Course 4: CRITICAL APPRAISAL OF ECONOMIC EVALUATIONS OF VACCINES

Basic Course

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Basic Course

CONTENTS

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Introduction

Vaccines are usually considered to be among the most efficient uses of scarce health care resources. Today, there are many under-used and new vaccines available and many more in the pipeline that in the short- to medium-term will not cost the few cents per dose that the traditional vaccines do, but will be ‘multi-dollar’ vaccines. (1)

To evaluate the introduction of new vaccines in the National Immunization Programs, decision-makers will require information on, among other things, their relative cost-effectiveness.

The evaluation of the cost-effectiveness information could be troublesome in some occasions, due to not be familiar with some concepts. In order to help to perform a systematic appraisal of these types of studies, and similarly to other study designs, several health economics evaluation critical appraisal guidelines exist to assist in this process. (1, 2, 3, 4)

The objective of this Course is go through the critical appraisal checklist proposed by WHO (1) to explain the different aspects that needs to be taken into account in the critical evaluation process of vaccine economic evaluations. This guide aims to evaluate the quality and validity of the studies and the interpretation of the results is not its main focus.

It is assumed that the user has a basic knowledge on health economics (which has been developed in the previous Courses of the present course), so this Course will focus on the application of the WHO checklist on a specific study.

The following study will be used as an example in this Course:


We now suggest that you stop here and have a first read of the article that we are going to appraise. This should take you about one hour.
Critical appraisal guidelines provide a checklist of questions aimed to evaluate the quality of a study.

The answers to the checklist of questions should be based on an evaluation of how successfully the key components of an analysis were included in the study write-up and the quality of the information provided. Readers may use the following responses to questions: YES, NO, PARTIALLY, UNCLEAR or NOT APPLICABLE.

YES: The study adequately develops the component.

PARTIALLY: The study partially develops the component.

NO: The study does not develop the component.

UNCLEAR: The study does not report this component or it is unclear its development.

NOT APPLICABLE: It is not applicable the development of the component due to the characteristics of the study.

The checklist will be divided in 8 different topics:

A. Study question and analytic framework
B. Modeling
C. Effects of the intervention
D. Costs
E. Discounting
F. Uncertainty
G. Other Factors
H. Conclusions

A. Question and framework analysis

The objective of this section is to evaluate if the outcomes of the study are adequately chosen regarding the health problem. Also the model structure and comparisons needs to be taken into account. The perspective of the analysis and its costs are also evaluated in this section.

1. Is there a clear statement of the study question?

Yes – but, in the objective it would be useful to state the outcomes to be evaluated (deaths, QALYs, cases).

In this case they stated the objective without naming the specific outcomes.

To assess the costs, health benefits and cost-effectiveness of introducing PCV into the routine child immunization program in Argentina.

2. Have the alternatives being compared been clearly stated?
Yes, the alternatives being compared were clearly stated. They did not include in the objectives the comparison between the two vaccines although vaccines comparison data is provided in the results.

3. Has a cost-utility analysis been performed? If not, has that decision been justified appropriately?

Yes, a CUA was performed. On the contrary there was not performed a CEA. It is advisable to estimate some quality of life outcome as QALY or DALY but also natural units as Life Years Gained is useful to be included.

borne by the healthcare system. Life-years gained are estimated by comparing YLL (years of life lost due to premature mortality) and DALYs (disability adjusted life-years lost due to morbidity and premature mortality) with and without vaccination. Average life expectancies and standard methods were used to calculate DALYs [23]. Age weighting was not assumed for the base case evaluation.

Cost-Effectiveness Ratio (ICER), which indicates the cost per DALY (Disability-Adjusted Life Year) averted expressed in 2009 American dollars (US$).

4. Is the perspective of the analysis clearly stated? If a societal or multiple perspectives have been adopted, have the costs and outcomes been disaggregated to allow judgments to be made from different perspectives? Are the costs and outcomes reported consistent with the perspective reported?

