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Evidence Base for Vaccine Introduction in Latin America and the Caribbean

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Acknowledgements

Jon K. Andrus[a,*], Damian G. Walker[b,1]

[a] Pan American Health Organization, 525 23 Street NW, Washington, DC 20037, United States
[b] Bill and Melinda Gates Foundation, 440 5th Avenue N., Seattle, WA 98109, United States

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* Corresponding author. Tel.: +1 202 974 3178.
E-mail addresses: andrusjo@paho.org (J.K. Andrus), Damian.Walker@gatesfoundation.org (D.G. Walker).
[1] Tel.: +1 206 709 3100.

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Foreword

New vaccines have an incredible potential to continue to be one of the most cost-effective interventions public health has to offer. To maximize the benefits of these interventions, governments need to have access to reliable evidence that will aid them in making informed decisions.

Immunization programs in Latin America and the Caribbean have provided leadership to put evidence at the center of policy-making. One important example is the long history of the Regional Technical Advisory Group on vaccine-preventable diseases (TAG) and the establishment of many National Immunization Technical Advisory Groups (NITAGs) in the region. Another is the existence of vaccine legislation which aims at protecting the achievements and sustainability of evidence-based decisions made by National Immunization Programs while promoting fiscal space and regulations that favor the introduction of cost-effective new vaccines.

With the arrival of new and more expensive vaccines, PAHO has acknowledged the need to provide greater capacity building support to countries on the use of economic analysis for decision making. In this light, with financial support from the Bill & Melinda Gates Foundation, PAHO established the ProVac Initiative with the aim of strengthening the national technical capacity for evidence-based decisions on new vaccine introduction. Over 30 countries have participated in regional training workshops and 14 countries have received direct technical assistance to develop locally derived cost-effectiveness analyses. These efforts have translated into a more equipped and informed group of immunization decision makers in the region.

These ProVac analyses provide valuable evidence for the decision making process around new vaccine introduction. Such analyses are instrumental in evaluating and improving data collection and reporting at the national level. Such work also provides opportunities for increasing the communication and coordination among technical groups within the government and with academic institutions. To this end, in 2010 the ProVac Initiative formed the ProVac Network of Centers of Excellence, which is comprised of academic institutions in the LAC Region with expertise in economic evaluations and decision analysis. These Centers of Excellence have developed methods, tools and practical guides to assist country teams in the generation of national-level evidence to support decisions on immunization, while serving also as a model for South-South cooperation. Findings, challenges and lessons learned from their work are reflected in the content of this supplement of *Vaccine*.

We are pleased to bring this supplement to publication and share some recent research aimed at closing the evidence gap for new vaccine introduction, with a special focus on conjugate pneumococcal and rotavirus vaccines.

PAHO Director
Carissa F. Etienne*
Pan American Health Organization,
525 23 Street NW, Washington,
DC 20037, United States

*Tel.: +1 202 974 3408.
E-mail address: etiennec@paho.org

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Preface

Evidence base for new vaccine introduction in Latin America and the Caribbean

In the past few years, new and underutilized vaccines against diseases associated with high disease burden in developing countries such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), *Neisseria meningitidis*, rotavirus and human papillomavirus (HPV) have become available. These vaccines should substantially contribute toward achieving the Millennium Development Goals by 2015 [1], and have been recommended for inclusion in national Immunization Programs [2–6]. However, these new vaccines are more complex and expensive, and the process of preparing for their introduction requires more time, better communication, and adequate planning for logistic and operational issues, compared to older vaccines. Therefore, national decision makers require a comprehensive evidence base to make informed decisions, including evidence about epidemiological and economic burden of disease as well as the cost-effectiveness and incremental costs to the immunization program.

Recognizing these challenges, Ministers of Health from countries in Latin America and the Caribbean (LAC) at the Pan American Health Organization's (PAHO) Directing Council meeting in 2006 requested PAHO to "support country activities to integrate economic studies into the decision-making process for the introduction of new and underutilized vaccines." In response to this request, the ProVac Initiative was launched, with financial support from the Bill & Melinda Gates Foundation. ProVac has been supporting countries in LAC since then to strengthen the decision making process, including the development of country-led cost-effectiveness analysis of new vaccines, and improving the operational procedures of National Immunization Technical Advisory Groups (NITAGs) [7,8].

