumption
Age distribution of disease cases and deaths				
<3 m:	11.5%	–	–	Sanderson 2013, WHO IVR schedule report
3–5 m:	16.2%	–	–	Sanderson 2013, WHO IVR schedule report
6–8 m:	15.2%	–	–	Sanderson 2013, WHO IVR schedule report
9–11 m:	13.0%	–	–	Sanderson 2013, WHO IVR schedule report
12–23 m:	30.2%	–	–	Sanderson 2013, WHO IVR schedule report
24–35 m:	10.1%	–	–	Sanderson 2013, WHO IVR schedule report
36–47 m:	3.0%	–	–	Sanderson 2013, WHO IVR schedule report
48–59 m:	0.9%	–	–	Sanderson 2013, WHO IVR schedule report

[a] In the absence of vaccination, CFRs are assumed to decline in each successive birth cohort in line with the general trend in mortality among children under 5. This is done by assuming that the fraction of deaths under age 5 caused by the disease remains fixed over time.

clinical otitis in children younger than 5, was used for the high-incidence scenario. It was assumed that AOM does not require hospitalization and that it is not associated with fatal cases.

For pneumococcal pneumonia, a recent publication from Rudan (2013) [15] was used, based on an epidemiological model that takes into account each country's profile and incorporates data from national Demographic and Health Surveys (DHS) for risk factors of pneumonia. It gave an estimate of 47,625 new cases of pneumococcal pneumonia in Egypt, which translates to 529 per 100,000 children under age 5. Data from the GBD 2000 [24] was used in the high-incidence scenario, with an incidence of *Spn* pneumonia of 980 per 100,000. On the national level, deaths due to pneumococcal pneumonia reported by the Maternal and Child Health department of the MOHP in 2012 were estimated as 1200, which corresponds to 40% of all-cause pneumonia deaths in Egypt. The case-fatality ratio (CFR)—i.e., the number of deaths divided by the number of new cases of this disease—was estimated at 2.5%. In Rudan 2013 [15], 1570 pneumonia deaths due to *Spn* were reported in Egypt, corresponding to a CFR of 3%; this was used in the high-CFR scenario.

The annual incidence of pneumococcal meningitis, based on the GBD project [24] estimates for the Middle East, was 14 per 100,000. Local data was also available from the Epidemiology Surveillance Unit, MOHP, which registered 35 cases (children younger than 5) in 2012, an incidence of 0.4 per 100,000. (This probably underestimates the real disease burden, so it was tested in a low-burden scenario.) The CFR for *Spn* meningitis was estimated at 7.9%, based on the Eastern Mediterranean regional study from Teleb 2013 [25]. A 15% rate was used in the high-burden scenario, based on a local surveillance study of bacterial meningitis in Egypt [26]. No local data was available on NPNM disease, so the 2000 GBD study was used instead; the incidence was 84 per 100,000 with a CFR of 4.6%.

Local data on sequelae in meningitis survivors is scarce, so data from a recent global systematic review [27] was used, showing a risk of 20.2% for major single sequelae among survivors and a risk of 4.5% for major multiple sequelae following pneumococcal meningitis. Disability weights of 0.28 for pneumonia and 0.62 for meningitis were applied [28]. For NPNM diseases, pneumonia disability weights were used as a proxy. Weighted disability averages were calculated for sequelae based on the reported global distribution of sequelae syndromes [27] and standard disability weights for conditions similar to each syndrome [28]. We used 0.24 for single pneumococcal sequelae and 0.63 for multiple pneumococcal sequelae [29]. The mean duration of illness was 6 days for AOM and NPNM and 10 days for *Spn* pneumonia and meningitis, based on local expert opinion.

2.4. Vaccine coverage and efficacy

The vaccine (PCV13) is presented as a 1-dose vial, Prevnar13® (Pfizer, NY). A 3-dose schedule without booster was considered, administered at 2, 4, and 6 months, together with the pentavalent vaccine three doses, as per the current EPI schedule. In the year of introduction, we assumed coverage rates for doses 1, 2, and 3 at 96.7%, 96.6%, and 96.5%, respectively, based on rates achieved in

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Table 2
Input parameters for estimating PCV vaccine coverage and timeliness.

Parameter	Estimate (%)	Scenarios		Source/s
		Low	High	
Coverage of DTP1 by age in year 2014 (proxy for PCV doses given with DTP1)				
3 m	97.0	–	–	EPI, MoHP
6 m	97.5	–	–	EPI, MoHP
9 m	98.0	–	–	EPI, MoHP
12 m	98.0	–	–	EPI, MoHP
24 m	99.0	–	–	EPI, MoHP
Coverage of DTP2 by age in year 2014 (proxy for PCV doses given with DTP2)				
3 m	0.0	–	–	EPI, MoHP
6 m	97.1	–	–	EPI, MoHP
9 m	98.0	–	–	EPI, MoHP
12 m	99.7	–	–	EPI, MoHP
24 m	100.0	–	–	EPI, MoHP
Coverage of DTP3 by age in year 2014 (proxy for PCV doses given with DTP3)				
3 m	0.0	–	–	EPI, MoHP
6 m	96.0	–	–	EPI, MoHP
9 m	97.8	–	–	EPI, MoHP
12 m	99.3	–	–	EPI, MoHP
24 m	100.0	–	–	EPI, MoHP

EPI: Expanded Program on Immunization; MoHP: Ministry of Health and Population.
Coverage projections over the period 2014–2023 were estimated by assuming that PCV will achieve the same coverage and timeliness as DTP.

2012 for the DTP3 (EPI, MOHP reports). The model also takes into account the timeliness of vaccination [30] (Table 2).

For all-cause AOM, full-dose efficacy data was derived from a meta-analysis by Pavia et al. in 2009 [31] that used efficacy rates from several trials conducted on PCV; the analysis demonstrated an efficacy of 6% against all-cause AOM. A meta-analysis in the Cochrane Review in 2009 [32] showed 81% vaccine efficacy against invasive pneumococcal disease, which was used for *Spn* pneumonia, meningitis, and NPNM. The reduced efficacy was estimated based on the ratio between one and two doses, or two and three doses, as reported by Mahon in 2006 [33] and multiplied by the full-dose efficacy. For AOM, one- and two-dose efficacy were estimated at 3% and 5.5%, respectively; for pneumococcal pneumonia, meningitis, and NPNM, one- and two-dose efficacy were estimated at 41% and 74.5%, respectively (Table 3).

2.5. Serotype coverage

Based on a systematic evaluation of global serotype coverage [34], we assumed serotype coverage for the region to be 100% for all-cause AOM and 74% for pneumococcal pneumonia, meningitis, and NPNM.

2.6. Indirect effects of vaccination

In the base-case scenario, we assumed a conservative 110% 'herd effect' multiplier. The multiplier accounts for herd effects of the vaccine in the under-5 age group. Because evidence on the herd effect of PCV13 is lacking, the 110% multiplier is an assumption, and due to the uncertainty surrounding this input, the team opted for a conservative assumption in the base case. In another scenario, the team used a "high" herd effect multiplier of 125%, based on evidence from the USA in PCV7 in order to account for indirect effects; In this latter study, the total impact of the vaccine – 94% – was divided by the direct impact (i.e. the efficacy observed in studies in the USA, 75%) in order to derive a 125% herd effect multiplier for the model [35]. A serotype replacement of 5.5% per year was included, based on a study of PCV7 conducted in England and Wales. [36]. Finally, we assumed a 5% annual decrease in vaccine efficacy (waning efficacy). In the model, the 'relative coverage of death' parameter is used to adjust the vaccination program coverage to account for high risk children who do not receive the vaccine. As a proxy for this value, we have used the vaccine coverage from the lowest wealth quintile, divided by the total coverage, based on what is reported in the Egyptian DHS (99%).

Other estimates of these impact assumptions, which are key drivers of the model, were tested in the scenario analysis.

2.7. Vaccination program costs

Vacsera, the local company that would import and commercialize the PCV13 in Egypt if the vaccine were adopted, priced it at US$ 14.24, plus an additional 3% for handling, 1% for delivery, and 1% for wastage (Table 4). Other costs include safety boxes (US$ 0.60) and the administering syringe for each dose (US$ 0.06). It was assumed that the price would decrease 3% per year.

Based on the opinion of EPI experts, US$ 1 per dose—about 7% of the vaccine per-dose price—was assumed for incremental system costs, including cold chain, transportation, training, and social mobilization such as awareness campaigns. (Based on 2013 exchange rates, US$ 1 is equivalent to 7 Egyptian pounds [EGPs]. US$ 14 is approximately EGP 100.)

Other scenarios with lower and higher prices were also tested, as vaccine price is a key driver of the result.

2.8. Health resource utilization

General access to care in Egypt is about 70%, according to the household health expenditure and utilization survey 2009/2010 [37]. But because it was assumed that not every child with access to care would visit a healthcare provider, we set outpatient visitation rates for all-cause AOM at 50%. For *Spn* pneumonia and meningitis, we assumed an outpatient visitation rate of 80%; for *Spn* NPNM, we assumed an outpatient visitation rate of 50%. In order to estimate the number of hospitalizations due to pneumococcal pneumonia, the number of new severe cases of *Spn* pneumonia from Rudan 2013 [15] was used (i.e., 14,318), multiplied by the proportion of hospitalizations of severe cases (80%). This was then divided by the number of new cases (47,625) to obtain a 24% utilization rate. Based on expert opinion, it was assumed that all meningitis cases are hospitalized, since nearly all diagnosed cases are admitted; it was also assumed that 75% of *Spn* NPNM cases are admitted to hospitals.

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Table 3
Input parameters for estimating the health impact of PCV13.

Parameter	Estimate (%)	Scenarios		Source/s
		Low (%)	High (%)	
Vaccine efficacy vs all-cause acute otitis media				
Dose 1	3.0	2.0	6.9	Mahon et al., 2006 (33)
Dose 2	5.5	3.7	9.0	Mahon et al. 2006 (33)
Dose 3	6.0	4.0	9.0	Pavia et al. 2009 (31)
Vaccine efficacy vs vaccine type pneumococcal pneumonia/meningitis/NPNM				
Dose 1	41.0	31.9	69.2	Mahon et al. 2006 [33]
Dose 2	74.5	58.0	90.0	Mahon et al. 2006 [33]
Dose 3	81.0	63.0	90.0	Lucero et al. 2009 [32]
% Vaccine serotype coverage				
Pneumococcal pneumonia cases	74.0	67.0	79.0	Johnson et al. 2010 [34]
Pneumococcal meningitis	74.0	67.0	79.0	Johnson et al. 2010 [34]
Pneumococcal NPNM	74.0	67.0	79.0	Johnson et al. 2010 [34]
Other vaccination impact assumptions				
% Relative coverage[a]	99	80	99.7	Assumption based on Egyptian DHS
% Decrease in dose efficacy per yr[b]	5.0	0.0	10.0	Assumption
% Contribution of herd effect in <5 years[c]	110	100	125	Conservative assumption
Decline in vaccine type coverage/yr[d]	5.5	0.0	6.0	Assumption

DHS: Demographic and Health Survey

[a] Relative coverage is the coverage in those at risk of getting the disease (i.e. effective coverage) relative to coverage in the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.

[b] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 m, 4–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, and 48–59 m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.

[c] Rather than endogenous modeling of transmission dynamics, the % of direct protection under 5 years is multiplied by a herd effect factor (e.g., 120%) to give the % of total protection in the cohort of interest before age 5 years. This excludes any herd effect in individuals aged 5 years+ and is therefore very conservative.

[d] Vaccine type disease replacement is handled by reducing the expected vaccine type coverage in successive vaccinated cohorts by a fixed % each year, thus reducing overall expected impact of the programme in each successive vaccinated cohort by a similar amount. Thus, for a given vaccinated cohort, the % vaccine type coverage is equal to: $[T(1-R)N]$ where, T = % of disease caused by vaccine types in the year of vaccine introduction, R = % reduction in vaccine type coverage per year following vaccine introduction, N = number in the sequence of vaccinated birth cohorts.

Table 4
Input parameters for estimating PCV13 program costs.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Vaccine dose price projection				
2014	$14.24	$10.00	$20.00	Local manufacturing company (Vacsera)
2015	$13.81	$9.70	$19.40	Model derived
2016	$13.40	$9.41	$18.82	Model derived
2017	$13.00	$9.13	$18.25	Model derived
2018	$12.61	$8.85	$17.71	Model derived
2019	$12.23	$8.59	$17.17	Model derived
2020	$11.86	$8.33	$16.66	Model derived
2021	$11.51	$8.08	$16.16	Model derived
2022	$11.16	$7.84	$15.67	Model derived
2023	$10.83	$7.60	$15.20	Model derived
Other vaccine dose costs				
International handling (% of vaccine price)	3.00%	–	–	Assumption
International delivery (% of vaccine price)	1.00%	–	–	EPI assumption
Wastage (% of doses discarded etc)[a]	1.00%	–	–	EPI assumption
Safety box cost (80 syringes per box)				
Price of each safety box	$0.60	–	–	CDCD, MoHP
International handling (%)	3.00%	–	–	Assumption
International delivery (%)	2.00%	–	–	Assumption
Wastage (% of doses discarded etc)[a]	5.00%	–	–	Assumption
Administering syringe cost per dose				
Price of each syringe	$0.06	–	–	CDCD, MoHP
International handling (%)	3.00%	–	–	Assumption
International delivery (%)	2.00%	–	–	Assumption
Wastage (% of doses discarded etc)[a]	10.0%	–	–	CDCD, MoHP
Incremental system costs of introduction				
Incremental system cost per dose	$1.00	–	–	EPI assumption

EPI: Expanded Program on Immunization; CDCD, MoHP: Communicable Disease Control Department, Ministry of Health and Population.

[a] The % wastage is converted into a factor [1/(1 – % wastage)] which is multiplied by the expected number of doses required to meet the anticipated level of coverage.

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Table 5
Input parameters for estimating health service utilization and costs (all costs are presented in 2013 US $).

Parameter	Estimate	Scenarios		Source/s
		Low	High	
OUTPATIENT VISITS				
Outpatient visits per disease episode				
All-cause acute otitis media (AOM)	0.50	0.48	0.53	National experts consensus
Pneumococcal pneumonia cases	0.80	0.76	0.84	National experts consensus
Pneumococcal meningitis	0.80	0.76	0.84	National experts consensus
Pneumococcal NPNM	0.50	0.48	0.53	National experts consensus
Government cost per outpatient visit[a]				
All-cause acute otitis media	$4.08	$3.67	$4.49	WHO-CHOICE
Pneumococcal pneumonia cases	$3.91	$3.86	$4.72	Field survey
Pneumococcal meningitis	$4.81	$3.86	$4.72	Field survey
Pneumococcal NPNM	$4.36	$3.92	$4.79	WHO-CHOICE
INPATIENT ADMISSIONS				
Inpatient admissions per disease episode				
Pneumococcal pneumonia cases	0.24	0.23	0.25	National experts consensus
Pneumococcal meningitis	1.00	0.95	1.05	National experts consensus
Pneumococcal NPNM	0.75	0.71	0.79	National experts consensus
Government cost per inpatient admission[b]				
Pneumococcal pneumonia cases	$147	$138	$152	Field survey
Pneumococcal meningitis	$270	$238	$263	Field survey
Pneumococcal NPNM	$145	$138	$152	Field survey

WHO-CHOICE: WHO initiative aimed at providing policy makers with evidence for deciding on interventions and programs that maximize health with available resources. (Available at http://www.who.int/choice/en/)

[a] Government costs per outpatient visit include the cost of visit, treatment, laboratory tests, and X-rays. Outpatient visits are distributed as follows: 25% public clinic, 25% primary hospital, 25% secondary hospital, 25% tertiary hospital for AOM; 10%/30%/30%/30% for pneumonia and meningitis; and 5%/30%/30%/35% for NPNM. The cost presented is the weighted average of the provider-specific costs.

[b] Government costs per inpatient admission include the cost per bed-day multiplied by the expected length of stay and the cost of any disease-specific drugs and diagnostics. Inpatient admissions are distributed as follows: 20% primary hospital, 40% secondary hospital, 40% tertiary hospital for pneumonia; 10%/40%/50% for meningitis; and 33.3%/33.3%/33.3% for NPNM. The cost presented is the weighted average of the provider-specific costs.

The distribution of visits and admissions across the different health providers was based on expert opinion. They are reported in Table 5.

2.9. Health services costs

All costs analyzed in this study are the cost of the four illnesses in the public sector whose treatment is funded by the government.

Resource utilization was estimated by surveying 100 physicians from 20 hospitals located in 4 governorates (Cairo, Giza, Bani-Sweif, and Gharbiya) representing three geographical areas of Egypt (traditionally upper Egypt, lower Egypt, and greater Cairo) with socioeconomic variations. Physicians were specialists in different areas (general pediatricians, neurologists, oto-rhino-laryngologists, and physicians in fever and respiratory diseases). The physicians were asked about the usual treatment in daily practice for a given syndrome. The weighted unit cost (costs for medicines, laboratory tests, and X-rays) for each intervention or practice was registered.

The average costs of outpatient and inpatient treatments were estimated from these field surveys when possible, based on the proportion of complicated and uncomplicated cases for each disease. An average of the government costs obtained was then computed by disease and by health provider (Table 5).

Because NPNM is not definitely diagnosed, it is treated like pyrexia of unknown origin, and corresponding costs were used.

For outpatient all-cause AOM and *Spn* NPNM, no local information could be obtained from the survey; instead we used the default data from WHO-CHOICE. (WHO-CHOICE is an initiative that provides policy makers with the evidence for deciding on the interventions and programs which maximize health for the available resources. (Available at: http://www.who.int/choice/en/.)

For admissions, a bed-cost of US$ 100 for the total length of stay was assumed, based on national pediatric experts. That sum includes cost of residence, service, and logistics. Reference prices for drugs used in hospitalization were obtained from information provided by surveyed hospitals. The price used is the hospitals' purchasing price.

The annual cost of major single and multiple sequelae from meningitis was not included in the base-case scenario because no significant data from Egyptian sources was available. However, to test the impact of this parameter, some annual household costs corresponding to Egypt's GDP per capita (based on Griffiths et al., 2012 [38]) were included in a tested scenario.

3. Results

3.1. Impact on pneumococcal disease burden and health service utilization

The introduction of PCV13 would avert 8583 deaths over 10 cohorts, or 41.9% of all pneumococcal-related deaths, and would prevent 106,401 inpatient admissions, 41.4% of all related hospitalizations (Tables 6 and 7).

3.2. Primary outcome

The introduction of PCV13 vaccine would be cost-effective with an incremental cost-effectiveness ratio (ICER) of US$ 3916 per DALY averted (government perspective), according to the WHO recommended threshold [21] (Table 8). This corresponds to 1.2 × GDP per capita in Egypt (US$ 3187 in 2012). The total incremental cost of introducing PCV vaccination program (10 years) is US$ 1,089,181,321 (approximately US$1.1 billion).

3.3. Sensitivity analysis

In order to test the robustness of the base-case results, we ran 18 different scenarios in the model and adjusted various parameters that were either key drivers of the model or for which we had

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Table 6
Discounted health benefits (10 cohorts vaccinated over the period 2014-2023).

	No vaccine (Status quo)	**PCV13** With vaccine	Averted
Total cases <5 years	**37,748,986**	**35,892,051**	**1,856,935**
All-cause acute otitis media	36,958,144	35,428,252	1,529,891
Pneumococcal pneumonia cases	667,159	391,263	275,896
Pneumococcal meningitis	17,656	10,355	7302
Pneumococcal NPNM	106,027	62,181	43,846
Total outpatient visits	**19,079,938**	**18,066,511**	**1,013,427**
All-cause acute otitis media	18,479,072	17,714,126	764,946
Pneumococcal pneumonia cases	533,727	313,011	220,717
Pneumococcal meningitis	14,125	8284	5841
Pneumococcal NPNM	53,013	31,090	21,923
Total inpatient admissions	**257,295**	**150,893**	**106,401**
Pneumococcal pneumonia cases	160,118	93,903	66,215
Pneumococcal meningitis	17,656	10,355	7302
Pneumococcal NPNM	79,520	46,635	32,885
Total deaths <5 years	**20,505**	**11,922**	**8583**
Pneumococcal pneumonia cases	14,878	8651	6228
Pneumococcal meningitis	1244	723	521
Pneumococcal NPNM	4383	2548	1834
Total children with permanent disability	**4054**	**2376**	**1678**
Sequelae group A	3315	1943	1372
Sequelae group B	739	433	306
DALYs Lost	**665,348**	**392,470**	**272,878**
YLDs – DALYs due to morbidity	57,255	38,766	18,488
YLLs – DALYs due to mortality	608,094	353,704	254,390

Health benefits are discounted at 3% per year.

uncertain values or different values depending on the source. Each of the 18 scenarios resulted in an ICER that was still cost-effective (highly cost-effective for three of the scenarios) from the government perspective (Fig. 1). As part of this analysis, two 'extreme' scenarios were tested:

- The most favorable scenario comprised a low vaccine price and a high incidence and case-fatality ratio: US$ 1404 per DALY averted (highly cost-effective).
- The least favorable scenario comprised a high vaccine price and a low incidence and case-fatality ratio: US$ 7833 per DALY averted (cost-effective).

Results from the government perspective should be considered robust because, despite testing a significant uncertainty, it was demonstrated that at a minimum the PCV13 intervention would be cost-effective.

4. Discussion

Primary results show that introduction of PCV13 would be a cost-effective intervention in Egypt.

In low- and middle-income countries, evidence-based decision-making and economic studies in particular are still limited, often due to a lack of relevant data or a systematic process. The ProVac IWG was an opportunity for some of these countries to be exposed to the methodology and gain support from partners to carry out their own analysis and promote evidence-based decision-making, especially regarding new vaccine introductions. This is especially relevant in the context of limited resources and in light of the high cost of the new vaccines (as compared to traditional vaccines of the EPI), particularly for middle-income countries that do not benefit from GAVI support [39].

Many of the published cost-effectiveness studies in these settings come from Latin America and the Caribbean, where the ProVac Initiative was first launched [18,40]. They have shown that, compared to no vaccination, either PCV10 or PCV13 would be

Table 7
Discounted economic benefits (10 cohorts vaccinated over the period 2014–2023).

	No vaccine (Status quo)	**PCV13** With vaccine	Averted
TOTAL GOV. HEALTH SERVICE COSTS[a]	**$117,656,726**	**$97,074,939**	**$20,581,788**
Total outpatient visit costs	**$77,821,729**	**$73,713,247**	**$4,108,482**
All-cause acute otitis media	$75,438,151	$72,315,370	$3,122,781
Pneumococcal pneumonia cases	$2,084,637	$1,222,559	$862,078
Pneumococcal meningitis	$67,883	$39,811	$28,072
Pneumococcal NPNM	$231,059	$135,507	$95,552
Total inpatient admission costs	**$39,834,997**	**$23,361,692**	**$16,473,305**
Pneumococcal pneumonia cases	$23,537,378	$13,803,766	$9,733,612
Pneumococcal meningitis	$4,767,225	$2,795,794	$1,971,431
Pneumococcal NPNM	$11,530,394	$6,762,132	$4,768,262

Costs are discounted at 3% per year.

[a] Government perspective includes all bed-days and disease-specific drug/diagnostic costs borne by the government at the following health providers: public clinic, public primary, secondary, and tertiary hospitals.

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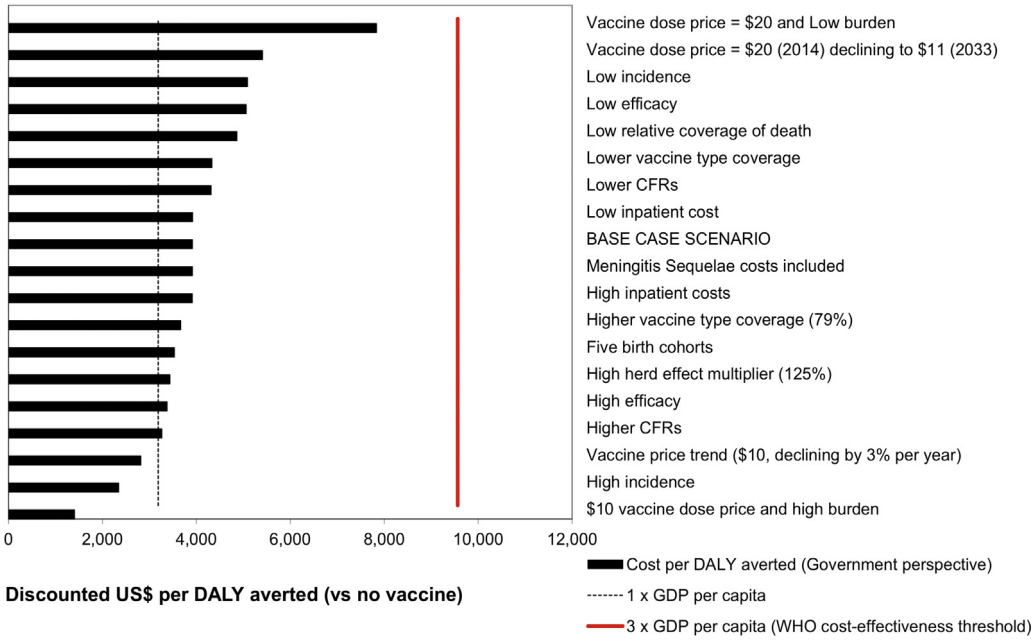

Fig. 1. Cost-effectiveness of introducing PCV13 and sensitivity analysis (government perspective).

cost-effective (Argentina, US$ 10,948 per DALY for PCV13 [41]; Brazil, US$ 9917 per DALY for PCV10 [42]; Colombia, US$ 1837 per DALY for PCV10 [43]). In African low-income countries, PCV13 vs. no vaccination was cost-effective in Gambia, with an ICER of US$ 570 per DALY corresponding to 1.6 × GDP per capita [44]; and highly cost-effective in Kenya, with an ICER of US$ 47 per DALY [45].

Our analysis has a few limitations. First, estimating some costs that are not directly associated with the healthcare system is difficult; opportunity costs such as parents' loss of productivity when taking care of sick children could not be included. Consequently, even though we were able to obtain partial information on household costs, the societal impact was not described. Second, data from the private sector was not available and private health facilities were not considered, even though some patients may go to private clinics. Third, sequelae costs incurred by the government were not included in the base-case analysis because no Egyptian data was available. This would affect the overall ICER by underestimating cost savings to the health system. Lastly, for a more comprehensive analysis, results would need to be strengthened by collecting additional accurate prospective data, and if possible, by adding the societal point of view.

Despite these limitations, the government perspective was the perspective of most interest because in Egypt, 70% of the population receives healthcare services from governmental institutions. The study allowed us to document the direct medical costs borne by the government (the public health sector) if the vaccine were introduced nationwide. Also, whenever possible, national, or regional data were used. Incomplete data was complemented by international literature and meta-analyses, and all data used to populate the model was validated by a multidisciplinary team of national and international experts, including different institutions and specialists in various fields, including epidemiologists, health economists, public health, and immunization experts.

Our results were shown to be robust. The scenario analysis allowed us to test several scenarios, and all of them showed that introduction of PCV13 would at least be cost-effective. Three scenarios showed PCV13 to be highly cost-effective. The scenario with the highest ICER was the least favorable one for the vaccine introduction. Therefore, in the base case, introduction of PCV13 in Egypt is cost-effective from the government point of view.

Finally, our results are likely to be conservative: we did not include societal and sequelae costs and the chosen herd effect multiplier of 110% is lower than what might be expected because it only took into account children under 5. Had older age groups been considered, it almost surely would lead to a more cost-effective analysis from the societal perspective.

Table 8
Discounted cost-effectiveness of PCV (10 cohorts vaccinated over the period 2014–2023).

	PCV13 Government perspective
Cost-effectiveness compared to no vaccine	
Net cost of vaccine introduction	**$1,068,599,533**
Costs of vaccine introduction	$1,089,181,321
Health service costs avoided	$20,581,788
DALYs averted	**272,878**
YLDs averted – DALYS due to morbidity	18,488
YLLs averted – DALYs due to mortality	254,390
US$ per DALY averted	**$3916**
Cost-effectiveness threshold	
1 × GDP per capita (2012) – WHO threshold for 'highly cost-effective'	$3187
3 × GDP per capita (2012) – WHO threshold for 'cost-effective'	$9562

Costs and DALYs are discounted at 3% per year.

5. Conclusion

Introduction of PCV13 would represent a high-impact public health intervention for Egypt and would respond to the NITAG resolution on reducing pneumonia cases and pneumococcal deaths. Strengthening epidemiological and laboratory surveillance will be of fundamental importance when making a decision about introducing this vaccine into the schedule, to measure the impact of the intervention. Intersectoral and multidisciplinary work within

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the framework of the MOHP allowed us to revise available data, producing solid evidence and facilitating evidence-based decision-making. Cost-effectiveness analysis could be an important part of a strong evidence-based decision-making process and needs to be considered for various public health interventions.

Funding

This study is part of the ProVac IWG and was funded by a grant from the Bill and Melinda Gates Foundation to the PAHO: OPP1032888. The Agence de Médecine Préventive (AMP) was PAHO's sub-grantee and implemented the project in the WHO Eastern Mediterranean region (EMRO) and the European region (EURO).

Acknowledgments

The authors are grateful to: Andrew Clark and Colin Sanderson (LSHTM), who provided support using and interpreting the TRIVAC model; Julia Blau, who coordinated the implementation of the project at AMP; our colleagues Antoine Durupt, Chloé Thion, and Aude Bruyas at AMP; Gabriela Felix (PAHO),who coordinated the ProVac IWG at PAHO; Diane Coraggio, who provided support to country teams regarding the effective communication of evidence to stakeholders; Dr Nadia Teleb, Regional Advisor, VPI for the Eastern Mediterranean (WHO-EMRO); Miloud Kaddar (formerly WHO-HQ); Dr. Loreis Ramses, Cairo governorate surveillance office; Dr. Mona Toson, Bani-Sweif governorate surveillance office, and Mrs. Heba Wali, Vacsera, holding company.

Conflicts of interest

All authors declare no conflict of interest.

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Vaccine 33S (2015) A192–A200

Contents lists available at ScienceDirect

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Cost-effectiveness analysis of the introduction of rotavirus vaccine in Iran

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ARTICLE INFO

Keywords:
Rotavirus diarrhea
Cost-effectiveness
Vaccine
Iran
DALY
TRIVAC model

ABSTRACT

Background: Although the mortality from diarrheal diseases has been decreasing dramatically in Iran, it still represents an important proportion of disease burden in children <5 years old. Rotavirus vaccines are among the most effective strategies against diarrheal diseases in specific epidemiological conditions. This study aimed to evaluate the cost-effectiveness of the introduction of rotavirus vaccine (3 doses of pentavalent RotaTeq® (RV5)) in Iran, from the viewpoints of Iran's health system and society.
Methods: The TRIVAC decision support model was used to calculate total incremental costs, life years (LYs) gained, and disability-adjusted life years (DALYs) averted due to the vaccination program. Necessary input data were collected from the most valid accessible sources as well as a systematic review and meta-analysis on epidemiological studies. We used WHO guidelines to estimate vaccination cost. An annual discount rate of 3% was considered for both health gain and costs. A deterministic sensitivity analysis was performed for testing the robustness of the models results.
Results: Our results indicated that total DALYs potentially lost due to rotavirus diarrhea within 10 years would be 138,161, of which 76,591 could be prevented by rotavirus vaccine. The total vaccination cost for 10 cohorts was estimated to be US$ 499.91 million. Also, US$ 470.61 million would be saved because of preventing outpatient visits and inpatient admissions (cost-saving from the society perspective). We estimated a cost per DALY averted of US$ 2868 for RV5 vaccination, which corresponds to a highly cost-effective strategy from the government perspective. In the sensitivity analysis, all scenarios tested were still cost-saving or highly cost-effective from the society perspective, except in the least favorable scenario and low vaccine efficacy and disease incidence scenario.

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http://dx.doi.org/10.1016/j.vaccine.2014.12.035
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Conclusion: Based on the findings, introduction of rotavirus vaccine is a highly cost-effective strategy from the government perspective. Introducing the vaccine to the national immunization program is an efficient use of available funds to reduce child mortality and morbidity in Iran.

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1. Introduction

The high prevalence and incidence of diarrhea are recognized as a major health problem. There were nearly 1.7 billion diarrhea episodes among children less than 5 years of age in low- and middle-income countries in 2010 [1]. Diarrheal disease is also the second leading cause of death in children under 5 years old, killing about one million children every year [2].

Rotavirus is the most important cause of severe diarrhea in infants and young children worldwide [3,4]. Rotaviruses are ubiquitous, and 95% of children are infected by the age of 5 years. Rotavirus is responsible for a large proportion of the above-mentioned deaths and 20–54% of acute diarrhea episodes worldwide [5–7].

Eesteghamati and his colleagues [8] reported that rotavirus is the most important cause of severe diarrhea among hospitalized children aged less than 5 years old in Iran. Those researchers also found that rotavirus disease accounts for more than one-half of all hospitalizations for severe diarrhea.

Recent studies show that rotavirus vaccines might be the best choice for preventing severe rotavirus disease and the deadly dehydrating diarrhea that it causes, particularly in low-income countries where access to treatment for RV is limited [9,10]. There are two rotavirus vaccines: the pentavalent RotaTeq® (RV5) (Merck and Co. Inc., West Point, Pennsylvania, USA) and the monovalent Rotarix® (RV1) (GlaxoSmithKline Biologicals, Rixensart, Belgium). Studies of the rotavirus vaccine have shown that the efficacy of RV5 and RV1, respectively, against rotavirus gastroenteritis of any severity was 74.0% (95% confidence interval (CI) 66.8–79.9) and 87% (95% CI 79.6–92.1) [11,12]. More importantly, the rotavirus vaccines can prevent approximately 98% of severe infections and 70% to 100% of emergency department visits and hospitalizations from rotavirus [12–14].

Decisions to adopt vaccination programs depend on multiple factors, including the disease prevalence and incidence, vaccine efficacy, and cost-effectiveness of a vaccination program. Although some studies have estimated the cost-effectiveness of rotavirus vaccination [15–18], most of them have been conducted in developed countries, not in developing nations. Results of cost-effectiveness studies can vary among countries due to differences in epidemiological patterns, patients' characteristics or health system variables (such as incidence/prevalence of disease, adherence to the treatment regimen, individuals' preferences for particular levels of health, unit costs of inputs into health care, and variation in how health care is delivered). Moreover, no simple rule is available to indicate how the results of cost-effectiveness studies in developed countries might translate to health care delivery settings in developing nations.

The major serotype of rotavirus in Iran is G4P [8] and other dominant strains are P [8] with G nontypeable, G4 with P nontypeable, G1 [P8], and G2 [P4] [8]. Although the major serotype can be covered by RV1 through cross-reactivity, RV5 provides direct protection against it. Also, based on a recent systematic review, RV5 was used in the unique study that reported vaccine efficacy against G4 and P [8] in middle-income countries [19]. Therefore, we conducted this study to evaluate the cost-effectiveness of RV5 vaccination compared to no vaccination in Iran.

2. Methods

2.1. Study design

This economic evaluation was conducted from the perspectives of Iran's government and its society; in the governmental perspective, those direct medical costs imposed on governmental health system were included and in the societal perspective, all direct medical costs that imposed on society including (patients' families or government) were included. The TRIVAC model, a decision-support model developed by the ProVac Initiative of the Pan American Health Organization (PAHO) in collaboration with the London School of Hygiene and Tropical Medicine (LSHTM) [20], was used to calculate total incremental costs, life years gained, disability adjusted life years (DALYs) averted due to the vaccination program, and an incremental cost-effectiveness ratio (ICER). A data collection procedure was used in order to obtain the necessary input data from the most valid accessible sources for the analysis.

We used the assumptions made by TRIVAC for the natural history of rotavirus. We classified rotavirus as non-severe or severe cases of rotavirus gastroenteritis (RVGE). TRIVAC is a static model that only crudely takes account of the indirect protection of the vaccination on unvaccinated children through herd immunity or of the negative effects of type replacement. A crude multiplier of direct vaccine efficacy can be applied to replicate a herd effect; also, vaccine efficacy can be decreased to reflect the circulating serotypes [20]. We assumed 2014 as the year of introduction of the vaccine and included children 1–59 months old for 10 sequential birth cohorts in the analysis (2014–2023). The time horizon for health and economic benefits has been defined in the TRIVAC model specifications [20]. An annual discount rate of 3% was considered for both health gain and costs.

2.2. Input epidemiological and effectiveness data

2.2.1. Demographic data

The number of live births was derived using data from Iran's National Organization for Civil Registration. We used the last Multiple-Indicator Demographic and Health Survey (IrMIDHS, 2010) to obtain mortality rates among children [21]. We also used the United Nations Population Division database to extract the estimates for current life expectancy of women and men in Iran and also estimates for the future [22].

2.2.2. Disease burden

An epidemiologic model was used to estimate the incidence of diarrheal diseases. According to the 2010 Demographic and Health Survey (DHS) report [21], the 14-day prevalence of all-cause diarrhea was 13.5% in Iran (the IrMIDHS study was performed between 22 December 2010 and 20 January 2011). This included all children who had a new episode of diarrhea within 14 days before survey or those whose episode started before the period, but still were symptomatic during the period. All cases of diarrhea started within (duration-1) days before the first day of study period, were among the prevalent cases at least in the first day of the period. We used the pooled estimate for the weighted median of duration of diarrhea in low- and middle-income countries for children 0–59 month old, which was 3.1 days (3.0–3.2) in a systematic review

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[23]. We rounded it to 3 days for calculation purposes. Considering a 3-day duration for all-cause diarrheal diseases, the daily incidence rate was estimated 8.4 per 1000 person-day based on the $I = \text{PP}/[\text{study period} + (D-1)]$ formula, where I, PP and D indicate incidence, period prevalence and duration, respectively. Assuming no systematic difference between the study period and whole calendar year, annual incidence rate of all-cause diarrhea was estimated to be 307,968 episodes per 100,000 children.