Yes – the analysis was carried out from a public health provider perspective and a societal perspective. As was done in this study is advisable to include more than one perspective to evaluate different cost categories that are related to different perspectives.
5. Are the time frame and analytic horizon clearly stated and justified?

Unclear – They report that the model estimate some outcomes during the first five years of life and also that life years and DALYs gained are estimated but it is not clear whether they modeled from five years till death.

B. MODELLING

6. Are the model structure and implicit or explicit assumptions clearly described?

Partially – the authors refers to another publication an explain succinctly the structure of the model. When is published elsewhere sometimes is useful to provide the structure of the model in an appendix or in a diagram that explains in general the model structure.

7. Is the model type (static, dynamic or stochastic) clearly stated and justified in light of likely changes to the force of infection and the role of chance in the
transmission process? Have the model’s strengths and weaknesses been discussed?

Partially – They report the model type (static cohort) in the discussion but they do not assess its strengths or weaknesses. It is advisable to justify the model structure used in the study.

8. Has the model been validated? If so, has it been validated in as many facets of validation as possible?

Unclear – It is not reported maybe it is reported in the reference mentioned about the model description. The validation of the models is a very useful thing to do, when you are applying the same model in different settings.

C. EFFECTS

9. Was the evidence identified systematically?

Partially - Demographic data were obtained from the Dirección de Estadística del Ministerio de Salud de la Nación. With respect to disease burden estimation they refer to published literature and in some cases (meningitis) national Epidemiology Department of the MOH. When they described the methods for the literature search only sources are stated but not inclusion criteria or literature search date for example.

Regarding vaccine efficacy serotype coverage adjustments were done for both vaccines in IPD but that was not the case for pneumonia or otitis media.
olated from PCV-7 [4,33]. For IPD, serotype coverage adjustments were done for both vaccines, but this was not the case for AOM or consolidated pneumonia, where reliable data on pneumococcal serotype distribution are not available and all-cause AOM and consolidated pneumonia were included. Considering this limitation, a

10. Were the methods of the sources described? If a single study was used, was its internal validity discussed? If multiple studies were used, was the method used to synthesize the results also discussed? Was the external validity of the evidence discussed?

No – It was not reported the internal validity of the sources used or the quality assessment of the sources used to estimate model parameters.

11. Was appropriate evidence of vaccine safety provided or referenced?

No reference was made to vaccine safety. An important point in a vaccine economic evaluation is to state where the vaccine efficacy evidence comes from.

12. If applicable, were the methods of valuation and source of the values described?

Partially – It is described that standard methods were used to calculate Disability-adjusted life years (DALYs).

Are adverse events from immunization impacts likely to have a substantial impact on the results of the analysis? If so, have they been included on both the costs and effects sides of the analysis?

No reference was made to adverse events, but it does not seem that they may have an impact on the results.

D. COSTS

13. Has a summary of the expected resource use and unit costs for each alternative been provided, including a specification of the assumptions behind calculations of the costs?

Yes – Sources of costs were reported and the methods to estimate resource use were stated. The cost estimate methodology is something that is sometimes poorly reported in economic evaluations.

14. If productivity losses were estimated have they been reported separately? Has their relevance been discussed?
Yes – They have been reported separately and also their relevance discussed. In some occasions productivity losses have great impact on the results so is very important to provide different scenarios with and without productivity losses.

Another limitation was the underestimation of household costs. In this study, the healthcare system perspective was the main scenario and only some expenses incurred by the family during hospitalization and the loss of parental labor productivity during such hospitalization were taken into account, but societal costs related to outpatient diseases and post-hospitalization days were not considered. This might account for the small differences observed between the base and alternative scenarios regarding costs per DALY averted for both vaccines.