To date, ProVac has supported 24 analyses in fourteen countries of the Region. National teams have led the process of obtaining and evaluating the best available evidence on disease burden, vaccine effectiveness, program cost, and disease costs, among others. These data are then used in models developed by the ProVac Initiative, which include TRIVAC, a cost-effectiveness model for *H. influenzae* type b (Hib), pneumococcal and rotavirus vaccine introduction [9] and CostVac, an immunization program costing tool [10]. These models are useful tools for supporting the decision making process only when there is sufficient quantity and quality data to drive them. The ProVac Initiative's first years of experience providing support to countries demonstrated a clear need for standardized methods to develop locally derived evidence to support real-time decisions concerning newer vaccines such as rotavirus and pneumococcal vaccine.

Central to ProVac's activities, a regional network of academic institutions with expertise in supporting public health decision making in the LAC Region – the ProVac Network of Centers of Excellence (CoE) – was established in 2010. As Toscano et al. describes in this supplement, the ProVac Network of CoE was tasked with providing technical support to ongoing activities of the ProVac Initiative, including developing methodological guides for generating accurate estimates on several key factors that are relevant for an informed decision. The Network also worked with developing, reviewing, or adapting models and tools to support economic analysis and evidence-based decision making [11]. This Vaccine journal supplement highlights this work from the ProVac CoE in the LAC region, including commentaries and original research on evidence-based decision making, disease burden, economic burden, cost of illness, cost-effectiveness analysis methods, EPI program costing and impact post-introduction.

Two systematic reviews of cost of illness studies of rotavirus and pneumococcal diseases in the LAC Region bring to light that a variety of methods, perspectives, currencies and approaches have been used to estimate the economic cost of illness in the Region, leading to substantial diversity in the available data [12,13]. Considering the limited external validity of cost data, standardized methods to develop locally derived pneumococcal and rotavirus healthcare service utilization and cost of illness estimates to support decisions have been proposed [14,15].

This supplement also highlights how immunization and surveillance program costs are often underestimated [16]. As a key parameter not only for program management and planning but also for estimating accurate routine immunization program costs and incremental costs of introducing new vaccines, standardized tools and methods to improve costing of immunization programs (EPI) have been developed [10]. CostVac is an EPI costing tool which is to be made available to all countries in the LAC Region and the world to help standardize methods for estimating immunization program costs at all relevant administrative levels.

The Global Framework for Immunization Monitoring and Surveillance (GFIMS) recommends that ministries of health enhance national surveillance of vaccine preventable diseases (VPDs), integrating surveillance when possible. Hyde et al. discusses the critical issues in implementing integrated VPD surveillance system [17]. Considering the experience of Costa Rica, which in 2009 became the first country to implement such integrated surveillance, Toscano et al. have estimated the costs for implementing and maintaining such surveillance in the country level [18].

All these methods and data can support the national decision making processes on new vaccine introduction. Once a decision has been made, operational issues must be considered, and introduction needs to be carefully planned to ensure an efficient and sustainable immunization program. Evidence-based decision making on new vaccines happens on a continuum. Vaccine effectiveness and impact should be assessed after introduction, and a

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decision regarding the new vaccine program continuation will take place [19,20]. Oliveira et al. highlights challenges and opportunities for rotavirus vaccine impact assessment post-introduction using surveillance data [19].

The pressing need for the approaches and methods described in this supplement are highlighted in a second study conducted by De Oliveira et al. [21]. These authors have conducted a qualitative assessment of new vaccine introduction in selected countries in the LAC region, demonstrating that the factors contributing to vaccine introduction in these selected countries generally are not well-grounded in a systematic approach. The authors reiterate a need to ground decisions in criteria including political, technical, programmatic and feasibility aspects [22].

Finally, comments from immunization experts globally will bring to the reader historical perspectives on new vaccines introduction in low-and-middle income countries [23], the importance of institutions for efficient spending in vaccines [24], key factors for sustainable vaccine introduction [25], challenges on estimating disease burden with available national data [26], and the experience of a developed country and early introducer of new vaccines, which can be valuable for developing countries in the Region [27]. The tools, training materials, methodological guides, and an online international vaccine economics and statistics data repository [8] described in this supplement are available to support countries to assess existing data and generate new evidence on new vaccine introduction. Additionally, this supplement shares valuable experience and information with national decision-makers, immunization technical experts, global partners and donors on methods to further strengthen the decision making process of new vaccine introduction in LAC and beyond.

