Discussion

Perspectives on the challenge of *Streptococcus pneumoniae* disease burden estimation for national policymakers in Latin America and the Caribbean: From theory to practice

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The United Nations Millennium Development Goals call for a two-third reduction in childhood mortality by 2015 [1]. New vaccines hold the promise of helping reach this goal but come at additional costs to government and society. Estimation of national disease burden is recognized as one of the key technical criteria for prioritizing new vaccine introduction and is a critical component of health economic evaluations [2,3]. Disease burden estimation is one of four sub-models within a cost-effectiveness analysis, complementing intervention effectiveness, intervention cost, and disease cost sub-models.

However, *Streptococcus pneumoniae* (pneumococcus) disease burden assessment remains challenging, particularly for national Ministries of Health, where available resources for such work are constrained. In addition, underreporting of disease burden is a significant problem, as diagnostic testing for pneumococcus misses many cases of invasive pneumococcal disease, due to physician’s choice not to obtain cultures, inadequate volume collection, antibiotic pretreatment, or laboratory practice [4]. Invasive pneumococcal disease is the most severe end of the pneumococcal disease burden spectrum and, for the reasons above, it is often challenging to diagnose. These difficulties are compounded when considering the far more common syndrome of pneumococcal pneumonia, which is almost always diagnosed on clinical grounds, without microbiological confirmation. Finally, uncomplicated pneumococcal acute otitis media is relatively mild and short in duration. It is very rarely microbiologically diagnosed but results in significant loss of parental productivity and increased healthcare resource utilization. Consequently, it can be highly influential in the value of pneumococcal conjugate vaccine [5].

Even high quality surveillance systems miss a large fraction of disease burden, resulting in the invisible base of the disease burden iceberg that is often discussed by pneumococcal disease experts [6]. In contrast, modeled disease burden estimates use available data to account for this undiagnosed fraction of disease. As an example, in the World Health Organization global pneumococcal disease burden model, O’Brien and colleagues used the fraction of pneumonia averted in pneumococcal conjugate vaccine trials to reveal more accurately the pneumonia disease burden caused by pneumococcus. This vaccine probe approach, using the impact of vaccine against syndromes difficult to diagnose microbiologically, is powerful [7] and results from the O’Brien analysis have been widely used [8]. Other models have produced analogous estimates regarding global and regional pneumococcal disease burden [9–11]. While these international disease burden models differ in the exact approaches taken, they have in common the need for extensive systematic review of the literature combined with meticulous development of mathematical algorithms estimating pneumococcal disease burden.
However, national Ministries of Health working at present are reluctant to use such internationally generated estimates for several reasons. In Latin America and the Caribbean, ongoing investments in surveillance and healthcare infrastructure have resulted in the availability of unpublished sources of data such as national health statistics reports, surveillance databases, and national health service data, not usually captured by systematic reviews. In the past ten years, secular declines in childhood mortality have been observed [12], and some international analyses conducted previously [8,11] may not reflect these trends, nor will the most recent published literature be incorporated. Although other international analyses are recent, they have not focused on pneumococcal disease [10].

National policy makers prefer to see national data incorporated into the evidence base supporting their decision making, but in so doing countries face several challenges:

**Challenge #1**: Technical staffs have multiple responsibilities; their time is constrained and project deadlines short. This is in contrast to the extensive resources that have been available to international disease burden exercises.

**Challenge #2**: Published reports providing usable local estimates are usually sparse and may not report the data needed.

**Challenge #3**: When published national data are available, the quality of the evidence, as judged by standard metrics, is often problematic.

**Challenge #4**: These quality issues are not restricted to published reports but are significant in unpublished sources, such as national health statistics, national health services data such as hospital discharge databases, and surveillance data.

**Challenge #5**: Sparse data and quality issues result in uncertainty that must be accounted for, as it will influence results and their interpretation.

Each of these challenges has solutions that can be effectively employed by national policymakers. We use the example of a successful analysis, concerning pneumococcal conjugate vaccine introduction in Argentina, to reflect on potential solutions [13,14].

**Solution #1, constrained professional staff time**: Developing the disease burden information necessary for cost-effectiveness analysis requires a large time investment. The Argentinean study’s leadership developed a multi-disciplinary study team, with reasonable time contributions made by many specialists. These included programmatic expertise from the Expanded Program in Immunizations, health economic experts from the Ministry of Health, clinical expertise from medical researchers in child health, and input on vital statistics and national databases from the governmental department of statistics. An external consultant with a background in clinical infectious diseases was hired to conduct systematic reviews of the literature, data synthesis, and model implementation. Her role proved catalytic, and as a result this consultant role was converted to a permanent position in the Ministry of Health, institutionalizing the capacity to conduct analyses in the future.

**Solution #2, sparse published national data**: When data are either sparse or absent, high quality regional or global data have been used in national models. For example, while Argentina had a number of relevant studies conducted concerning incidence of chest X-ray confirmed pneumonia and invasive pneumococcal disease, no data were available regarding incidence of acute otitis media, a potentially influential syndrome in this low mortality, upper middle income country. After a systematic review of the published literature, the investigators chose to use otitis incidence estimates drawn from a North American study [15]. Their choice was influenced by the full disease burden estimation in this prospective cohort, with active case ascertainment and long follow-up time. In the investigators’ judgment, they used the best quality data available, even though this meant going to an international source.

**Solution #3, quality issues in published data**: Quality assessment is a necessary first step to the employment of available published national data. For example, the Argentinean investigators identified two prospective population-level national studies to estimate the incidence of chest X-ray-confirmed pneumonia in under-five-year-olds. One of them was deemed of superior quality by the investigators but only estimated incidence for under-two-year-olds; the other one was of lesser quality but estimated incidence for under-five-year-olds. Therefore, the investigators decided to use the under-two-year-old incidence from the stronger study and three-to-five-year-old incidence from the alternative study, then calculated an average incidence for all under-five-year-olds. Because both study-derived case fatality ratios were considered unrealistically low due to potential selection bias, the investigators used Ministry of Health statistics regarding all-cause pneumonia mortality rates to estimate deaths, in essence deriving morbidity from two data sources, and mortality from a third data source, allowing for a more accurate estimation of the case fatality ratio.

**Solution #4, quality issues in unpublished data**: As with published data, quality assessment is essential to determining which unpublished data can be used in disease burden estimation. In the Argentinean case, national sentinel surveillance data for invasive pneumococcal disease were available from 1993 onwards and used to evaluate serotype coverage. However, secular trends in the numbers of isolates identified suggested maturation of the surveillance system over time and changes in clinical laboratory practice could not be excluded. As a result, the investigators opted to use the most recent five years of data to develop serotype coverage estimates for use in their model.

**Solution #5, uncertainty regarding results**: As recommended in guidelines and standard references [3,16,17], the investigators performed extensive sensitivity and scenario analysis, particularly focusing on parameters related to acute otitis media and chest X-ray-confirmed pneumonia, as well as vaccine’s potential indirect effects. These uncertainty analyses were a focus of their presentation of results and key messages for decision makers.

The Argentinean case illustrates how key challenges to disease burden estimation for use in cost-effectiveness analysis can be addressed, through mobilization of resources for study conduct, the strategic use of both international and national data, careful consideration of quality when choosing input data, and extensive uncertainty analysis. As countries work to reduce child mortality and avert serious childhood illness, the dissemination of methods, tools and resources and the expansion of technical capacity to conduct these analyses within Ministries of Health will further promote the incorporation of scientific evidence into decision making, contributing to better choices regarding new vaccine introduction.

**Conflicts of interest statement**

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