To estimate the proportion of rotavirus diarrhea from all-cause diarrhea, we used the results of a systematic review and meta-analysis [24]. That review included all Iranian studies indexed in the international and national databases, including PubMed, Ovid Medline, Science Direct, Google Scholar, Institute for Scientific Information (ISI), and Scopus as well as Iran Medex and Irandoc for Farsi-language papers [25]. The systematic review included 21 studies on hospital cases from 11 different provinces (10,997 cases) and 15 studies on outpatient cases from 7 different provinces (4371 cases). For hospital and outpatient settings, the pooled estimates with random effect were 39% (95% CI: 32–47%) and 31% (95% CI: 23–38%), respectively. Based on the opinion of clinical expert in the research team, in our model we used the pooled estimate of the outpatient setting (31%) as the percentage of all-cause diarrhea incidence that is attributable to rotavirus. That is because the incidence in community was the parameter of interest in the model, rather than hospitalizations.

We estimated the number of deaths attributed to rotavirus diarrhea based on statistics from the national registry of childhood deaths. Their database reports cause-specific mortality for children <5 years old, with nationwide coverage. For our estimate, we multiplied the proportion of severe cases of diarrheal disease that are due to rotavirus (39%) by the total number of deaths due to diarrheal diseases extracted from that national registry. The disability weight for diarrhea episodes was considered to be 0.119, as used in the model and the 1st global burden of disease (GBD) study. There are updated disability weights for diarrheal diseases [26], but we did not use them, so that our results would be comparable with the results of other local and international studies. The age distribution of disease cases was obtained from an Iranian study on sentinel sites for rotavirus surveillance [8].

2.2.3. Vaccine coverage and efficacy

We assumed that the new vaccine would be administered jointly with another vaccine in the routine schedule [27] (DTP vaccine at 2, 4, and 6 months), with a coverage of 99% and a maximum achievable coverage of 99.5%. Ministry of Health collects administrative data from all rural health houses and urban health posts which are responsible for routine immunization. Those information have good consistency with nationally representative surveys [21]. The vaccination coverage of DTP3 and Hepatitis-B3 are around 99% based on estimates of the Ministry. The rotavirus vaccine efficacy (VE) has not been reported for Iran. Therefore, three scenarios were modeled in order to explore how different scenarios of vaccine efficacy would impact the cost-effectiveness profile in Iran, based on evidence from countries in the same WHO mortality stratum, B (low adult and low children mortality). The first scenario, which was the base-case scenario, incorporated estimates of three-dose VE of 82.2% (70.0–90.1%) against Vesikari scale ≥11 (severe) rotavirus gastroenteritis (RVGE), based on a multi-country study in Latin America [28]. The second scenario used full dose efficacy estimates from Vietnam of 63.9% (7.6–90.9%) against severe RVGE. We also used a very low estimate of VE from the same study (48.3%) in our sensitivity analysis; that was an overall estimate for Vietnam and Bangladesh (WHO mortality stratum B and D, respectively) which is a pessimistic estimate for Iran condition. [29]. The third scenario used efficacy estimates from the Linhares et al. Latin American study against very severe RVGE (Vesikari scale ≥19) of 97.3% (83.8–99.9%) [28]. While RV1 was used in this study instead of RV5, immunogenicity and efficacy estimates for the two vaccines are similar across a range of countries [30]. Partial schedule efficacy, that is, efficacy of only one or two doses (which has been estimated to take into account drop-outs and children who do not receive their full schedule), was calculated according to published studies of Latin America and Asia [28,29]. Efficacy for 1 and 2 doses was equal to 52% and 71% of full doses, respectively. The ratio of VE of non-severe (all who need medical attention except admitted) versus severe cases (admitted) was estimated at 83%, based on the Vesikari et al. study [11]. The relative coverage of deaths was considered to be 90%. This is an adjustment that accounts for a concentration of deaths in the children who are not reached by vaccination—and so the true effectiveness may be lower than the equal distribution of deaths [31]. The annual decrease in dose efficacy, which was used to simulate waning protection, was considered to be 4.8% [28]. In the base-case analysis we assumed no herd immunity exist. We tested a 110% multiplier for VE in sensitivity analysis to estimate the impact of herd immunity. The serotype coverage of RV5 was considered 100% based on frequency of common serotypes in Iran [8] and cross-reactivity; in sensitivity analysis, a 52.7% serotype coverage was tested as low serotype coverage.

2.3. Cost estimation

2.3.1. Vaccination program costs

We used WHO guidelines [32] to estimate the incremental cost of introducing the rotavirus vaccine into the current national vaccination system. The cost of vaccine supplies was calculated using the formula of $C = P \times I \times B \times D \times (1/(1-w))$, where P is the vaccine price per dose, I is the immunization coverage rate, B is the birth cohort population, D is the number of doses per fully immunized child, and w is the wastage rate.

The price of each dose (US$ 10) was obtained from the local representative of the vaccine's manufacturer. A Ministry of Health representative provided the company with the number of required vaccine doses and officially asked about and negotiated on the price. Finally, we received a pro forma for the vaccine price. The number of doses per child fully immunized for rotavirus was considered as three, and the wastage rate was assumed to be 5%. To estimate the incremental system cost per dose, we included the cost of distribution system, cold chain, surveillance monitoring, training, maintenance, personnel expenses, and the required facilities that are needed beyond the currently available facilities of Iran's Ministry of Health. The total annualized capital cost was estimated based on equipment prices and their useful life and an annualizing factor. In addition, health care personnel costs (all heath care workers involved in this program, including vaccinators) were assessed on the basis of exclusive time allocations for this vaccine and other incentive payment.

2.3.2. Health service utilization and costs

To estimate the total outpatient health care utilization costs, we extracted data on health care seeking during an episode of childhood diarrhea from a representative nationwide study on 14,625 children with diarrheal diseases [33]. The study showed that 70% of cases had at least one visit with a health care provider. Those included visits with a physician in 61.6% of cases and with either a *behvarz* (rural health care worker) or a health post officer (non-physician care provider in urban area) in 8.4% of cases. The rest of the cases (30%) had not had a visit with any health care provider. The personnel cost for physicians was estimated based on a weighted mean of the official price of outpatient visits of general practitioners and specialists in private and public sectors.

We estimated the pattern of prescribing diagnostic tests and medications in severe and non-severe cases by interviewing a wide

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Table 1
Input parameters for estimating disease burden.

Parameter	Estimate	Scenarios		Source (s)
		Low	High	
Annual incidence per 100,000 aged 1–59 mo				
Rotavirus (non-severe) cases	92,315	68,492	113,160	[21,36]
Rotavirus (severe) cases	2864	2125	3511	[21,36]
% Case fatality ratios (CFRs) in ages 1–59 mo[a]				
Rotavirus (severe) cases	0.02%	0.01%	0.03%	Child mortality surveillance system of Iran
Disability weight for DALY calculations				
Rotavirus (non-severe) cases	0.119	–	–	[26]
Rotavirus (severe) cases	0.119	–	–	[26]
Mean duration of illness (in days)				
Rotavirus (non-severe) cases	6	–	–	Assumption
Rotavirus (severe) cases	6	–	–	Assumption
Age distribution of disease cases and deaths				
<3 mo	2.4%	–	–	[8]
3–5 mo	7.8%	–	–	[8]
6–8 mo	20.0%	–	–	[8]
9–11 mo	20.0%	–	–	[8]
12–23 mo	35.0%	–	–	[8]
24–35 mo	5.0%	–	–	[8]
36–47 mo	5.0%	–	–	[8]
48–59 mo	4.8%	–	–	[8]

[a] In the absence of vaccination, CFRs are assumed to decline in each successive birth cohort in line with the general trend in under-5 mortality. This is done by assuming the fraction of under-5 deaths caused by the disease remains fixed over time.

range of health professionals, including general practitioners, pediatric assistants, and pediatricians, in the public and private sectors. The average cost of each inpatient episode was estimated based on medical records of 60 patients who were hospitalized for viral diarrhea (based on ICD-10-CM Diagnosis Code A08) in the Mofid Children's Hospital, in Tehran, Iran, in 2012 (average length of stay was 3.1 days and mean age was 2.3 years). All costs were estimated using 2013 price levels or were inflated from previous years to 2013 values using the health sector pay and prices index when appropriate. To have an international perspective all costs were converted from Iranian Rials [IRR] into United State dollars (US$) at an official 2013 currency exchange rate of 24,000 IRR per US$ 1.00 [34].

2.4. Cost-effectiveness measures and sensitivity analysis

The incremental cost-effectiveness ratio (ICER) of vaccination versus no vaccination in the base-case scenario was defined in terms of the ratio of the difference in costs to the difference in effect measures ((vaccine cost – cost saving)/DALY averted).

We also defined our threshold (ceiling rate) for labeling an intervention as being cost-effective or not based on WHO guideline [35]. We conducted a series of deterministic sensitivity analyses to detect those parameters that had the most impact on the ICER, with different input parameters being changed in a sequence to the upper and lower limit, while the other variables were held constant.

Table 2
Input parameters for estimating health service utilization and costs (all costs are presented in 2013 US$).

Parameter	Estimate	Scenarios		Source (s)
		Low	High	
Outpatient visits				
Outpatient visits per disease episode				
Rotavirus (non-severe) cases	0.70	0.50	0.90	[33,36]
Rotavirus (severe) cases	1.00	0.70	1.30	[33,36]
Government cost per outpatient visit[a]				
Rotavirus (non-severe) cases	$2.23	$2.01	$2.45	Calculated
Rotavirus (severe) cases	$4.69	$4.22	$5.16	Calculated
Household cost per outpatient visit[b]				
Rotavirus (non-severe) cases	$3.85	$3.47	$4.24	Calculated
Rotavirus (severe) cases	$6.60	$5.94	$7.26	Calculated
Inpatient admissions				
Inpatient admissions per disease episode				
Rotavirus (severe) cases	0.90	0.80	1.00	[33,36]
Government cost per inpatient admission[c]				
Rotavirus (severe) cases	$174.52	$157.06	$191.97	Calculated
Household cost per inpatient admission[d]				
Rotavirus (severe) cases	$45.29	$40.76	$49.82	Calculated

[a] Government costs per outpatient visit include visit, medications, and diagnostic tests. Outpatient visits in cases who seek medical attention (70%) are distributed as follows: specialist physician (public: 8%, private: 41%), general practitioner (public: 17%, private: 22%), health post officers: 4% and *behvarz* personnel: 8%. The cost presented is the weighted average of the provider-specific costs.

[b] Household costs per outpatient visit include direct medical cost (out-of-pocket payments for consultations and drugs). Outpatient visits in cases who seek medical attention (70%) are distributed as follows: specialist physician (public: 8%, private: 41%), general practitioner (public: 17%, private: 22%), health post officers: 4% and *behvarz* personnel: 8%. The cost presented is the weighted average of the provider-specific costs.

[c] Government costs per inpatient admission include direct medical cost [the cost per bed day multiplied by the expected length of stay (3.1 days) and the cost of any disease-specific drugs and diagnostics]. Inpatient admissions are distributed as follows: 4.8% Social Security hospital, 5.2% private hospitals, and 90.0% public hospitals. The cost presented is the weighted average of the provider-specific costs.

[d] Household costs per inpatient admission include out-of-pocket expenditure for medical cost of medication, hospital care, and diagnostics. Inpatient admissions are distributed as follows: 4.8% social security hospital, 5.2% private hospitals, and 90.0% public hospitals. The cost presented is the weighted average of the provider-specific costs.

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Table 3
Input parameters for estimating rotavirus vaccine (RV) coverage and timeliness.

Parameter	Estimate (%)	Scenarios		Source(s)
		Low	High	
Coverage of DTP1 by age in year 2014 (proxy for RV doses given with DTP1)				
3 mo	96.2	–	–	EPI & [37]
6 mo	97.5	–	–	EPI & [37]
9 mo	97.9	–	–	EPI & [37]
12 mo	98.3	–	–	EPI & [37]
24 mo	99.0	–	–	EPI & [37]
Coverage of DTP2 by age in year 2014 (proxy for RV doses given with DTP2)				
3 mo	0.0	–	–	EPI & [37]
6 mo	97.4	–	–	EPI & [37]
9 mo	97.6	–	–	EPI & [37]
12 mo	98.1	–	–	EPI & [37]
24 mo	99.0	–	–	EPI & [37]
Coverage of DTP3 by age in year 2014 (proxy for RV doses given with DTP3)				
3 mo	0.0	–	–	EPI & [37]
6 mo	97.0	–	–	EPI & [37]
9 mo	97.5	–	–	EPI & [37]
12 mo	98.0	–	–	EPI & [37]
24 mo	99.0	–	–	EPI & [37]

Coverage projections over the 2014–2023 period were estimated by assuming RV will achieve the same coverage and timeliness as DTP and by assuming a 5% annual decrease in the gap between final coverage in the cohort (coverage by age 24 mo) and a ceiling of 100% (DTP1), 100% (DTP2), and 100% (DTP3).

Table 4
Input parameters for estimating RV5 program costs.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Vaccine dose price projection				
2014	$10.00	$7.00	$12.00	Local representative of the manufacturer
2015	$10.00	$7.00	$12.00	Assumption
2016	$10.00	$7.00	$12.00	Assumption
2017	$10.00	$7.00	$12.00	Assumption
2018	$10.00	$7.00	$12.00	Assumption
2019	$10.00	$7.00	$12.00	Assumption
2020	$10.00	$7.00	$12.00	Assumption
2021	$10.00	$7.00	$12.00	Assumption
2022	$10.00	$7.00	$12.00	Assumption
2023	$10.00	$7.00	$12.00	Assumption
Other vaccine dose costs				
International handling (% of vaccine price)[a]	3.00%	1.00%	5.00%	Assumption
International delivery (% of vaccine price)[b]	2.00%	1.00%	3.00%	Assumption
Wastage (% of doses discarded etc.)[c]	5.00%	3.00%	7.00%	Assumption
Incremental system costs of introduction[d]				
Incremental system cost per dose	$1.13	$1.02	$1.24	Calculated

[a] The handling percentage refers to the international service charges (documents, airports).
[b] Delivery percentage refers to the international shipping cost (international freight), which includes insurance.
[c] The percentage of wastage is converted into a factor [1/(1 − % wastage)] that is multiplied by the expected number of doses required to meet the anticipated level of coverage.
[d] Estimated incremental system costs include cost of personnel (88.4% of cost), training material (8.6% of cost), vehicles and transport (1.7% of cost), and cold chain (1.3% of cost). They are assumed to be recurrent costs each year.

3. Results

Input parameters for estimating disease burden, disease-related service utilization and costs, vaccine coverage, vaccination program costs, and vaccine efficacy are summarized in Tables 1–5. The model's results for outcomes and costs for 10 cohorts from 2014 to 2023 for the entire country are presented below.

3.1. Effectiveness measures

As shown in Table 6, without a vaccination program, there would be 64,464,813 cases of diarrhea over 10 birth cohorts from 2014 to 2023, including 62,524,950 non-severe cases and 1939,863 severe cases. In contrast, with a vaccination program, 35,129,919 cases of diarrhea could be averted. During this period of time, 266 deaths could also be avoided via the vaccination program. Life years gained through vaccination were estimated 7888. Without vaccination, total DALYs lost due to mortality and morbidity from rotavirus diarrhea would be 138,161, while vaccination could prevent 76,591 of them in the same period (Table 6).

3.2. Cost and health care utilization measures

From a societal perspective, our results revealed that within the modeling time horizon, without vaccination there would be 45,125,369 outpatient visits, of which 24,590,943 could be averted via vaccination (Table 6). In addition, the total estimated number of inpatient admissions without vaccination would be 1745,877; 65% of them (1139,256) could be avoided through vaccination. Based on the average cost of each outpatient visit, the total cost of outpatient visits would be US$ 402.08 million without vaccination. Furthermore, the total estimated cost of inpatient admissions would be US$ 383.76 million. Our results show that about US$ 470.6 million would be saved by preventing outpatient visits and inpatient

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Table 5
Input parameters for estimating the health impact of RV5.

Parameter	Estimate (%)	Scenarios		Source(s)
		Low (%)	High (%)	
Vaccine efficacy vs non-severe RVGE				
Dose 1	35.4	19.2	42.6	[11,38]
Dose 2	35.4	35.4	42.6	[11,38]
Dose 3	68.1	37.1	68.1	[11,38]
Vaccine efficacy vs severe RVGE				
Dose 1	42.7	41.0	44.1	[28,39]
Dose 2	42.7	42.7	89.4	[28,39]
Dose 3	82.1	63.9	97.0	[28,29]
Other vaccination impact assumptions				
% Vaccine serotype coverage	100	57	100	[8,40]
% Relative coverage[a]	90	80	100	Assumption
% Decrease in dose efficacy per yr[b]	4.8	0.0	5.0	[28]
% Contribution of herd effect in <5 yr[c]	100	100	110	Assumption

[a] Relative coverage is the coverage in those at risk of getting the disease (i.e., effective coverage) relative to coverage in the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.
[b] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 mo, 4–5 mo, 6–8 mo, 9–11 mo, 12–23 mo, 24–35 mo, 36–47 mo, 48–59 mo) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.
[c] Rather than endogenous modeling of transmission dynamics, the % direct protection <5 yr is multiplied by a herd effect multiplier (e.g., 110%) to give the % total protection in the cohort of interest before age 5.0 yr. This excludes any herd effect in individuals aged 5 yr+ and is therefore very conservative.

Table 6
Discounted health benefits (discounted at 3% per year) for 10 cohorts vaccinated over the 2014–2023 period.

	No vaccine (status quo)	RV5 With vaccine	Averted
Total cases <5 yr (×1000)	64,465	29,335	35,130
Rotavirus (non-severe) cases (×1000)	62,525	28,661	33,864
Rotavirus (severe) cases (×1000)	1940	674	1266
Total outpatient visits (×1000)	45,125	20,534	24,591
Rotavirus (non-severe) cases (×1000)	43,767	20,063	23,705
Rotavirus (severe) cases (×1000)	1358	472	886
Total inpatient admissions (×1000)	1746	607	1139
Rotavirus (severe) cases (×1000)	1746	607	1139
Total deaths <5 yr	408	142	266
Rotavirus (severe) cases	408	142	266
DALYs lost	138,161	61,569	76,591
Due to morbidity (YLDs)	126,073	57,370	68,703
Due to mortality (YLLs)	12,088	4200	7888

Table 7
Discounted economic benefits (costs are discounted at 3% per year) for 10 cohorts vaccinated over the 2014–2023 period.

	No vaccine (status quo)($)	RV5 With vaccine ($)	Averted ($)
Total gov. health service costs[a] (×1000)	453,208	172,937	280,270
Total outpatient visit costs (×1000)	148,524	67,072	81,452
Rotavirus (non-severe) cases (×1000)	139,421	63,909	75,512
Rotavirus (severe) cases (×1000)	9103	3163	5940
Total inpatient admission costs (×1000)	304,683	105,865	198,818
Rotavirus (severe) cases (×1000)	304,68	105,865	198,818
Total societal health service costs[b] (×1000)	785,841	315,221	470,619
Total outpatient visit costs (×1000)	402,083	181,881	220,202
Rotavirus (non-severe) cases (×1000)	380,177	174,270	205,907
Rotavirus (severe) cases (×1000)	21,907	7612	14,295
Total inpatient admission costs (×1000)	383,757	133,340	250,417
Rotavirus (severe) cases (×1000)	383,757	133,340	250,417

[a] Government perspective includes all bed day and disease-specific drug/diagnostic costs borne by the government at the following health providers: health center, public primary/secondary/tertiary hospital.
[b] Societal perspective includes all costs included in the government perspective. In addition, it includes all household costs incurred when visiting both government and private health providers.

admissions (Table 7). The total vaccination cost for the 10 cohorts would be US$ 499.91 million (Table 8).

3.3. Cost-effectiveness estimates

Our final results in this section showed that rotavirus vaccine is a highly cost-effective intervention compared to no vaccination from the government perspective. The estimated cost per DALY averted was US$ 2868 from the government perspective (Iran's GDP per capita as used in the model was equal to US$ 4763). Also from the government's perspective, the estimated costs were US$ 27,844 per life-year gained, US$ 825,098 per death averted, US$ 203 per inpatient admission averted, and US$ 6 per case averted. From the society perspective, the estimated cost per DALY averted was US$ 382.

3.4. Sensitivity Analysis

The results of the deterministic sensitivity analysis showed that disease incidence, vaccine price, case fatality ratio, and vaccine efficacy were among the most important parameters that can change the ICER. As shown in Fig. 1, on the basis of the WHO threshold, from both the societal and government perspectives, the rotavirus vaccine was not cost-effective in the least favorable scenario for vaccine introduction, that is, lowest disease incidence, low vaccine efficacy (a 63.9% low and a 48.3% very low estimate), low serotype coverage, low health care utilization cost, low relative coverage of death, and highest vaccine price and system costs. In other cases, the intervention was always cost-saving, very cost-effective or cost-effective.

4. Discussion

Based on the results of TRIVAC, rotavirus vaccination was highly cost-effective from the societal and governmental perspective. It

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Table 8
Discounted cost-effectiveness of RV5 (costs and DALYs discounted at 3% per year) for 10 cohorts vaccinated over the 2014–2023 period.

	RV5 Government perspective	Societal perspective
Cost-effectiveness compared to no vaccine		
Net cost of vaccine introduction (×1000)	$219,640	$29,291
Costs of vaccine introduction (×1000)	$499,911	$499,911
Health service costs avoided (×1000)	$280,270	$470,619
DALYs averted	76,591	76,591
Due to morbidity (YLDs)	68,703	68,703
Due to mortality (YLLs)	7888	7888
US$ per DALY averted	2868	382
Cost-effectiveness threshold		
1 × GDP per capita (2013)—WHO threshold for "highly cost-effective"	$4763	$4763
3× GDP per capita (2013)—WHO threshold for "cost-effective"	$14,289	$14,289

also will be cost-saving from the government perspective at a vaccine price per dose less than US$ 5.2.

Our analysis estimated that vaccination could prevent more than 35.1 million cases of rotavirus-associated diarrhea within the study time horizon (2014–2023). A national rotavirus immunization program was estimated to prevent 65% of all rotavirus-related deaths. The economic burden of rotavirus-associated hospitalizations and outpatient visits among children aged less than 5 years in Iran during the study time horizon was calculated to be US$ 785.84 million from the societal perspective. About 60% (US$ 470.61 million) of this cost could be prevented through vaccination.

Results of previous studies have shown that rotavirus vaccination would be a cost-effective public health intervention in various developing countries. For example, in Kenya, Rotarix® and RotaTeq® have a cost-effectiveness ratio of US$ 142 and 288 per DALY averted from a societal perspective [41]. In Vietnam, universal vaccination of infants at a cost of US$ 7.26 or less per vaccine dose would be a cost-effective public health intervention [42]. In Thailand, as part of the national immunization program, the rotavirus vaccine would be cost-effective at the price of US$ 6.20 per dose; at a maximum vaccine price of US$ 6.20–10.50 per dose, the cost-effectiveness ratio is approximately US$ 185–759 per DALY averted [43]. In Uzbekistan, rotavirus vaccination could be cost-effective with vaccine prices in the range of US$ 2–25 per child [44].

One study evaluated the cost-effectiveness of introducing rotavirus vaccination in GAVI-eligible countries [9]. The results showed that in a baseline scenario with an initial vaccine price of US$ 7 per dose for a 2-dose vaccine, and with a gradual decrease in vaccine price over time, vaccination was highly cost-effective in all the GAVI-eligible countries, based on their GDP-based thresholds. In addition, a national rotavirus immunization program for Brazilian children would be cost-saving with a price less than US$ 2.2 per dose [45].

The estimated ICER in our study is higher than in most of the other developing countries. This can be explained partially by a low case fatality ratio of rotavirus in Iran, a lower level of health care utilization in terms of frequency and intensity, and a higher vaccine price.

Although a rotavirus vaccine program has the potential to be cost-effective, cost-effectiveness results should be interpreted with consideration to country-specific comparators for improving the health of children. For instance, there are other completed or undergoing studies in Iran on the cost-effectiveness of vaccines against *Haemophilus Influenzae* type b [46], pneumococcal diseases, influenza virus, and acellular pertussis. All these vaccines could possibly be introduced to the national program of immunization [27]. Sustainability is another important issue for introducing a new vaccine, and it can be influenced by such factors as vaccine price,

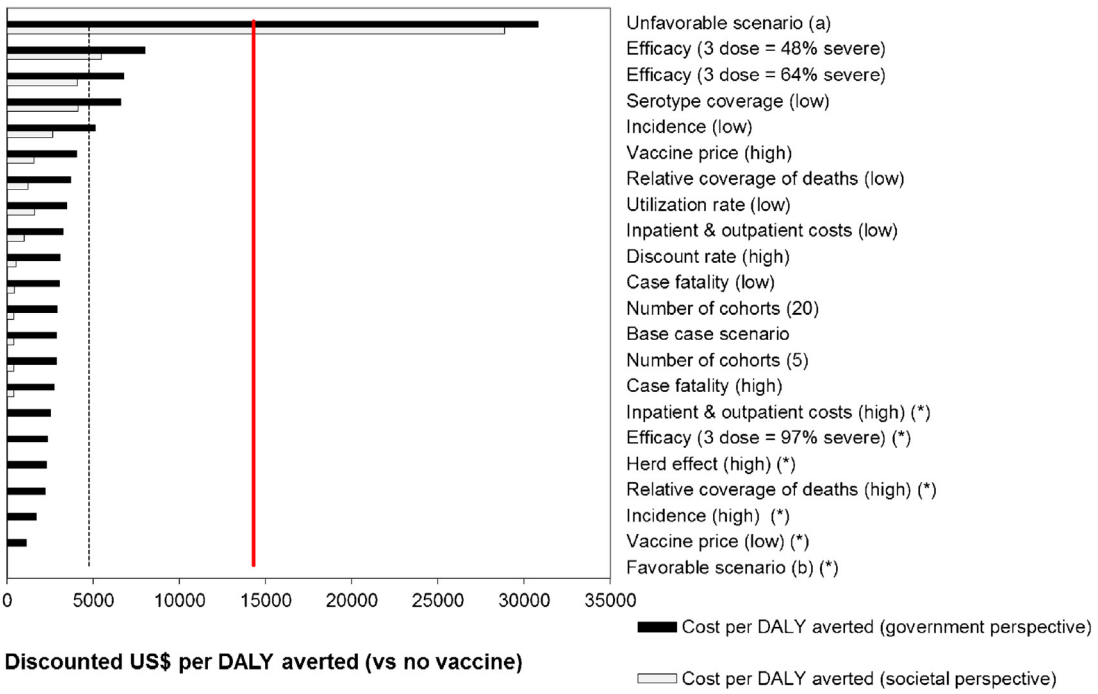

Fig. 1. *US$ per DALY averted for base case RV5 scenario and alternative "what-if" scenarios: government perspective and societal perspective.*(1) [a] Unfavorable scenario = low disease incidence, low serotype coverage, low death coverage, low vaccine efficacy (64%), low health care utilization cost, low relative coverage of death, and high vaccine price and system cost. (2) [b] Favorable scenario = high disease incidence, high serotype coverage, high death coverage, high vaccine efficacy, high health care utilization cost, high relative coverage of death, and low vaccine price and system cost. (*) Scenario is cost-saving from a societal perspective, i.e., the health service costs avoided (by both the government and households) exceeds the cost of introducing the vaccine.

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availability of financial resources in the health system, and country potential for technology transfer.

Using local cost and epidemiological data in our analysis is a good base for local health policy-making. However, there are some limitations in the study. We made several assumptions that could affect the results of the analysis. We estimated the case fatality ratio in severe cases at 0.02%, based on national death registries and expert opinion. This figure is lower than the WHO estimation [47], but it seems to be the closest to the country reality. Our estimation for incidence of RVGE was higher than estimates of Bilcke et al. (0.31 per person-year), however we preferred to use our estimate which is based on the local data from Iran and is also more compatible with Walker et al. systematic review on incidence of diarrhea in low and middle income countries [48,49]. We obtained vaccine efficacy data from the international literature, using estimates from Latin American and Asian countries with fairly high VE rates, so the efficacy might be different in Iranian patients. However, we used data from the same WHO mortality stratum, B. Moreover, vaccine effectiveness may be lower than trial efficacy because of suboptimal vaccine storage and administration and differences in disease epidemiology. We assumed a 90% relative coverage of deaths because of their potential concentration among unvaccinated children; however, since the expected vaccine coverage is very high, this is a pessimistic assumption and real efficacy of vaccine for preventing deaths should be higher. We assumed vaccine coverage based on that for other vaccines, which may not be an accurate estimation of coverage for the rotavirus vaccine. However, the majority of parameters with uncertain values could be tested in the scenario analysis (using high and low values). That testing showed that the results of the base-case scenario were robust, and with most scenarios resulting in the vaccine being highly cost-effective or cost-effective. The exception was the least favorable scenario. We ran the model again after using a very low vaccine efficacy of 48.3% for full dose based on the overall Vietnam and Bangladesh estimates from the Asian study [29]. This led to an intervention that was still cost-effective from the government and societal perspective. Also, uncertainties about the VE of diverse genotypes of rotavirus have not been seen in the literature [50,51].

We did not have access to the proportion of episodes of non-severe diarrhea that are related to Rotavirus in the community setting. We used the proportion estimated through outpatient cases for this purpose that might not be an exact assumption. We did not consider the extra cost of visits by *behvarz* and health post officer personnel, who are non-physician care providers (applicable in 8.4% of cases of diarrhea where health care is sought). This was mainly because of the type of their contract (fixed monthly salary) and available unused capacities in most parts of the health network. We think that considering this opportunity cost would have a small effect on the cost-effectiveness profile in favor of doing vaccination.

Finally, it is evident that when allocating scarce community resources, the adopted perspective should reach beyond that of the provider (the health care system), which can be too restrictive. This study considered two different perspectives (societal and government) but only direct medical cost was included in the cost estimation. Such other costs as productivity loss of the parents, deceased cases due to diarrhea, and direct non-medical costs could change our results in the base-case analysis. However, we are confident that our results are conservative and that the vaccine cost-effectiveness profile in Iran probably would be better if we included those costs.

5. Conclusion

Due to the high morbidity and incidence of rotavirus diarrhea, rotavirus vaccine should be included in the Expanded Program on Immunization in Iran in the future. This cost-effectiveness analysis demonstrated that introducing rotavirus vaccine into the program could be highly cost-effective from the government and societal perspective.

Competing interest

The authors have declared that no competing interests exist.

Funding

This work was supported by the ProVac International Working Group, which is funded entirely by a grant from the Bill & Melinda Gates Foundation (grant number: OPP1032888).

Acknowledgments

This technical and collaborative project gained significant strength by thoughtful advice and great technical assistances from Iran MOHME, the National Immunization Technical Advisory Group (NITAG), WHO-Iran, Regional Office for the Eastern Mediterranean, Agence de Médecine Préventive (AMP), PATH, London School of Hygiene & Tropical Medicine (LSHTM), Pan American Health Organization (PAHO), and the Sabin Vaccine Institute. The authors would like to thank kindly all advisors and colleagues, especially Céline Hoestlandt, Carlos Lara, Julia Blau, Dr. Andy Clark, Gabriela Felix, Diane Coraggio, and Dr. Nadia Teleb for their valuable technical support.

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Vaccine 33S (2015) A201–A208

Contents lists available at ScienceDirect

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Cost-effectiveness of rotavirus vaccination in Albania

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ARTICLE INFO

Keywords:
Albania
Cost-effectiveness
Diarrhea
Evidenced-based medicine
Rotavirus
Vaccine

ABSTRACT

Background: Rotavirus vaccines have been introduced in several European countries but can represent a considerable cost, particularly for countries that do not qualify for any external financial support. This study aimed to evaluate the cost-effectiveness of introducing rotavirus vaccination into Albania's national immunization program and to inform national decision-making by improving national capacity to conduct economic evaluations of new vaccines.

Methods: The TRIVAC model was used to assess vaccine impact and cost-effectiveness. The model estimated health and economic outcomes attributed to 10 successive vaccinated birth cohorts (2013–2022) from a government and societal perspective. Epidemiological and economic data used in the model were based on national cost studies, and surveillance data, as well as estimates from the scientific literature. Cost-effectiveness was estimated for both the monovalent (RV1) and pentavalent vaccines (RV5). A multivariate scenario analysis (SA) was performed to evaluate the uncertainty around the incremental cost-effectiveness ratios (ICERs).

Results: With 3% discounting of costs and health benefits over the period 2013–2022, rotavirus vaccination in Albania could avert 51,172 outpatient visits, 14,200 hospitalizations, 27 deaths, 950 disability-adjusted life-years (DALYs), and gain 801 life-years. When both vaccines were compared to no vaccination, the discounted cost per DALY averted was US$ 2008 for RV1 and US$ 5047 for RV5 from a government perspective. From the societal perspective the values were US$ 517 and US$ 3556, respectively.

Conclusion: From both the perspectives, the introduction of rotavirus vaccine to the Albanian immunization schedule is either cost-effective or highly cost-effective for a range of plausible scenarios. In most scenarios, including the base-case scenario, the discounted cost per DALY averted was less than three times the gross domestic product (GDP) per capita. However, rotavirus vaccination was not cost-effective when rotavirus cases and deaths were based on plausible minimum estimates. Introduction of RV1 would yield similar benefits at lower cost.

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1. Introduction

Rotavirus diarrhea is among the main causes of childhood illnesses in developing and developed countries [1]. Children experience their first episode of rotavirus diarrhea before reaching 12 months of age in developing countries and between 2 and 5 years of age in developed countries [2,3]. The World Health Organization (WHO) estimated that approximately half a million children died from rotavirus gastroenteritis (RVGE) in the year 2008, and the majority of this burden was borne by low-income countries [4]. RVGE often accounts for a large number of outpatient visits and inpatient admissions and can therefore represent significant health care costs to governments and households [3].

In Albania, rotavirus has been observed since 1988. In Tirana, rotavirus was detected in 25.1% of young children hospitalized with severe gastroenteritis during 1988–1991 [3] and in 10.3% of cases during 1993–1994 [5]. In 2000, rotavirus was the cause of a large gastroenteritis outbreak, mainly among children under 5 years old [6]. Despite the declining trend observed during the 1990s, unpublished data from the Institute of Public Health (IPH) indicates that in 2011–2012 rotavirus was detected in 31.7% of samples collected from five sentinel hospitals in the country. The main rotavirus serotypes circulating in Albania are G4 (the majority of cases), G1, G2, G9, P4, and P8 [7,8].

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http://dx.doi.org/10.1016/j.vaccine.2014.12.075
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Several studies have shown that rotavirus vaccination is a cost-effective intervention in different economic and epidemiological contexts [9–12]. The two rotavirus vaccines available today are the monovalent vaccine (RV1, Rotarix®, *GlaxoSmithKline*) and the pentavalent vaccine (RV5, RotaTeq®, *Merck*) [13].

RV1 has a recommended schedule of two doses, whereas RV5 requires three doses. Both vaccines are considered safe by the WHO [14] and are included in immunization programs of several countries [1].

The Albanian immunization program has historically been a success story; 99% of children are expected to be covered. The rotavirus vaccine is planned to be introduced by 2015 in Albania and efforts were made to change from an oral polio vaccine (OPV) to an inactivated polio vaccine (IPV), in line with European Union (EU) immunization schedules [15]. Lately, rotavirus vaccination has been a matter of energetic public debate in Albania. This has highlighted the pressing need for the group of experts that is the national advisory committee on immunization to assess the cost-effectiveness of introducing new vaccines and provide further evidence to the country decision-makers.

To conduct this exercise, Albania requested technical support from the WHO's Regional Office in Europe. The support came from the ProVac International Working Group (IWG) with the contribution from WHO Office in Europe, the United States' Centers of Diseases Control and Prevention, the Agence de Médecine Préventive, the Program for Appropriate Technology in Health, the Sabin Vaccine Institute, and the London School of Hygiene and Tropical Medicine. ProVac is an Initiative of the Pan American Health organization that was officially launched in 2006 [16]. Albania was the first country outside of the Americas to conduct a cost-effectiveness analysis (CEA) with ProVac tools, assisted by the ProVac IWG.

The aim of this paper is to evaluate the cost-effectiveness of introducing rotavirus vaccine in the Albanian national immunization schedule by comparing rotavirus vaccination to the status quo (i.e., no rotavirus vaccination).

2. Materials and methods

2.1. Analytic framework

The cost-effectiveness of introducing the rotavirus vaccine was estimated using the TRIVAC model, version 2.0. TRIVAC is a decision-support model designed for use by a national country team to explore the impact and cost-effectiveness of rotavirus vaccination under a range of plausible scenarios [17]. The model provides information on disability-adjusted life-years (DALYs) over the lifetime of the cohorts evaluated, with and without vaccine introduction, and provides an incremental cost-effectiveness ratio (ICER), which indicates the cost-effectiveness of rotavirus vaccination in terms of US$ per DALY averted. The TRIVAC model was used to evaluate both RV1 and RV5.

In each analysis, 10 consecutive birth cohorts of children between 0 and 59 months of age were considered; 2014 was assumed as the year of introduction. The model tracked each birth cohort from birth until death. All costs, cases, and deaths were calculated from birth up to age 5 years. The analysis accounted for the full stream of life years and DALYs lost following a death using life expectancy estimates. The costs and benefits attributed to each birth cohort were aggregated to provide results for a 10-year vaccination program, thus allowing the model to capture trends in vaccine price and rotavirus mortality over time. The input parameters included in the TRIVAC model are demography, burden of disease, vaccine coverage and efficacy, health services utilization, and costs of both vaccination and health services. Based on the WHO guide [18], a 3% discount rate was used for both benefits and costs.