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Jon K. Andrus *
Pan American Health Organization, 525 23 Street NW, Washington, DC 20037, United States

Damian G. Walker [1]
Bill and Melinda Gates Foundation, 440 5th Avenue N., Seattle, WA 98109, United States

* Corresponding author. Tel.: +1 202 974 3178.
E-mail addresses: andrusjo@paho.org (J.K. Andrus), Damian.Walker@gatesfoundation.org (D.G. Walker)

[1] Tel.: +1 206 709 3100.

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Discussion

Historical perspectives on new vaccine introduction in Latin America and the Caribbean

Ciro de Quadros*

Sabin Vaccine Institute, 2000 Pennsylvania Ave NW, Suite 7100, 20006, Washington DC, USA

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Few social programs rival what the Expanded Program on Immunization (EPI) has been able to accomplish for child health [1]. In the Americas, vaccines have transformed the regional disease landscape. The Americas was the first region to eliminate smallpox and the region has been free of wild poliovirus for over 20 years, measles for over 11 years and rubella for over 3 years [2–4]. Today immunization remains a key regional priority for achieving health for all and increasingly countries are expanding their national immunization programs to protect against more disease pathogens [4]. The countries in the Americas continue to be trail blazers in the global efforts to eliminate and eradicate vaccine-preventable diseases.

The advent of new vaccines such as pneumococcal conjugate and rotavirus vaccines have the potential to save countless lives in the Region and globally. Many countries in the Americas have been early introducers of these vaccines [5]. This tendency for early adoption may be rooted in historical evolution of the EPI in the Americas. There are four key historical factors that have contributed to the successful expansion of the EPI in the Americas:

1. Technical cooperation provided by key international and regional players

Efforts to mass immunize children in Latin America and the Caribbean began in 1977, with the establishment of the Expanded Program on Immunization (EPI). In the first few years of these efforts, the Pan American Health Organization (PAHO) was the sole agency providing technical cooperation to the Region. In 1985, the push to eradicate polio from the Western Hemisphere created a need to form an Inter-Agency Coordination Committee (ICC), which included those agencies that were providing either technical or financial support to the program. Agencies represented in the ICC included UNICEF, USAID, Rotary International, the Inter-American Development Bank (IADB) and PAHO. Among these agencies, PAHO continued to lead technical cooperation efforts, while UNICEF provided inputs in the area of social communication and advocacy. USAID, Rotary International and the IDB only provided financial support. At the same time, a Regional Technical Advisory Group on Vaccine-Preventable Diseases (TAG) was formed. This group was charged with providing expert advisory support to PAHO and its Member-States on the technical aspects of the EPI. The Centers for Disease Control (CDC), although not part or either the ICC or TAG was financially supported by PAHO to provide technical expertise for the organization of the polio laboratory network. To this end PAHO provided CDC with the financial support to buy equipment for its virology lab and to support the salary of three virologists. This is quite interesting, as usually CDC would be supporting the program financially as it is now happening. Finally, PAHO also supported Schools of Public Health in the region, for example in Argentina, Brazil and Mexico, and they contributed to the development of EPI training modules, which went on to be used extensively in the Region to train EPI staff at all levels of the health system. The contribution of these key actors led to a more technically and financially strong EPI. In addition, the extensive coordination among actors enabled the Regional program to be more flexible in the face of new challenges, including the arrival of new vaccines.

2. Concrete strategies to promote high-level support for sustainable new vaccine introduction

Several issues favored the early introduction of vaccines in Latin America and the Caribbean. There is a long tradition of the use of vaccines in the Region, which was the first area of the world to eradicate Smallpox. With the establishment of the EPI (1977), the governments of PAHO Member-States demonstrated an early

* Tel.: +1 202 842 5025; fax: +1 202 842 7689.
E-mail address: ciro.dequadros@sabin.org

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commitment to the program with the early appointment and training of EPI Managers and their staff in all countries [6]. This created a cadre of individuals that started advocating for intensive use of vaccines. PAHO developed an EPI newsletter as a platform to share data and best practices between Member-States in the Region, which continues to be an important information sharing tool. PAHO also supported efforts to periodically evaluate the progress of national programs through multidsicplinary evaluations, drawing together a group of professional peers to critically assess the strengths and weaknesses of the EPI. These evaluations motivated national programs towards continuous improvement and corrective action. During the same period, PAHO created the Revolving Fund for Vaccine Procurement which would eventually go on to facilitate new vaccine introduction, since countries could use local currency to pay for the products and the economies of scale provided by the Fund made the prices affordable to their governments. Simultaneously, PAHO and partners worked with the Parliaments in the various countries to promote and advocate for legislation that protects immunization financing from year to year and therefore ensures sufficient budget to allow for a sustainable introduction of new vaccines to the program. The commitment of the governments was key to ensure that the EPI was equipped early on with sufficient financial resources, political visibility and a highly skilled workforce.