15. Have the methods used to estimate them been described and justified?

Partially – They mentioned a study that evaluates these costs.

during the hospitalization. The estimate was based on a study conducted within the framework of the scholarship “Ramón Carrillo-Arturo Oñativia 2004” granted by the Ministerio de Salud de la Nación, which investigated societal costs associated with hospitalizations due to acute respiratory infections in children in different public hospitals in Buenos Aires [30]. The estimate has

16. Is the currency stated? If so, is the date of the currency and prices used in the model stated, with details of any adjustments or conversions provided?

Yes – Year and exchange rate was provided.

tividad Clínica y Sanitaria (JECs). All these costs were updated to year 2009 according to variations of the healthcare section of the Consumer’s price index (CPI). The exchange rate used from Argentine pesos to American dollars was $3.70 = US$1.

E. DISCOUNTING

17. Is the discount rate clearly stated and justified?

Yes – all future costs and outcomes were discounted at 3% and justified.
18. Has a sensitivity analysis been conducted to explore the impact of varying the discount rate?

Yes – sensitivity analysis was done although results are presented only in a discounted scenario.

F. UNCERTAINTY

19. Have the costs and effects been presented for all alternatives?

Yes – see Table 5.

20. Have dominated interventions been identified and excluded?

Not applicable – vaccination is both more costly and more effective. There were no dominated strategies.

21. Has sensitivity analysis been conducted to assess the robustness of the findings to changes in the value of key parameters? Has the choice of parameters and the ranges over which they have been subjected to SA, been stated and justified?

Yes – the authors undertook sensitivity analysis for certain parameters, they were reported in Figure 2. However, the reason to choose those parameters was not stated nor was the range used.

22. Has the national CE threshold been used, if one exists? If there is no national CE threshold, have the results of the evaluation been classified according to the per capita national GDP of the country in question?

Yes – the authors used the WHO recommendation that an intervention may be considered very cost-effective if the costs per DALY averted are less than the country’s per-capita GDP.
23. Have the findings been compared to other economic evaluations undertaken in the same or neighboring countries?

Yes – the authors observed that the results are comparable to other studies done in the region.

So far, as our analysis, all of them have shown that vaccination against S. pneumoniae in the region is cost-effective and would represent a high-impact intervention for the national public health status due to the high disease burden related to this pathogen, and the costs of the healthcare system associated with treatment.

G. OTHER FACTORS

24. Is there a discussion of other important factors in the decision under consideration, such as affordability, equity or social acceptance?

Yes - The authors make some reference of the underestimation of household costs and also the scarcity of information available in the region. But aspects as affordability, equity or social acceptance were not mentioned.

H. CONCLUSIONS

25. Is an answer given to the study question?

Yes – Both vaccines PCV-10 and PCV-13 are cost-effective when compared to a strategy of no vaccination, taking into account a threshold of U$S 22,000. But when compared PCV-13 against PCV-10, the ICER between both vaccines was U$S 28,147 per DALY saved when using PCV13 instead of PCV10.

26. Do the conclusions follow from the data reported?

Yes

27. Are the conclusions accompanied by the appropriate caveats?

Yes – the authors mention some aspects that can affect the results (PCV10 non-typeable Haemophilus influenzae protection influence on the prevention of AOM, the underestimation of household costs and the exclusion of herd effects).

In general is a good quality economic evaluation study with minor limitations.
REFERENCES


ADVANCED COURSE

Specific aspects to be considered when reading an economic evaluation about vaccines

In the economic evaluations some aspects to be considered are specific when the intervention to be evaluated is a vaccine program.

To facilitate the evaluation of this type of studies WHO published a guideline with the main components to be taken into account (1). Some aspects of this guideline were developed in a previous Course.

Here we will focus on the components that are specifically applied when the objective is the critical appraisal of a study.

Assessing the cost of a vaccination program

In the costing of a vaccination program one important factor is taking into account the cost of the administration of the vaccine and not only the vaccine itself.