2.2. Demographic data

The following demographic data were used: (1) number of live births per year (34,498 in 2011), from the cohort database (1–12 months old) of the National Immunization Program (NIP) housed by the IPH; (2) infant mortality per 1000 live births, from the Bureau of Statistics Ministry of Health; and (3) mortality in children under 5 per 1000 live births and life expectancy at birth, from the National Institute of Statistics (INSTAT). The life expectancy projections from the United Nations Population division (UNPOP) were rescaled using the national estimates.

2.3. Burden of disease

We estimated the incidence of rotavirus outpatient visits and rotavirus admissions and the rotavirus mortality rate in children younger than 5 (see Table 1). To estimate the timely burden of rotavirus diarrhea in children in that age cohort, a sentinel surveillance system was set up in 2010–2011 in Tirana, Durres, Lezha, Vlora, and Fier hospital districts. In 2011, records show that there were 8649 rotavirus gastroenteritis (RVGE) outpatient visits and 2400 inpatient RVGE admissions. Because there were no reliable national data available on rotavirus mortality, the WHO projections for mortality figures due to rotavirus were used [19] instead.

2.4. Costs related to rotavirus burden: governmental and societal perspectives

We addressed the rotavirus costs from governmental and societal perspectives. The governmental perspective includes the costs of medical care related to rotavirus disease incurred by the public sector because the cases are generally handled by public facilities. Albania's healthcare system has a single entity that pays for healthcare services delivered by public and private providers: the Health Insurance Fund (HIF), a government agency.

2.5. Governmental perspective: health utilization costs

Healthcare costs saved by preventing rotavirus infection were estimated for three levels of service providers: primary (health centers), secondary (district hospitals and emergency rooms [ER]), and tertiary (Tirana hospital and ER). According to the sentinel system, 60% of outpatient visits were treated in primary care clinics and 40% in the ER of public hospitals. The methodology used for estimating the economic burden of rotavirus consists of a bottom-up technique [18], including direct medical costs such as salaries of pediatricians and nurses, costs of examinations, food, consumables, and pharmaceuticals, as well as utility, cleaning, laundry, administration, maintenance, and depreciation costs (Table 2). The costs were calculated in Albanian Lek (ALL) currency and then expressed in United States dollars (US$) using the 2011 exchange rate of 100.812 ALL = US$1 [20].

2.6. Societal perspective: household costs as social costs

Societal costs included all government costs plus costs to households. Household costs were calculated based on transportation cost and costs in the form of loss of productivity (LoP) due to caretakers taking time off from work. To estimate lost productivity, we used the WHO guide, which is based on the GDP per capita [18].

Rotavirus disease in a child is likely to have an impact on parents. However, in Albania, the impact is not expected to be the same for both parents, since mothers bear the weight of childcare. Consequently, the cost of only one caregiver was used to measure lost productivity (Table 2).

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Table 1
Input parameters for estimating disease burden.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Annual incidence per 100,000 aged 1–59 m				
Rotavirus outpatient visits	5146	3859	6433	Mid=[a], Low = Surveillance[b], High = Surveillance[c]
Rotavirus admissions	1428	1071	1785	Mid = [a], Low = Surveillance[b], High = Surveillance[c]
Rotavirus deaths[d]	3	0	6	Mid = [19], Low = Surveillance[b], High = [19]
Disability weight for DALY calculations				
Rotavirus outpatient visits	0.12	–	–	WHO GBD 1990 [33]
Rotavirus admissions	0.12	–	–	WHO GBD 1990 [33]
Mean duration of illness (in days)				
Rotavirus outpatient visits	7	–	–	Surveillance[c]
Rotavirus admissions	7	–	–	Surveillance[c]
Age distribution of outpatient visits and admissions				
<3 m	3.0%	–	–	Surveillance[c]
3–5 m	8.0%	–	–	Surveillance[c]
6–8 m	17.0%	–	–	Surveillance[c]
9–11 m	12.0%	–	–	Surveillance[c]
12–23 m	31.0%	–	–	Surveillance[c]
24–35 m	14.0%	–	–	Surveillance[c]
36–47 m	8.0%	–	–	Surveillance[c]
48–59 m	6.0%	–	–	Surveillance[c]

[a] The mid value or estimated value is calculated [(low + high)/2].
[b] Surveillance sentinel from 5 districts: Tirana, Durres, Vlora, Fieri, Lezha (only positive cases); IPH; 2011 (cases for Tirana district).
[c] Surveillance sentinel from 5 districts: Tirana, Durres, Vlora, Fieri, Lezha (only positive cases); IPH; 2011.
[d] The rotavirus mortality incidence has been derived by multiplying the incidence of rotavirus admissions by the admission: deaths ratio, a parameter requested in TRIVAC. This ratio is calculated by dividing the number of rotavirus deaths nationally (irrespective of whether treated or not) by the number of rotavirus admissions nationally. In the absence of vaccination, this ratio is assumed to decline in each successive birth cohort in line with the general trend in mortality under age 5. This is done by assuming that the fraction of deaths under age 5 caused by the disease remains fixed over time.

2.7. *Vaccination program: coverage, timeliness, cost, and efficacy*

Rotavirus vaccine coverage and timeliness are based on reported DTP-Hib-HepB vaccine coverage because rotavirus would be given during the same visits (i.e., at 2, 4, and 6 months in the case of RV5, and at 2 and 4 months in the case of RV1). The data from the recent Albanian Demographic and Health Survey (DHS) [21] were used to estimate timeliness [22] (Table 3).

Vaccination program costs included delivery costs, handling costs, vaccine wastage, vaccine cost per dose, and extra system costs (information systems, education, and communication campaigns, short-term training costs, vaccinator's salaries, etc.) (Table 4). The vaccines are procured through UNICEF, and Albania is eligible for UNICEF's pooled procurement. From consultation with the UNICEF, it was agreed that irrespective of the number of doses used, the price per dose could vary no more

Table 2
Input parameters for estimating health service costs (all costs are presented in 2012 US$).

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Outpatient visits				
Government cost per outpatient visit[a]				
Rotavirus outpatient visits	$12.52	$10.14	$21.34	Authors' calculation [e]
Household cost per outpatient visit[b]				
Rotavirus outpatient visits	$15.10	$9.94	$40.05	Authors' calculation[e]
Inpatient admissions				
Government cost per inpatient admission[c]				
Rotavirus admissions	$227.12	$101.03	$342.58	Authors' calculation[e]
Household cost per inpatient admission[d]				
Rotavirus admissions	$45.29	$29.82	$120.16	Authors' calculation[e]

[a] Government costs per outpatient visit includes medical costs, salary of medical staff, consumables, and pharmaceutical costs as well as overhead costs of health facilities such as utilities (electricity, water, heating, telephone), administration, and maintenance costs. Outpatient visits are distributed as follows: 40% in ER in public hospital, 60% primary care clinic. The cost presented is the weighted average of the provider-specific costs.
[b] Household costs per outpatient visit includes productivity losses to families due to lost wages, travel expenses. Outpatient visits are distributed as follows: 40% in ER in public hospital, 60% primary care clinic. The cost presented is the weighted average of the provider-specific costs.
[c] Government costs per inpatient admission – includes medical costs, salary of medical staff, examinations, food, consumables, and pharmaceutical or treatment costs as well as utilities, cleaning, laundry, administration, maintenance, and depreciation costs. Inpatient admissions are distributed as follows: 100% in public hospital. The cost presented is the weighted average of the provider-specific costs.
[d] Household costs per inpatient admission include productivity losses to families due to lost wages, and travel expenses for an average 3 days of hospitalization. Inpatient admissions are distributed as follows: 100% public hospital.
[e] Authors' calculation: Government costs were estimated for three levels of service providers: the primary health care services, hospital services, and ER services in 5 surveillance sentinel cities – Tirana, Durres, Lezha, Fier, and Vlora. The methodology used for estimating the economic burden of rotavirus consists of a bottom-up technique, including direct medical costs such as salary of pediatricians and nurses, examinations, food, consumables, and pharmaceutical costs as well as utilities, cleaning, laundry, administration, maintenance, and depreciation costs. Societal costs included all government costs plus additional costs to households. Household costs were calculated based on transportation costs and costs in the form of loss of productivity (LoP) due to caretakers taking time off work in 5 surveillance sentinel cities – Tirana, Durres, Lezha, Fier and Vlora. The WHO guide was used to estimate the LoP using the gross domestic product (GDP) per capita.

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Table 3
Input parameters for estimating rotavirus vaccine (RV) coverage and timeliness.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Coverage of DTP1 by age in year 2014 (proxy for RV doses given with DTP1)				
3 m	91.0%	–	–	DHS Albania 2008–09 [21,22]
6 m	98.7%	–	–	DHS Albania 2008–09 [21,22]
9 m	98.8%	–	–	DHS Albania 2008–09 [21,22]
12 m	98.8%	–	–	DHS Albania 2008–09 [21,22]
24 m	99.9%	–	–	DHS Albania 2008–09 [21,22]
Coverage of DTP2 by age in year 2014 (proxy for RV doses given with DTP2)				
3 m	0.4%	–	–	DHS Albania 2008–09 [21,22]
6 m	95.0%	–	–	DHS Albania 2008–09 [21,22]
9 m	97.2%	–	–	DHS Albania 2008–09 [21,22]
12 m	97.3%	–	–	DHS Albania 2008–09 [21,22]
24 m	98.3%	–	–	DHS Albania 2008–09 [21,22]
Coverage of DTP3 by age in year 2014 (proxy for RV doses given with DTP3)				
3 m	0.0%	–	–	DHS Albania 2008–09 [21,22]
6 m	0.9%	–	–	DHS Albania 2008–09 [21,22]
9 m	95.3%	–	–	DHS Albania 2008–09 [21,22]
12 m	96.4%	–	–	DHS Albania 2008–09 [21,22]
24 m	97.4%	–	–	DHS Albania 2008–09 [21,22]

Coverage projections over the period 2014–2023 were estimated by assuming RV will achieve the same coverage and timeliness as DTP, and by assuming a 0% annual decrease in the gap between final coverage in the cohort (coverage by age 24 m) and a ceiling of 100% (DTP1), 100% (DTP2) and 100% (DTP3).

than US$ 8–9 for both vaccines, with a mean value of US$ 8.5 [23]. Consequently, RV5 (which requires 3 doses) was assumed to be more expensive per course than RV1 (which requires 2 doses).

The efficacy of both vaccines was set at 83% for a complete schedule, with a range between 67% and 92% [24]. Based on the De Palma study, the efficacy of preventing RVGE with only one dose was set at 51% for both vaccines [25]. Due to insufficient data, it was assumed that a complete schedule of RV1 has the same efficacy as 2 doses of RV5. For waning vaccine efficacy, the figure of 4.8% per year was used [24]. The low estimate used for waning efficacy in the model for sensitivity analysis for RV1 and RV5 was 0%, based on estimates from Europe [13]; the high estimate was 53%, based on estimates from Nicaragua [26]. Dose-specific efficacy estimates are shown in Table 5.

The only difference in assumptions used for the two vaccines was the number of doses administered. The evidence to date suggests very similar levels of vaccine performance. Based on a meta-analysis, the efficacy of RV1 and RV5 against severe RVGE was 80% (95% with a confidence interval (CI) of: 65–89) and 93% (50–99%), respectively. While the point estimates of efficacy differ somewhat, the 95% CIs are large, so there is insufficient data to assume a different vaccine efficacy [27]. Thus, from the outset RV1 will dominate RV5, but results for both vaccines are presented for comparison.

2.8. Cost-effectiveness threshold

WHO recommends using the GDP per capita as a threshold to interpret the results [18]. An intervention is considered highly

Table 4
Input parameters for estimating RV1/RV5 program costs.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Vaccine dose price projection				
2014	$8.50	$8.00	$9.00	Mid=[a], Low = [23], High = [23]
2015	$8.33	$7.84	$8.82	Assumption: National multidisciplinary team[b]
2016	$8.16	$7.68	$8.64	Assumption: National multidisciplinary team[b]
2017	$8.00	$7.53	$8.47	Assumption: National multidisciplinary team[b]
2018	$7.84	$7.38	$8.30	Assumption: National multidisciplinary team[b]
2019	$7.68	$7.23	$8.14	Assumption: National multidisciplinary team[b]
2020	$7.53	$7.09	$7.97	Assumption: National multidisciplinary team[b]
2021	$7.38	$6.95	$7.81	Assumption: National multidisciplinary team[b]
2022	$7.23	$6.81	$7.66	Assumption: National multidisciplinary team[b]
2023	$7.09	$6.67	$7.50	Assumption: National multidisciplinary team[b]
Other vaccine dose costs				
International handling (% of vaccine price)	15.1%	15.0%	15.2%	Mid=[a], Low = [23], High = [23]
International delivery (% of vaccine price)	0.0%	0.0%	0.0%	N/A
Wastage (% of doses discarded, etc.)[c]	10.0%	10.0%	10.0%	Assumption: National multidisciplinary team
Incremental system costs of introduction[d]				
Incremental system cost per dose	$0.88	$0.88	$0.88	Author calculation

[a] The mid value or estimated value is calculated [(low + high)/2].
[b] Assumption: National multidisciplinary team: the price decline is calculated by 2%.
[c] The % wastage is converted into a factor [1/(1 − % wastage)] which is multiplied by the expected number of doses required to meet the anticipated level of coverage.
[d] Estimated incremental system costs include: vaccinator's salary (6% of cost), supervision, monitoring, and disease surveillance (1.8% of cost), short-term training (0.09% of cost), information education and communication materials (IEC) + social mobilization (0.2% of cost). Two first cost categories (vaccinator's salary and supervision, monitoring, and surveillance) are assumed to occur each year. The other costs (short term training, IEC and social mobilization) are assumed to be recurrent in the first two years.
[e] Incremental system costs calculation is based on recent experiences from new vaccine introduction such as Hib and Pneumo using the data from Financial Sustainability Plan of the National Immunization Program 2004, the data from Health Insurance Fund related the salary of vaccinator cost. The average length for performance of one vaccine is estimated based on assessment done in one of the big districts (district of Shkodra with 40 health centers) before starting the pilot of the immunization register.

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Table 5
Input parameters for estimating the health impact of RV1/RV5.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Vaccine efficacy vs rotavirus outpatient visits				
Dose 1	51.0%	26.0%	67.0%	Mid=[25], Low = [25], High = [25]
Dose 2	83.0%	67.0%	92.0%	Mid = [24], Low = [24], High = [24]
Dose 3	83.0%	67.0%	92.0%	Mid = [24], Low = [24], High = [24]
Vaccine efficacy vs rotavirus admissions				
Dose 1	51.0%	26.0%	67.0%	Mid = [25], Low = [25], High = [25]
Dose 2	83.0%	67.0%	92.0%	Mid = [24], Low = [24], High = [24]
Dose 3	83.0%	67.0%	92.0%	Mid = [24], Low = [24], High = [24]
Other vaccination impact assumptions				
% relative coverage[a]	100%	80%	100%	Mid = [25], Low = [25], High = [25]
% decrease in dose efficacy per yr[b]	4.8%	0.0%	53.0%	Mid = [24], Low = [13], High = [26]
% contribution of herd effect in <5yrs[c]	100%	100%	120%	Assumption: National multidisciplinary team

[a] Relative coverage is the coverage in those at risk of getting the disease (i.e., effective coverage) relative to coverage in the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.
[b] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 m, 4–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.
[c] Rather than endogenous modeling of transmission dynamics, the % direct protection <5 years is multiplied by a herd effect factor (e.g., 120%) to give the % of total protection in the cohort of interest before age 5 years. This excludes any herd effect in individuals aged 5 years+ and is therefore very conservative.

cost-effective if the value of the ICER (discounted US$ per DALY averted) is less than 1 GDP per capita; it is considered cost-effective if the value of the ICER is between 1 and 3 times the GDP per capita, and it is considered not to be cost-effective if the ICER is greater than 3 times the GDP per capita.

2.9. Scenario analysis (SA)

Given that the study included many assumptions, it was important to assess the uncertainty surrounding the results and how much they might vary if inputs were altered. To evaluate the uncertainty of the cost-effectiveness results, a multivariate scenario analysis was conducted (see Figs. 1 and 2) [28]. This analysis examined the impact of varying different combinations of input parameters including the discount rate, vaccine price and coverage, burden of disease, vaccine efficacy, timing of vaccination, costs of health services, and waning of vaccine efficacy. The upper and lower values of these variables have been used and modified in order to obtain scenarios which are both favorable and unfavorable to the vaccine. An ad-hoc analysis was carried out by combining different levels of efficacy for RV5. Even when RV5 efficacy was set at 100%, it was still less cost-effective than RV1.

3. Results

3.1. No-vaccination alternative

In the no-vaccination alternative, the situation is similar for both evaluations. The expected outcomes are presented in Table 6.

Table 6
Discounted health benefits (10 cohorts vaccinated over the period 2014–2023).

	No vaccine (Status quo)	RV1/RV5 With vaccine	Averted
Total outpatient visits <5 yrs	74,951	23,779	51,172
Total inpatient admissions <5 yrs	20,799	6599	14,200
Total deaths <5 yrs	39	12	27
DALYs lost	1391	441	950
YLDs – DALYS due to morbidity	218	69	149
YLLs – DALYs due to mortality	1173	372	801

Health benefits are discounted at 3% per year.

From both the government and societal perspective, the discounted health service cost savings due to vaccine introduction was approximately US$ 387,000 and US$ 528,000 per year, respectively. (The savings were the same for both vaccines because their efficacy is assumed to be the same.)

3.2. Vaccination alternative for monovalent and pentavalent vaccines

Regardless of the type of vaccine introduced, over the 10 cohorts analyzed, there would be 51,172 outpatient and 14,200 inpatient visits averted. Additionally, 27 deaths due to acute RVGE would be averted in children less than 5 years old (Table 6). This means 950 DALYs would be averted and 801 life-years gained (LYGs). The summary of the results for models with RV1 and RV5 is shown in Tables 6–8. The RV1 model is highly cost-effective from both a governmental and societal perspective (ICER is less than or equal to the GDP per capita, US$ 4149) [29]; in comparison, the RV5 model is cost-effective from a governmental perspective and highly cost effective from a societal perspective.

The much higher 'course' price for RV5 means that it would cost US$ 2.89 million more than RV1 (Table 8). Similarly, the total net cost is higher for RV5 ($4.79 million) than for RV1 (US$ 1.91 million) from both a governmental and societal perspective ($3.38 million vs. $0.49 million, respectively) (Table 7).

3.3. Scenario analysis

The scenario analysis investigated the impact of different inputs on cost and health outcomes for RV1, shown in Fig. 1, and for RV5, shown in Fig. 2.

In most of the scenarios, including the base-case scenario, the vaccine would be considered cost-effective or highly cost-effective. However, when the rotavirus mortality rate is low (or zero, in fact, given the relatively small birth cohort in Albania) and the disease incidence is also low, the ICER exceeds 3 times GDP for both vaccines, and so the vaccine would not be considered cost-effective.

If the high waning-vaccine rate (53% loss of protection per year, based on estimates from Nicaragua) is applied, it reduces the results of ICER for both vaccines from highly cost-effective to cost-effective (Figs. 1 and 2).

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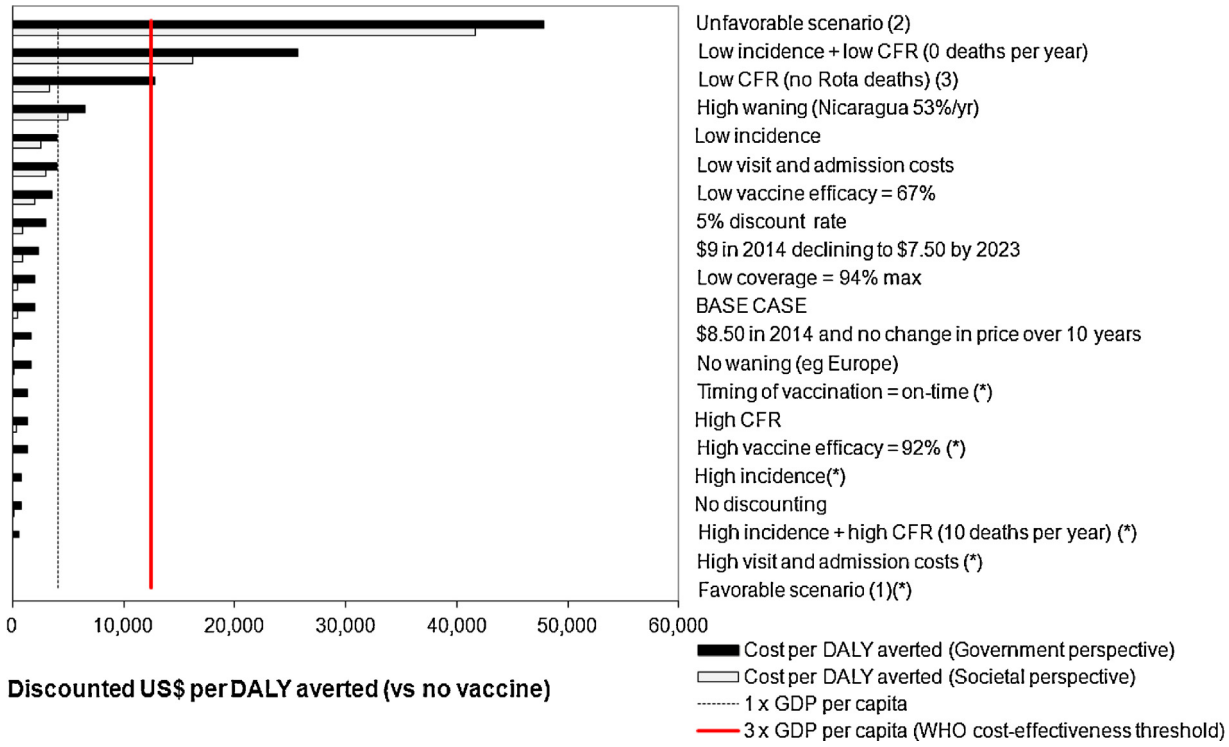

Fig. 1. US$ per DALY averted for base-case RV1 scenario and alternative 'what-if' scenarios: government perspective and societal perspective. (1) Favorable scenario = high visit and admission costs + (high incidence + high rotavirus mortality) + no discounting + high vaccine efficacy. (2) Unfavorable scenario = (low incidence + low rotavirus mortality) + low rotavirus mortality. (3) Not cost-effective from government perspective, but highly cost-effective from societal perspective. (*) Scenario is cost-saving from a societal perspective, i.e., the health service costs avoided (both by the government and households) exceed the cost of introducing the vaccine.

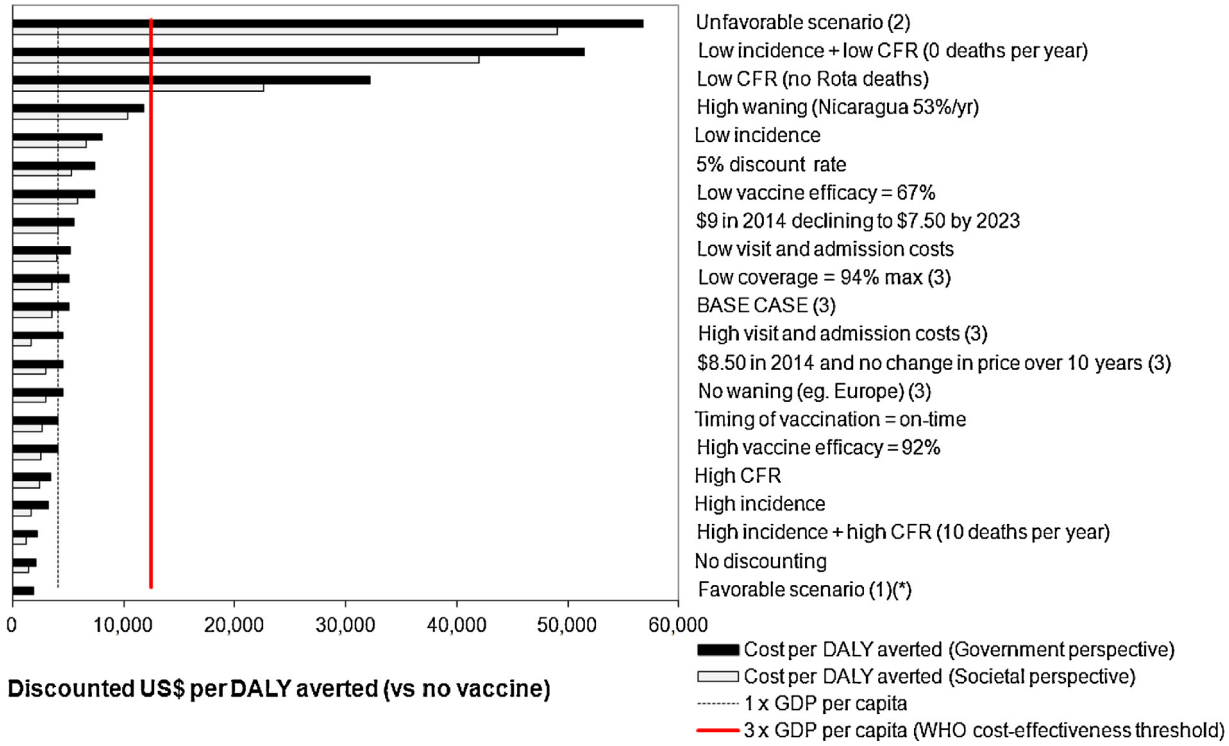

Fig. 2. US$ per DALY averted for base-case RV5 scenario and alternative 'what-if' scenarios: government perspective and societal perspective. (1) Favorable scenario = no discounting; +(high incidence + high rotavirus mortality) + high incidence + high rotavirus mortality. (2) Unfavorable scenario = (low incidence + low rotavirus mortality) + low rotavirus mortality. (3) Cost-effective from government perspective, and highly cost-effective from societal perspective. (*) Scenario is cost-saving from a societal perspective, i.e., the health service costs avoided (both by the government and households) exceed the cost of introducing the vaccine.

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Table 7
Discounted economic benefits (10 cohorts vaccinated over the period 2014–2023).

	No vaccine (Status quo)	RV1/RV5 With vaccine	Averted
Total Gov. Health Service Costs[a]	**$5,662,013**	**$1,796,351**	**$3,865,662**
Total outpatient visit costs	$938,233	$297,667	$640,566
Total inpatient admission costs	$4,723,780	$1,498,684	$3,225,096
Total Societal Health Service Costs[b]	**$7,735,738**	**$2,454,269**	**$5,281,469**
Total outpatient visit costs	$2,069,989	$656,732	$1,413,257
Total inpatient admission costs	$5,665,749	$1,797,537	$3,868,212

Costs are discounted at 3% per year.
[a] Government perspective includes direct costs, which include medical costs, salary of medical staff, diagnosis, consumables, foods, treatment, etc., plus direct non-medical costs, which include costs for utilities, laundry, cleaning, administration, and depreciation borne by the government at the following health providers: health centers, public and primary, secondary, and tertiary hospitals.
[b] Societal perspective includes loss of productivity (LoP) and transport cost of caretakers, which are household costs incurred when visiting government health providers.

Table 8
Discounted cost-effectiveness of RV (10 cohorts vaccinated over the period 2014–2023).

	RV1		RV5	
	Government perspective	Societal perspective	Government perspective	Societal perspective
Net cost of vaccine introduction	**$1,906,868**	**$491,060**	**$4,793,132**	**$3,377,325**
Costs of vaccine introduction	$5,772,529	$5,772,529	$8,658,794	$8,658,794
Health service costs avoided	$3,865,662	$5,281,469	$3,865,662	$5,281,469
DALYs averted	**950**	**950**	**950**	**950**
YLDs averted – DALYS due to morbidity	149	149	149	149
YLLs averted – DALYs due to mortality	801	801	801	801
US$ per DALY averted	**$2008**	**$517**	**$5047**	**$3556**
Net cost of vaccine introduction	–	–	**$2,886,265**	**$2,886,265**
Costs of vaccine introduction	–	–	$2,886,265	$2,886,265
Health service costs avoided	–	–	$0	$0
DALYs averted	–	–	–	–
YLDs averted – DALYS due to morbidity	–	–	–	–
YLLs averted – DALYs due to mortality	–	–	–	–
US$ per DALY averted	–	–	**Dominated**	**Dominated**
1 × GDP per capita (2012) – WHO threshold for 'highly cost-effective'	$4149	$4149	$4149	$4149
3 × GDP per capita (2012) – WHO threshold for 'cost-effective'	$12,447	$12,447	$12,447	$12,447

Costs and DALYs are discounted at 3% per year.

4. Discussion

This is the second CEA performed in Albania; the first was for introducing the Hib vaccine in 2006. That experience was led by an international consultant; in contrast, this current study was country-led. The current effort highlights the importance of such analyses in helping national health authorities gain a better understanding of the situation regarding rotavirus diarrhea in children less than 5 years old.

The economic evaluation was done from both government and societal perspectives for both vaccines. The universal rotavirus immunization program was found to prevent about 68% of the hospitalizations and outpatient visits due to RVGE.

In this study, RV1 was highly cost-effective from both a governmental and societal perspective in the base case; in contrast, RV5 proved to be merely cost-effective from a governmental perspective and highly cost-effective from societal perspective. The number of administrated doses per vaccine clearly increased the cost of the vaccination program.

The fact that RV5 is surpassed by RV1 is not surprising since the only assumption that differed was the price per course. The same efficacy levels were assumed for both vaccines against rotavirus-associated hospitalizations and outpatient visits after the full doses were administered, which is a limitation. However, variation of efficacy level in a pessimistic scenario has a significant impact only on RV5 results: it drops from highly to cost-effective.

The NIP has a specific budget from the Ministry of Health and used for vaccine procurement, cold chain, transport, maintenance, and supervision. The cost of the program for the existing vaccines is approximately US$ 3.5 million per year. Our findings suggest that if RV1 were introduced in Albania, the total discounted cost of a 10-year program would be approximately US$ 5.77 million. In the case of RV5, the total discounted cost of a 10-year program would be US$ 8.66 million. However, CEA is not a proper budget analysis; therefore, the differences expressed in Table 8 should be interpreted with caution.

Under most scenarios, we found the RV vaccination to be either highly cost-effective or cost-effective, which contrasts with assessments for high-income European countries, where costs per DALY averted were generally greater than $30,000 for most scenarios [30,31]. However, these countries also typically have a higher threshold for cost-effectiveness because the price of vaccination and costs for health services are likely to be much higher. This finding in Albania likely is a function of the higher incidence of severe disease and deaths, and of the lower expected price of vaccination. But even at this lower price, some scenarios were not cost-effective, so a price above the value assumed in this analysis is not likely to be acceptable.

This study has additional limitations, primarily related to gathering national health data and the quality of the data obtained. The main limitation is the lack of reliable national data related to deaths from diarrhea. Because data was limited, we found it necessary to rely instead on WHO recommendations [18]. As seen in the scenario analyses section, data related to deaths from diarrhea is a key driver of the study and therefore critical.

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A second limitation is the lack of proper protocols for case management and treatment of diarrheal disease in primary, secondary, and tertiary care settings.

A third limitation is that no consideration was given to any effects that the differences in the serotypes may have on the vaccine efficacy figures obtained from literature review. In order to avoid assumptions and limitations as much as possible, we developed an optimistic and pessimistic scenario of uncertainty parameters for both vaccines and for both governmental and societal perspectives.

Omitting the costs of vaccines' adverse effects is also a limitation. Safety is a separate criteria evaluated by decision-makers and WHO has developed a specific analysis on the risks and benefits of RV introduction in Albania [32]. Additional cases of intussusception would be very unlikely to alter the cost-effectiveness results because they are rare and represent very few additional hospitalizations to the children concerned. Put in the context of the much larger rotavirus diarrhea hospitalization costs prevented, this would not make a difference to the conclusions.

5. Conclusion

Introducing the rotavirus vaccine to the National Immunization Program would be cost-effective according to the WHO interpretation of results [18]. Although further scenario analyses deserve particular attention, there is a high probability that the vaccine introduction would be, at minimum, cost-effective. However, the critical element that significantly affects results is the number of rotavirus deaths; this needs to be precisely estimated. This analysis demonstrates that this type of study can produce evidence to inform decision-makers and stakeholders on how to best spend limited resources and to decide on what to include in a package of health services to better respond to the population's health needs.

Acknowledgments

The authors would like to thank Liudmila Mosina from the World Health Organization (WHO) regional office for Europe and Benjamin Lopman from the US Centers of Disease Control and Prevention (CDC) for their fine contribution to the present paper. Also, we would like to thank Mariana Bukli from the UNICEF, Albania.

In addition, we wish to thank the team of consultants from the Ministry of Health of Albania and Tirana University Hospital Center's "Mother Teresa," as well as representatives from the Public Health Institute and Health Insurance Institute (now known as the Health Insurance Fund) who were part of this project.

Authors' contributions: AA, SB, and IP helped in the conception and design of the study and data analysis; AS provided epidemiological data and disease burden estimation; IP and EN provided immunization data; AC and GF provided assistance for running the TRIVAC model for Albania; CL, CH, and JB helped with the critical revision of the content of the paper. All authors have participated in drafting the paper and have read and approved the manuscript.

Conflict of interest: The authors report no conflict of interest for this work.

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Vaccine 33S (2015) A209–A218

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of pneumococcal conjugate vaccination in Croatia

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ARTICLE INFO

Keywords:
Croatia
Pneumococcal
Cost-effectiveness
Decision-making
Evidence-based medicine
Vaccine

ABSTRACT

Objective: Pneumococcus is a known cause of meningitis, pneumonia, sepsis, and acute otitis media in children and adults globally. Two new vaccines for children have the potential to prevent illness, disability, and death, but these vaccines are expensive. The Croatian Ministry of Health has considered introducing the vaccine in the past, but requires economic evidence to ensure that the limited funds available for health care will be used in the most effective way.

Methodology: Croatia appointed a multidisciplinary team of experts to evaluate the cost-effectiveness of introducing pneumococcal conjugate vaccination (PCV) into the national routine child immunization program. Both 10-valent and 13-valent PCV (PCV10 and PCV13) were compared to a scenario assuming no vaccination. The TRIVAC decision-support model was used to estimate cost-effectiveness over the period 2014–2033. We used national evidence on demographics, pneumococcal disease incidence and mortality, the age distribution of disease in children, health service utilization, vaccine coverage, vaccine timeliness, and serotype coverage. Vaccine effectiveness was based on evidence from the scientific literature. Detailed health care costs were not available from the Croatian Institute for Health Insurance at the time of the analysis so assumptions and World Health Organization (WHO) estimates for Croatia were used. We assumed a three-dose primary vaccination schedule, and an initial price of US$ 30 per dose for PCV10 and US$ 35 per dose for PCV13. We ran univariate sensitivity analyses and multivariate scenario analyses.

Results: Either vaccine is estimated to prevent approximately 100 hospital admissions and one death each year in children younger than five in Croatia. Compared to no vaccine, the discounted cost-effectiveness of either vaccine is estimated to be around US$ 69,000–77,000 per disability-adjusted life-years (DALYs) averted over the period 2014–2033 (from the government or societal perspective). Only two alternative scenarios were borderline cost-effective (US$ per DALY averted less than 3 × GDP per capita of approximately US$ 40,000). The first was a scenario based primarily on the WHO 2008 pneumococcal disease burden estimates for Croatia. The second was a scenario that assumed a fairly dramatic drop in the price of the vaccine over the period. Both vaccines would need to be priced at approximately US$ 20 per dose or less to be considered cost-effective under base-case assumptions. PCV10 would be more cost-effective than PCV13 with base-case assumptions, but this is sensitive to the price of each vaccine.

Conclusion: Based on estimated health and economic benefits in children alone, PCV is unlikely to be cost-effective in Croatia. Both vaccines would need to be priced at less than US$ 20 per dose to be considered cost-effective for children. Further analyses should be conducted to estimate the health and economic burden of pneumococcal disease in older age groups, and to assess the influence on cost-effectiveness results when short-term and long-term indirect effects are included for older individuals. While there are important uncertainties around the price and effectiveness of both vaccines, our analysis suggests there is insufficient evidence to warrant a significant difference in the price of the two vaccines.

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http://dx.doi.org/10.1016/j.vaccine.2014.12.043
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1. Introduction

Vaccines used in the childhood immunization program in Croatia have been sequentially added since 1948, when BCG and diphtheria vaccines were introduced.

The program is mandatory and free of charge for children. Since 2010, vaccination against pneumococcal disease has been financed by the Croatian Institute for Health Insurance (CIHI) for some risk groups, e.g. bone marrow transplant. Three vaccines are used: 10- and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13), and a polysaccharide pneumococcal vaccine. Recommendations for the immunization program are based on criteria such as epidemiological data, availability of vaccines, vaccine characteristics, vaccine safety, and on other criteria such as public acceptance and affordability.

In the process of discussions at the national level about introducing new vaccines, the Croatian health system was offered assistance from the World Health Organization (WHO) and other ProVac International Working Group (IWG) partners to help evaluate the potential cost-effectiveness of adding PCV to the national immunization program. Two PCVs are licensed in Croatia, the 10-valent (PCV10) and the 13-valent (PCV13).

The National Immunization Technical Advisory Group (NITAG) recommended introducing PCV into the immunization program in 2011, but the decision has been postponed because the Ministry of Health (MoH) was not sure that the introduction of pneumococcal vaccine should be prioritized. The MoH requires economic evidence to ensure that the limited funds available for health care programs will be used in the most effective way. The results of this cost-effective analysis (CEA) will be used by the MoH to help make a more informed decision about whether introducing PCV would represent an appropriate allocation of funds. Another important study objective was to define the vaccine price required for PCV introduction to be cost-effective so that it can be used in negotiations with manufacturers and to help make an informed decision about choosing one of the two available PCVs. Because Croatia is a high-income country, it is not eligible to procure vaccines through UNICEF or any other mechanism, so it is particularly important to consider economic and financial evidence as well as clinical data when making a decision.