3. Strong immunization advisory bodies at all levels

Recognizing the diverse policy issues that arise at the country level, many governments established National Immunization Technical Advisory Groups (NITAGs) to support the country decision making process with technical recommendations. NITAGs were created starting in the early 1990s and generally followed the strategies and technical recommendations proposed by the Regional TAG. Subsequently, Chairs of NITAGs began participating in the TAG meetings and this facilitated a seamless translation of Regional recommendations by NITAGs to their countries' realities. The clear and important link between the Regional advisory body and national advisory bodies and the technical support they provide to the EPI has led to programmatic policies that are rather consistent throughout the Region and an accelerated uptake of new vaccines.

4. Immunization policy grounded in a broad and national evidence base

The Region has made tremendous progress in the area of evidence-based policymaking due to the intense efforts to ensure that the EPI was equipped with well-trained staffed and sufficient capacity to collect, analyze and disseminate relevant programmatic and technical data to policymakers. In turn, policymakers have come to expect this from the program. In recent years, the economic and disease burden studies conducted in the Region, particularly on the newer vaccines that prevent rotavirus, pneumococcal disease and Human papilloma virus, have been instrumental in the process of early adoption. The Sabin Vaccine Institute is proud to have collaborated with PAHO in these studies, which were groundbreaking. The ProVac Initiative, launched by PAHO about 7 years ago takes this to another level, by creating regional centers of excellence and providing technical cooperation for nationally-owned cost-effectiveness analyses. As we enter the Decade of Vaccines, this initiative will be critical in the years to come to continue providing governments with the best available information, which will allow for informed decisions as new technologies become available to the control and eradication of other infectious diseases.

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Discussion

Beyond methods and studies: Building institutions for better public spending on vaccination

Amanda Glassman*

Center for Global Development, 1800 Massachusetts Avenue NW, Third Floor, Washington, DC 20036, United States

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While overall public spending on health as a percentage of GDP remains relatively low, as their economies grow, most governments in Latin America and the Caribbean (LAC) are spending more per person on health care and public health. In the area of vaccines, public spending has also grown; between 2010 and 2011 alone, the World Health Organization (WHO) estimated that public spending on vaccination in LAC grew by 15% on average [1], although there is considerable heterogeneity in per capita spending between countries.

In many ways, LAC has been and remains a leader in vaccine introduction relative to other regions. Even so and in spite of increasing spending overall and global evidence on the potential value of new and underutilized vaccines [2], there is uneven consideration and adoption of new vaccines. As of 2012, less than half of the 48 LAC countries and territories have adopted the Rotavirus vaccine, 21 countries and 5 territories have adopted the pneumococcal vaccine, and six countries have adopted HPV as part of their national immunization programs [3].

Many LAC governments have established WHO-recommended National Immunization Technical Advisory Groups (NITAG) to advise on new vaccine adoption and the national immunization program in general [4]. In spite of these efforts, Andrus et al. identified instances of decision making without reference to available evidence, limited use of cost-effectiveness analyses in decision making, and limited technical capacity to carry out economic evaluation [5]. Further, a 2008 report of the independent Commission on the Future of Vaccines in Latin America also noted the absence of cost-effectiveness analyses using national data, information on costs and risk groups for specific preventable diseases, and disaggregated data on local and municipal levels as major obstacles to better priority-setting for vaccines [6].

Even where countries had undertaken cost-effectiveness analyses, the Commission found that the budgetary impact of a vaccine was not studied and, as a result, a major gap persisted between evidence generation activities and budget decisions to authorize necessary funding for a recommended vaccine. A study of new vaccine adoption processes in five Latin American countries by Oliveira et al. (2013, in this volume) concludes that "the factors contributing to new vaccine introduction in the countries evaluated are not generally grounded in a systemized approach."