This administration cost includes wastage, transportation, storage, personnel and facilities but sometimes a vaccine is administered in conjunction with others vaccine making the cost of an additional vaccine not the simple sum of the costs included.

Other aspects were methodology can vary and the approach used needs to be justified is the estimation of productivity loss.

Costs are recommended to be expressed in local currency, and also to allow global comparisons it is advisable that there are also expressed in US$ official and purchasing power parity (PPP) exchange rate.

Assessing the cost of the outcomes

One important component to be considered are the sequelae if there is any. The costing of the sequelae are in general greater in the first years and less in the following ones. Also the description of the costs of the events and sequelae needs to be described in terms of quantity and price of the resources included.

Assessing the effects of a vaccination program

Vaccine efficacy is obtained from published data; ideally these data should come from a systematic review.

This efficacy needs to be adjusted by vaccination coverage.

Also, if considered important, adverse effects should be included.
Outcomes should be expressed in natural units (cases or deaths), but also in years life lost (YLL) and disability adjusted years life lost (DALYs).

**Modeling**

To estimate the population impact some form of mathematical model in general is used.

Models can be divided in static and dynamic models.

In a dynamic model the force of infection varies over time according to the proportion of the population that is infected. In a static model the force of infection is independent from the percentage of infected population. One should evaluate if the model is the correct one to the problem in question.

In general when the transmission human to human does not exist (rabies, tetanus) and the group infected is not an influential one (elderly for influenza or travelers from low to high endemic areas) one tend to choose a static model. If the otherwise situation occurs a dynamic model would be more appropriate.

Also two important aspects to evaluate in when in the appraisal of a study is the transparency and if possible validation of the model.

Transparent: the structure and assumptions are clearly described

Validated: if possible calibrated or with its predictive value tested.

**Epidemiological inputs**

Another important aspect when reading an economic evaluations is to understand the epidemiological parameters and sources used in the model.

Sometimes these estimations need to be based on some data but some calculations needs to be made to estimate others. These data sources and calculations needs to be described in a detailed way so as to be confident that these parameters are correct.

**Discounting**

The cost effectiveness of vaccination programs is largely affected by discounting, because the intervention is in the present but the benefits are in the future.

It is recommended that the discount rate should be the same that the country in question, but also adding alternate scenarios with 3% discount rate as recommended by WHO and DCP2 and a sensitivity analysis ranging from 0 to 10%.

**Estimating presenting and interpreting data**
It is important that interpretation of cost effective or cost ineffective interventions should not be made on point estimations only. At least one way sensitivity analysis on the following parameters should be performed (vaccine effectiveness and cost, disease incidence, discount rate).

It also recommended when possible that probabilistic sensitivity analysis should be performed on all parameters and acceptability curves be constructed.

This is also more important in countries were the availability of data is scarce so the sensitivity analysis is more important due to the uncertainty of the results.

For the interpretation of the results also it is recommended that the rule proposed by the Commission on Macroeconomics and Health of less than 1 PBI per capita as “highly cost-effective”, between 1 and 3 PBI per capita as “cost-effective” and more than 3 PBI per capita as ineffective, should be used (2).

Other criteria to consider when making decisions about vaccination programs

Cost effectiveness is one of the factors influencing health policy decisions but others as equity, adequacy of demand and public attitudes play also an important role.

An important factor is the degree to which the intervention is culturally accepted and this has a great influence in the compliance. The same interventions can be accepted in one country but not in other due to cultural differences that make the intervention not acceptable in one of them.

Conclusion

Vaccine decision-making is getting more complicated due to the cost of the new vaccines that are much larger than the traditional ones.

Also in many cases these new vaccines are a cost effective intervention taking into account the PBI per capita threshold but the countries are facing the decision of which of these new vaccines they should incorporate because they do not have budget for all of them although they tend to be cost effective.

Taking this into account the others factors mentioned before affecting the decision making process become more relevant.
REFERENCES