2. Methods

2.1. Model overview

The CEA was carried out using the TRIVAC vaccine impact and cost-effectiveness model, version 2.0. This is a static cohort model, developed in Microsoft Excel® by modelers from the London School of Hygiene and Tropical Medicine (LSHTM) for the Pan American Health Organization' ProVac Initiative [1]. The model includes the following parameters: demography, disease burden, health services utilization and costs, vaccination coverage, vaccine efficacy, and vaccination costs. Four syndromes were included: all-cause acute otitis media (AOM), pneumococcal pneumonia, pneumococcal meningitis, and pneumococcal non-pneumonia non-meningitis (NPNM). In this analysis, NPNM was used to refer to pneumococcal bacteremia/sepsis. The outcomes of the model include: number of pneumococcal disease cases averted due to the vaccine, deaths averted, costs of introducing PCV and costs prevented in health services if the vaccine was introduced as a result of cases of disease averted. The model also provides information on life-years saved and disability-adjusted life years (DALYs) averted through the lifetime of targeted cohorts. Numbers of deaths and life expectancy were used to calculate years of life lost (YLL) and numbers of cases, mean duration of illness and disability weights were used to calculate years of life with disability (YLD). Finally, the model provides a cost-effectiveness ratio which gives the cost in United States dollars (US$) per DALY averted.

For each alternative, CEA compares the relationship between health costs and benefits. This type of analysis does not explicitly take a sectoral perspective where the costs and effectiveness of all possible interventions are compared in order to select the mix that maximizes health for a given set of resource constraints. The estimated cost-effectiveness of a single proposed new intervention is compared either with the cost-effectiveness of a set of existing interventions reported in the literature or with a fixed-price cut-off point representing the assumed social willingness to pay for an additional unit of health [2]. The cost-effectiveness was determined by calculating the incremental net cost of the vaccination program (estimated as the total cost of the vaccination program less the costs saved from disease prevention) and dividing by the number of DALYs that would be averted by the vaccination program.

2.2. Analytic framework

This CEA compared the introduction of the PCV into the immunization program versus no introduction. The model was run twice, once for PCV10 and once for PCV13.

2014 was considered as the year of vaccine introduction and the model was used to estimate costs and effects for 20 successive birth cohorts of children vaccinated between 2014 and 2033. The primary outcome measure is the cost-effectiveness ratio (US$ per DALY averted), which is based on the total costs and benefits aggregated over the 20 cohorts. Both the governmental and societal cost perspectives were considered, with the latter also including household costs. Only the public health care system was considered; the private sector was not taken into account because all children in Croatia have access to health care with all costs covered through social security. Evaluated providers are social security clinics (for outpatient visits) and social security hospitals (mainly for inpatient admissions). For both vaccines, a schedule of three primary series doses (at 2, 4, and 6 months) and no booster dose was chosen. Procurement of administering syringes was not considered because PCV is presented as a prefilled syringe. Based on WHO recommendations, a discount rate of 3% was applied for both future health outcomes and future costs [2].

2.3. Demographic data

The demographic data required are number of live births per year, infant mortality rate, mortality in children under age 5, life expectancy at birth, and proportion of infant death before 1 month. These are used to estimate life-years at risk for each birth cohort between birth and age 5. For all inputs, national data were provided by the National Bureau of Statistics (Population Census 2001 and 2011) and by the Croatian National Institute for Public Health [3,4]. Demographic projections were estimated by scaling the United Nations population division projections to the Croatian data [5].

2.4. Disease burden data

(Table 1) Based on the number of reported inpatient- and outpatient-managed pneumonia cases, the annual number of all-cause pneumonia cases of children younger than 5 was estimated to be approximately 6000 [4]. The fraction of all-cause pneumonia due to pneumococcal is a contentious and uncertain parameter, and in Croatia, 95% of pneumonia cases reported through the mandatory notification system do not have a confirmed etiology. For the base case, and in accordance with previous WHO methods [7], we assumed that 8% of pneumonia cases were due to pneumococcal. This assumption was based on the percent of clinical

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Table 1
Input parameters for estimating disease burden.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Annual incidence per 100,000 aged 1–59 m				
All-cause acute otitis media	23,581	800	25,939	[4] +/− 10%
Pneumococcal pneumonia cases	226	186	297	Low = [4], Low = WHO, High = WHO
Pneumococcal meningitis	2.5	1.9	3.9	Mid = [8], Low = [4], High = WHO
Pneumococcal NPNM	18.0	8.5	23.0	Mid = [8], Low = [4], High = WHO
% Case fatality ratios (CFRs) in ages 1–59 m[a]				
Pneumococcal pneumonia cases	0.08%	0.07%	0.32%	Mid = assumption, mortality department, High = [10]
Pneumococcal meningitis	18.6%	16.74%	20.47%	Mid = assumption, mortality department, High = [10]
Pneumococcal NPNM	2.6%	2.35%	2.87%	Mid = assumption, mortality department, Low = [10]
% Sequelae in pneumococcal meningitis survivors				
% Major sequelae (single)	20.2%	–	–	[9]
% Major sequelae (multiple)	4.5%	–	–	[9]
Disability weight for DALY calculations				
All-cause acute otitis media	0.02	–	–	[10]
Pneumococcal pneumonia cases	0.28	–	–	[10]
Pneumococcal meningitis	0.62	–	–	[10]
Pneumococcal NPNM	0.28	–	–	[11]
% Major sequelae (single)	0.24	–	–	[11]
% Major sequelae (multiple)	0.63	–	–	[11]
Mean duration of illness (in days)				
All-cause acute otitis media	7	–	–	Assumption, pediatricians ($n = 3$)
Pneumococcal pneumonia cases	10	–	–	Assumption, pediatricians ($n = 3$)
Pneumococcal meningitis	14	–	–	Assumption, pediatricians ($n = 3$)
Pneumococcal NPNM	14	–	–	Assumption, pediatricians ($n = 3$)
Age distribution of disease cases and deaths				
<3 m	1.3%	–	–	[22]
3–5 m	2.5%	–	–	[22]
6–8 m	3.4%	–	–	[22]
9–11 m	3.8%	–	–	[22]
12–23 m	24.5%	–	–	[22]
24–35 m	23.8%	–	–	[22]
36–47 m	22.9%	–	–	[22]
48–59 m	17.8%	–	–	[22]

[a] In the absence of vaccination, CFRs are assumed to decline in each successive birth cohort in line with the general trend in mortality under age 5. This is done by assuming that the fraction of deaths under age 5 caused by the disease remains fixed over time.

pneumonia prevented by PCVs in the four pivotal clinical trials (Gambia, Philippines, South Africa, USA). Pneumococcal pneumonia incidence was estimated to be 226 per 100,000 annually in children younger than 5. The data on number of cases of bacterial meningitis were obtained from the national communicable disease surveillance system for the year 2011. In that year, there were 36 all-cause meningitis cases in children younger than 5; of those, 4 were pneumococcal meningitis (annual incidence of 1.89 per 100,000 under age 5). There were 148 cases of bacterial sepsis; of those, 18 were pneumococcal sepsis (annual incidence of 8.5 per 100,000 under age 5). These estimates were used in the low-incidence scenario. For the mid-incidence scenario, we used pooled data from three years derived from Guzvinec et al. (pneumococcal meningitis 2.5 and NPNM 18.0 per 100,000 per year under age 5, respectively) [8]. For the high-incidence scenario we used estimates published by the WHO for Croatia (3.9 and 23.0 per 100,000 per year under age 5, respectively) [7].The incidence estimates for all-cause AOM were obtained from primary care physicians reports [4]. Case fatality ratios (CFR) were calculated by combining the incidence rates described above with data from the national mortality statistics department (2009–11). (Table 1)

Given the lack of national published data on meningitis sequelae, we used estimates from a global systematic literature review for the proportion of meningitis survivors with single (20.2%) or multiple (4.5%) sequelae [9] and estimates from Griffiths et al. for the sequelae disability weights [10].

2.5. Health service utilization and cost

(Table 2) Detailed health care costs were not available from the CIHI at the time of the analysis, so assumptions and WHO estimates for Croatia were used. The government bears the direct medical cost of pneumococcal disease treatment, including days in hospital, medical staff time, diagnostic tests, and medications. Households bear direct non-medical costs such as transportation to healthcare facilities, and time spent by parent or caregiver caring for a sick child. These costs and out-of-pocket costs were based on assumptions by the national team. For sequelae costs, no national data were available. We therefore assumed one outpatient visit per year for the government cost; for the household cost we assumed 1 × gross domestic product (GDP) per capita in lost productivity for each year of life until death [11]. We also ran a scenario without any productivity losses included.

2.6. Vaccination schedule and coverage

Since PCV would be administered together with DTP, polio and *Haemophilus influenzae* type b (Hib), a vaccination coverage rate similar to those reported for the first three doses of pentavalent vaccine was assumed [12] (Table 3). Vaccination is planned to be carried out through health institutions only.

2.7. Vaccine efficacy data

Vaccine efficacy against four syndromes is presented in Table 5. Vaccine type coverage from the study by Guzvinec et al. was derived for the group younger than 5 years. (82% for PCV10 and 95% for PCV13) [8]. Assumptions were made to account for vaccine-induced waning, herd effects and serotype replacement in children younger than 5 years. Because overall vaccine coverage is very high in Croatia, no adjustment was made for relative coverage (worse coverage among high risk children). Relative coverage is the coverage for

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Table 2
Input parameters for estimating health service utilization and costs. All costs are presented in 2014 US $.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
OUTPATIENT VISITS				
Outpatient visits per disease episode				
All-cause acute otitis media	2.00	1.80	2.20	Assumption, pediatricians ($n = 3$)
Pneumococcal pneumonia cases	2.00	1.80	2.20	Assumption, pediatricians ($n = 3$)
Pneumococcal meningitis	1.00	0.90	1.10	Assumption, pediatricians ($n = 3$)
Pneumococcal NPNM	1.00	0.90	1.10	Assumption, pediatricians ($n = 3$)
Government cost per outpatient visit[a]				
All-cause acute otitis media	$22	$11	$33	Mid = [18], Low/High = assumption
Pneumococcal pneumonia cases	$32	$16	$48	Assumption, Croatian Institute for Health Insurance
Pneumococcal meningitis	$32	$16	$48	Assumption, Croatian Institute for Health Insurance
Pneumococcal NPNM	$32	$16	$48	Assumption, Croatian Institute for Health Insurance
Household cost per outpatient visit[b]				
All-cause acute otitis media	$5	$3	$8	Assumption, Croatian Institute for Health Insurance
Pneumococcal pneumonia cases	$5	$3	$8	Assumption, Croatian Institute for Health Insurance
Pneumococcal meningitis	$5	$3	$8	Assumption, Croatian Institute for Health Insurance
Pneumococcal NPNM	$5	$3	$8	Assumption, Croatian Institute for Health Insurance
INPATIENT ADMISSIONS				
Inpatient admissions per disease episode				
Pneumococcal pneumonia cases	0.43	0.39	0.90	Estimate = [4]
Pneumococcal meningitis	1.00	0.90	1.10	Assumption, ProVac national team ($n = 6$)
Pneumococcal NPNM	1.00	0.90	1.10	Assumption, ProVac national team ($n = 6$)
Government cost per inpatient admission[c]				
Pneumococcal pneumonia cases	2000	1000	3000	[18], Assumption ProVac national team ($n = 6$)
Pneumococcal meningitis	8000	1400	15,000	[18], Assumption ProVac national team ($n = 6$)
Pneumococcal NPNM	4000	1000	5000	[18], Assumption ProVac national team ($n = 6$)
Household cost per inpatient admission[d]				
Pneumococcal pneumonia cases	50	25	75	Assumption, ProVac national team ($n = 6$)
Pneumococcal meningitis	50	25	75	Assumption, ProVac national team ($n = 6$)
Pneumococcal NPNM	50	25	75	Assumption, ProVac national team ($n = 6$)
MENINGITIS SEQUELAE				
Government cost of meningitis sequelae per year[e]				
Major sequelae (single)	22	11	1100	[18]
Major sequelae (multiple)	22	11	1100	[18]
Household cost of meningitis sequelae per year[f]				
Major sequelae (single)	13,227	11,904	14,550	[19]
Major sequelae (multiple)	13,227	11,904	14,550	[19]

[a] Government costs per outpatient visit include medical staff time, diagnostic tests, medications. Outpatient visits are distributed as follows: 50% Social Security hospital, 50% Social Security clinic. The cost presented is the weighted average of the provider-specific costs.
[b] Household costs per outpatient visit include travel expenses and out-of-pocket payments for drugs. Outpatient visits are distributed as follows: 50% Social Security hospital, 50% Social Security clinic. The cost presented is the weighted average of the provider-specific costs.
[c] Government costs per inpatient admission include the cost per bed-day and the cost of any disease-specific drugs and diagnostics. Inpatient admissions are distributed as follows: 50% Social Security hospital, 50% Social Security clinic. The cost presented is the weighted average of the provider-specific costs.
[d] Household costs per inpatient admission include travel expenses, out-of-pocket payments for drugs. Inpatient admissions are distributed as follows: 50% Social Security hospital, 50% Social Security clinic. The cost presented is the weighted average of the provider-specific costs.
[e] Sequelae costs borne by the government include medical staff time, diagnostic tests, medications and are applied annually from the age of meningitis onset until full life expectancy. These costs are included/excluded and discounted over time in the base-case (best-estimate) scenario.
[f] Sequelae costs borne by households include travel expenses and out-of-pocket payments for drugs and are applied annually from the age of meningitis onset until full life expectancy. These costs are included/excluded and discounted over time in the base-case (best-estimate) scenario.

those at risk of getting the disease (i.e. effective coverage) relative to coverage for the entire birth cohort (i.e., overall coverage).

2.8. Vaccine cost

Data from the CIHI, based on the publicly published list of drugs covered by the basic health insurance, indicate that price per dose for PCV10 is approximately US$ 63 and for PCV13 is approximately US$ 67 [16]. This is the price paid by the CIHI for vaccines used for high-risk groups. Based on experience with pentavalent vaccine, it was assumed that the price would be lower if the vaccine were implemented in the universal childhood immunization program. We assumed a price of US$ 30 per dose for PCV10 and US$ 35 per dose for PCV13. The price of safety boxes from UNICEF was used, and we assumed an incremental health system cost of US$ 1 per dose [11] and a 1% vaccine wastage rate (Table 4).

2.9. Uncertainty analysis

Each parameter was varied, one at a time, by 10% to assess which parameters had the greatest influence on the cost-effectiveness ratio (sensitivity analysis). Several multivariate scenarios were then evaluated using more realistic changes in parameter values. Contrasting scenarios combining sets of 'favorable' and sets of 'unfavorable' assumptions can suggest a plausible range of cost-effectiveness values. The model produces graphs to show the US$ per DALY averted for each scenario [1] Finally, we ran a two-way threshold analysis for two of the most uncertain parameters (dose price and vaccine efficacy against AOM) to determine the price required for the vaccine to be cost-effective, and which vaccine would be preferable under different scenarios of AOM effectiveness.

3. Results

3.1. Estimated health benefits of PCV

(Table 6) Both vaccines are estimated to prevent approximately 36,000 discounted episodes of pneumococcal illness over the period 2014–2033. PCV13 is expected to prevent around 17 discounted deaths and 2000 hospital admissions; in

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Table 3
Input parameters for estimating PCV vaccine coverage and timeliness.

Parameter (m)	Estimate (%)	Scenarios		Source/s
		Low	High	
Coverage of DTP1 by age in year 2014 (proxy for PCV doses given with DTP1)				
3	80.4	–	–	[12]
6	95.1	–	–	[12]
9	97.0	–	–	[12]
12	97.5	–	–	[12]
24	98.0	–	–	[12]
Coverage of DTP2 by age in year 2014 (proxy for PCV doses given with DTP2)				
3	1.6	–	–	[12]
6	86.3	–	–	[12]
9	94.1	–	–	[12]
12	96.0	–	–	[12]
24	97.0	–	–	[12]
Coverage of DTP3 by age in year 2014 (proxy for PCV doses given with DTP3)				
3	0.1	–	–	[12]
6	34.6	–	–	[12]
9	82.6	–	–	[12]
12	91.2	–	–	[12]
24	96.0	–	–	[12]
Coverage of measles dose 1 by age in year 2014 (proxy for PCV booster doses given with measles dose 1)				
3	0.0	–	–	[12]
6	0.0	–	–	[12]
9	0.0	–	–	[12]
12	56.4	–	–	[12]
24	94.0	–	–	[12]

Coverage projections over the period 2014–2033 were estimated by assuming PCV will achieve the same coverage and timeliness as DTP, and by assuming a 0% annual decrease in the gap between final coverage in the cohort (coverage by age 24 m) and a ceiling of 98% (DTP1), 97% (DTP2) and 96% (DTP3) and 94% (measles dose 1)

comparison, PCV10 is expected to prevent around 15 deaths and 1800 admissions. This is roughly equivalent to around one undiscounted death and 100 undiscounted admissions prevented each year. Approximately 80% of the averted DALYs were due to avoided mortality and 20% to avoided morbidity.

3.2. Estimated economic benefits

(Table 7) From a government perspective, both vaccines were estimated to avert approximately US$ 6–7 million discounted health service costs over the 20-year period. From a societal

Table 4
Input parameters for estimating PCV program costs, All costs are presented in 2014 US $.

Parameter	PCV10 Estimate	Scenarios Low	High	PCV13 Estimate	Scenarios Low	High	Source/s
Vaccine dose price projection							
2014	**30.00**	30.00	30.00	**35.00**	35.00	35.00	Assumption*
2015	**29.40**	27.00	30.00	**34.30**	31.50	35.00	Assumption*
2016	**28.81**	24.30	30.00	**33.61**	28.35	35.00	Assumption*
2017	**28.24**	21.87	30.00	**32.94**	25.52	35.00	Assumption*
2018	**27.67**	19.68	30.00	**32.28**	22.96	35.00	Assumption*
2019	**27.12**	17.71	30.00	**31.64**	20.67	35.00	Assumption*
2020	**26.58**	15.94	30.00	**31.00**	18.60	35.00	Assumption*
2021	**26.04**	14.35	30.00	**30.38**	16.74	35.00	Assumption*
2022	**25.52**	12.91	30.00	**29.78**	15.07	35.00	Assumption*
2023	**25.01**	11.62	30.00	**29.18**	13.56	35.00	Assumption*
2024	**24.51**	10.46	30.00	**28.60**	12.20	35.00	Assumption*
2025	**24.02**	9.41	30.00	**28.03**	10.98	35.00	Assumption*
2026	**23.54**	8.47	30.00	**27.47**	9.89	35.00	Assumption*
2027	**23.07**	7.63	30.00	**26.92**	8.90	35.00	Assumption*
2028	**22.61**	6.86	30.00	**26.38**	8.01	35.00	Assumption*
2029	**22.16**	6.18	30.00	**25.85**	7.21	35.00	Assumption*
2030	**21.71**	5.56	30.00	**25.33**	6.49	35.00	Assumption*
2031	**21.28**	5.00	30.00	**24.83**	5.84	35.00	Assumption*
2032	**20.85**	4.50	30.00	**24.33**	5.25	35.00	Assumption*
2033	**20.44**	4.05	30.00	**23.84**	4.73	35.00	Assumption*
Other vaccine dose costs**							
Wastage (% of doses discarded, etc.)[a]	**1.00%**	0.00%	2.00%	**1.00%**	0.00%	2.00%	Assumption*
Safety box cost (150 syringes per box)							
Price of each safety box	**1.08**	–	–	**1.08**	–	–	[21]
Incremental system costs of introduction[b]							
Incremental system cost per dose	**1.00**	0.00	10.00	**1.00**	0.00	10.00	[11]

* National multidisciplinary team ($N = 6$).
** Cost assumptions include delivery, insurance, and handling.
[a] The % wastage is converted into a factor [1/(1% wastage)] which is multiplied by the expected number of doses required to meet the anticipated level of coverage.
[b] Estimated incremental system costs include logistics of vaccination [11]. They are assumed to only occur in the first year.

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Table 5
Input parameters for estimating PCV health benefits.

Parameter	PCV10 Estimate (%)	Scenarios Low (%)	High (%)	PCV13 Estimate (%)	Scenarios Low (%)	High (%)	Source/s
Vaccine efficacy vs. all-cause acute otitis media							
Dose 1	**3.0**	2.0	6.9	**3.0**	2.0	6.9	[17]
Dose 2	**5.5**	3.7	9.0	**5.5**	3.7	9.0	[17]
Dose 3	**6.0**	4.0	9.0	**6.0**	4.0	9.0	[13]
Vaccine efficacy vs. vaccine type pneumococcal pneumonia/meningitis/NPNM							
Dose 1	**41.0**	31.9	69.2	**41.0**	31.9	69.2	[17]
Dose 2	**74.5**	58.0	90.0	**74.5**	58.0	90.0	[17]
Dose 3	**81.0**	63.0	90.0	**81.0**	63.0	90.0	[14]
% Vaccine serotype coverage							
Pneumococcal pneumonia cases	**82.3**	71.0	87.0	**94.9**	82.0	95.0	[8]
Pneumococcal meningitis	**82.3**	71.0	87.0	**94.9**	82.0	95.0	[8]
Pneumococcal NPNM	**82.3**	71.0	87.0	**94.9**	82.0	95.0	[8]
Other vaccination impact assumptions							
% Relative coverage[a]	**100**	–	–	**100**	–	–	Assumption[*]
% Decrease in dose efficacy per yr[b]	**5.0**	0.0	10.0	**5.0**	0.0	10.0	Assumption[*]
% Contribution of herd effect in <5yrs[c]	**120**	100	–	**120**	100	–	[20]
Decline in vaccine type coverage/yr[d]	**3.0**	0.0	5.5	**3.0**	0.0	5.5	Assumption[*]

[*] ProVac national team ($n = 6$).
[a] Relative coverage is the coverage for those at risk of getting the disease (i.e. effective coverage) relative to coverage for the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.
[b] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 m, 4–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.
[c] Rather than endogenous modeling of transmission dynamics, the % direct protection <5yrs is multiplied by a herd effect multiplier (e.g. 120%) to give the % total protection in the cohort of interest before age 5yrs. This excludes any herd effect in individuals aged 5yrs+ and is therefore very conservative.
[d] Vaccine type disease replacement is handled by reducing the expected vaccine type coverage in successive vaccinated cohorts by a fixed % each year, thus reducing overall expected impact of the program in each successive vaccinated cohort by a similar amount. Thus, for a given vaccinated cohort, the % vaccine type coverage is equal to $[T(1 - R)N]$ where, T = % of disease caused by vaccine types in the year of vaccine introduction, R = % reduction in vaccine type coverage per year following vaccine introduction, and N = number in the sequence of vaccinated birth cohorts.

Table 6
Discounted health benefits (20 cohorts vaccinated over the period 2014-2033).

	No vaccine	PCV10		PCV13	
	(Status quo)	With vaccine	Averted	With vaccine	Averted
Total cases <5yrs	680,474	644,125	36,348	643,543	36,931
All-cause acute otitis media	673,426	640,863	32,563	640,863	32,563
Pneumococcal pneumonia cases	6460	2990	3470	2456	4003
Pneumococcal meningitis	72	33	39	28	45
Pneumococcal NPNM	515	239	277	196	319
Total outpatient visits	1,360,359	1,287,978	72,381	1,286,862	73,497
All-cause acute otitis media	1,346,852	1,281,726	65,126	1,281,726	65,126
Pneumococcal pneumonia cases	12,920	5981	6939	4913	8007
Pneumococcal meningitis	72	33	39	28	45
Pneumococcal NPNM	515	239	277	196	319
Total inpatient admissions	3365	1558	1808	1280	2086
Pneumococcal pneumonia cases	2778	1286	1492	1056	1721
Pneumococcal meningitis	72	33	39	28	45
Pneumococcal NPNM	515	239	277	196	319
Total deaths <5yrs	27	12	15	10	17
Pneumococcal pneumonia cases	4	2	2	2	3
Pneumococcal meningitis	11	5	6	4	7
Pneumococcal NPNM	11	5	6	4	7
Total children with permanent disability	15	7	8	6	9
Major sequelae (single)	12	6	7	5	8
Major sequelae (multiple)	3	1	1	1	2
DALYs lost	1297	738	559	654	643
YLDs-DALYS due to morbidity	494	374	120	358	136
YLLs-DALYs due to mortality	803	364	440	296	507

Health benefits are discounted at 3% per year.

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Table 7
Discounted economic benefits (20 cohorts vaccinated over the period 2014-2033) All costs are presented in 2014 US $.

	No vaccine	PCV10		PCV13	
	(Status quo)	With vaccine	Averted	With vaccine	Averted
TOTAL GOV. HEALTH SERVICE COSTS	**38,268,859**	**32,196,562**	**6,072,297**	**31,482,790**	**6,786,069**
Total outpatient visit costs	**30,062,983**	**28,398,048**	**1,664,935**	**28,362,331**	**1,700,652**
All-cause acute otitis media	29,630,742	28,197,964	1,432,778	28,197,964	1,432,778
Pneumococcal pneumonia cases	413,433	191,378	222,056	157,215	256,218
Pneumococcal meningitis	2315	1071	1243	880	1435
Pneumococcal NPNM	16,492	7634	8858	6272	10,221
Totalinpatientadmissioncosts	**8,195,734**	**3,793,792**	**4,401,942**	**3,116,571**	**5,079,163**
Pneumococcal pneumonia cases	5,555,511	2,571,637	2,983,874	2,112,580	3,442,931
Pneumococcal meningitis	578,679	267,870	310,809	220,053	358,626
Pneumococcal NPNM	2,061,544	954,286	1,107,259	783,938	1,277,606
Total sequelae costs	**10,142**	**4722**	**5420**	**3888**	**6,254**
Major sequelae (single)	8294	3862	4433	3180	5115
Major sequelae (multiple)	1848	860	988	708	1139
TOTAL SOCIETAL HEALTH SERVICE COSTS	**51,476,356**	**41,618,309**	**9,858,047**	**40,318,663**	**11,018,008**
Total outpatient visit costs	**36,864,780**	**34,837,939**	**2,026,841**	**34,796,642**	**2,068,138**
All-cause acute otitis media	36,365,002	34,606,592	1,758,409	34,606,592	1,758,409
Pneumococcal pneumonia cases	478,032	221,280	256,752	181,780	296,252
Pneumococcal meningitis	2676	1239	1437	1018	1659
Pneumococcal NPNM	19,069	8827	10,242	7251	11,818
Total inpatient admission costs	**8,364,008**	**3,871,686**	**4,492,322**	**3,180,560**	**5,183,448**
Pneumococcal pneumonia cases	5,694,398	2,635,928	3,058,470	2,165,394	3,529,004
Pneumococcal meningitis	582,296	269,544	312,752	221,428	360,868
Pneumococcal NPNM	2,087,313	966,214	1,121,099	793,737	1,293,576
Total sequelae costs	**6,247,568**	**2,908,684**	**3,338,884**	**2,341,461**	**3,766,422**
Major sequelae (single)	5,109,347	2,378,762	2,730,585	1,914,879	3,080,231
Major sequelae (multiple)	1,138,221	529,922	608,299	426,582	686,190

Costs are discounted at 3% per year.

perspective, the savings is approximately US$ 10–11 million. The difference is primarily due to the lost productivity attached to cases of meningitis sequelae.

3.3. Cost-effectiveness

Table 8 presents a summary of the costs and cost-effectiveness of both vaccines compared to no vaccine, and the cost-effectiveness of PCV13 compared directly to PCV10. Compared to no vaccine, the cost-effectiveness of PCV10 and PCV13 is estimated to be around US$ 69,000–77,000 per DALY averted from either the government or societal perspective. The WHO Commission on Macroeconomics and Health has previously suggested that a discounted cost per DALY averted of less than 3 × gross domestic product (GDP) per capita should be considered cost-effective [15]. In Croatia, 3 × GDP per capita is approximately US$ 40,000, which means the base-case scenario would not be cost-effective.

Also, the PCV introduction would cost 1 376 $ (PCV13) and 1 164 $ (PCV 10) per case averted.

3.4. Uncertainty analysis

The US$ per DALY averted was most sensitive to the herd effect for children under age 5, the vaccine dose price, and parameters related to pneumococcal meningitis, i.e., incidence, vaccine efficacy, and type coverage.

Figs. 1 and 2 show the results of multivariate and univariate scenario analysis. In most scenarios the vaccine is much more than the cost-effectiveness threshold so is not cost-effective from either the government or societal perspective. Only two scenarios were borderline cost-effective for both vaccines: (1) a scenario largely based on the WHO 2008 pneumococcal estimates for Croatia and (2) a scenario assuming a fairly dramatic drop in the price of the vaccine over the period.

Table 9 shows the results of a threshold analysis. This shows that both vaccines would need to be priced at around US$ 20 per dose to be considered cost-effective (i.e., less than US$ 40,000). This also optimistically includes the assumption of a gradual decrease in the dose price over time. With base-case assumptions, PCV10 would be more cost-effective than PCV13, despite the much higher serotype coverage associated with PCV13 and the assumption that both PCV10 and PCV13 have equivalent effectiveness against AOM. Thus, the difference in price is a more influential factor. According to the threshold analysis the price at which vaccine becomes cost-saving is US$ 2,5 and "higly cost-effective",using the treshold of 1 × per capita GDP, US$ 3,5, from governmental perspective, with slight differences whether PCV 10 or PCV 13 is evaluated.

4. Discussion

This study assessed whether introduction of either PCV10 or PCV13 would be cost-effective in Croatia. Results show that based on the estimated health and economics benefits in children alone, introducing either vaccine into the immunization program is not likely to be cost-effective. In conducting the study we faced some uncertainties that limit the interpretation of the results. The price of introducing the vaccines into the immunization program was the primary uncertainty; it was not possible to obtain reliable estimates of vaccine price. In the analysis, a price of US$ 20 per dose of vaccine, with a gradual decrease each year, would be cost-effective in a base scenario for both vaccines. In our base scenario, PCV10 was more cost-effective than PCV13. However, there are important uncertainties around the price and effectiveness of both vaccines, and our analysis suggests there is insufficient evidence to warrant a significant difference in the price of the two. The second uncertainty relates to the disease burden; passive population-based surveillance is likely to underestimate the pneumococcal disease burden, either by not reporting cases, not testing them, or failing to detect them in the laboratory. This bias is common for all types of passive surveillance. Pneumonias may be underestimated also by misclassification. In addition, there are several challenges in identifying the etiology of meningitis, e.g., the capacity of hospitals to collect and handle specimens during off-work hours or the use of antibiotics prior to collecting specimens. For example, the incidence used

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Table 8
Discounted cost-effectiveness of PCV (20 cohorts vaccinated over the period 2014-2033) All costs are presented in 2014 US $.

	PCV10		PCV13	
	Government perspective	Societal perspective	Government perspective	Societal perspective
Cost-effectiveness compared to no vaccine				
Net cost of vaccine introduction	**42,206,050**	**38,420,300**	**49,233,621**	**45,001,682**
Costs of vaccine introduction	48,278,347	48,278,347	56,019,690	56,019,690
Health service costs avoided	6,072,297	9,858,047	6,786,069	11,018,008
DALYs averted	**559**	**559**	**643**	**643**
YLDs averted—DALYS due to morbidity	120	120	136	136
YLLs averted—DALYs due to mortality	440	440	507	507
US$ per DALY averted	**75,467**	**68,698**	**76,557**	**69,977**
Cost-effectiveness of PCV13 compared to PCV10				
Net cost of vaccine introduction	–	–	**7,027,571**	**6,581,382**
Costs of vaccine introduction	–	–	7,741,343	7,741,343
Health service costs avoided	–	–	713,772	1,159,961
DALYs averted	–	–	**84**	**84**
YLDs averted—DALYS due to morbidity	–	–	16	16
YLLs averted—DALYs due to mortality	–	–	68	68
US$ per DALY averted	–	–	**83,830**	**78,507**
Cost-effectiveness threshold				
1 × GDP per capita (2012)—WHO threshold for 'highly cost-effective'	13,530	13,530	13,530	13,530
3 × GDP per capita (2012)—WHO threshold for 'cost-effective'	40,590	40,590	40,590	40,590

Costs and DALYs are discounted at 3% per year.

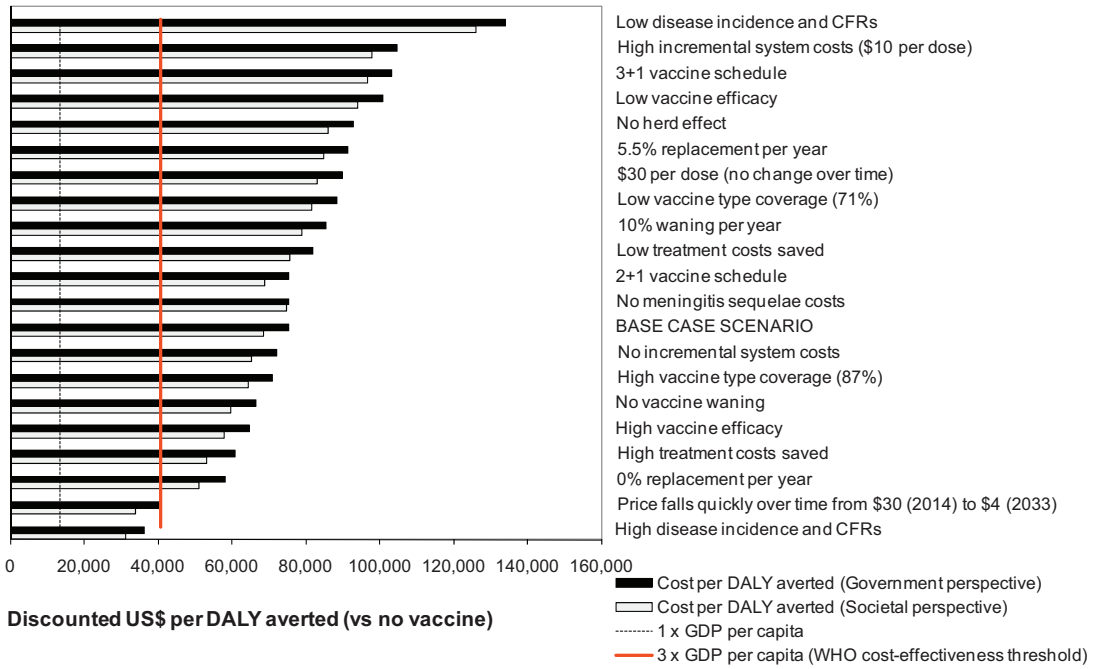

Fig. 1. US$ per DALY averted for base case PCV10 scenario and alternative 'what-if' scenarios: government perspective and societal perspective.

Table 9
Two-way sensitivity analysis evaluating PCV dose price, and the three dose vaccine efficacy of PCV10 against all-cause AOM, All costs are presented in 2014 US $.

		Vaccine efficacy against all-cause AOM				
		PCV13	PCV10			
		6%	6%	12%	18%	24%
Price per dose	**$5**	4331	6257	3603	1078	cost savings
	$10	16,369	20,099	17,098	14,244	11,526
	$15	28,407	33,941	30,594	27,410	24,378
	$20	40,444	47,783	44,089	40,576	37,230
	$25	52,482	61,625	57,585	53,742	50,082
	$30	64,520	75,467	71,080	66,908	62,934
	$35	76,557	89,309	84,576	80,073	75,786

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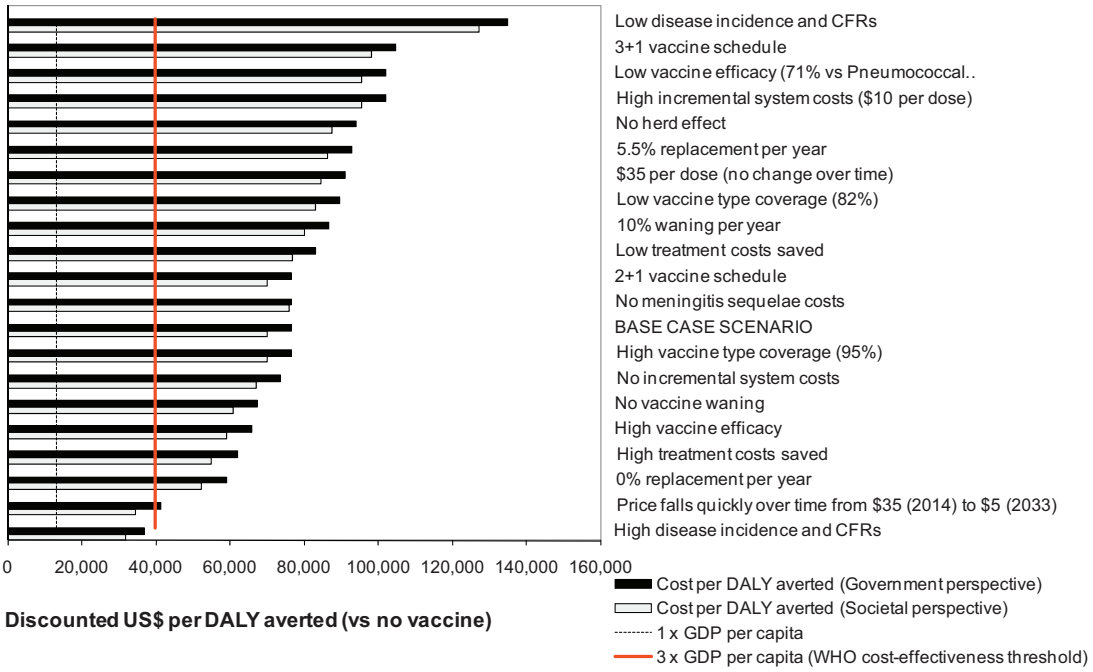

Fig. 2. US$ per DALY averted for base case PCV13 scenario and alternative 'what-if' scenarios: government perspective and societal perspective.

for meningitis is based on reports where only 50% of etiology of bacterial meningitis was diagnosed. Similarly, deaths due to pneumococcal may be underestimated because children may have died prior to collecting a specimen for laboratory confirmation. Our scenario analysis with higher incidence for each disease showed that the introduction of PCV would be borderline cost-effective (based on benefits in children alone), so this is a very relevant limitation to consider.