Increased investment may be needed, as NITAG in the region are often ad hoc, poorly funded and staffed entities, without an explicit legal, institutional or budgetary framework for operation. In many countries it is unclear how a NITAG's technical recommendations will connect with budget decision-making. This may be one reason why some countries in the region may miss early introduction of potentially cost-effective vaccines during a period of growing public spending.

The need for increased technical input when considering the introduction of new vaccines and immunizations is not unique to LAC, but a more general problem facing priority-setting efforts in the health sector in middle-income countries. A recent Center for Global Development working group on priority-setting in low- and middle-income countries found that many public budgets continue to be input-based (salaries, facilities, supplies), ad hoc and reflect historical allocations, rather than intervention-based and proactive toward new technology adoption [7]. Although countries are increasingly interested in explicit priority-setting as demonstrated by the widespread adoption of essential medicines lists and health benefits plans or guarantees, existing processes frequently lack an organizational home and budget that would allow for on-going use of economic evaluation, budget impact analysis and deliberation to assess alternatives and make recommendations on coverage and reimbursement choices. Further, there are many methodological, data and capacity challenges: epidemiological, demographic and cost data – sometimes very dated – from other countries are used

* Tel.: +1 202 416 4000; fax: +1 202 416 4050.
E-mail address: aglassman@cgdev.org

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in economic evaluation; cost-effectiveness thresholds are based on a WHO rule of thumb never intended to be generalized worldwide; the budget impact of new technologies is not usually considered; and appropriate counterfactuals in economic evaluations are often missing.

Launched in 2006, the Pan American Health Organization's ProVac Initiative is intended to fill some of these gaps in immunization decision-making, and has focused and led on the development of economic evaluation methodologies, tools and studies using national data and building a network of academic centers of excellence in economic evaluation of vaccines to generate greater capacity to carry out and interpret studies. The ProVac Network of Centers of Excellence is currently home to five academic institutions, and functions as a communication hub and knowledge center, providing methodological guides and training material [8]. ProVac also supports the TRIVAC decision support model, which has been used to provide evaluative support for the pneumococcal, rotavirus, and Hib vaccines – and to date has been used in cost-effectiveness evaluations in 14 countries in Latin America [9]. ProVac uses technical cooperation with countries to "strengthen the structure and the processes for decision making at the country level" [10]. In this regard, it provides support to Ministries of Health to establish, formalize and strengthen NITAGs.

This is certainly the way forward for support to priority-setting: building the capacity to generate economic evaluation and related analyses, while also building the capacity to use this information in decision-making.

In building the capacity to use the evidence, the Center for Global Development working group found that the existence of an explicit legal and institutional framework for policy making, a routinely-allocated budget and staff, a transparency and conflict of interest policy, and a clear connection to decisions on coverage or reimbursement are essential features of successful priority-setting in the health sector [7].

A key question in designing support to NITAGs in the future then is whether these should be part of or separate from a broader and improved priority-setting process on the uses of public spending. Building on experiences in OECD countries, NITAGs tend to be independent from decision-making processes on the uses of broader public budgets for health, such as health benefits plans and related. This arrangement may be justified by the existence of separate budgets for vaccination and for the rest of health spending, as is the case in 25 LAC countries with a separate budget line item for vaccination [11].

However, the incentives implicit in this separateness may also be problematic for priority-setting as trade-offs in the use of public monies may not be adequately addressed on either side of the divide. For example, vaccine costs and effectiveness may not be compared to the costs and effectiveness of the existing standard of care for a disease or compared to other new uses of health spending, resulting in overstated or understated cost-effectiveness ratios. Savings associated with a coverage/reimbursement decision on a vaccine may not accrue to the non-vaccine budget, thus limiting incentives to reallocate toward vaccines. General budgets funding health benefits plans may be attached to individuals or households and will grow automatically as populations grow, whereas vaccination budgets are treated separately and may not benefit from an automatically growing budget allocation and thus the space to consider new vaccines.

The articles in this supplement lay out lessons learned in generating the evidence base necessary to support the decision making process around new vaccine introduction. Together, the work suggests that better priority-setting institutions are needed to translate evidence on the cost-effectiveness of new and underutilized vaccines into public budget decisions. And importantly, priority-setting should not be seen as solely a methods, data or technical issue, but also as an institutional, political and budgetary process that requires attention in its own right.

Conflicts of interest statement

None declared.

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Discussion

Perspectives on sustainable vaccine introduction

Alan R. Hinman*

The Task Force for Global Health, 325 Swanton Way, Decatur, GA 30030, United States

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The articles in this issue describe the results of ProVac, an exciting initiative in the Americas to develop capacity at the national level to assess the costs and benefits of use of a particular vaccine, thus enabling evidence-based decision making about its potential use. Although evidence-based decision making is always desirable, it has become increasingly important as new vaccines are developed that are considerably more expensive than "traditional" Expanded Program on Immunization (EPI) vaccines. New vaccines cost dollars, not cents, as was the case for "traditional" EPI vaccines (BCG, DPT, polio, and measles). Consequently, policy makers are increasingly demanding information about what they will get in return for their investment in new vaccines. The ProVac tool helps assess the situation based on an individual country's epidemiological circumstances. National Immunization Technical Advisory Groups (NITAGs) can then interpret the information and make specific recommendations.

Making an evidence-based decision to introduce a new vaccine, however, is merely the first step to realizing the benefits that can result from its use. Sustaining use of the vaccine depends on a number of factors:

- An infrastructure strong enough to appropriately handle and administer the vaccine – cold chain and service delivery. Vaccines do not give themselves, they require physical and human infrastructure. New vaccines may pose additional burdens on the cold chain and additional personnel may be needed to deliver the vaccines to current or new target populations.
- A surveillance system capable of detecting and investigating occurrence of vaccine preventable diseases as well as monitoring progress in disease reduction, vaccine coverage, and potential adverse events following immunization.
- An effective procurement strategy to get the most advantageous price for the vaccine. Most countries in the Americas participate in PAHO's revolving fund, which gets very advantageous prices for participating countries. In other parts of the world, countries may use UNICEF as a purchasing mechanism. Additionally, some countries may participate in pooled procurement.
- Public support – as immunization reduces the occurrence of vaccine preventable diseases, public concern about the diseases wanes and concerns about possible adverse consequences of vaccination (real or imagined) become more important. Around the world, issues of vaccine hesitancy or vaccine refusal are becoming more prominent and we must develop more effective communication strategies to convey the continuing importance of immunization.
- Political support – in the Americas, virtually all countries have line items in their national budgets to support vaccines and immunizations. This is not the case in many other countries in the developing world.
- Long-term financing. The poorest countries in the world now receive support from the GAVI Alliance for introduction of new vaccines. However, this support is time-limited and countries are expected to gradually increase their co-payment until they are paying for the vaccines, either from domestic or external sources. Legislation to assure continuing funding for immunizations can be very effective. The Sabin Vaccine Institute is working in 15 countries (12 in Africa, 3 in Asia) to bring together representatives from Ministries of Health, Ministries of Finance, and Parliament to recognize the importance of legislative backing for immunizations.

* Tel.: +1 404 687 5636.
E-mail address: ahinman@taskforce.org

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Identifying long-term financing for continued use of existing and new vaccines, whether from internal or external sources, is a major challenge for developing countries. Although not a magic bullet, good evidence about the burden of disease and impact of vaccination, such as that developed through the ProVac initiative, can provide substantial assistance in this task.

Conflicts of interest

Dr. Hinman has a 3-year ($100,000/year) policy grant from Novartis to assess the feasibility of establishing emergency stockpiles of rabies vaccine and immune globulin in high-risk countries where they are not readily available.

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Discussion

What do policy makers need to know? Lessons from the decision to add pneumococcal conjugate and rotavirus vaccines to the US immunization program

Cynthia G. Whitney*, Umesh D. Parashar

National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, United States

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The decisions to introduce pneumococcal conjugate and rotavirus vaccines into the US immunization programs were good ones. The vaccines have performed even better than expected, markedly reducing disease not only among young children who received them but also among unvaccinated persons in the community [1,2]. But when the US Centers for Disease Control and Prevention (CDC) first considered whether to recommend routine use of these vaccines, several pieces of information – such as data on disease burden and vaccine efficacy, safety, and cost-effectiveness – had to be gathered before the decision to use these vaccines became clear.