TRIVAC model was initially developed to help facilitate a decision-support process in countries with limited technical capacity and data quality, i.e., low- and middle-income countries. In this context, disease mortality is typically higher and vaccine prices lower, so often very conservative assumptions (e.g. no herd effect, low vaccine efficacy) will tend to suggest that introducing a vaccine will be cost-effective. This is the first application of the TRIVAC model in a high-income country. In this context, mortality is much lower and vaccine prices are higher, so disease morbidity and associated costs of treatment are more influential. In addition, the threshold for what is considered cost-effective might be lower than the 3 × GDP threshold commonly used in low- and middle-income settings. For example, in England and Wales, the cost-effectiveness threshold is around 1 × GDP per capita. In these circumstances, a vaccine is less likely to be cost-effective based on conservative assumptions alone and there is a greater responsibility to make the base case as realistic as possible, accounting for potential biases. Positive indirect effects, such as herd immunity, should be included to make the base case scenario more realistic, and equally, negative indirect effects, such as serotype replacement, should be included to avoid over-stating the case for vaccination. Our analysis focused entirely on children under age 5; therefore, we are likely to have underestimated to the true benefit of the vaccine in older age groups (due to the herd effect). This would make the results of the cost-effective analysis more favorable to the vaccine. Further analyses should therefore be conducted to estimate the health and economic burden of pneumococcal disease in older age groups, and to assess the influence on cost-effectiveness results when short-term and long-term indirect effects are included for older individuals. This was beyond the scope of the model and this initial study.

5. Conclusion

Based on estimated health and economic benefits in children alone, PCV is unlikely to be cost-effective in Croatia. There is insufficient evidence to warrant a significant difference in the price of the two available vaccines and both vaccines would need to be priced at less than US$ 20 per dose to be considered cost-effective. Further analyses should be conducted to assess the influence on cost-effectiveness results when indirect effects are included for older individuals.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgments

The authors would like to thank the members of multidisciplinary team for their time and valuable contributions: Mario Šekerija, Romana Katalinić, Marina Lichter Štajduhar, and Đurđa Španović. The authors would also like to thank Liudmila Mosina, Viktor Galayda, Anushua Sinha, and Aude Bruyas for their support in implementing the project.

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Vaccine 33S (2015) A219–A226

Contents lists available at ScienceDirect

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Cost-effectiveness of pneumococcal conjugate vaccination in Georgia

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ARTICLE INFO

Keywords:
Georgia
Cost-effectiveness analysis
Pneumococcal conjugate vaccine
Decision-making process
Evidence-based medicine

ABSTRACT

Objective: Financial support from the Global Alliance for Vaccines and Immunization (GAVI) to introduce the 10-valent pneumococcal conjugate vaccine (PCV10) into the routine childhood immunization schedule in Georgia is ending in 2015. As a result, the Interagency Coordination Committee (ICC) decided to carry out a cost-effectiveness analysis to gather additional evidence to advocate for an appropriate evidence-based decision after GAVI support is over. The study also aimed to strengthen national capacity to conduct cost-effectiveness studies, and to introduce economic evaluations into Georgia's decision-making process.

Methodology: A multidisciplinary team of national experts led by a member of the ICC carried out the analysis that compared two scenarios: introducing PCV10 vs no vaccination. The TRIVAC model was used to evaluate 10 cohorts of children over the period 2014–2023. National data was used to inform demographics, disease burden, vaccine coverage, health service utilization, and costs. Evidence from clinical trials and the scientific literature was used to estimate the impact of the vaccine. A 3 + 0 schedule and a vaccine price increasing to US$ 3.50 per dose was assumed for the base-case scenario. Alternative univariate and multivariate scenarios were evaluated.

Results: Over the 10-year period, PCV10 was estimated to prevent 7170 (8288 undiscounted) outpatient visits due to all-cause acute otitis media, 5325 (6154 undiscounted) admissions due to all-cause pneumonia, 87 (100 undiscounted) admissions due to pneumococcal meningitis, and 508 (588 undiscounted) admissions due to pneumococcal non-pneumonia and non-meningitis (NPNM). In addition, the vaccine was estimated to prevent 41 (48 undiscounted) deaths. This is equivalent to approximately 5 deaths and 700 admissions prevented each year in Georgia. Over the 10-year period, PCV10 would cost the government approximately US$ 4.4 million ($440,000 per year). However, about half of this would be offset by the treatment costs prevented. The discounted cost-effectiveness ratio was estimated to be US$ 1599 per DALY averted with scenarios ranging from US$ 286 to US$ 7787.

Discussion: This study led to better multi-sectoral collaboration and improved national capacity to perform economic evaluations. Routine infant vaccination against *Streptococcus pneumoniae* would be highly cost-effective in Georgia. The decision to introduce PCV10 was already made some time before the study was initiated but it provided important economic evidence in support of that decision. There are several uncertainties around many of the parameters used, but a multivariate scenario analysis with several conservative assumptions (including no herd effect in older individuals) shows that this recommendation is robust. This study supports the decision to introduce PCV10 in Georgia.

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1. Introduction

Georgia has faced civil conflicts and economic and social decline since it gained independence from the Soviet Union in 1991. However, over the past decade, the socio-economic situation has improved due to substantial economic and social reforms. While

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http://dx.doi.org/10.1016/j.vaccine.2014.12.070
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economic growth was adversely affected by the August 2008 conflict, growth rebounded again in 2010 and the World Bank now classifies Georgia as a lower middle-income country. Similarly, over the last 10 years (2002–2012) the infant mortality rate was cut by nearly half, dropping from 20.1 to 10.8 deaths per 1000 live births, according to national health statistics, and from 23.6 to 12.6 deaths per 1000 live births, according to vital statistics.

Among the main causes of infant deaths are diseases of the respiratory system, certain conditions originating in the perinatal period, infectious and parasitic diseases, congenital malformations, and external causes such as accidents, injuries, and poisoning. The highest proportion of child morbidity is related to respiratory system diseases. Two efficacious and safe pneumococcal conjugate vaccines (PCV) are currently available to help reduce mortality and morbidity due to pneumonia, meningitis, and other invasive diseases caused by *Streptococcus pneumoniae* (Spn). Both vaccines can currently be procured with the financial support of the Global Alliance for Vaccines and Immunization (GAVI), but the support ends December 2015 and the government will then bear the total cost of the program. Georgia had planned to introduce the 10-valent pneumococcal conjugate vaccine (PCV10) in 2013 but due to healthcare system reorganization and the late introduction of a rotavirus vaccination (RV), a decision was made to postpone introducing PCV until 2014. Therefore, in consultation with the World Health Organization (WHO) Regional Office for Europe, the Interagency Coordination Committee (ICC), which is the national advisory committee on immunization, decided to conduct a cost-effectiveness analysis (CEA) on the introduction of PCV10 with support from the ProVac International Working Group (IWG). The aim of the study was to inform the government about the economic and epidemiological impact of introducing PCV10. A multidisciplinary team of national experts from several organizations (including and led by a member of the ICC), was established and met regularly to collect and review the best available national data. The team conducted the CEA to evaluate whether or not introduction of PCV10 would be cost-effective compared to no introduction, and through this process, to decide whether or not to advocate for an appropriate evidence-based decision after GAVI support has ended.

2. Methods

The ProVac Initiative was begun in the Americas by the Pan American Health Organization (PAHO) and during a two-year pilot phase, it was expanded to other regions through the ProVac IWG [1]. Georgia was supported by the Agence de Médecine Préventive (AMP), an implementing partner of the ProVac IWG, in collaboration with WHO Europe. The TRIVAC decision support model, version 2.0, was used. This is an internationally recognized transparent Excel®-based model, described in detail elsewhere [2]. The parameters of the model required collection of data that included demography, burden of disease, health services utilization and costs, vaccine coverage, vaccine efficacy, and vaccination program costs.

2.1. Analytic framework

The analysis evaluated the costs and benefits of two alternative situations: (1) universal introduction of the PCV10 vaccination into the Georgian National Immunization Program and (2) no PCV vaccination. Ten consecutive births cohorts were modeled over the period 2014–2023. Following WHO recommendations, a 3% discount rate was used for both costs and health outcomes [18]. We assumed that PCV10 would be administered in three primary doses without a booster dose (3p + 0). Realistic estimates of vaccination coverage and timeliness were based on estimates available for DTP vaccination. Four clinical outcomes related to *S. pneumoniae* were included: (1) outpatient visits due to all-cause acute otitis media (AOM), (2) inpatient admissions due to all-cause pneumonia, (3) inpatient admissions due to pneumococcal meningitis, and (4) inpatient admissions due to pneumococcal non-pneumonia non-meningitis (NPNM) invasive disease. It was the opinion of expert members of the team, that all cases of severe pneumonia, pneumococcal meningitis and pneumococcal NPNM would be admitted to a hospital in Georgia; as a result, it was practical and reasonable to focus on admissions rather than all cases in the community. A government perspective was taken, so no household costs were considered. In Georgia, the majority of providers are private and costs of treatment are partly or fully covered by the government. Three types of providers were taken into account: primary care providers (private individual entrepreneurs, who receive salaries from government), secondary care (polyclinics), and tertiary care (hospitals). All three providers handle outpatient visits for AOM, but only hospitals (tertiary care) handle inpatient admissions for invasive pneumococcal disease.

2.2. Demography

The National Statistics Office of Georgia (Geostat) provided all demographic data [4]. The number of births for 2012 was 56,890. In the base-case scenario, a declining trend (based on the projection of the United Nations Population Division [UNPOP]) was applied to this figure to estimate the number of births in future years [5]. To take into consideration the uncertainty around the assumption of a declining population, a second scenario with no year-over-year trend was also evaluated. Estimates on mortality rates for infants and children younger than 5 years of age were provided by the National Centre for Disease Control and Public Health (NCDC). In 2012, 14 of every 1000 live births died before the age of 1; 16 of every 1000 live births died before the age of 5. The life expectancy for those born in 2012 was assumed to be 75. This was used to estimate the number of life-years lost and disability-adjusted life-years (DALY) due to mortality related to *S. pneumoniae*. The UNPOP projections for Georgia were applied to these estimates to generate a projection for the period 2014–2023 [3].

2.3. Burden of disease

Data concerning AOM and pneumonia were based on national statistical reports published in the statistical yearbook 2012 [6]. Two types of reports were available to estimate AOM incidence; therefore, two estimates of incidences were calculated. Both report types gather data from health facilities based on the International Classification of Diseases (ICD) 10th revision codes. However, one is from the Tbilisi-level case-based reporting system and the other one is from the national reporting system of notifiable diseases. These two reporting systems were used to estimate a Tbilisi annual incidence of 1695 cases of AOM per 100,000 under 5 years old and a national annual incidence of 3073 per 100,000 under 5 years. The more conservative Tbilisi incidence was used in the base-case analysis; the national incidence was used in the scenario analysis. The national-level reporting was sufficient to estimate the incidence of pneumonia admissions, 1603 per 100,000 under 5 years old. For pneumococcal meningitis and pneumococcal NPNM, no national data were available; instead, WHO 2008 estimates for Georgia were used [7], with annual incidences, respectively, of 10 and 62 per 100,000 under 5 years.

Data on the number of pneumonia deaths was based on the national reporting system. A case fatality ratio (CFR) was calculated by dividing the number of pneumonia deaths by the estimated number of pneumonia admissions. The CFR of 25% for

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Table 1
Input parameters for estimating disease burden.

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Annual incidence per 100,000 aged 1–59 m				
All-cause acute otitis media	1695	1695	3073	National reporting system
All-cause pneumonia admissions	1603	1603	1603	Estimate
Pneumococcal meningitis admissions	10.5	5.8	17.4	GBD 2000
Pneumococcal NPNM admissions	61.5	33.8	102.1	GBD 2000
% Case fatality ratios (CFRs) in ages 1–59 m[a]				
All-cause pneumonia admissions	0.20%	0.16%	0.24%	NCDC Georgia
Pneumococcal meningitis admissions	25.0%	12.96%	29.87%	Sentinel surveillance (NCDC Geo)
Pneumococcal NPNM admissions	2.6%	2.33%	5.14%	GBD 2000 (adjusted to 2014)
% Sequelae in pneumococcal meningitis survivors				
% Major sequelae (single)	20.2%	–	–	[5]
% Major sequelae (multiple)	4.5%	–	–	[5]
Disability weight for DALY calculations				
All-cause acute otitis media	0.02	–	–	WHO GBD 1990
All-cause pneumonia admissions	0.28	–	–	WHO GBD 1990
Pneumococcal meningitis admissions	0.62	–	–	WHO GBD 1990
Pneumococcal NPNM admissions	0.28	–	–	Assumption (Griffiths PhD, page 107)
% Major sequelae (single)	0.24	–	–	Assumption (Griffiths PhD, page 107)
% Major sequelae (multiple)	0.63	–	–	Assumption (Griffiths PhD, page 107)
Mean duration of illness (in days)				
All-cause acute otitis media	6	–	–	Expert opinion (2)
All-cause pneumonia admissions	6	–	–	Expert opinion (2)
Pneumococcal meningitis admissions	10	–	–	Expert opinion (2)
Pneumococcal NPNM admissions	6	–	–	Expert opinion (2)
Age distribution of disease cases and deaths				
<3 m	9.4%	–	–	WHO IVR Schedule Report
3–5 m	13.0%	–	–	WHO IVR Schedule Report
6–8 m	13.3%	–	–	WHO IVR Schedule Report
9–11 m	12.2%	–	–	WHO IVR Schedule Report
12–23 m	32.5%	–	–	WHO IVR Schedule Report
24–35 m	13.3%	–	–	WHO IVR Schedule Report
36–47 m	4.7%	–	–	WHO IVR Schedule Report
48–59 m	1.6%	–	–	WHO IVR Schedule Report

[a] In the absence of vaccination, CFRs are assumed to decline in each successive birth cohort in line with the general trend in mortality under 5 years of age. This is done by assuming that the fraction of deaths under age 5 that are caused by the disease remains fixed over time.

pneumococcal meningitis was based on estimates from sentinel surveillance for bacterial meningitis. The CFR for pneumococcal NPNM was based on the WHO estimate for Georgia. No national data were available on the proportion of children with long-term sequelae following meningitis; instead, global estimates from Edmond et al. were used [8]. In order to estimate DALYs, each syndrome was assigned a disability weight provided by the WHO global burden of disease (GBD) [3]. The age distribution of pneumococcal disease was based on estimates for Europe by Sanderson et al. [18] and mean duration of illness was estimated after consulting national experts.

2.4. *Health services cost related to* S. pneumoniae *(Spn)*

Only government expenditures were taken into consideration. Based on data from Ministry of Health (MoH) state health programs, the weighted average cost of a visit for AOM was equivalent to US$ 11.84. This sum was calculated from two costs: professional

Table 2
Input parameters for estimating health service utilization and costs (all costs are presented in US $) 2013.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Outpatient visits				
Government cost per outpatient visit[a]				
All-cause acute otitis media	$12	$9	$14	MoH (mix of inpatient and outpatient)
Inpatient admissions				
Government cost per inpatient admission[b]				
All-cause pneumonia admissions	$301	$241	$361	MoH
Pneumococcal meningitis admissions	$494	$395	$593	MoH
Pneumococcal NPNM admissions	$800	$640	$960	MoH

[a] Government costs per outpatient visit for AOM included professional services and a lab exam. The costs of AOM visits were also inflated to account for some of these cases being hospitalized. Outpatient visits are distributed as follows: 50% polyclinic 10% hospital, 40% private individual entrepreneur (PIE). The cost presented is the weighted average of the provider-specific costs.
[b] Government costs per inpatient admission include the cost per bed-day multiplied by the expected length of stay, the cost of disease-specific drugs and diagnostics. Inpatient admissions are 100% hospital.

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Table 3
Input parameters for estimating PCV vaccine coverage and timeliness.

Parameter (m)	Estimate (%)	Scenarios		Source(s)
		Low	High	
Coverage of DTP1 by age in year 2014 (proxy for PCV doses given with DTP1)				
3	69.9	–	–	www.provac-olives.com, [16]
6	86.4	–	–	www.provac-olives.com, [16]
9	91.6	–	–	www.provac-olives.com, [16]
12	93.9	–	–	www.provac-olives.com, [16]
24	97.8	–	–	www.provac-olives.com, [16]
Coverage of DTP2 by age in year 2014 (proxy for PCV doses given with DTP2)				
3	6.7	–	–	www.provac-olives.com, [16]
6	70.5	–	–	www.provac-olives.com, [16]
9	82.4	–	–	www.provac-olives.com, [16]
12	87.0	–	–	www.provac-olives.com, [16]
24	94.3	–	–	www.provac-olives.com, [16]
Coverage of DTP3 by age in year 2014 (proxy for PCV doses given with DTP3)				
3	0.1	–	–	www.provac-olives.com, [15,16]
6	41.4	–	–	www.provac-olives.com, [16]
9	68.0	–	–	www.provac-olives.com, [16]
12	78.9	–	–	www.provac-olives.com, [16]
24	91.4	–	–	www.provac-olives.com, [16]

Coverage projections over the period 2014–2023 were estimated by assuming that PCV will achieve the same coverage and timeliness as RV in the early period of introduction, and the same coverage as DTP thereafter.

services and lab exams. In addition, the costs of AOM-related visits were inflated to reflect the fact that some of the AOM cases are indeed hospitalized and incur substantial cost. The visit cost was assumed to be equal for all three types of providers. According to the MoH, the cost of one hospital admission for pneumonia was estimated at US$ 301.18, for pneumococcal meningitis at US$ 494.12, and for pneumococcal NPNM at US$ 800.00. Sequelae costs borne by the government were not considered due to lack of data.

2.5. Vaccine coverage, efficacy, and other impact assumptions

Coverage of PCV1 over the 2014–2023 period was assumed to be 67%, 75%, 87%, 90%, 94%, 96%, and 98% thereafter. This was based on data on DTP immunization coverage for 2013 obtained from the national immunization reporting system and provided by the NCDC immunization department. Rotavirus vaccine coverage was used to inform the estimates of PCV coverage in the first few years, as this vaccine was introduced relatively

Table 4
Input parameters for estimating PCV10 program costs.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Vaccine dose price projection				
2014	$0.70	–	–	MoH assumption
2015	$1.40	–	–	MoH assumption
2016	$2.10	–	–	MoH assumption
2017	$2.80	–	–	MoH assumption
2018	$3.50	–	–	MoH assumption
2019	$3.50	–	–	MoH assumption
2020	$3.50	–	–	MoH assumption
2021	$3.50	–	–	MoH assumption
2022	$3.50	–	–	MoH assumption
2023	$3.50	–	–	MoH assumption
Other vaccine dose costs				
International handling (% of vaccine price)	0.0%	–	–	
International delivery (% of vaccine price)	5.0%	–	–	Freight costs from GAVI proposal
Wastage (% of doses discarded, etc)[a]	10.0%	–	–	Estimate—measles vaccine
Safety box cost (80 syringes per box)				
Price of each safety box	$0.55	–	–	NCDC Geo
International handling (% of vaccine price)	0.0%	–	–	
International delivery (% of vaccine price)	10.0%	–	–	Freight costs from GAVI proposal
Wastage (% of doses discarded, etc)[a]	5.0%	–	–	NCDC Geo
Incremental system costs of introduction[b]				
Incremental system cost per dose	$0.63	–	–	Calculations based on cMYP Georgia 2010–2015

[a] The % wastage is converted into a factor [1/(1−% wastage)] which is multiplied by the expected number of doses required to meet the anticipated level of coverage.
[b] Estimated incremental system costs per-dose spending was estimated to be US$ 0.63. The operational launch cost was estimated to be US$ 1.06 in the first year, with costs of US$ 0.60 thereafter.

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Table 5
Input parameters for estimating the health impact of PCV10.

Parameter	Estimate (%)	Scenarios		Source(s)
		Low (%)	High (%)	
Vaccine efficacy vs all-cause AOM outpatient visits				
Dose 1	17.0	10.5	34.0	[14] (Mahon—20%, Whitney 2006 ratio)
Dose 2	30.9	19.1	44.3	[14] (Mahon—20%, Whitney 2006 ratio)
Dose 3	33.6	20.8	44.3	[9]
Vaccine efficacy vs all-cause pneumonia admissions				
Dose 1	14.4	14.4	20.1	[14] (Mahon—20%, Whitney 2006 ratio)
Dose 2	24.1	24.1	26.2	[14] (Mahon—20%, Whitney 2006 ratio)
Dose 3	26.2	19.0	33.0	[7] (meta analysis)
Vaccine efficacy vs vaccine type pneumococcal meningitis/NPNM				
Dose 1	41.0	31.9	69.2	[14] (Mahon—20%, Whitney 2006 ratio)
Dose 2	74.5	58.0	90.0	[14] (Mahon—20%, Whitney 2006 ratio)
Dose 3	81.0	63.0	90.0	[12]
% Vaccine serotype coverage				
Pneumococcal meningitis admissions	81.0	78.0	82.0	[19]
Pneumococcal NPNM admissions	81.0	78.0	82.0	[19]
Other vaccination impact assumptions				
% Relative coverage[a]	95	80	100	[17]
% Decrease in dose efficacy per yr[b]	5.0	0.0	5.0	Assumption
% Contribution of herd effect in <5 yrs[c]	120	100	120	Reingold/CDC (based on PCV7)
Decline in vaccine type coverage/yr[d]	5.5	0.0	5.5	Assumption

[a] Relative coverage is the coverage of those at risk of getting the disease (i.e., effective coverage) compared to coverage of the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.
[b] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 m, 4–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.
[c] Rather than endogenous modeling of transmission dynamics, the % of direct protection for <5 yrs is multiplied by a herd effect multiplier (e.g., 120%) to give the % of total protection in the cohort of interest <5 yrs. This excludes any herd effect in individuals aged 5 yrs+ and is therefore very conservative.
[d] Vaccine type disease replacement is handled by reducing the expected vaccine type coverage in successive vaccinated cohorts by a fixed % each year, thus reducing overall expected impact of the program in each successive vaccinated cohort by a similar amount. Thus, for a given vaccinated cohort, the % vaccine type coverage is equal to: $[T(1-R)\times N]$ where, T = % of disease caused by vaccine types in the year of vaccine introduction, R = % reduction in vaccine type coverage per year following vaccine introduction, and N = number in the sequence of vaccinated birth cohorts.

recently. Estimated coverage of DTP doses 1, 2, and 3 was used as a proxy for the expected drop-out rate between PCV doses 1, 2, and 3. The timeliness of PCV doses 1, 2, and 3 was based on estimates for the European region by Clark and Sanderson [18].

Two studies were considered for PCV10 vaccine efficacy against all-cause AOM. One was from Czech and Slovak Republic [9]; the second was a study nested [10] within a recent clinical trial from Finland [11]. The evidence from the study in the Czech and Slovak Republic, 33.6% (20.8%; 44.3%), was assumed for the base case. For

Table 6
Discounted health benefits (10 cohorts vaccinated over the period 2014–2023).

	No vaccine	PCV10	Averted
	(Status quo)	With vaccine	
Total outpatient visits	34,444	27,274	7170
All-cause acute otitis media	34,444	27,274	7170
Total inpatient admissions	34,042	28,122	5919
All-cause pneumonia admissions	32,578	27,253	5325
Pneumococcal meningitis admissions	213	127	87
Pneumococcal NPNM admissions	1250	742	508
Total deaths <5 yrs	137	96	41
All-cause pneumonia admissions	59	50	10
Pneumococcal meningitis admissions	49	29	20
Pneumococcal NPNM admissions	29	17	12
Total children with permanent disability	41	24	17
Sequelae group A	33	20	14
Sequelae group B	7	4	3
DALYs Lost	4744	3305	1438
YLDs—DALYS due to morbidity	666	458	208
YLLs—DALYs due to mortality	4078	2848	1230

Health benefits are discounted at 3% per year.

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Table 7
Discounted economic benefits (10 cohorts vaccinated over the period 2014–2023).

	No vaccine	PCV10	Averted
	(Status quo)	With vaccine	
Total Gov. health service costs[a]	$11,325,355	$9187,383	$2137,972
Total outpatient visit costs	$407,915	$323,006	$84,909
All-cause acute otitis media	$407,915	$323,006	$84,909
Total inpatient admission costs	$10,917,440	$8864,377	$2053,063
All-cause pneumonia admissions	$9811,714	$8208,083	$1603,631
Pneumococcal meningitis admissions	$105,341	$62,524	$42,817
Pneumococcal NPNM admissions	$1000,385	$593,770	$406,615

Costs are discounted at 3% per year.
[a] Government perspective includes bed days covered by the government and disease-specific diagnostic costs borne by the government at the following health providers: polyclinic, hospital and private individual entrepreneur (PIE).

efficacy against all-cause pneumonia, 26.2% efficacy was assumed based on a meta-analysis of the fraction of radiological pneumonia (proxy for pneumonia admissions) prevented in clinical trials in California, the Philippines, and South Africa [7]. The estimate from the Gambian trial was much higher than in the other three trials and since it was not considered relevant to the Georgian context, it was excluded. For pneumococcal meningitis and NPNM, we used 81% vaccine efficacy based on the Cochrane review [12] and we considered the uncertainty around these estimates in the scenario analysis.

There is a good deal of uncertainty around assumptions for herd effects, serotype replacement, waning vaccine-induced protection, and relative coverage (i.e., the extent to which high-risk children are covered by the vaccine). We therefore varied these assumptions in scenario analyses to assess their influence on the cost-effectiveness result. For the base case, we assumed 95% relative coverage by dividing DTP2 coverage in the poorest quintile by DTP2 coverage in the entire birth cohort. Overall program coverage was then multiplied by 95% to provide a more realistic estimate of coverage for children at the highest risk of mortality from invasive pneumococcal disease. The 95% value was based on estimates from Demographic and Health Surveys (DHS) in other middle-income countries [16]. We assumed that the direct effectiveness in children younger than 5 could be multiplied by 120% to reflect the observed herd effect in this age group with PCV7 in the USA [13].We did not consider herd effects in older age groups. Waning vaccine-induced protection and type replacement were assumed to be 5% and 5.5% per year, respectively, but these were both varied in scenario analyses (Tables 1–3).

Table 8
Discounted cost-effectiveness of PCV (10 cohorts vaccinated over the period 2014–2023).

	PCV10
	Government perspective
Cost-effectiveness compared to no vaccine	
Net cost of vaccine introduction	$2300,242
Costs of vaccine introduction	$4438,214
Health service costs avoided	$2137,972
DALYs averted	1438
YLDs averted—DALYS due to morbidity	208
YLLs averted—DALYs due to mortality	1230
US$ per DALY averted	$1599
Cost-effectiveness threshold	
1 × GDP per capita (2012)—WHO threshold for 'highly cost-effective'	$3508
3 × GDP per capita (2012)—WHO threshold for 'cost-effective'	$10,525

Costs and DALYs are discounted at 3% per year.

2.6. Vaccination program cost

To estimate the price of the vaccine and injection supplies, we used NCDC data and the country GAVI proposal for introducing PCV. In the base-case scenario we used a per-dose vaccine price of US$ 3.50, which was then adjusted for the initial years because national co-financing is progressive (see Table 4). The additional freight cost was taken at 5% of the vaccine price. Based on the NCDC data, the wastage rate for the two-dose vaccine presentation was assumed to be 10%. Prices for safety boxes and administering syringes were also considered.

The incremental system cost per dose for introducing PCV vaccine was estimated based on the country comprehensive multi-year plan (cMYP) 2010–2015. The per-dose spending was estimated to be US$ 0.63. For the first year of introduction, the team calculated the difference between expected costs in 2012 and in 2013; the only difference between these two years was the expected introduction of PCV10. This cost was divided by the number of doses (with a 3 + 0 schedule) expected in the first year of introduction. Using this data, we estimated the operational cost of the launch to be US$ 1.06 in the first year and US$ 0.60 in subsequent years (Table 5).

2.7. Scenario analysis

A scenario analysis was performed to evaluate the uncertainty of results due to the shortage of reliable national data. The scenarios tested were: (1) high and low burden of disease (i.e., incidence and deaths), (2) no change in the number of births over time, (3) high and low vaccine efficacy, (4) waning vaccine-induced protection, (5) high and low health services costs (i.e., outpatients and inpatients), (6) no discount rate, (7) worst case (unfavorable for introduction), (8) best case (favorable for introduction), and (9) high and low coverage. We also considered a scenario in which no adjustment was made for herd effects or type replacement.

3. Results

3.1. Without vaccination

With no introduction of PCV10 over the period 2014–2023, we estimate 34,444 (39,838 undiscounted) outpatient visits due to all-cause AOM, 32,578 (37,680 undiscounted) admissions due to all-cause pneumonia, 213 (247 undiscounted) admissions due to pneumococcal meningitis, and 1250 (1446 undiscounted) admissions due to pneumococcal NPNM. In addition, there would be 4744 discounted DALYs and US$ 11.33 million discounted health service costs borne by the government.

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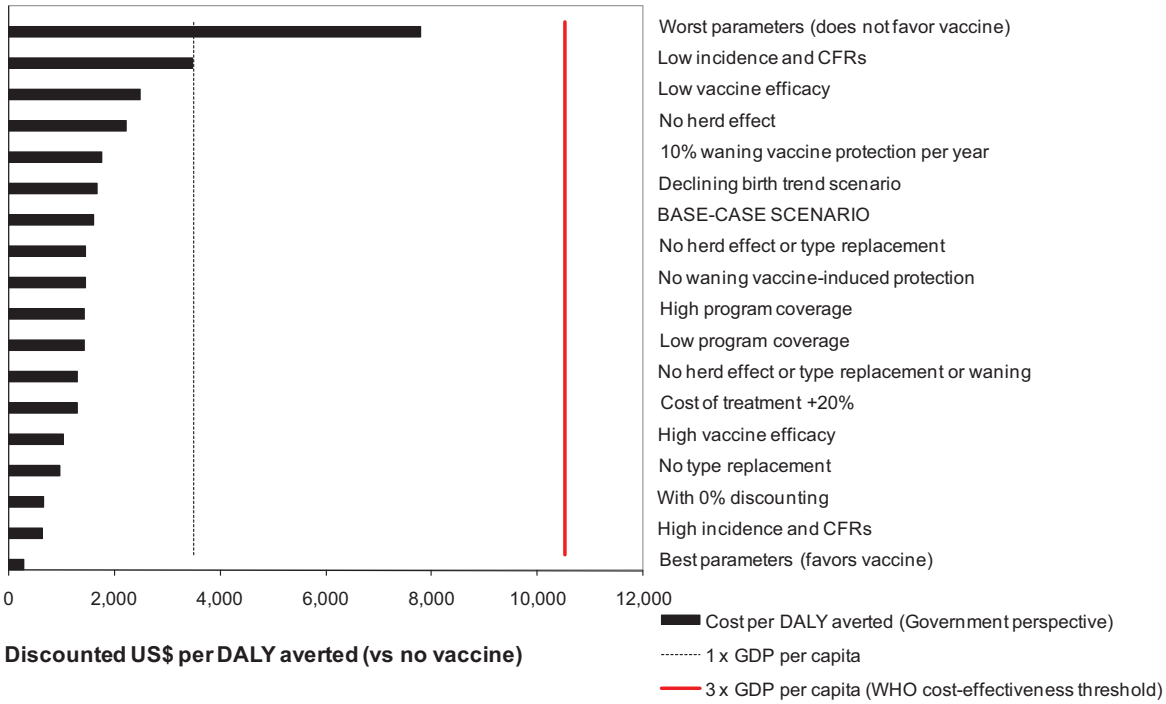

(1) Favorable scenario = High annual incidence rates, high CFRs, low vaccine price projections, low systems costs, high efficacy parameters, 0% waning in dose efficacy, high serotype coverage parameters, a 125% herd effect multiplier, a high vaccine coverage projection, high inpatient and outpatient costs.

(2) Unfavorable scenario = Low annual incidence rates and CFRs, high vaccine price projections and system costs, low efficacy parameters, a 10% yearly waning in dose efficacy, low serotype coverage parameters, low vaccine coverage projections and low outpatient and inpatient costs.

Fig. 1. US$ per DALY averted for base case PCV10 scenario and alternative 'what-if' scenarios: government perspective. Favorable scenario = high annual incidence rates, high CFRs, low vaccine price projections, low systems costs, high efficacy parameters, 0% waning in dose efficacy, high serotype coverage parameters, a 125% herd effect multiplier, a high vaccine coverage projection, high inpatient and outpatient costs. Unfavorable scenario = low annual incidence rates and CFRs, high vaccine price projections and system costs, low efficacy parameters, a 10% yearly waning in dose efficacy, low serotype coverage parameters, low vaccine coverage projections and low outpatient and inpatient costs.

3.2. *With vaccination*

Clinical benefits expected with the vaccination program for the ten cohorts are summarized in Table 6. In brief, over the period 2014–2023, PCV10 is estimated to prevent 7170 (8288 undiscounted) outpatient visits for all-cause AOM, 5325 (6154 undiscounted) admissions for all-cause pneumonia, 87 (100 undiscounted) admissions for pneumococcal meningitis and 508 (588 undiscounted) admissions for pneumococcal NPNM. In addition, the vaccine is estimated to prevent 41 (48 undiscounted) deaths. This is equivalent to preventing approximately 5 deaths and 700 admissions each year in Georgia (Table 7).

Over the 10-year period, PCV10 would cost the government approximately US$ 4.4 million (US$ 440,000 per year). However, about half of this would be offset by averted treatment costs of approximately US$ 2.14 million. (Of that figure, US$ 1.6 million are averted treatment costs for pneumonia.) The net cost borne by government would be equal to US$ 2.30 million. This amount is derived from the total cost of vaccination minus the savings from averted treatment (Table 8). The incremental cost-effectiveness ratio (i.e., the cost per DALY averted) from governmental perspective is equal to US$ 1599 per DALY averted. According to the WHO recommendation of using the gross domestic product (GDP) per capita as thresholds to interpret this ratio, the introduction of PCV in Georgia is highly cost-effective, which means that taking into account the end of GAVI's support, the intervention is still a valuable investment for the government [15].

All results of the scenario analysis are shown in Fig. 1. Almost all are below the GDP per capita threshold (i.e., highly cost-effective). Even the worst-case scenario, which gathers unfavorable figures of several parameters, still results in a cost-effective intervention. Therefore, from the governmental perspective, the results of this analysis are robust.

4. Discussion

This study assessed the potential impact of introducing the vaccine in terms of health benefits, incremental costs to the immunization program, health system costs averted, and cost-effectiveness of the introduction of the pneumococcal vaccine. These criteria are all relevant to the decision-making process in Georgia. This analysis shows that introduction of PCV10 is likely to be highly cost-effective in Georgia. It also provides evidence about the clinical and economical burden of the *S. pneumoniae* in Georgia, and about the benefit of introducing PCV10 to the national immunization program. The introduction of PCV10 is estimated to cost approximately US$ 4–5 million over a decade, but about half this cost would be offset by savings from reduced hospital admissions and outpatient visits.

This cost-effectiveness analysis is the first country-led economic evaluation of a vaccine in Georgia. Utilization of a transparent model to perform the study made it possible to obtain useful evidence and multiple relevant results. The methodology used to collect data included several experts from different fields and was

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an effective way to produce a snapshot of the current economic and epidemiological burden associated with pneumococcal disease in Georgia.

However, the study faced some limitations. (1) Data on community pneumonia were not available, so no outpatient visits were assumed for pneumonia; this resulted in underestimating the burden of disease. (2) Only expert opinion was available for estimates of parameters such as duration of illness or health service utilization; because no local data were available for sequelae and associated costs, the benefits of vaccination were underestimated. (3) The societal perspective was not explored due to lack of available data and also due to the recent change in the health financing system. (4) Herd immunity effect among people older than 5 years old, especially elderly people, was not modeled although the herd effect is likely to have a significant impact on the cost-effectiveness and would make the result even more favorable. (5) Although global estimates used for incidence of pneumococcal meningitis and NPNM are reasonable placeholders, a good quality national source would be more appropriate.

Nonetheless, as much as possible, many of these limitations were evaluated in the scenario analyses and the fact that the vaccine remained cost-effective despite very conservative assumptions (e.g., no herd effect in older individuals) suggests that the conclusion is robust. In addition, it should also be mentioned that AOM inclusion would improve CE ratio further.

Other benefits of the national study included the identification of important gaps in national data, such as health service utilization and costs, and the increased capacity of the national team to conduct economic evaluations in the future.

5. Conclusion

The decision to introduce PCV10 was already made some time before the study was initiated but this study provides important economic evidence in support of that decision. Not only is it highly cost-effective, it is also likely to prevent approximately 5 child deaths and a substantial number of hospital admissions annually. This analysis also created the opportunity to identify some gaps in national data, especially on health care utilization, for which we relied mainly on expert opinion. It is important to work on the collection of these data. This analysis was a good capacity building process and led to better understanding of cost-effectiveness, better multi-sectorial collaboration and an improved national capacity to perform the economic evaluations. In conclusion, it would be interesting to extend this type of evaluation to other health interventions in order to compare their cost-effectiveness and provide a new source of information for decision-makers.