First, policy makers had to determine the need. Do pneumococci and rotavirus cause enough hospitalizations and deaths in the US to warrant vaccinating every child? In the US, as in most parts of the world that use *Haemophilus influenzae* type b vaccine, pneumococcus was the most common cause of severe pneumonia and bacterial meningitis in young children [3]. Likewise, rotavirus was the most common cause of diarrhea requiring hospitalization [4]. While sub-populations at greater risk of both severe pneumococcal and rotavirus disease were identified (e.g., premature infants), targeting vaccination to these groups would miss the vast majority of cases and thus universal vaccination was the best option.

Next, policy makers had to determine that the vaccines were both safe and effective, turning to evidence from randomized controlled clinical trials. For rotavirus vaccines, data were carefully reviewed to assess risk of intussusception, an adverse event that led to the withdrawal of a previous rotavirus vaccine from the US market in 1999, and age restrictions were put in place to keep the theoretical risk as low as possible [4]. The pneumococcal conjugate vaccine (Prevnar) was safe and highly efficacious in a large US trial [5]. While the two rotavirus vaccines (RotaTeq and Rotarix) differed in composition and schedule, they were similarly efficacious [6,7]. Policy makers also discussed practical matters, such as how the new vaccines would fit into the existing schedule of vaccinations and well-baby visits.

Cost-effectiveness models assessed the balance between disease burden and its associated costs (medical and societal) with the cost of providing vaccine routinely to children. Even though the first cost-effectiveness estimates for pneumococcal conjugate vaccine did not include money saved through indirect effects, these early estimates helped justify the decision to provide vaccine through a 'catch-up' program to all children up to age 2 years [8]. For rotavirus vaccines, the cost of lost time from work for parents caring for sick children who did not require medical care comprised a significant proportion of total costs and was a key consideration [9].

The data were reviewed in detail by technical working groups that included selected members of CDC's Advisory Committee on Immunization Practices (ACIP), subject matter experts, and representatives of professional organizations for pediatrics and family medicine. After this, the full ACIP reviewed summarized data and voted on vaccine recommendations, which were ultimately adopted by CDC [3,4]. Once the vaccines were recommended, CDC conducted post-marketing surveillance and epidemiological studies to evaluate the effect of the vaccination programs and make sure that the recommendations were sound. These evaluations reaffirmed the health benefits of vaccination including documenting indirect benefits, a finding that came somewhat as a surprise for both vaccines [1,2]. Continued monitoring for intussusceptions as millions of children are vaccinated against rotavirus has provided additional assurance on the safety of the vaccination program [10].

The US added pneumococcal and rotavirus vaccines in 2000 and 2006, respectively, when these vaccines were first licensed. Today, a lot more information is available on their safety and performance in routine use as well as efficacy in clinical trials conducted in a variety of settings. In addition, we have new pneumococcal conjugate vaccine products that cover more serotypes, making these products potentially more cost effective than the original 7-valent formulations. Taken together, these additional data should make it

* Corresponding author. Tel.: +1 404 639 4727; fax: +1 404 235 9973.
E-mail address: cwhitney@cdc.gov (C.G. Whitney).

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easier for each additional country to make an informed decision. Where there are gaps in local data, information on disease burden, efficacy, safety and cost effectiveness from countries with similar populations can help answer questions.

Conflict of interest statement

None declared.

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Review

TRIVAC decision-support model for evaluating the cost-effectiveness of *Haemophilus influenzae* type b, pneumococcal and rotavirus vaccination

Andrew Clark[a,*], Barbara Jauregui[b], Ulla Griffiths[a], Cara B. Janusz[b], Brenda Bolaños-Sierra[a], Rana Hajjeh[c], Jon K. Andrus[b], Colin Sanderson[a]

[a] *London School of Hygiene and Tropical Medicine, UK*
[b] *Pan American Health Organization, USA*
[c] *Centers for Disease Control and Prevention (CDC), USA*

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ABSTRACT

The TRIVAC decision support model has been used widely in Latin America and other regions to help national teams evaluate the cost-effectiveness of *Haemophilus influenzae* type b (Hib) vaccine, pneumococcal conjugate vaccine (PCV) and rotavirus vaccine (RV). We describe the structure and functioning of this model, and identify the parameters with the greatest influence on the results.

The TRIVAC model is a spreadsheet software program that calculates incremental cost-effectiveness ratios (ICERs) and other indicators for three childhood vaccines (Hib, PCV and RV) utilising parameters such as demography, disease burden, vaccine costs, vaccine coverage, vaccine efficacy, health service utilisation and costs. There is a good deal of uncertainty about the local values of many of the parameters that have most influence on the cost-effectiveness of these new vaccines. Cost-effectiveness models can be used to explore the implications of different values of these parameters. However, for such models to be seen as relevant and helpful by decision-makers, they need to be transparent, flexible, easy to use, and embedded in a process which is owned and led by national teams.