Acknowledgements

The authors would like to thank Liudmila Mosina from WHO Europe, Dr. Tamara Pilishvili from US CDC, and Dr. Viktor Galayda for fruitful collaboration and their contribution to this study. We would also like to thank Giorgi Kurtsikashvili from WHO CO, and Chris Duggar and Julia Morgan and Add Maes from US CDC for their kind contributions, as well as the team from the NCDC immunization department.

Conflict of interest statement

Authors declare no conflicts of interest for this work. The current manuscript was supported by the ProVac IWG, which is funded entirely by a grant from the Bill & Melinda Gates Foundation (Grant number OPP1032888).

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Vaccine 33S (2015) A227–A232

Contents lists available at ScienceDirect

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Economic analysis of the single-dose immunization strategy against hepatitis A in Argentina

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ARTICLE INFO

Keywords:
Hepatitis A
Single-dose vaccination
Economic analysis
Argentina

ABSTRACT

Background: Vaccination against hepatitis A (HA) was carried out only as part of a limited outbreak control strategy in Argentina until June 2005, when universal immunization in infants was introduced into the national immunization calendar. A single-dose strategy was chosen instead of the standard two-dose schedule used elsewhere. This study aimed to estimate preventive, medical, and non-medical costs related to HA and to compare these costs in the periods before and after mass vaccination.
Methods: A retrospective analysis estimated treatment costs of HA and unspecified hepatitis cases reported to the National Health Surveillance System from 2000 to 2010. Costs related to immunization, fulminant hepatitis (FH), liver transplantation, and death were projected as well. Using a social perspective and a healthcare system perspective, costs in two 5-year periods were compared: 2000–2004 versus 2006–2010. Finally, we evaluated the impact of different discount rates, FH risk, and exclusion of unspecified hepatitis cases in the sensitivity analysis.
Results: Total HA and unspecified hepatitis cases decreased from 157,871 in 2000–2004 to 17,784 in 2006–2010. Medical and non-medical costs decreased from US$11,811,600 and US$30,118,222 to US$1,252,694 and US$4,995,895 in those periods, respectively. Immunization costs increased from US$6,506,711 to US$40,912,132. Total preventive, medical, and non-medical costs decreased from US$48,436,534 to US$47,160,721, representing a 2.6% reduction in total costs between the two periods. When a healthcare system perspective was considered or unspecified hepatitis cases were excluded, total costs were 130.2% and 30.8% higher in 2006–2010 than in the previous period, respectively.
Conclusion: After implementation of the universal single-dose vaccination against HA in infants in Argentina, an impressive decline was observed in HA cases, with a decrease in medical and non-medical costs in the first 5 years. The single-dose strategy, which is simpler and less expensive than the standard two-dose scheme, can be a good alternative for future vaccination policies in other countries where HA is endemic.

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1. Background

Hepatitis A (HA) virus is one of the most frequently reported vaccine-preventable diseases, which affect more than 200 million people annually worldwide [1]. Although different vaccines against HA have demonstrated safety, efficacy, and cost-effectiveness, the high cost and the need for a two-dose schedule may explain their limited use globally [2–5].

Hepatitis A infection has always been endemic in Argentina, but during 2003–2004 there was a country-wide outbreak and disease rates reached 113.3 cases per 100,000 population [6,7]. Vaccination of contacts of index cases was part of the outbreak control strategy at that time, but this approach was not sufficient to control the disease, and the epidemic continued spreading throughout the country. Hepatitis A at that time was the leading cause of fulminant hepatitis (FH) and liver transplantation (LT) in children [8–10].

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http://dx.doi.org/10.1016/j.vaccine.2014.12.077
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In this context, and aiming to reduce the high morbidity and mortality associated with this endemic disease, the National Ministry of Health, in agreement with national experts, decided to introduce a single dose of inactivated hepatitis A vaccine into the regular immunization schedule for all children 12 months of age, beginning in June 2005 [11,12]. A single-dose strategy was chosen based on the high immunologic response that can be achieved in vaccinated individuals 4–6 weeks after the first dose; the predicted long-lasting protection induced by immune memory response; and, finally, the expectation that this strategy would interrupt transmission not only in infants but in other age groups as well, due to the herd protection that has been documented in other countries, at an affordable cost for the country [2–5,13–15].

This vaccination policy, which has continued to the present, has required the use of public economic resources, and this cost should be compared to the benefits generated for society in both epidemiological–clinical and economic terms. The epidemiological–clinical impact of this intervention has been demonstrated through the impressive decline in the post-vaccination period in HA cases and rates, pediatric HA-associated fulminant hepatic failure, and liver transplantation [16–18]. Estimating potential costs averted can help us assess the value of the vaccination strategy as a social investment from an economic standpoint. Therefore, the aim of this study was to estimate preventive, medical, and non-medical costs related to HA from 2000 to 2010 and to compare these costs between the pre- and post-mass vaccination periods.

2. Methods

2.1. General description

We performed a retrospective analysis estimating medical and non-medical costs of hepatitis A and unspecified hepatitis cases reported to the National Health Surveillance System (SNVS), and the immunization program costs, for the period 2000–2010 from a social perspective, which takes into account both medical and non-medical costs, and from a healthcare system perspective, which considered only medical costs [19]. We then compared two 5-year periods in terms of preventive (outbreak control and universal vaccination), medical, and non-medical costs: the period before the adoption of the universal single-dose vaccination approach (2000–2004), and the period after mass HA vaccination of infants was implemented (2006–2010). As the vaccination strategy started in June 2005, medical and non-medical costs were not considered for 2005, and only preventive costs of that year were included in the analysis, and allocated to the post-universal vaccination period .

2.2. Burden of disease

HA cases reported through passive clinical surveillance to the SNVS from 2000 to 2010 were used to estimate direct medical and non-medical (social) costs related to hepatitis A [7]. "Unspecified" hepatitis cases were also included in this analysis as >90% of these cases are presumed to be HA cases, based on the strong epidemiology nexus and similar age distribution [18]. These "unspecified" hepatitis cases represent a 35% of the total number of cases (HA and unspecified hepatitis), according to the SNVS, for the entire period analyzed.

Fulminant hepatitis is an infrequent complication of HA. National studies report a probability between 0.6% and 1.9% that HA cases will develop FH, while data from other countries indicate a lesser probability in the range of 0.1–0.5% [20–24]. In our study we assumed a 0.1% risk in the base case, but considered a higher risk in the sensitivity analysis. We considered the other 99.9% of HA cases as non-fulminant hepatitis (NFH) cases and classified them as non-complicated, cholestatic, prolonged and relapsing, with probabilities of 92.1%, 2.4%, 1.3%, and 4.2%, respectively, based on local reports [20,25]. We assumed that all NFH cases recovered ad integrum. On the other hand, we estimated that 31.2% of FH cases recover without needing LT, 43.0% receive LT, and 25.8% die while waiting for an organ [10].

Regarding post-transplant survival, we assumed a 25.6% mortality rate in the first year after LT based on a national multicenter study. We assumed that after the first year, transplanted individuals had the same survival rate as the general population [17].

2.3. Health resource utilization, medical costs, and non-medical costs

Micro-costing methodology was used. All costs were first estimated in Argentine current pesos (AR$) for each year (2000–2010) and then were converted at 2013 constant prices using the general consumer price index [26]. Finally, we converted all constant prices to US dollars according to the average official exchange rate of the year 2013 (AR$5.49 = US$1) [27].

Medical costs were valued based on regulated lists, agreements with self-administered hospitals, data provided by public hospitals, and the pharmacist workbook (*Vademecum* price list). Cost data from private or social security sources were not available, so only medical costs from the public sector were used in this analysis. National experts were consulted to estimate health resources utilization for NFH and FH. For LT cases, resource utilization and costs were estimated by the National Central Unique Institute for Coordination of Ablation and Implant (INCUCAI), taking into account pre-transplantation diagnostic tests, organ procurement and implantation, first-year monitoring and care, and lifelong annual immunosuppressive therapy.

Non-medical costs, included costs of school absenteeism among children [28,29], lost productive time during illness (based on the human capital method) among adults, and lost productive time due to premature death adjusted by age. We also included out-of-pocket costs (transportation costs between the place of residence and transplant centers, accommodation, and food expenses) and lost productive time of caregivers while HA patient was hospitalized and during follow-up after LT discharge.

The cost of school absenteeism was estimated based on the cost of providing a day of school (adjusted for school holidays) according to the Provincial Educational Public Expenditure of each year [30]. In order to estimate productivity loss, we considered the average monthly salary of employed persons adjusted by the unemployment rate of each year, both according to National Institute of Statistics and Census (INDEC), and we assumed that adults with HA and their caregivers were paid employees throughout the analyzed period [31–33].

A 6.25% annual discount rate was used only for lifelong immunosuppressive therapy future costs as well as for premature death costs, in both periods, based on the discount rate proposed by the MERCOSUR structural convergence fund (FOCEM) for social investment in Latin-America [34]. Discount rate was not applied to any other medical or non-medical costs that occurred during the 2000–2010 period. Nor discount rate was applied to outcomes/benefits for the assessed period as we did not estimate future health benefits of vaccination after 2010.

2.4. Preventive costs

Outbreak control and universal mass vaccination costs were obtained from the National Program for the Control of Vaccine-Preventable Diseases (ProNaCEI). There was no purchase of HA vaccine at the national level for the period 2000–2002. During

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this period each jurisdiction acted independently to administer vaccines and conduct outbreak control actions. Since 2003, coinciding with the start of the nationwide outbreak, the ProNaCEI has purchased and distributed HA vaccine for the whole country, so immunization analysis covers the 2003–2010 period.

The following items were considered within the category of immunization costs: vaccine price; service charge of the PAHO Revolving Fund; delivery, freight, and insurance; safety boxes and syringes; and distribution from central level to all provinces. These costs were used to obtain the *total vaccination cost per dose*.

Countrywide, 131,888 and 230,370 doses were distributed in 2003 and 2004, respectively. Since 2005, it is estimated that 800,000 doses/year have been distributed throughout the country, based on the total target population (approximately 730,000 live births per year) and a presumed 10% wastage. Main input data for this study are summarized in Table 1.

3. Results

Total HA and unspecified hepatitis cases decreased from 157,871 cases in 2000–2004 to 17,784 cases in 2006–2010, representing an 88.7% decrease in total cases (Fig. 1). Among these, estimated FH cases showed a continuous decline during the second period, and no cases of FH or LT were observed in 2010 (Table 2).

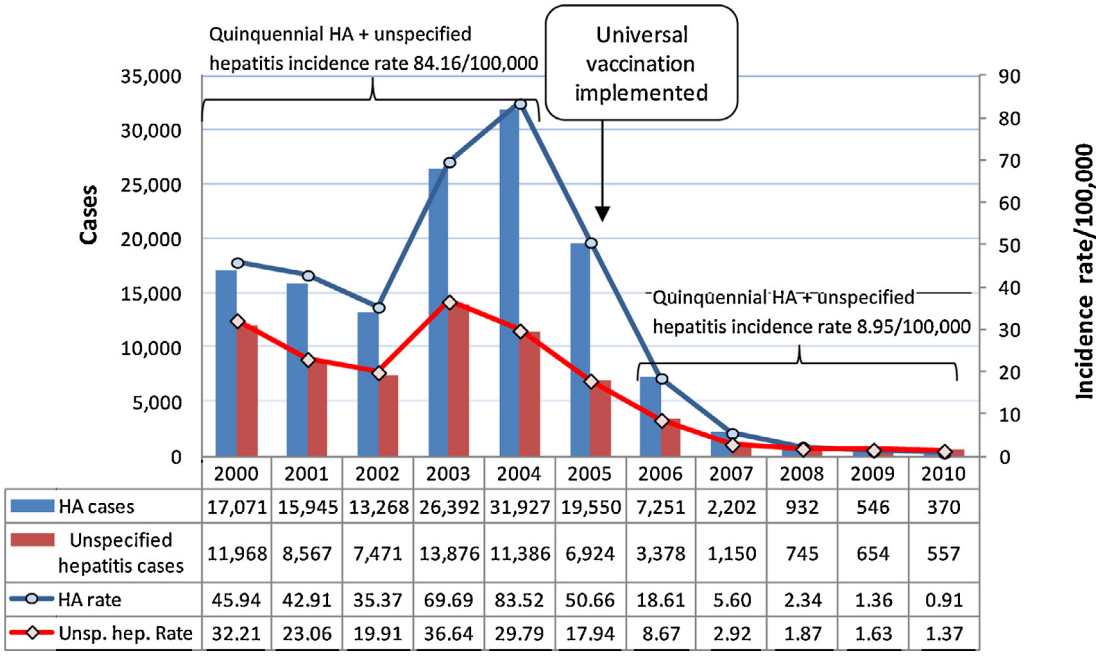
After universal mass vaccination was implemented in 2005, medical costs decreased, falling from US$11,811,600 in 2000–2004 to US$1,252,694 in 2006–2010. Non-medical costs decreased from US$30,118,222 to US$4,995,895 in the two periods. Medical and non-medical costs of the 2006–2010 period represent a reduction of 85.1% between the two periods. Although preventive costs related to vaccination increased by 528.8% (from US$6,506,711 in 2000–2004 to US$40,912,132 in 2005–2010), overall costs, including preventive, medical, and non-medical costs, still decreased from US$48,436,534 in 2000–2004 to US$47,160,721 in 2006–2010, a reduction of 2.6%. An analysis from a healthcare system perspective (only including medical and immunization costs) was also done. In this case, total costs increased in 130.2%, from US$18,318,311 to US$42,164.826 (Table 3).

Table 1
Main burden of disease and cost-related variables: base case.

Quinquennial disease rate/100,000 population	
(HA + unspecified hepatitis) 2000–2004	84.16
(HA + unspecified hepatitis) 2006–2010	8.95
Burden of disease	
Non-fulminant hepatitis [22–24]	99.9%
Non-complicated [20,25]	92.1%
Cholestatic [20,25]	2.4%
Prolonged [20,25]	1.3%
Relapsing [20,25]	4.2%
Fulminant hepatitis [22–24]	0.1%
Survival without liver transplant [10]	31.2%
Undergo liver transplant [10]	43.0%
Death on transplant waiting list [10]	25.8%
First-year liver transplant mortality [17]	25.6%
Medical and non medical costs (US$ 2013) [26, 30–33]	
Non-fulminant hepatitis[a]	$272
Fulminant hepatitis[a]	$2958
Liver transplant[b]	$36,177
First year post-liver transplant[b]	$7702
Annual immunosuppressive therapy[b]	$4454
Annual productivity loss	$4640
Immunization program cost per dose (US$ 2013)	
2003–2004	$18.92
2005	$10.11
2006–2010	$8.21
Annual discount rate [30]	6.25%

Note: Numbers in square brackets indicate reference documents.
[a] *Source*: Regulated lists, agreements with self-administered hospitals, data provided by public hospitals, and the pharmacist workbook (*Vademecum* price list). Average from 2000 to 2010 values expressed in 2013 values.
[b] *Source*: National Central Unique Institute for Coordination of Ablation and Implant (INCUCAI).

Trends in absolute and relative HA-associated medical, non-medical, and immunization costs for the entire study period (2000–2010) are shown in Fig. 2. Medical and non-medical costs show a peak during the 2003–2004 outbreak and decrease dramatically, both in absolute and relative terms, in the post-mass vaccination period. Preventive costs related to immunization also increase in 2003–2004 as part of the outbreak control strategy and they keep rising until 2005, when universal mass vaccination starts.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
HA cases	17,071	15,945	13,268	26,392	31,927	19,550	7,251	2,202	932	546	370
Unspecified hepatitis cases	11,968	8,567	7,471	13,876	11,386	6,924	3,378	1,150	745	654	557
HA rate	45.94	42.91	35.37	69.69	83.52	50.66	18.61	5.60	2.34	1.36	0.91
Unsp. hep. Rate	32.21	23.06	19.91	36.64	29.79	17.94	8.67	2.92	1.87	1.63	1.37

Fig. 1. HA and unspecified hepatitis cases and rates reported to the SNVS, 2000–2010.

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Table 2
Hepatitis A-associated estimated fulminant and non-fulminant hepatitis cases and their outcomes from 2000 to 2010.

Year	Fulminant hepatitis A cases			Non-fulminant hepatitis A cases[a]	Total
	Survivors without liver transplant	Deaths while on waiting list	Liver transplant cases		
2000	9	8	12	29,010	29,039
2001	8	6	11	24,487	24,512
2002	6	5	9	20,718	20,739
2003	13	10	17	40,228	40,268
2004	14	11	19	43,270	43,313
2005	8	7	11	26,448	26,474
2006	3	3	5	10,618	10,629
2007	1	1	1	3349	3352
2008	1	0	1	1675	1677
2009	0	0	1	1199	1200
2010	0	0	0	926	926
2000–2004	50	40	68	157,713	157,871
2006–2010	5	4	8	17,767	17,784

[a] NFH includes non-complicated (92.1%), relapsing (4.2%), cholestatic (2.4%) and prolonged (1.3%) forms.

Table 3
HA-related medical, non-medical, and immunization program costs, 2000–2010.

Year	Medical costs (US$)		Non-medical costs (US$)		Immunization program costs	Social perspective	Healthcare system perspective
	HA and liver transplant medical treatment	Lifelong immunosuppressive therapy[a]	School absenteeism, lost wages, and out-of-pocket costs	Lost wages due to premature death[a]			
2000	1,516,978	587,322	6,076,369	398,313	–	8,578,982	2,104,300
2001	1,299,884	510,325	5,145,060	337,601	–	7,292,869	1,810,209
2002	1,082,636	552,727	3,188,864	210,972	–	5,035,199	1,635,363
2003	1,975,072	1,065,729	6,036,889	395,038	2,960,064	12,432,791	6,000,865
2004	2,112,571	1,108,356	7,785,462	543,655	3,546,647	15,096,692	6,767,574
2005	1,218,683	625,250	5,137,350	338,875	8,087,848	15,408,006	9,931,781
2006	508,388	245,790	2,449,022	162,045	7,381,433	10,746,678	8,135,612
2007	156,803	71,786	898,852	60,666	6,667,375	7,855,482	6,895,964
2008	81,598	35,760	531,457	36,959	6,024,229	6,710,003	6,141,588
2009	60,450	25,771	432,776	30,386	6,622,878	7,172,261	6,709,099
2010	46,400	19,948	367,234	26,498	6,128,369	6,588,448	6,194,717
2000–2004	7,987,141	3,824,459	28,232,643	1,885,579	6,506,711	48,436,534	18,318,311
2006–2010	853,639	399,055	4,679,341	316,554	40,912,132[b]	47,160,721[b]	42,164,826[b]
Difference between periods			−85.10%		528.8%	−2.6%	130.2%

[a] Discounted 6.5%/year.
[b] Subtotal costs include the immunization cost of year 2005.

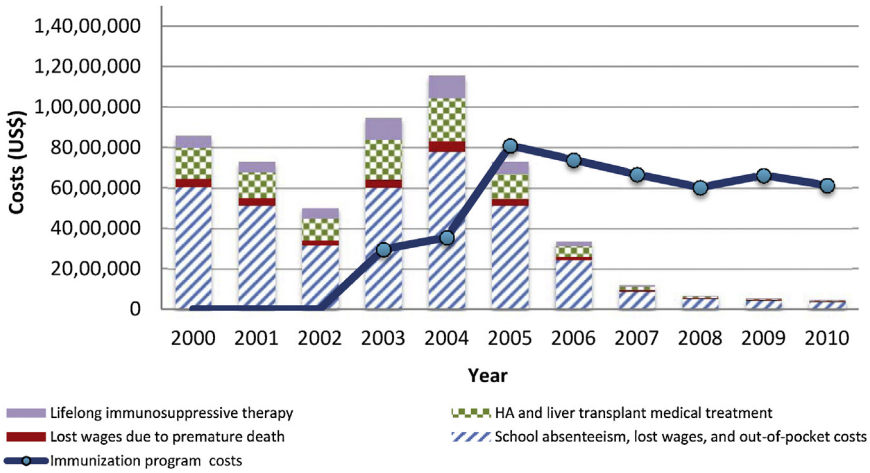

Fig. 2. Trends in HA-associated medical, non-medical, and immunization costs, 2000–2010.

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Table 4
Composition of HA-associated costs, 2000–2010.

Period	Medical costs		Non-medical costs		Immunization program costs
	HA and liver transplant medical treatment	Lifelong immunosuppressive therapy	School absenteeism, lost wages, and out-of-pocket costs	Lost wages due to premature death	
2000–2004	16.5%	7.9%	58.3%	3.9%	13.4%
2006–2010	1.8%	0.8%	9.9%	0.7%	86.8%[a]

[a] Immunization program cost includes the year 2005.

Then, it is observed a slow decline in absolute terms but vaccination costs continue to increase in proportion during the period 2006–2010 when compared with medical and non-medical costs for the same period.

A relative cost analysis shows that non-medical costs were the largest component of total costs in 2000–2004, representing 62.2%. During the 2006–2010 period, by contrast, prevention of HA through vaccination represented 86.8% and non-medical costs only 10.6% of total costs (Table 4).

3.1. Sensitivity analyses

We assessed the robustness of our results when different assumptions and parameters were used at critical points of our model (Table 5). With respect to disease burden, we considered an increase in the probability of developing FH from 0.1% to 0.6%, based on local reports [21]. Another scenario excluded "unspecified" hepatitis cases on the grounds that there could be some other etiologies included in this group [20]. The annual discount rate was also changed to 3% and to 10%, following regional and international recommendations [19,35].

As a result, in the 2006–2010 period, total cost reduction rates reached a −10.4% when annual discount rate was changed to 3% and a −43.8% when a higher probability of FH was considered. On the other hand, total costs in the post-mass vaccination period exceeded costs of the previous period when a discount rate of 10% was considered (+1.37%), and reached a maximum when "unspecified" hepatitis cases were excluded from the analysis (+30.8%).

4. Discussion

After universal mass vaccination of Argentine infants began in 2005, an impressive decline was observed in the HA burden of disease. These results, along with the high persistence of protective antibodies against HA for up to 4 years after single-dose vaccination, led the World Health Organization Strategic Advisory Group of Experts on Immunization to recommend this strategy for other countries in April 2012 [36,37]. Moreover, a decline in total HA disease management and preventive costs was observed (2.6% reduction), even though program immunization costs were more than five times higher in the 2005–2010 period compared to 2000–2004. In this sense, Argentina made a shift in the management of HA disease, moving from a *treatment-based strategy*, in which HA was poorly controlled and represented a significant productivity loss for the country, to a more efficient and less expensive *preventive strategy* based on universal mass vaccination.

These cost calculations, however, are strongly influenced by social costs. Thus, from an exclusive healthcare perspective, total costs increased in 130.2% in the post-mass vaccination period. Given that Argentina is considered an upper-middle-income country, the results would be probably different in countries with a lower or higher income status.

Our study has some limitations. Regarding burden of disease, we considered "HA and unspecified hepatitis" cases reported to the SNVS as primary data. This choice could have led us to overestimate the burden of disease and therefore treatment cost reductions, as other forms of hepatitis may have been included. However, it is presumed that hepatitis A accounts for >90% of the cases in the unspecified group, which also showed a downward trend parallel to that of HA cases. On the other hand, HA cases could have been underestimated because of underreporting, which is common when passive surveillance is used, as it was in this study.

LT-related costs could also have been underestimated, as we considered lifelong immunosuppressive therapy costs but complications and control visit costs only during the first year post-LT. Moreover, taking into account that the survival rate after HA-related LT is not clear, we assumed the same life expectancy for LT survivors as for the general population from the second post-LT year onward.

We could also have underestimated medical costs, because we only considered public healthcare system costs, which are often lower than those of social security or the private sector. However, we assumed that public costs better represent our reality, since approximately 95% of cases notified to the SNVS are from the public healthcare sector.

We assumed that wages and the cost of immunosuppressive medication remain constant throughout the life of a patient, but this assumption may reduce the accuracy of estimated future costs since it implies that prices and the structure of the labor market will remain unchanged over the long term.

To address some of these limitations, we performed a sensitivity analysis using different assumptions and parameters, although retaining the social perspective. Total costs in the 2006–2010 period still declined, and the reduction rate increased from the base case when a smaller discount rate (3%) or a higher probability of HF risk was considered. On the other hand, those costs exceeded the costs of the previous period when a higher discount rate was considered or when unspecified hepatitis cases were excluded.

Table 5
Sensitivity analysis under alternative assumptions.

Alternative assumptions	2000–2004 (US$)				2006–2010 (US$)				Percentage variation between periods
	Medical costs	Non-medical costs	Immunization program costs	Total	Medical costs	Non-medical costs	Immunization program costs	Total	
Base case	11,811,600	30,118,223	6,506,711	48,436,534	1,252,694	4,995,895	40,912,132	47,160,721	−2.6%
0.6% probability of FH	45,188,327	41,751,230	6,506,711	93,446,267	4,771,437	6,843,271	40,912,132	52,526,839	−43.8%
Annual discount rate 3%	14,680,774	32,065,934	6,506,711	53,253,419	1,536,370	5,267,732	40,912,132	47,716,234	−10.4%
Annual discount rate 10%	10,517,077	29,244,494	6,506,711	46,268,282	1,120,851	4,867,359	40,912,132	46,900,342	1.4%
Unspecified hepatitis cases excluded	7,832,256	19,905,195	6,506,711	34,244,162	797,355	3,095,355	40,912,132	44,804,842	30.8%

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In conclusion, single-dose immunization against hepatitis A in Argentina not only had a remarkable epidemiological impact, but also brought about a reduction in medical and non-medical costs in the first 5 years after its implementation. This strategy, which is simpler and less expensive than the standard two-dose schedule used elsewhere, can be a good alternative for future vaccination policies in countries where HA is endemic.

Authors' contributions

Carla Vizzotti, Tomás Pippo, Analía Urueña, Juan Altuna, Gastón Palópoli, Fernanda Artola, Hugo Fernández, Pablo Orellano, and Máximo Diosque contributed to the conception and design of the study. Carla Vizzotti, Tomás Pippo, Analía Urueña, Juan Altuna, Gastón Palópoli, María Fernanda Artola, María Laura Hernández, Hugo Fernández, María Cristina Cañero-Velasco, Mirta Ciocca, and Margarita Ramonet contributed to the study by acquiring relevant data. Carla Vizzotti, Tomás Pippo, Analía Urueña, Juan Altuna, Gastón Palópoli, María Fernanda Artola, and Máximo Diosque contributed to the analysis and interpretation of data. Carla Vizzotti, Tomás Pippo, Analía Urueña, Juan Altuna, and María Fernanda Artola drafted the article. All authors have revised it critically for intellectual content and approved the final article.

Acknowledgments

The authors are grateful to Cara Janusz (Pan American Health Organization) for revising the manuscript. Thanks also go to Felipe Aguerre and Liliana Bisigniano of the Instituto Nacional Central Único Coordinador de Ablación e Implante (INCUCAI) and to the Epidemiology Office of the National Ministry of Health for kindly sharing their information.

Conflict of interest statement: All authors declare no conflicts of interest in relation to this article.

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Vaccine 33S (2015) A233–A239

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Thirty years of vaccination in Vietnam: Impact and cost-effectiveness of the national Expanded Programme on Immunization

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ARTICLE INFO

Keywords:
Cost-effectiveness
Diphtheria
Immunization
Measles
Pertussis
Polio

ABSTRACT

Introduction: Countries like Vietnam transitioning to middle-income status increasingly bear the cost of both existing and new vaccines. However, the impact and cost-effectiveness of the Expanded Programme on Immunization (EPI) as a whole has never been assessed on a country level.
Methods: Data on vaccine-preventable disease incidence and mortality from Vietnam's national surveillance was analysed to estimate the likely impact that vaccination in 1980–2010 may have had. Adjustment for under-reporting was made by examining trends in reported mumps incidence and in case-fatality risks for each disease. The same data were separately analysed using the Lives Saved Tool (LiST) to give an alternative estimate of impact. The financial cost of EPI in 1996–2010 was also estimated from the perspective of service provider.
Results: National surveillance data suggests that up to 5.7 million diseases cases and 26,000 deaths may have been prevented by EPI. Analysis using LiST suggests that even more deaths (370,000) may have been prevented by measles and pertussis vaccination alone. The cost-effectiveness of EPI is estimated to be around $1000–$27,000 per death prevented.
Conclusion: Two separate approaches to assessing EPI impact in Vietnam give different quantitative results but a common conclusion: that EPI has made a substantial impact on mortality and represents good value for money.
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1. Introduction

The Expanded Programme on Immunization (EPI) was established by the World Health Organization (WHO) in 1974 to support countries in increasing uptake of vaccines against measles, diphtheria, pertussis, tetanus, poliomyelitis and tuberculosis. Between 1980 and 2011, global coverage of the third dose of diphtheria–pertussis–tetanus vaccine (DPT) increased from 20% to 83%, while that of measles-containing vaccine increased from 16% to 85% [1].

A World Bank report [2] considered that vaccines covered by EPI are among the most cost-effective interventions available, with measles immunization estimated to cost $10 per disability life year (DALY) prevented, and DPT immunization $25 per DALY prevented. A more recent analysis [3] suggested that the incremental cost per death averted of EPI ranges from $274 in South Asia to $1754 in Europe and Central Asia in 2001 US$, and is about $478 in East Asia and the Pacific. However, the impact and cost-effectiveness

Abbreviations: DALY, disability adjusted life year; DPT, diphtheria–pertussis–tetanus vaccine; EPI, Expanded Programme on Immunization; LiST, Lives Saved Tool.

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http://dx.doi.org/10.1016/j.vaccine.2014.12.017
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of the EPI vaccine package has never been formally evaluated on a national level. Hence previous cost-effectiveness analyses have relied on extrapolation of limited data to a global level.

A key indicator of EPI success is observed reductions in vaccine-preventable disease incidence and mortality [4]. However, passive surveillance of trends in disease incidence may be affected by underreporting, particularly of cases that do not present for health care. Furthermore, the degree of underreporting may change over time as case definitions, access to care and surveillance systems evolve. On the other hand, active surveillance methods such as cross-sectional surveys without major sources of bias are normally too resource-intensive to be conducted regularly in low and middle income countries. For mortality, establishing the cause of death is difficult when symptoms are non-specific and children have multiple co-morbidities at the time of death. Lastly, even if declines in severe disease and mortality are well-documented, these may be due to improved access to care, nutrition and general health as well as vaccination.

EPI was first introduced in Vietnam in 1981, and became one of six national targeted health programmes in 1985. The programme originally vaccinated infants against six diseases (diphtheria, tetanus, pertussis, poliomyelitis, measles, and tuberculosis). By 2009, 96% of children less than 1 year old were recorded as having received three doses of DPT. EPI's successes include elimination of polio in 2000 and of maternal and neonatal tetanus in 2005.

Vietnam has benefitted from Gavi support for vaccine introduction and health systems strengthening, but eligibility for these funds may end as Vietnam transitions to middle-income status. Hence both the current EPI as well as new vaccine introductions will be increasingly funded by national resources. Yet there are competing priorities for Vietnam's public investments both within and outside the health sector. As the government plans for future investments, it is critical to understand the impact and value of Vietnam's EPI.

The goal of this study is to assess the impact and cost-effectiveness of Vietnam's EPI in reducing mortality and morbidity associated with vaccine-preventable diseases over its 30 year history. The study addresses a key evidence gap in providing the first national impact and economic evaluation of EPI. To do so, two complementary methods were used. First, data on vaccine-preventable disease incidence and mortality from national surveillance were analysed to estimate the likely impact that 30 years of vaccination may have had. Second, the Lives Saved Tool (LiST) was used. LiST is a model to estimate the number of lives saved by different packages and coverage levels of health interventions by combining evidence about the effectiveness of maternal, neonatal and child health interventions with country specific information about cause of death and current coverage of health interventions.

2. Methods

2.1. Statistical modelling based on surveillance data

The National Institute of Hygiene and Epidemiology records notifications of cases and deaths attributed to measles, diphtheria, pertussis, tetanus and polio in 1980–2010 in all ages. Surveillance was based on clinical, epidemiological and microbiological confirmation for polio (since 1992) and measles (since 2000), and clinical diagnosis only for other diseases. Case definitions are given in Appendix A.1; these were unchanged over the entire period 1980–2010, apart from a change in the measles case definition in 2003 by which time measles incidence had reached very low levels.

Decreases in notified cases give an indication of the impact of vaccination. However, incidence may have declined due to reasons unrelated to vaccination, such as changes in case ascertainment and disease risk factors. To control for non-vaccine related changes, annual vaccine-preventable disease notifications were adjusted based on changes in mumps incidence in the same year (see Appendix A.3). Mumps was chosen as a control variable because there is no mumps vaccination programme currently in place in Vietnam, so any changes in reported mumps incidence must be due to non-vaccine related causes. A regression curve was fitted to annual mumps incidence to smooth out year-to-year variations (see Appendix A.2).

The National Institute of Hygiene and Epidemiology records administrative coverage for measles, DPT and polio vaccines in 1980–2010, except for 1988. Reported incidence for measles, diphtheria, pertussis and polio was related to routine dose coverage in order to investigate the temporal association between increasing vaccine coverage and decreasing disease incidence (hence providing evidence that vaccination is a cause of disease decline). Tetanus was not modelled since reductions in neonatal tetanus incidence are not easily associated with infant DPT vaccination alone, and are due also to maternal vaccination. For parsimony, coverage of catch-up, second dose and booster programmes was not considered; these programmes took place in the latter years of the period 1980–2010 when disease incidence had already reached fairly low levels. Twelve linear regression models were used to explore the association between incidence (with or without the mumps adjustment factor) and vaccine coverage over the past three years (see Table 1). The reduction in disease incidence attributed to vaccination in a particular year was assumed to be equal to the difference between incidence in that year estimated by each model (unless this was negative, in which case it was rounded to zero) and incidence predicted to occur by the same model when vaccine coverage was 0%. Models giving the largest and smallest estimated number of vaccine-prevented deaths were selected to provide an uncertainty range. If notification data alone or mumps-adjusted notification data (without regression modelling) gave the largest or smallest number this was selected instead.

The number of deaths attributed to vaccine-preventable diseases may have declined due to reasons unrelated to vaccination, such as improved healthcare and nutrition. To adjust for this, it was assumed that reductions in deaths due to reasons unrelated to vaccination reduced the case-fatality risk of disease without affecting disease incidence. On the other hand, vaccination is assumed to simply prevent disease from occurring in the first place, rather than to reduce the severity (and hence risk of death) of cases. Hence the number of deaths prevented by vaccination in a particular year was assumed to be the estimated number of disease cases prevented by vaccination in that year (as described above), multiplied by the case-fatality risk for the disease in that year estimated using national surveillance data (see Appendix A.5 for equations).

2.2. Estimation of the number of deaths prevented using the Lives Saved Tool (LiST)

LiST was used to model under-five mortality due to measles and pertussis in 1980–2010. Polio and diphtheria have limited roles in under-five mortality while neonatal pertussis is not directly prevented by infant vaccination alone. Details of LiST methodology have been published elsewhere [5]. Briefly, a complete LiST projection was constructed for 2000 using all coverage data, health status information and mortality rates. The 1980 coverage and health status rates were entered for the years 2001–2005 in order to extrapolate the most likely proportionate cause of death in neonates and 1–59 months olds using a method previously reported in the literature [6]. These values were then used in the baseline LiST projection for the years 1980–2010. Full details of data sources and methodology are given in Appendix A.6.

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Table 1
Linear regression models used to relate disease incidence to vaccine coverage. Symbols: x_i = incidence of notified cases in year i, y_i = incidence of notified cases in year i adjusted using mumps data, c_i = vaccine coverage in year i ($c_i = 0$ for $i < 1980$).

Model number	Model equation	Dependent variable		Independent variable(s)		
		Disease incidence x_i	Mumps-adjusted disease incidence y_i	Vaccine coverage in the same year c_i	Vaccine coverage in the previous year c_{i-1}	Vaccine coverage two years ago c_{i-2}
1	$x_i \sim c_i$	√		√		
2	$x_i \sim c_i + c_{i-1}$	√		√	√	
3	$x_i \sim c_i + c_{i-1} + c_{i-2}$	√		√	√	√
4	$x_i \sim c_i + c_{i-2}$	√		√		√
5	$x_i \sim c_{i-1}$	√			√	
6	$x_i \sim c_{i-1} + c_{i-2}$	√			√	√
7	$y_i \sim c_i$.		√	√		
8	$y_i \sim c_i + c_{i-1}$		√	√	√	
9	$y_i \sim c_i + c_{i-1} + c_{i-2}$		√	√	√	√
10	$y_i \sim c_i + c_{i-2}$		√	√		√
11	$y_i \sim c_{i-1}$		√		√	
12	$y_i \sim c_{i-1} + c_{i-2}$		√		√	√

The LiST analysis was compared to the reduction over time in the number of cases of and deaths due to measles and pertussis (in 1980–2010) according to national surveillance data. To do this, the average annual number of cases and deaths between 1980 and 1986 was calculated and compared to the average annual value between 2000 and 2010, for both measles and pertussis, to calculate a percent reduction over time.

2.3. EPI costs

The financial cost of Vietnam's EPI in 1996–2010 was estimated from the perspective of the service provider. Records prior to 1996 (including start-up costs) were not available. All the inputs (ingredient) used in implementing the programme were captured. The cost per vaccine dose was estimated by incorporating all relevant ingredients, such as personnel, supplies, vaccine procurement, operations and logistics (see Appendix A.7). The total annual cost of each vaccine was estimated by multiplying the average cost per dose by the total number of doses used by the program in that year. Costs were presented in 2010 US$.

3. Results

Models relating notifications incidence and vaccine coverage for each of the four diseases appear to fit data well, based on visual inspection and by comparing their Akaike Information Criterion (see Appendix A.4 for results). They capture initial high disease incidence prior to vaccination as well as its rapid decline as EPI was rolled out nationally. Coefficients relating disease notifications to vaccine coverage were negative (including the entire 95% confidence interval; data not shown), supporting the hypothesis that vaccination has been a cause of disease decline. Models predict a spike in diphtheria and pertussis incidence around 2002 which did not occur in practice, despite a sharp decline in DPT coverage from 96% in 2001 to 75% in 2002. The reason for this may be herd protection from existing vaccinated cohorts; these indirect effects are poorly captured by a linear model [7]. The best fitting model was model 11 for polio, and model 9 for all other diseases.

Case-fatality risks for measles, pertussis, diphtheria and polio declined in 1980–2010 (Fig. 1). Temporary increases in 1993 (measles), 2005 (pertussis) and 1990–1996 (polio) may represent outbreaks in socioeconomically disadvantaged areas with a higher case-fatality risk, due to lower vaccine coverage in these geographically restricted regions. High reported case-fatality risk for polio in the decade prior to elimination may reflect improved ascertainment of polio deaths due to the attention being given to this disease. The annual number of disease cases prevented by vaccination has increased since 1980, due to both improved vaccine coverage and increasing birth cohort size (Fig. 2). However, the number of deaths prevented has decreased, because of declining case-fatality risks, particularly for measles. In total, 2.3–5.7 million diseases cases and 10,000–26,000 deaths are estimated to have been prevented by EPI in 1980–2010. The largest impact (in terms of deaths prevented by vaccination) was obtained when using model 12 for pertussis, and using unadjusted surveillance data alone for other diseases. The least impact was obtained when using model 5 for polio, and model 1 for other diseases.

LiST estimates even greater benefit from EPI. According to LiST, about 370,000 under-five deaths may have been prevented by two EPI vaccines (measles and pertussis), primarily through prevention of measles mortality. This is mainly because LiST estimates of mortality for measles (based on WHO estimates) are about 70–200 times higher than those estimated from adjusted surveillance data, although estimates for pertussis are similar. However, the proportionate reduction in the number of deaths between 1980 and 2010 is similar: 99–100% and 97–100% for measles and pertussis using national data, compared to 96% and 83% using LiST. LiST suggests that EPI may have been responsible for around 15% of under-five mortality decline in Vietnam since 1980, mainly due to measles vaccination. Results for all four diseases are shown in Table 2, together with corresponding figures using LiST.

The cost of EPI over 15 years (1996–2010) is estimated at $154.5 million, consisting of $41.8 million for routine DPT, $28.3 million for polio, $8.6 million for first measles dose, $5.41 million for second measles dose, $0.25 million for DPT campaigns, $46.8 million for polio campaigns and $23.4 million for measles campaigns (see Appendix A.7 for costs disaggregated by year). Using the lowest estimate of the number of deaths prevented in 1996–2010 (9400 deaths), EPI cost $27,000 per life saved. Since costs are only available for half time period 1980–2010 over which deaths prevented are estimated, we use half the much higher estimate of deaths prevented in 1980–2010 according to LiST (half of 370,000 deaths). This suggests that EPI only cost $1000 per life saved. Indeed EPI may be even more cost-effective than suggested here, and may even be net cost-saving, as neither estimate incorporates cost savings to the health sector due to reduced treatment. Furthermore, almost half the cost of EPI was spent on polio vaccination, whose main aim is not mortality prevention.

4. Discussion

We have used two methods to assess the impact of EPI on disease incidence and mortality in Vietnam since 1980. Statistical analysis of national surveillance data suggests that up to 5.7 million

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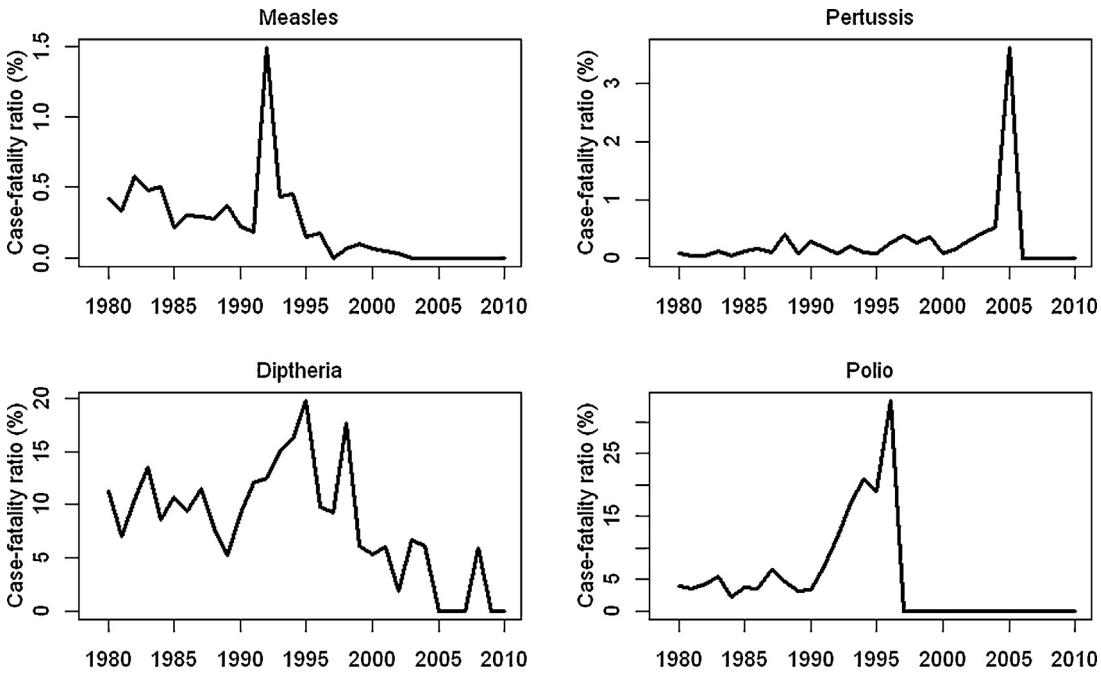

Fig. 1. Case-fatality risk of measles, diphtheria, pertussis and polio from 1980 to 2010, based on notified cases and deaths. The case-fatality risk for polio after 1996 could not be calculated as polio had been eliminated by then.

disease cases and 26,000 deaths may have been prevented by EPI. A significant temporal association between disease incidence and vaccine coverage was found. Using LiST suggests that about 370,000 deaths may have been prevented by two EPI vaccines (measles and pertussis). Cost-effectiveness analysis using financial data suggests that EPI costs around $1000–$27,000 per death prevented.

The lower end of the range for cost-effectiveness, based on LiST estimates of mortality, is close to a Disease Control Priorities

Table 2
Estimated EPI impact on cases and deaths due to measles, pertussis, diphtheria and polio.

	Measles		Pertussis		Diptheria		Polio		Total	
	Low[1]	High[1]	Low[1]	High[1]	Low[1]	High[1]	Low[1]	High[1]	Low[1]	High[1]
Using national surveillance data										
Cases 1980	40,000	110,000	35000	78,000	1300	3900	580	1800	76,880	19,3700
Cases 2010	2900	15,000	0	6900	6	610	0	540	2906	23,050
Deaths 1980	170	460	26	59	150	440	22	70	368	1029
Deaths 2010	0.85	4.4	0	2.1	0.11	12	0	12	0.96	30.5
Deaths per 1000 cases 1980	4.2	4.2	0.76	0.76	110	110	38	38	0.0048	0.0053
Deaths per 1000 cases 2010	0.3	0.3	0.31	0.31	19	19	23	23	0.00033	0.0013
Vaccine prevented cases 1980–2010	1.2	3.1	1	2.4	0.038	0.11	0.019	0.058	2.257	5.668
Vaccine prevented deaths 1980–2010[2]	1900	5300	3700	8200	2800	8800	960	3200	9360	25,500
Vaccine prevented cases 1996–2010[3]	0.81	2.2	0.77	1.7	0.028	0.08	0.017	0.045	1.625	4.025
Vaccine prevented deaths 1996 - 2010[2,3]	380	1100	3300	7300	1500	4400	600	1600	5780	14,400
% reduction in cases due to vaccination (2010 vs. 1980)	93	86	100	91	100	85	100	71	96%	88%
% reduction in deaths due to vaccination (2010 vs. 1980)	99	99	100	96	100	97	100	82	87%	96%
Using LiST										
Deaths 1980	23,000		300						26,800	
Annual deaths 2000–2010	1000		50						1250	
Vaccine prevented deaths 1980–2010	366,000		5000						411,000	
% reduction in deaths due to vaccination (1980 to 2000–2010)	96%		83%						95%	

[1] "Low" and "high" represent figures from the highest and lowest results (in terms of disease impact) of twelve linear regression models used.
[2] Calculated as number of cases prevented by vaccination in each year × case-fatality risk in the same year.
[3] Vaccine impact for 1996–2010 only was used to calculate cost-effectiveness, since financial costs were only available starting from 1996.

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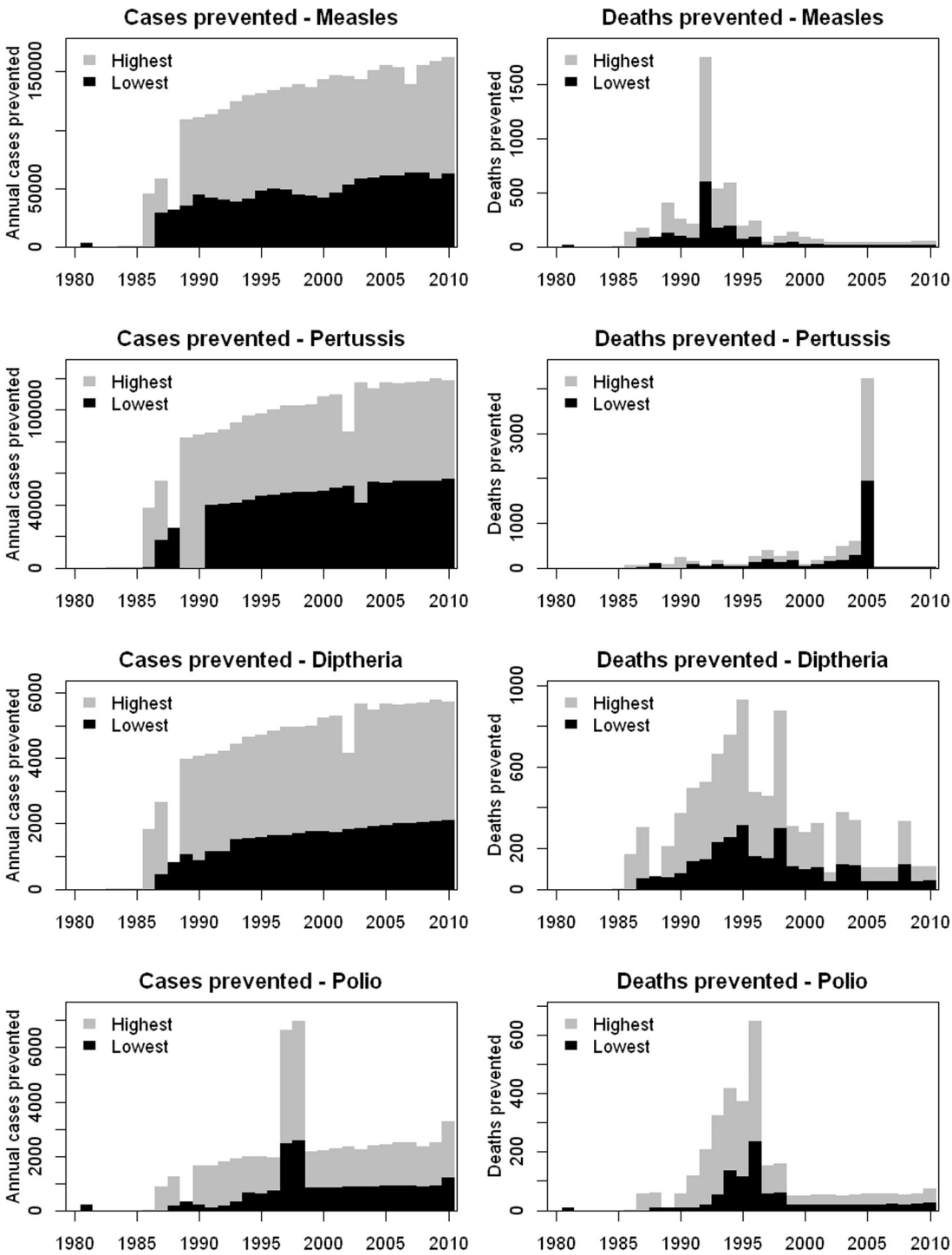

Fig. 2. Highest and lowest numbers of disease cases and deaths prevented by EPI from 1980 to 2010 based on models fitted to national surveillance data.

Network estimate for East Asia and the Pacific of EPI costing $434 per death prevented [3]. This is unsurprising since both LiST and the Disease Control Priorities Network estimate vaccine-preventable mortality based on WHO cause-specific mortality figures. However, the cost-effectiveness ratio estimated using national surveillance data is much greater. This is because LiST estimates more than ten times the number of measles deaths prevented by EPI compared to national surveillance data, although the proportionate reduction in deaths is much more similar between the two approaches.

The difference in absolute numbers may stem from under-ascertainment of measles deaths in national surveillance data due to either misattribution of measles deaths to other causes, or measles patients not seeking health care. Furthermore, if under-ascertainment has decreased since 1980 (as may be expected due to improved surveillance and health care access) then the magnitude of decline in measles deaths from 1980 to 2010 will be underestimated.

To adjust for underascertainment, we use mumps notifications as a control variable to represent changes in infectious disease notifications that are not related to vaccination. Mumps-containing vaccines are not routinely administered in Vietnam; hence any changes in notifications of mumps cases must be due to the other factors, which are assumed to equally affect other communicable diseases. The control variable accounts for both (i) improvements

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in disease ascertainment which may have caused incidence to rise, and (ii) changes in disease risk factors (such as improved hygiene) which may have caused incidence to fall. There was a decreasing trend in mumps incidence between 1980 and around 1990 (see Appendix A.2), suggesting that declines in disease risk factors outweighed the effect of improved ascertainment until the latter part of the study period. This means that mumps-adjusted disease incidence is higher than unadjusted incidence in our model for the first part of the study period. Unfortunately, it is not possible to disentangle the individual effects of both changes through a single control variable. Another limitation is that this method would not have captured changes in diphtheria, pertussis, measles or polio ascertainment that did not affect mumps. For example, case ascertainment for measles may have improved more than for mumps, due to the regional focus on measles elimination [8].

Several studies have examined underascertainment in Vietnamese surveillance sources. A household study in Bavi District compared mortality recorded through the Commune Population Registration System (CPRS) in 1999–2000 with that estimated using three other methods (re-census, communal death registration and neighbourhood surveys) [9]. This suggested that the CPRS may have missed around 19% of deaths, particularly in infant and the elderly, but did not examine deaths that may have been assigned to the wrong cause. A cross-sectional survey in 2008/2009 comparing surveillance case reports with cases recorded in health care logbooks of commune health stations found a shortfall of 61.3%, 47.5% and 56.3% for influenza-like illness, pneumonia and severe pneumonia, respectively [10]. Our own estimates using mumps as a control variable suggests that in 1999, 48% more mumps cases were missed compared to 2010.

A second potential cause of the difference between the analysis of surveillance data and LiST is that the former analysis adjusts for reductions in incidence and mortality that may have occurred due to non-vaccine related factors such as health care access, population structure, overall health, crowding and sanitation. Reduction in infectious disease incidence due to non-vaccine causes is captured using the adjustment factor based on mumps notifications. Indeed, the incidence of mumps notifications decreased between 1980 and 1990, possibly due to improvements in health, before increasing after 1990, possibly due to improved surveillance. Reduction in mortality due to non-vaccine causes is captured by assuming that case-fatality risks in a particular year would still hold in the absence of these non-vaccine factors, even if vaccination had not taken place, and vaccination would only reduce the number of cases of the disease.

One limitation of our statistical analysis of surveillance data is that it relates vaccine coverage to disease incidence using linear regression models that do not capture non-linear effects such as herd protection [7]. The models adequately describe the overall pattern of disease decline as coverage increases from zero to close to 100% since herd effects are minimal at both extremes of the coverage range. However, outbreaks due to short-term fluctuations in coverage are less well captured.

LiST takes a different approach. LiST is a multi-cause model of mortality, which captures the interactions between different interventions that prevent or allow deaths to occur. This relies on WHO estimates of mortality using natural history models [11]. However, LiST assigns mortality reductions due to preventive interventions (such as vaccination) before therapeutic interventions (such as nutritional supplementation and improved access to hospital care). For instance, the impact of measles vaccination is applied to measles mortality first, and the effect of vitamin A therapy on measles mortality is only applied to the measles deaths that remain after the application of vaccination. Consequently, LiST is likely to assign a greater proportion of the decline in measles mortality since 1980 to vaccination compared to the analysis of surveillance data. Hence the difference in the two model estimates may be due to under-ascertainment in national data, overestimation by LiST, or a combination of both.

Table 3
Two approaches to retrospectively estimate the impact of a vaccination programme.

	Surveillance based estimation	Impact model based estimation
Description	Monitor cases and deaths due to a disease both before and during vaccination	Model the likely reduction in morbidity and/or mortality based on disease natural history and vaccine effectiveness
Strengths	Direct observation of changes in incidence. Hence able to capture complex nonlinear effects such as herd protection	Less affected by surveillance biases
Limitations	Affected by underascertainment or misattribution of disease/deaths, as well as changes in morbidity/mortality due to non-vaccine related causes	Estimated vaccine impact is dependent on the order in which interventions are applied when there are multiple interventions that can affect disease incidence and mortality (such as vaccination and treatment)

These methodologies can be used in other settings with vaccine-preventable disease surveillance to retrospectively estimate the impact of EPI. The regression method can be used in any setting with (i) an adequate time series of case and death notifications, and (ii) vaccine coverage for both diseases prevented by EPI vaccines as well as another disease (such as mumps) not affected by existing vaccines. LiST has also been used in other settings. For example, one analysis showed that 11% of recent child mortality reduction in Niger is likely due to vaccines [12]. LiST has also been used to prospectively estimate the potential impact of introducing vaccines or accelerating broader vaccine introduction [13,14].

The difference in deaths averted between the two methods in our analysis is very large, even after adjusting surveillance data for under-ascertainment. This highlights the importance of using multiple methods to estimate vaccine impact when directly observed and actively reported data are not available, as is the case in most low and middle income countries. Having multiple estimates allows triangulation of a likely range in which the true value of deaths averted is likely to lie. However, further investigation into the extent of under-ascertainment in surveillance data and the importance of non-vaccine causes of mortality decline is needed in order to determine which of the two estimates is closest to the truth.

Despite these differences, it is highly reassuring that the broad conclusion from both approaches is the same: Vietnam's EPI has made a substantial impact on mortality and is very likely to be cost-effective, even under conservative assumptions. As more countries graduate from Gavi funding and rely on internal resources, impact and economic analyses of national vaccination programmes such as EPI are likely to become increasingly important. Furthermore, our methodology suggests that both surveillance and modelling play important and complementary roles in such estimates (Table 3).

Acknowledgments

This study was funded by the World Health Organization (WHO reference number SPHQ12-APW-377), and conducted with the support of Vietnam's National Institute of Hygiene and Epidemiology. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the World Health Organization or National Institute of Hygiene and Epidemiology.

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Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.12.017.

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Vaccine 33S (2015) A240–A247

Contents lists available at ScienceDirect

Vaccine

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Estimating costs of care for meningitis infections in low- and middle-income countries

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ARTICLE INFO

Keywords:
Costs
Meningitis
Hospital
Resource-limited settings

ABSTRACT

Meningitis infections are often associated with high mortality and risk of sequelae. The costs of treatment and care for meningitis are a great burden on health care systems, particularly in resource-limited settings. The objective of this study is to review data on the costs of care for meningitis in low- and middle-income countries, as well as to show how results could be extrapolated to countries without sound data.

We conducted a systematic review of the literature from six databases to identify studies examining the cost of care in low- and middle-income countries for all age groups with suspected, probable, or confirmed meningitis. We extracted data on treatment costs and sequelae by infectious agent and/or pathogen, where possible. Using multiple regression analysis, a relationship between hospital costs and associated determinants was investigated in order to predict costs in countries with missing data. This relationship was used to predict treatment costs for all 144 low- and middle-income countries.

The methodology of conducting a systematic review, extrapolating, and setting up a standard database can be used as a tool to inform cost-effectiveness analyses in situations where cost of care data are poor. Both acute and long-term costs of meningitis could be extrapolated to countries without reliable data. Although only bacterial causes of meningitis can be vaccine-preventable, a better understanding of the treatment costs for meningitis is crucial for low- and middle-income countries to assess the cost-effectiveness of proposed interventions in their country. This cost information will be important as inputs in future cost-effectiveness studies, particularly for vaccines.

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1. Introduction

Infectious meningitis is a major cause of morbidity and mortality worldwide, resulting in 422,900 deaths and 2628,000 years lived with disability (YLDs) in 2010 [1,2]. While meningitis results from all four of the main causative agents – bacteria, viruses, fungi and parasites – bacterial meningitis accounts for over 65 percent of meningitis deaths [1].

Accurately assessing the economic burden of meningitis is integral to evidence-based decision making in low- and middle-income countries (LMICs) with limited resources to implement public health programs [3]. Costs of care are key components to evaluating the cost-effectiveness of disease interventions. However, costs of care can be difficult to collect, particularly in resource-limited settings and for diseases that are rare and/or have long-term effects. The objective of this study is to review data on the costs of care for meningitis in LMICs – including all 144 low-income, lower middle-income, and upper middle-income

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http://dx.doi.org/10.1016/j.vaccine.2014.11.061
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countries as classified by the World Bank (see Appendix 1) – in the published literature, as well as to show how results can be extrapolated to countries without sound data.

The objectives of this review are (1) to assess the direct medical and indirect costs for different types of meningitis infections; (2) to estimate the standardized treatment cost for meningitis infections in LMICs with primary data; and (3) to extrapolate costs from country settings with available data to 144 LMICs.

2. Methods

2.1. Search strategy and selection criteria

Studies were identified from a systematic review of literature with primary data in low- and middle-income countries for all age groups with suspected, probable, or confirmed bacterial meningitis. The following databases were searched:

- The Cochrane Central Register of Controlled Trials (CENTRAL) (current issue);
- PubMed (1950 to present);
- EMBASE (1980 to present);
- CINAHL (1981 to present).
- WHO Regional Country Databases (all);
- Econ Lit (all).

The search strategy used a combination of controlled vocabulary (MeSH) terms and free text terms. Key search terms included terms related to meningitis or meningitis-causing bacteria, costs or economic analyses, and LMICs. Articles that did not include primary data, did not discuss meningitis or the meningitis cases resulting from a non-infectious etiology, did not look at costs, were not human studies, or contained a non-English abstract were excluded. During the full text analysis, articles containing outcomes from a study already reported in another article were also excluded. Titles and abstracts were initially scanned, followed by a full text review.

2.2. Data extraction and cost adjustment

We extracted data on costs of care and sequelae by infectious agent and/or pathogen, where possible. Cost data from each included study were extracted for direct and indirect costs. All costs were adjusted to 2012 US dollars (USD) through an initial conversion of study year costs to local currency (LCU), followed by an application of Consumer Price Index (CPI) growth in LCU, and then a conversion between 2012 LCU and 2012 USD [4].

2.3. Quality scoring of included studies

Using the GRADE working group framework as a model, a quality scoring methodology was adapted to the context of costing studies [5]. Factors that decreased confidence in the methodological quality included costs that were based on interviews, small sample size (<100), a study without a country-specific setting, and other limitations in study design such as author-acknowledged study design biases. In order to assess quality, studies were assigned a starting quality rating of 5 and deductions were made for study limitations according to criteria on primary data collection, sample size, and study design. Specifically, the quality score of 5 remained unchanged if these factors did not apply to the specific study, but the score decreased by one level for a serious risk and two levels for a very serious risk to quality.

2.4. Calculating a standardized cost of care for meningitis

In order to estimate standardized costs of care for the treatment of meningitis, direct and indirect costs were averaged among the available data points by cost component. For studies that examined a unique country-specific setting, total treatment costs were determined by summing the relevant cost components. In some instances, articles provided a total treatment cost figure, which was utilized where appropriate (8 articles). The quality scores were used to calculate a weighted average cost across a country setting if that setting had more than one costing study available (20 articles). The full list of quality scores by study can be found in Table 2. For two articles, multiple hospital settings or treatment options for costs were presented, and the following methods were applied to estimate a total cost per case: (1) the number of patients per each hospital setting was used to estimate a weighted average cost per case for that study [6]; or (2) a simple average was taken for different treatment options for meningitis infections and given equal weight [7].

We defined the cost estimation to capture the cost of care provided in a hospital setting [8–10]. Therefore, the costs estimated concern direct medical costs for the treatment of meningitis in a hospital setting.

2.5. Data analysis

We aggregated the following list of covariates as ones that are often associated with treatment costs, according to background documents for the WHO-CHOICE database [11–13], including WHO region (*region*); World Bank income level (*income*) [14]; gross domestic product (GDP) per capita (*gdp*) [14]; population density (*density*) [15]; percentage of population in urban areas (*urban*) [14]; under 5 mortality rate per 1000 live births (*mortality*) [16]; number of hospital beds per 10,000 population (*beds*) [16]; physician density per 10,000 population (*physician*) [16]; health care expenditure

Table 1
Study characteristics.

Region	**Studies (n)**
AFRO	9
AMRO	9
EMRO	3
EURO	2
SEARO	2
WPRO	2
Income[a]	**Studies (n)**
Low-income	5
Lower middle-income	7
Upper middle-income	17
Setting	**Studies (n)**
Country-wide	10
Regional	1
City or province	16
Costs	**Studies (n)**
Direct costs only	18
Direct + indirect costs	9
Sequelae costs	8
Classification of disease	**Studies (n)**
Bacterial	18
• *Haemophilus influenzae type b (Hib)*	8
• *Streptococcus pneumoniae*	8
• *Neisseria meningitidis*	3
Viral	1
Other (including fungal, parasitic, or unspecified)	8
Laboratory confirmed	9

[a] Low income: GNI per capita of $1035 or less; Lower middle-income: GNI per capita of $1036 to $4085; upper middle-income: GNI per capita of $4086 to $12,615.
Note: Income and disease numbers do not sum to the total number of papers included (n = 27) because some papers included countries in multiple income levels or with multiple causes of disease.

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Table 2
Assessment of quality and study characteristics indicators.

Lead Author	Year	Country	Direct costs only included	Direct + indirect costs included	Sequelae costs included	Costs based on interviews	Type of meningitis specified	Meningitis laboratory confirmed	Has a country-wide setting	Has a city or province level study setting	Hs a regional study setting	Has a sample size <100	Quality Score	Ref. No.
Low-income														
Van Damme, W.	2004	Guinea	X				X			X			3	[87]
Akumu AO	2007	Kenya	X				X	X	X			X	4	[88]
Ayieko, P.	2009	Kenya		X		X			X				3	[6]
Nelson, E.	1995	Malawi	X							X			3	[89]
Rajasingham, R.	2012	Uganda	X				X	X		X			2	[7]
Lower middle-income														
Gessner, B. D.	2008	Indonesia	X				X	X		X			4	[90]
Veeken, H.	1998	Nigeria	X				X			X			3	[91]
Hussain, H.	2006	Pakistan	X			X				X		X	1	[83]
Griffiths, U. K.	2012	Senegal		X		X	X			X		X	1	[82]
Anh, D. D.	2010	Viet Nam	X					X		X			3	[92]
Upper middle-income														
Augustovski, F. A.	2009	Argentina	X		X	X	X		X				3	[79]
Lucarevschi, B. R.	2012	Brazil	X				X			X		X	3	[27]
Colombini, A.	2009	Burkina Faso		X	X	X				X			3	[81]
Colombini, A.	2011	Burkina Faso		X		X				X			2	[80]
Levine, O. S.	1993	Chile	X				X			X		X	3	[93]
Lee, K. K.	2009	China		X	X	X	X			X		X	1	[84]
Alvis Guzmán, N.	2006	Colombia		X			X	X	X			X	3	[22]
Arciniegas, W.	2006	Colombia	X				X		X				4	[23]
Sabayan, B.	2007	Iran	X				X			X			3	[94]
Talbird, S. E.	2010	Mexico		X	X	X	X		X			X	1	[86]
Platonov, A. E.	2006	Russia		X	X		X	X		X		X	3	[95]
Wright, P.	2007	Thailand	X				X	X		X		X	3	[96]
Soltani, M. S.	2005	Tunisia	X		X		X	X	X			X	3	[28]
Larraz, G. G.	2010	Uruguay		X	X		X	X	X				4	[25]
Multiple country setting														
Griffiths, U. K.	2011	Belarus and Uzbekistan	X		X		X	X	X				4	[97]
Constenla, D.	2007	Brazil, Chile, and Uruguay	X				X		X				5	[98]
Sinha, A.	2008	Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Panama, Uruguay, Venezuela	X			X	X				X		1	[85]

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per capita (*healthexp*) [15]; and general government expenditure on health as % of total government expenditure (*govtexp*) [17].

Each covariate was obtained for all 144 low- and middle-income countries except the World Bank income level for the Cook Islands, Nauru, and Niue, as these small Pacific islands are not categorized by the World Bank. For the purpose of this analysis, these three nations were assigned to the lower middle-income category based on the average Western Pacific region (WPRO) GDP per capita of $3260.

Multiple linear regression was used to analyze the impact of these covariates on the 27 available country costs. Given that this cost data was right-skewed, treatment costs were log transformed. The covariates were investigated for nonlinearity and the variables for WHO region and World Bank income level were included using indicator variables. All covariates were then tested for significance both individually with likelihood ratio testing and as a set with a nested models *F* test [18]. Possible interactions between the categorical variables for *region* and *income* were also assessed with each continuous covariate. We also examined Akaike's Information Criteria (AIC) to determine the more parsimonious model from the original list of covariates adequate for prediction [19], which led to the exclusion of the categorical variables *region* and *income* along with the continuous variables *beds*, *physician*, and *govtexp*. We also cross-checked significance tests with non-parametric bootstrap significance tests, to detect possible weaknesses in model assumptions or small sample size [20]. The selected model was used to predict hospital treatment costs. To correct for the retransformation bias, we included a correction term to the regression equation (Duan's smearing estimate [21]).

3. Results

3.1. Study selection

In the systematic review, our initial search resulted in 1817 articles as shown in Fig. 1. After reviewing titles and abstracts, 94 of these articles were considered potentially relevant. Of these, four were in Spanish [22–25], two in Portuguese [26,27], one in French [28], and one in Romanian [29], with the remaining papers in the English language. Thirteen articles were excluded before the full text review as conference abstracts. The full texts of the remaining articles were further screened for inclusion in the review. Fourteen articles were excluded for not including any cost discussion or cost figures [30–43]. A further eight were excluded for not discussing costs specific to meningitis [24,29,44–49]. Another 29 articles were excluded as not having primary data [26,50–71]. Two articles were also excluded for studying a high-income country setting [72,73]. Finally, we were not able to obtain one article, which was excluded as missing [74].

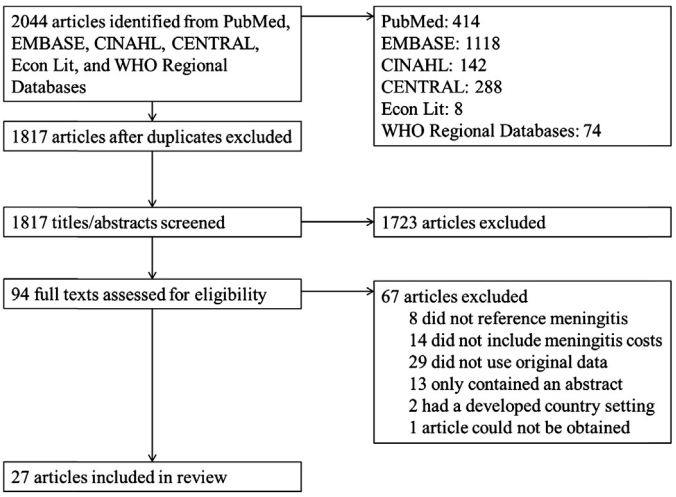

Fig. 1. Search results of the literature review.

A total of 27 articles were selected for inclusion in the final review. Table 1 provides characteristics on the study settings, types of costs, and etiology of meningitis discussed in these articles. More than half of the studies (17 studies) came from upper middle-income countries, examined bacterial meningitis (18 studies), and focused primarily on direct costs (18 studies).

3.2. Assessment of quality and study characteristics

Table 2 provides study-by-study information of the indicators of quality that were assessed as well as characteristics of the studies. Every article included in the final review was of observational study design; therefore, observational studies started out with the highest quality rating (as compared to GRADE, which ranks randomized controlled trials of higher quality than observational studies) [5].

3.3. Cost results

Articles provided data on costs for 27 different countries, where some of the studies had overlapping settings and some analyzed more than one setting. The resulting standardized costs of care for meningitis infections in 2012 USD are presented in Table 3.

The direct medical costs of hospital treatment of meningitis infections ranged widely from approximately $37 in Malawi to nearly $25,000 in China, suggesting differences both in infection severity and facility-level costs by setting (Fig. 2).

3.4. Regression results

The equation used to predict treatment costs for meningitis infections relied on GDP per capita, population density, the percentage of the population in urban areas, the mortality rate for children under 5, and the health expenditure per capita. The final model

Table 3
Standardized and aggregated overall costs of care for meningitis.

Country	WHO Region	World Bank Income Level	Costs (2012 USD)
Argentina	AMRO	Upper middle-income	$2413
Belarus	EURO	Upper middle-income	$1341
Brazil	AMRO	Upper middle-income	$3111
Burkina Faso	AFRO	Upper middle-income	$81
Chile	AMRO	Upper middle-income	$4916
China	WPRO	Upper middle-income	$24,700
Colombia	AMRO	Upper middle-income	$6679
Dominican Republic	AMRO	Upper middle-income	$2230
Guinea	AFRO	Low-income	$43
Honduras	AMRO	Lower middle-income	$2012
Indonesia	SEARO	Lower middle-income	$301
Iran	EMRO	Upper middle-income	$6133
Kenya	AFRO	Low-income	$246
Malawi	AFRO	Low-income	$37
Mexico	AMRO	Upper middle-income	$12,909
Nigeria	AFRO	Lower middle-income	$99
Pakistan	EMRO	Lower middle-income	$5188
Panama	AMRO	Upper middle-income	$2523
Russia	EURO	Upper middle-income	$2104
Senegal	AFRO	Lower middle-income	$2609
Thailand	SEARO	Upper middle-income	$549
Tunisia	EMRO	Upper middle-income	$2199
Uganda	AFRO	Low-income	$313
Uruguay	AMRO	Upper middle-income	$4173
Uzbekistan	EURO	Lower middle-income	$300
Venezuela	AMRO	Upper middle-income	$1934
Viet Nam	WPRO	Lower middle-income	$164

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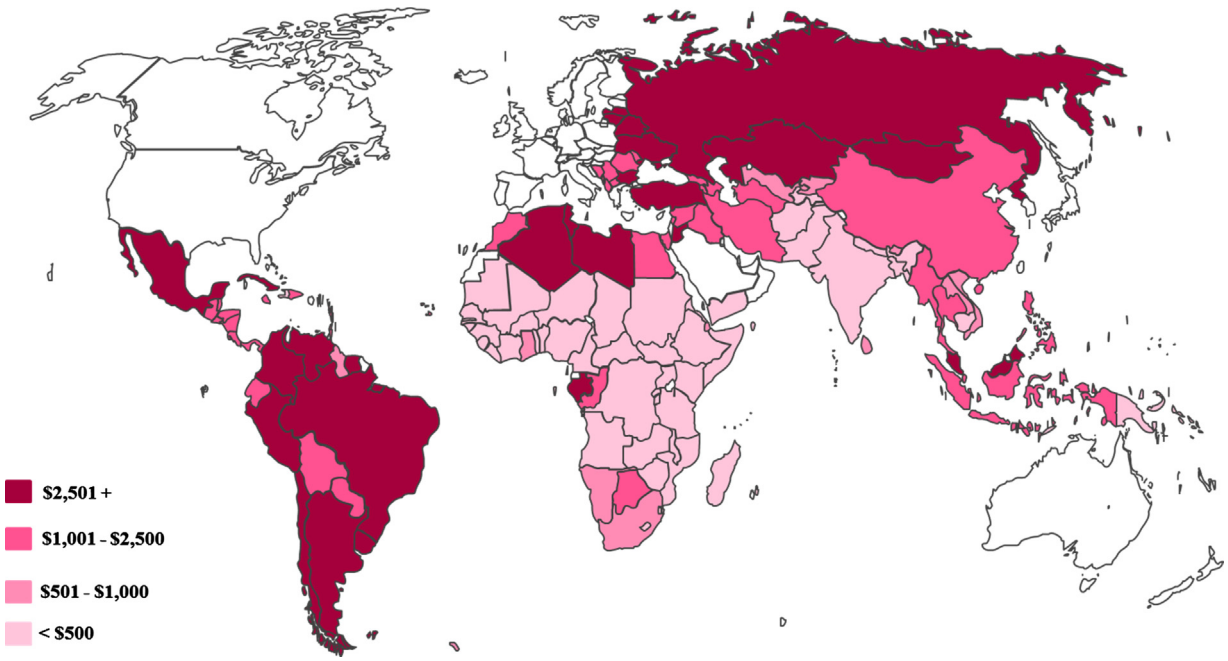

Fig. 2. Map of treatment costs (2012 USD).

Table 4
Results of multiple linear regression analysis before predicted costs.

Variable	Coefficient	Standard Error	*P*-Value	(95% Confidence Interval)
GDP per capita	0.0002	0.0002	0.359	(−0.0002,0.0006)
Population density	−0.0015	0.0044	0.731	(−0.0107,0.0077)
% urban population	2.3796	2.3858	0.330	(−2.5819,7.3411)
<5 mortality rate per 1000 live births	−17.9943	7.7752	0.031	(−34.1637, −1.8249)
Health care expenditure per capita	−0.0027	0.0028	0.348	(−0.0086,0.0032)

posits that these determinants logically predict treatment costs by acting as proxies for how meningitis treatment costs are likely to differ across countries by assuming that costs scale by the income level of the country, the regional differences based on the distribution of the population, and the level of health care provided in that country.

While several of the covariates were not significant in the regression results (Table 4), nested model *F* tests indicated that the covariates significantly contributed to the model as a group ($p < 0.001$). In addition, the AIC criterion indicated that the final model performed best in terms of possible out-of-sample prediction, i.e., balancing model parsimony and fit on the available sample. Regression diagnostics of the residuals showed no systematic relationship between residual and fitted values, also indicating good model fit to the data. The final model used to predict costs had an *R*-squared of 0.62.

We extrapolated the treatment costs from the 27 settings to 144 low- and middle-income countries using the following equation:

$$\text{Cost}_i = \exp\left[\beta_0 + \beta_1 \times \text{GDP}_i + \beta_2 \times \text{density}_i + \beta_3 \times \text{urban}_i + \beta_4 \times \text{mortality}_i + \beta_5 \times \text{health}\ \exp_i + \sum_j \frac{e_j}{N}\right],$$

with e_j denoting the residuals of the dataset used for analysis with sample size N and the term $(\sum_j e_j/N)$ correcting for retransformation bias.

Overall, these costs ranged from $42 to $9300. The median treatment cost by income level was $170 for low-income countries; $790 for lower-middle income countries; and $2100 for upper-middle income countries. The median treatment cost by WHO region was $250 for AFRO; $2000 for AMRO; $1500 for EMRO; $2100 for EURO; $630 for SEARO; and $890 for WPRO. The full list of predicted treatment costs can be found in Appendix 1.

4. Discussion

This review found that primary data on the costs of care for meningitis are available in a fifth of the LMICs and suggest a standardized costing methodology using multiple linear regression analysis to model costs in other countries. These extrapolated estimates can not only be useful for cost-effectiveness analyses at the global or regional levels, but also in the absence of quality data at the country level. For example, instead of using neighboring country data or regional data when primary cost data are unavailable [39,75], this method may provide a more informed estimate. Specifically, this type of analysis can contribute to future country-level analysis conducted by projects like WHO-CHOICE by providing revised inputs to update facility cost estimates [76]. While in-country cost-effectiveness analyses strive to rely upon rigorously validated country-specific cost data based on large, population-linked databases or prospective data collection, these studies are expensive and rare. Econometrically modelled country-specific costs provide a broad indication of treatment costs that may be preferable to raw country-level data without reliable, standardized review.

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Table 5
Predicted model fit (2012 USD).

Country	WHO region	Level of data (*n*)	Treatment costs	Predicted costs	% Difference
Argentina	AMRO	Country (1) + Regional (1)	$2413	$5151	113
Belarus	EURO	Country (1)	$1341	$4423	230
Brazil	AMRO	City (1) + Regional (2)	$3111	$2693	−13
Burkina Faso	AFRO	Province (2)	$81	$51	−38
Chile	AMRO	Regional (3)	$4916	$5679	16
China	WPRO	City (1)	$24,700	$2083	−92
Colombia	AMRO	Country (2) + Regional (1)	$6679	$3001	−55
Dominican Republic	AMRO	Regional (1)	$2230	$1957	−12
Guinea	AFRO	City (1)	$43	$152	251
Honduras	AMRO	Regional (1)	$2012	$1495	−26
Indonesia	SEARO	Facility (1)	$301	$1598	431
Iran	EMRO	City (1)	$6133	$2116	−65
Kenya	AFRO	Country (2)	$246	$253	3
Malawi	AFRO	City (1)	$37	$152	315
Mexico	AMRO	Country (1) + Regional (1)	$12,909	$3971	−69
Nigeria	AFRO	Province (1)	$99	$149	50
Pakistan	EMRO	Facility (1)	$5188	$289	−94
Panama	AMRO	Regional (1)	$2523	$2128	−16
Russia	EURO	City (1)	$2104	$9319	343
Senegal	AFRO	Facility (1)	$2609	$477	−82
Thailand	SEARO	Facility (1)	$549	$1599	191
Tunisia	EMRO	Country (1)	$2199	$2716	24
Uganda	AFRO	Facility (1)	$313	$127	−59
Uruguay	AMRO	Country (2) + Regional (1)	$4173	$4709	13
Uzbekistan	EURO	Country (1)	$300	$628	109
Venezuela	AMRO	Regional (1)	$1934	$5756	198
Viet Nam	WPRO	Province (1)	$164	$655	300

The main limitation of this analysis is the small sample size, which also affects checks on distributional assumptions for the regression analysis. Although we cannot adequately test the normality assumption of the error term, studies have shown that the *F*-test, utilized in this analysis, behaves conservatively [18]. We also cross-checked our results utilizing the non-parametric bootstrap method, which has been shown to work well for small sample sizes [77]; both methods produced very similar results.

The quality of these figures are impacted by the low level of primary data in the literature and the lack of standardization across study designs and types of costs presented. The findings of the systematic review suggest that only 19% of LMICs have primary data available for treatment costs of meningitis. Of the 27 countries with primary cost data available, the majority were from AFRO (8) and AMRO (10) regions, while the remaining regions relied on data from 1–3 countries, which may limit the robustness of the predictions for these regions. In addition, while 18 articles focused on the direct medical costs of care for meningitis, nine articles were also able to include indirect costs, such as transportation and caregiver costs. Because indirect costs such as transportation costs and productivity losses were not standardized study by study, the exclusion of these costs, as well as costs accrued in facilities other than a hospital, in the standardized costs of care is an additional limitation of this study.

In order to present treatment costs by country, the method to weight costs for country settings with multiple primary data points was developed as a means to standardize to a single treatment cost figure for each country. While this method was systematically used for multi-study countries, the weighting factor has not been externally validated. For the regression model, non-parametric methods may have provided additional advantages in accounting for large errors in the investigation of these data, but those advantages are likely to be negligible given the small number of country treatment costs available. While this statistical analysis is limited by the sparse availability of primary data [78], the current data included could also be improved in the quality and the level of reporting, as nine articles in the review included cost figures that were based on physician, patient, or expert interviews [6,79–86].

The model does a fair job of predicting treatment costs in the countries which had primary data available from the facility, city, province, or country level, apart from a few countries with results based on regional analyses (Table 5). While predicted model fit would be expected to have projected treatment costs that are more closely aligned with the observed treatment costs, we see that predicted costs often differ due to the large variability of the original cost data across countries. The generalizability of the original cost data to the national level is a further limitation of the sample costs, which were sometimes collected at the facility, city, or province level. In addition, the robustness of the fit may be affected by the limited sample size.

Despite these limitations, the methodology employed in this systematic review and subsequent cost analysis enables the useful estimation of the costs of care for meningitis infections across 144 low- and middle-income countries. The quality score was designed to be relevant to the context of costing studies in order to estimate meningitis treatment costs across a variety of cost categories. Beginning with 27 studies of varying quality, we determined standardized meningitis treatment costs for 27 different countries, enabling a more disease-specific look at hospital treatment costs in addition to providing a foundation for our cost extrapolation.

This study also underscores the need for future research, not only for gathering additional primary cost data, but also for developing additional methods for this type of cost extrapolation. Future research on standardizing cost databases specific to vaccine-preventable diseases, among others, will be important for cost-effectiveness studies in countries without reliable data.

Data sources for this type of analysis are subject to many forms of bias and measurement error. The results of this analysis can be useful for providing an understanding of what costs might be for countries where data availability is poor, and may help to inform policy-making around disease interventions such as immunization. The science in this field of cost estimation is still rapidly evolving.

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This exploratory data analysis can provide valuable insight into cost estimation in data-limited environments.

Authorship

AP, MJ, SO, MS, and RH designed the study. AP, MJ, JL, AB, and RH developed the methodology. AP and JM collected the data and performed the analysis. All authors contributed to drafting and critical revision of the manuscript and have approved the final article.

Sources of support

Department of Immunization, Vaccines & Biologicals, World Health Organization, Geneva, Switzerland.

Conflict of interest statement

None declared. The views expressed in this article are that of the authors and do not necessarily represent the views of the World Health Organization.

Acknowledgements

We thank the World Health Organization, for its financial and intellectual support of this research; Damian Walker for advice on particular issues; and Marie-Pierre Preziosi for sharing information and expertise.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.11.061.

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Vaccine 33S (2015) A248–A254

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Rotavirus vaccine effectiveness in Latin American and Caribbean countries: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Rotavirus vaccines
Rotavirus vaccine effectiveness
Meta-analysis
Latin America and the Caribbean region

ABSTRACT

Introduction: There are two group A rotavirus (RVA) vaccines available worldwide since 2006: monovalent (Rotarix®, RV1) and pentavalent (RotaTeq®, RV5). Currently, 16 countries and 1 territory in Latin America and the Caribbean (LAC) have introduced RVA vaccines and since their introduction several impact and effectiveness studies have been conducted in different countries. The purpose of this study was to assess RVA vaccine effectiveness in LAC countries.

Methodology: We conducted a systematic review and meta-analysis of studies in children under-five who were admitted with laboratory-confirmed RVA diarrhea. We searched Medline, WOS, LILACS, Scopus, and other sources from 2006 to October 2013. Two independent evaluators identified the studies that met predefined selection criteria and extracted relevant information according to a protocol. Pooled estimates were obtained with fixed and random-effects models and stratified according to selected effect modifiers.

Results: Of the 806 articles meeting the initial criteria, 8 case-control studies which involved 27,713 participants (6265 cases and 21,448 controls) were included in the final analyses. The pooled estimates were calculated using different types of controls, leading to different degrees of effectiveness. The effectiveness of two doses of RV1 against rotavirus-related hospitalizations ranged from 63.5% (95% CI: 39.2–78.0) to 72.2% (95%CI: 60.9–80.2). Effectiveness ranged from 75.4% (95%CI: 64.6–82.9) to 81.8% (CI 95%:72.3–88.1) among infants <12 months for RV1, and from 56.5% (95%CI: 26.2–74.3) to 66.4% (95%CI: 54.1–75.5) for infants >12 months. The RV5 effectiveness for diarrhea with a Vesikari score >11 in infants 6 to 11 months old ranged from 76.1% (95%CI: 57.6–86.6) to 88.8% (95%CI: 78.3–94.3). Also, it showed 63.5% (95%CI: 29.4–82.6) of effectiveness against G2P [4].

Conclusion: RVA vaccines consistently showed protection against diarrhea-related hospitalizations in LAC. Results were more robust for RV1. Effectiveness was shown with different types of controls, but appeared somewhat higher with community controls. Effectiveness was higher among infants <12 months and lower in older children.

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1. Introduction

Group A RVA infect nearly every child by the age of 3–5 years and are globally the leading cause of severe, dehydrating diarrhea in children under five years of age [1,2]. Globally, RVA diarrhea in 2008 resulted in 453,000 deaths in children under five, comprising 37% of deaths attributable to diarrhea and 5% of all deaths in children <5 years [3]. It was estimated for 14 countries in Latin America that RVA caused 6302 deaths and 229,656 hospitalizations annually in the absence of RVA vaccination [4]. More recently, was estimated that RVA caused approximately 197,000 deaths in 2011 which means that it still is the most important cause of diarrhea-related mortality worldwide [5].

RVA are non-enveloped dsRNA viruses with a segmented genome (11 gene segments) and based on their two outer capsid proteins, VP7 and VP4, RVA have been classified into G (glycoprotein) and P (protease-sensitive) genotypes [6,7]. In 2006, two new human, live-attenuated oral vaccines, RotaTeq® (RV5) (Merck and Co.) and Rotarix® (RV1) (GSK Biologicals, Rixensart, Belgium), were licensed. RotaTeq® (RV5) is an oral pentavalent human-bovine reassortant vaccine (G1, G2, G3, G4, P [8]) that is administered in a 3-dose schedule. Rotarix® (RV1) is an oral attenuated human

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http://dx.doi.org/10.1016/j.vaccine.2014.11.060
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monovalent vaccine (G1P [8]) that is administered in a two-dose schedule. These vaccines have proven to be safe and effective in clinical trials in different countries [8,9]. They are recommended for use in all countries by the World Health Organization (WHO), particularly in those countries with high diarrhea-related mortality in children <5 years [10].

As of May 2014, 16 LAC countries and one territory have introduced RVA vaccines into their universal immunization program: Brazil, El Salvador, Mexico, Nicaragua, Panama, and Venezuela in 2006; Ecuador in 2007; Bolivia in 2008; Colombia, Honduras, Peru, and Cayman Island in 2009; Guatemala, Guyana, and Paraguay in 2010; Dominican Republic in 2012 and Haiti in 2014[11,12].

In LAC, since the introduction of RVA vaccines, several studies have demonstrated their effectiveness, especially for severe diarrhea leading to hospitalizations and deaths. However, these studies have shown reductions in child hospitalization and mortality with a variation in the magnitude of the protective effect of the vaccines, also when comparing the effect of two different vaccines that are currently available [13–19]. In this paper we reviewed the benefits, limitations, and consistency of results in studies measuring RVA vaccine effectiveness in LAC children. We critically assess the similarities and differences in methodology and findings of observational studies and compare RVA vaccine effectiveness.

2. Methods

2.1. Inclusion criteria

We selected the studies using the following criteria: those conducted in LAC countries in hospitalized children <5 years; intervention restricted to monovalent or pentavalent RVA vaccines; RVA cases confirmed with laboratory diagnosis; and comparative studies where it was possible to calculate vaccine effectiveness. If data were duplicated or shared in more than one study, we included the most recent publication.

2.2. Literature search

We searched Medline (PubMed data base), LILACS, Scopus and Web of Science, from 2006 to October 2013 using key words related to rotavirus, such as “rotavirus infection”, “rotavirus disease”, “rotavirus hospitalization”, “rotavirus death” “rotavirus vaccines” and “rotavirus impact and effectiveness studies” in all countries of LAC. We also contacted 10 experts on RVA studies from LAC looking for unpublished articles, thesis, and reviewed the literature of relevant articles to locate additional publications. Additionally, we obtained and confirmed some data from researchers. There was no restriction regarding languages.

2.3. Study selection and data extraction

In the first phase three independent evaluators reviewed the abstracts in order to identify the studies that met predefined criteria. In the second phase two independent evaluators selected studies where all the relevant information should be abstracted in a data-collection form based on a standardized protocol. Disagreements between evaluators were resolved through discussion. That process was summarized in a flow chart (PRISMA) [20].

2.4. Quality assessment of the methodology

We assessed the methodological quality of the selected studies using the Newcastle–Ottawa Scale (NOS) for observational studies in meta-analysis [21]. A NOS system score ranges from 0 to 9, with 7 or higher being generally considered satisfactory.

We calculated the pooled odds ratios and the respective 95% confidence intervals using fixed and random effect models. The pooled odds ratios were converted into vaccine effectiveness (VE) using the following formula: $VE = (1 - \text{odds ratio}) \times 100$. As the case-control studies presented different control groups such as community, hospitalized controls, RVA negative test (EIA), and combined controls, we decided to summarize the effectiveness of the most common control groups established in the studies which was the hospitalized controls. However, we also pooled estimations using the other control groups when the number of studies allowed for this type of analysis.

Heterogeneity among studies was assessed through: (i) visual inspection of forest-plots; (ii) chi-squared for heterogeneity and; (iii) Higgins *I*-squared (I^2). In the case of the latter, values over 40% were considered as indicative of relevant inconsistency between studies.

The main exposition variables studied were vaccine type (RV1 or RV5) and vaccine schedule (complete or incomplete). A subgroup analysis was also performed to explore the role of potential effect modifiers such as the Vesikari score (>11 and >15), age (6 to 12 months and >12 months); Vesikari score >11 and >15 by ages 6 to 12 months and >12 months.

A sensitivity analysis was conducted both to explore possible sources of heterogeneity and assess the accuracy of our findings [22]. We performed an analysis to evaluate the impact on effectiveness by using different types of controls and removing some studies.

Statistical analysis was performed using Stata software. StataCorp 2007. Stata Statistical Software: Release 10.College Station, TX: StataCorp LP.

3. Results

3.1. Identification and characteristics of selected studies

We selected 806 records meeting protocol eligibility criteria and excluded 58 duplicated articles. We excluded an additional 670 articles that did not meet the selection criteria after a thorough revision of titles, abstracts and, in many cases, methodologies. After reviewing the full text of 12 records, four were excluded (Fig. 1).

The remaining eight records were case-control studies considered to have a satisfactory methodological quality based on NOS score 7 or higher. Two studies had not been published when the systematic review was conducted and were located by contacting specialists [23,24].

The final eight studies included a total of 27,713 participants (6265 cases and 21,448 controls) and all of them were among children <5 years of age. Six studies estimated VE for the RV1 vaccine and two for the RV5 vaccine. From the selected studies, three were conducted in Brazil, two in Nicaragua, and one in each of the following countries: Bolivia, Colombia and El Salvador. Severe diarrhea hospitalizations were the main outcome to estimate VE of complete vaccination schedules using different types of controls (Table 1). Six case-control studies were designed using individual matching, at least for age, and one used frequency matching. The pooled measures of VE for the different outcome definitions showed an important variation according to the type of control. We could not perform any meta-analysis including all of the eight case-control studies together due to the different interventions and specific objectives across studies.

3.2. Effectiveness of Group A RVA vaccines

VE according to different subgroups used primarily hospital controls. If the study was not designed using hospital controls, we performed an analysis using another type of control.

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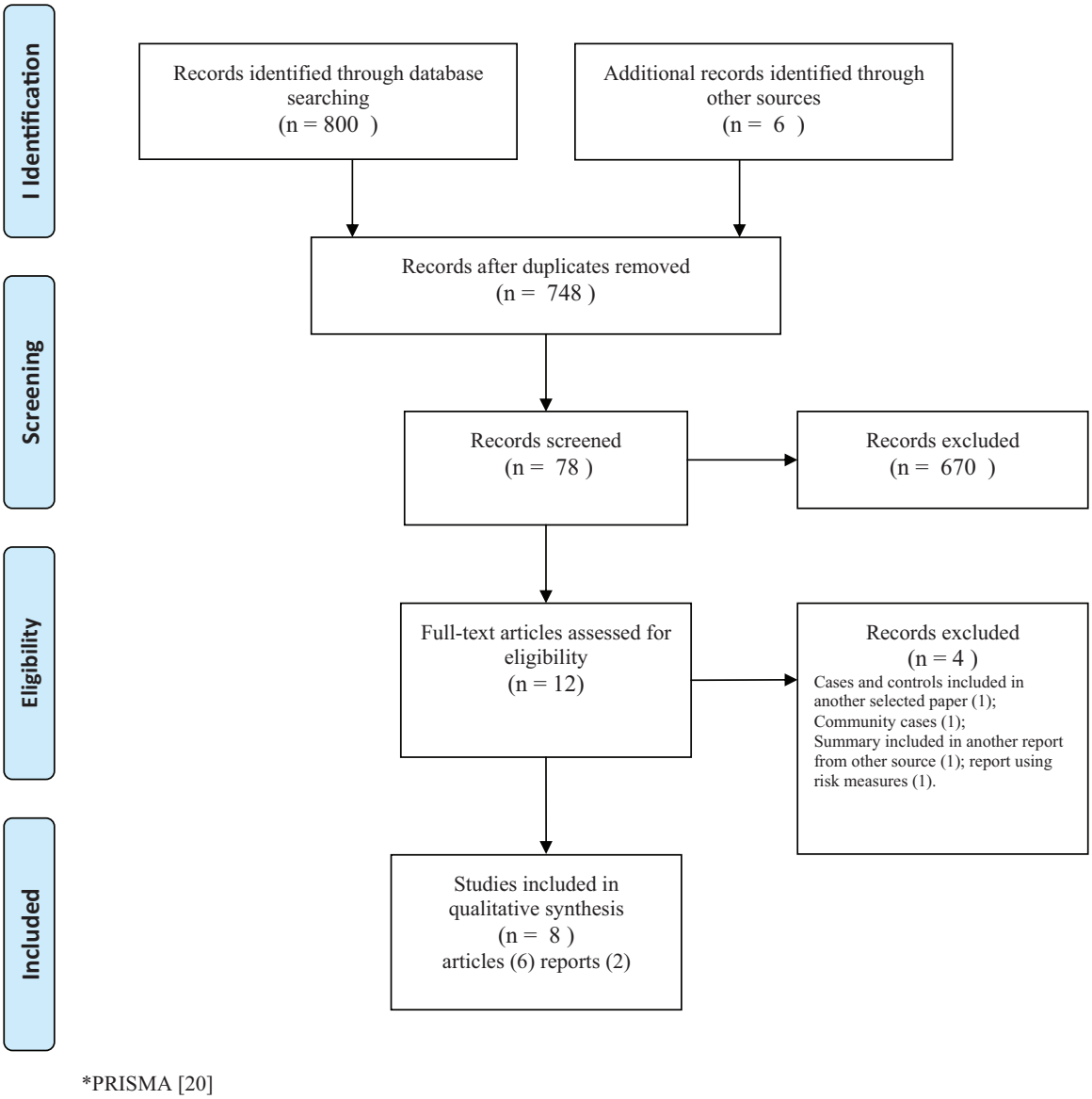

Fig. 1. Flow of information through the different phases of a systematic review*. * PRISMA [20].

Table 1
Characteristics of 8 case-control studies selected for the meta-analysis by year, country, vaccine, objective, number of cases and controls.

Author	Year	Country	Vaccine	Study objective	Number of cases	Type and number of controls
Correia et al.	2010	Brazil	RV1	VE against severe diarrhea and hospitalization caused by infection with fully heterotypic G2P4 strains	70	Hospital = 416 EIA test negative = 484
De Palma et al.	2010	El Salvador	RV1	VE of 2 doses of the vaccine against rv diarrhea requiring hospital admission	323	Neighborhood = 969
Justino et al.	2011	Brazil	RV1	VE of 2 or 1 dose of vaccine in hospitalized children	538	Neighborhood = 346 Hospital = 507
Mast et al.	2012	Nicaragua	RV5	VE in reducing risk of RVA resulting in hospitalization and emergency department visit with 3 doses of vaccine	502	Neighborhood = 1685 Hospital = 1894 Combined = 3579
Patel et al.	2012	Nicaragua	RV5	To define the duration of protection of 3 doses of vaccine	1016	EIA test negative = 4930 Neighborhood and hospital = 5627
Patel et al.	2013	Bolivia	RV1	VE against hospital admission with 2 doses of vaccine	400	Hospital = 1200 EIA test negative = 718
Ichihara et al.*	2013	Brazil	RV1	VE in preventing hospitalization against RVA and genotype specific with 2 doses of vaccine	215	Hospital = 1961
Cotes-Cantillo et al.*	2013	Colombia	RV1	VE against severe diarrhea with 2 doses of vaccine	173	Rapid test negative for RVA confirmed for EIA test negative = 711

* Ichihara and Cotes-Cantillo were selected from specialist reports in 2013 and published in 2014.

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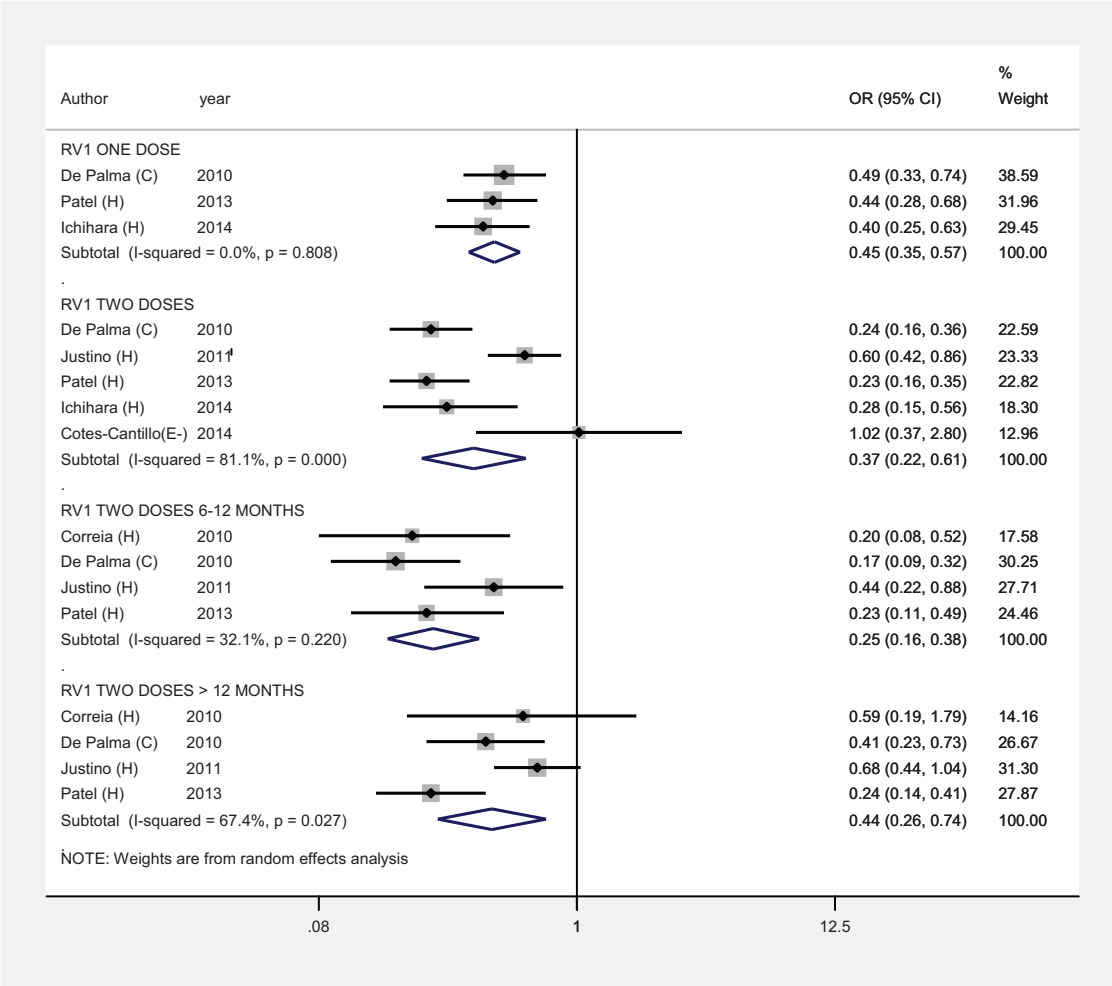

RV1: Monovalent vaccine

C: Community control

H: Hospital control

E-: EIA test negative

Fig. 2. Monovalent rotavirus vaccine effectiveness, according number of doses and age. RV1: monovalent vaccine. C: community control. H: hospital control. E-: EIA test negative.

Fig. 2 presents the results obtained in our study using random-effect models due to the heterogeneity of estimates across studies.

The pooled estimate of three studies [13,19,25] which assessed VE of one dose of RV1 was 55.5% (Fig. 1); however, when we performed the analysis using EIA test negative as a control group in the Patel et al. study [13], the pooled VE was reduced to 49.8%.

As shown also in Fig. 2, five studies [13,23–26] evaluated VE of two doses of RV1 against RVA hospitalizations and the pooled measure was 63.5%. When the VE estimate with hospitalized controls was replaced by community controls, used in the Justino et al. study [26], the VE improved to 72.2%.

VE for two doses of RV1 in children from 6 to 12 month was 75.4% in the primary analysis [13,26–28], and improved to 81.8% when the alternative estimate using community controls of Justino et al. [26] was considered. Regarding the VE in children >12 month, effectiveness was also improved, when using the community control of Justino et al. [26], increasing to 66.4% compared with the results shown on Fig. 2 [13,26–28].

The random-effects pooled measure including three studies [23,25,26] for RV1 Vesikari >11 score in all ages presented a VE of 48.2% (Table 2). A sensitivity analysis was done without considering the Cotes-Cantillo et al. study [23], to explore the degree of VE variation. The results changed significantly and VE was 65.0% (95%CI: 40.6 to 79.3). For RV5 Vesikari >11, including two studies [14,18], pooled VE was 68.4%. Analysis for RV1 Vesikari >15 contemplated three studies [23,25,26] and VE was 39.2% (Table 2). Sensitivity analysis disregarding Cotes-Cantillo et al. [23] showed a pooled VE of 65.3% (95%CI: −98.6 to 91.5), which is similar to the previous analysis, with both estimates presenting large confidence intervals.

Some of the studies [14,18,23,25] allowed to stratify the subset with Vesikari >11 score by age. The pooled VE in children from 6 to 12 months was 76.2% and 76.1% for RV1 and RV5, respectively, with no substantial heterogeneity between them. However, it is important to note that these analyses contemplated only two studies for RV1 and two for RV5 (Fig. 1). The same analysis for RV5 was performed with community controls [14,18], increasing the VE to

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Table 2
Summary of RV1 and RV5 effectiveness, according type of control and Vesikari subgroups, using random effects model.

Study/country	Type of control	Weight (%)	Heterogeneity, I^2%	Summary VE	95%CI
Vesikari >11 all ages by vaccine RV1 and RV5					
De Palma et al.—BOL	Community	21.6			
Justino et al.—BRA	Hospital	20.6	79.2	**48.2***	**−83.6 to 97.6**
Cotes-Cantillo et al.—COL	EIA test negative	11.8			
Mast et al.—NIC		22.7	0	**68.4****	**56.4 to 77.1**
Patel et al.—NIC		23.3			
Vesikari >15 all ages by vaccine RV1					
De Palma et al.—BOL	Communiny	25.4			
Justino et al.—BRA	Hospital	25.1	78.4	**39.2***	**−97.5 to 84.9**
Cotes-Cantillo et al.—COL	EIA test negative	22.9			
Vesikari >11 in children from 6 to 11 months by vaccine RV1 and RV5 with complete schedule					
De Palma et al.—ELS	Community	27.43			
Cotes-Cantillo et al.—COL	EIA test negative	7.6	0	**76.2***	**47.9 to 89.1**
Mast et al.—NIC	Hospital	23.9			
Patel et al.—NIC	Hospital	41.1	0	**76.1****	**57.6 to 86.6**
Vesikari >11 in children >12 months by vaccine RV1 and RV5 with complete schedule					
De Palma et al.—ELS	Community	26.7			
Cotes-Cantillo et al.—COL	EIA test negative	14.8	77.7	**22.8***	**−1.91 to 79.6**
Mast et al.—NIC	Hospital	29.9			
Patel et al.—NIC	Hospital	28.6	0	**61.6****	**42.8 to 70.8**

* RV1 (monovalent vaccine).
** RV5 (pentavalent vaccine).
ELS—El Salvador; BRA—Brazil; COL—Colombia; NIC—Nicaragua; BOL—Bolivia.

88.8% (95%CI: 78.3 to 94.3), and using combined controls, VE was 76.0% (95%CI: 68.0 to 82.0).

Two studies measured RV1 effectiveness in the subgroup Vesikari >15, by age [23,25]. The pooled VE for 6 to 11 months was 82.0% (CI 95%:20.8 to 95.9) using community controls for the De Palma et al. study [25] and EIA test negative for the Cotes-Cantillo et al. study [23]. In the subgroup Vesikari >15, age >12 months, the pooled VE was 81.8% (CI 95%:29.9 to 95.3). In both age groups, the accuracy of the pooled estimates was affected by the large confidence intervals in the Cotes-Cantillo et al. study [23]. The random effects pooled VE from three studies of RV1 [13,24,26] was 63.5% (95%CI: 29.4 to 82.6) for the genotype G2P [4] in all ages with a complete vaccination schedule.

4. Discussion

According to our knowledge, this is the first meta-analysis studying RVA effectiveness in LAC which is the main strength of this study. Overall, our findings showed that both vaccines, RV1 and RV5, protected against RVA-diarrhea hospitalizations, especially in children <5 years with a complete vaccination schedule, for whom the effectiveness estimate was around 75%. We highlight the 63.5% effectiveness of RV1 against genotype G2P [4] since this strain seems to be naturally re-emerging in Latin America [29]. Also of interest was the pooled 55.4% VE for one dose of RV1 among infants <12 months. That implies substantial protection in settings where it is difficult to reach children to complete vaccination schedules and, when it is not possible to administer the complete schedule before 12 months of age. Another important point to be considered is that a significant proportion of RVA cases occur before the age in which the vaccine schedule should be completed [30].

In general, we did not find significant differences in the magnitude of the pooled measures for the main outcomes when compared with the results of the selected studies included in our meta-analysis. Overall, the magnitude of VE across studies indicated the vaccine afforded substantial protection in several countries, which was consistent across different programmatic conditions, peak seasons of RVA infection, and environmental and social and economic status.

The results from this study represent the protective effect of the vaccines in the "real world", which is often lower compared to the artificial settings of clinical trials. The efficacy of the RV1 against severe RVA gastroenteritis and against RVA-associated hospitalization was 85%, and reached 100% in the case of more severe RVA gastroenteritis in the clinical trial [9]. For the RV5, the efficacy was 94.5% for hospitalizations and emergency visits related to RVA genotypes G1–G4 causing gastroenteritis [8]. This discrepancy of RVA efficacy and the effectiveness of immunization programs for RVA is consistent with results that have been reported in the literature in low and middle income countries of Africa [31].

In this meta-analysis, all studies were case-controls, their case definitions were based on WHO recommendations [32], effectiveness was measured by adjusting for potential confounding variables, and presence of RVA was tested by EIA. Also, cases and controls established the vaccination status based on records which show a degree of accuracy in measuring the main exposure. Many of them remark the exclusion criteria of controls when infants presented a vaccine-preventable disease, avoiding selection bias. Those features give confidence that the studies included in the meta-analysis are homogenous. However, we found an important variation regarding the type of controls in the studies identified. Primarily, we tried to analyze the data using hospital controls, but some of the studies did not use this type of controls as mentioned in Section 3. Consequently, we performed different analysis using different control groups and the effectiveness consistently increased when we included community controls in the pooled measure for all of the outcomes studied.

These findings deserve special attention because it has been recognized that case studies using multiple control groups occasionally produce discordant results [33]. Also, some authors consider the presence of a control selection bias if results are different depending on the control group utilized. However, the case-control approach is widely used to evaluate VE and all of the observational studies must control confounding variables to ensure estimates are not biased. Nevertheless, protocol studies must evaluate the possibility of a control selection bias which is liable to be introduced when they are not representative of the population producing the cases [34]. Some of the studies in this meta-analysis, and

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also other authors, refer that neighborhood controls provide the advantage of controlling potential confounding variables, particularly, socio-demographic status and vaccination access [25,26,33]. On the other hand, it is recognized that the "ideal" control group rarely exists in epidemiologic studies [35].

Our study has some limitations, especially regarding the issue discussed above, where different types of controls were used in the studies and different subgroups were also analyzed across the studies. This has shown a variation in the estimates resulting from studies with different types of controls, but the pooled measure of some critical endpoints was performed with a few studies. This also hampered the analysis of the publication bias and the performance of meta-regression. Some of the analyses are not sufficiently robust to conclude the real effectiveness in these different subgroups. This was of particularly concern in the case of RV5, which was assessed in only two studies, one of them sponsored by the vaccine manufacturer. On the other hand, consistent results from different outcomes provided wider and complementary perspectives of the performance of RVA vaccination. Another possible limitation refers to selecting only case-control studies as mentioned before. The definition and selection of controls from studies were assessed with a good score in the NOS. However, it could be possible that this score did not identify some of the weaknesses of the study design, in particular, the control selection.

The studies of Cotes-Cantillo et al. [36] and Justino et al. [26] presented discrepant VE results when compared with other studies, since they showed that the estimation of effectiveness had an important variation in its magnitude. The sensitivity analyses, when we excluded Cotes-Cantillo et al. study [23], significantly increased the effectiveness of the outcomes in the meta-analysis which also occurred when the community control from the Justino et al. study [26] was used. Authors explored some explanations for this discrepancy. In the Justino et al. [26] study, it is recognize that hospital controls are under-vaccinated; in the Cotes-Cantillo et al. study [23] – which found a lower VE – authors raised the issue of the high vaccine coverage when the study was conducted.

In the systematic review we found a significant number of studies in LAC that measured the impact of these vaccines, focusing mainly on RV1, but they were conducted with different designs and estimation measures; thus, it was not possible for us to include them in the meta-analysis. However, all of these studies showed that vaccines had a significant impact in reducing RVA-diarrhea hospitalizations in children under five years of age [16,17,37] which is consistent with the vaccine effectiveness results presented in our findings.

In LAC, 16 countries and one territory had introduced the RVA vaccines up to May 2014, but few of them performed studies measuring effectiveness, according to our systematic review. Nonetheless, it would be difficult to conduct effectiveness studies in other LAC countries due to the high vaccine coverage in most of them [38], which hampers the contrast of the odds of exposure between cases and controls. Fifty seven countries – mostly middle-and high-income countries – have introduced RVA vaccines into their national immunization programs [39]. Therefore, there are many opportunities to conduct effectiveness studies in countries where coverage still allows it, as well as in those that will be introducing the vaccines in the future. These studies should consider analyzing the same outcomes and using the same group of controls that could generate a meta-analysis involving a greater number of studies in different settings.

In summary, in our meta-analysis on RVA vaccine effectiveness in LAC we found evidence that these vaccines provide good protection against hospitalizations caused by RVA diarrhea in children from 6 to 12 months; lower protection with incomplete schedule and in children >12 months, especially when considering RV1, since there was a greater number of studies to meta-analyze. This evidence ratifies the importance of these vaccines as a public health intervention, reducing the burden of severe RVA disease and supports WHO recommendation to introduce the vaccine into the routine immunization program [10].

Conflict of interest statement

We declare that we have no conflicts of interest.

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