In this paper the key drivers of cost-effectiveness in the model are identified by one-way sensitivity analyses, run for each vaccine in 147 countries. The data used are mainly from standard international sources and the published literature. The primary indicator was the discounted cost per Disability Adjusted Life-Year (DALY) averted, from a government perspective, over a 20-year period (2013–2032). For all three vaccines, the ICER was most sensitive to changes in *relative coverage* (the coverage of the children who would have become diseased or, more importantly, died if the population had not been vaccinated, as a % of overall national coverage) and the herd effect multiplier. Other influential parameters for all three vaccines were: the incidence and case fatality of disease, the baseline trend in disease mortality in the absence of vaccination, vaccine efficacy, vaccine price and the % decline in vaccine price per year. Important vaccine-specific parameters included the cost of Hib meningitis sequelae, PCV serotype coverage and the rotavirus gastro-enteritis (RVGE) admission rate. While vaccine efficacy, herd effects, disease mortality and vaccine price are commonly cited as important drivers of cost-effectiveness, this analysis highlights the potentially important influence of *relative coverage*, a parameter rarely considered in models of vaccine impact and cost-effectiveness.

Contents

* Corresponding author at: Department of Health Services Research and Policy, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, UK.
E-mail address: andrew.clark@lshtm.ac.uk (A. Clark).

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1. Introduction

The Expanded Programme on Immunization (EPI) has already had a major impact on the numbers of deaths and episodes of disease caused by diphtheria, pertussis, tetanus, polio and measles [1]. In more recent years a new generation of vaccines has become available. Two of these (*Haemophilus influenzae* type b [Hib] vaccine and pneumococcal conjugate vaccine [PCV]) protect against pneumonia, meningitis and other invasive bacterial diseases, and one (rotavirus vaccine [RV]) protects against severe diarrhoea. In the year 2008, diarrhoea and pneumonia were estimated to have caused 28% of all deaths in children aged less than 5 years. With the inclusion of meningitis and other invasive bacterial diseases, this fraction increases to around one-third [2]. Hib vaccine, PCV and RV have the potential to prevent a significant proportion of these deaths and have already been introduced in many countries.

Historically, vaccines have been among the 'best buys' for public health programmes, costing a matter of cents per dose [3]. The newer vaccines are more expensive. If the aim is universal coverage, even a relatively modest cost for each child can add up to a large amount for a population, so budgetary constraints and prioritisation emerge as critical issues.

Inevitably government decisions about the introduction of new vaccines will be subject to advocacy and lobbying by interested parties. However, if the maximum public health benefit is to be had from health care spending, prioritisation should be based on how much improvement in health an intervention produces in relation to its cost. Cost-effectiveness depends on factors such as the incidence and severity of the diseases in question, the effectiveness and cost of the vaccine, and to some extent the health care costs avoided by preventing disease. Most of these factors vary considerably between countries, so cost-effectiveness will also vary by country. Ideally then, each country should determine its own priorities using evidence relevant to its own circumstances. There is growing recognition of and support for this principle, both in general and for vaccines in particular [4].

The evidence is not straightforward however. There is a good deal of uncertainty about the scale of the burden of disease and how much of it could be prevented by these new vaccines. There is also uncertainty about the future prices of new vaccines and the extent and duration of funding support from the GAVI Alliance and other donors. Uncertainties of this kind can lead to a view that evidence-based decision-making is 'too hard', leading in turn either to decision paralysis or to decisions based on less worthy considerations. This is where decision support models (DSMs) can be helpful, not so much to provide *the* answer as to provide a framework within which data and assumptions are made explicit, and the implications of choosing different options under different scenarios can be explored. In particular, they allow the implications of the evidence, and the uncertainties about the evidence, to be presented in a transparent and coherent way.

In this paper we describe the structure, methods and assumptions of the TRIVAC decision support model. The model has been designed for use at country level by teams led by the Ministry of Health [5,6]. The development of the model was funded by the Pan American Health Organization (PAHO) ProVac Initiative (www.paho.org/provac) and GAVIs Hib Initiative (www.hibaction.org). To date, it has been used to perform national and/or sub-national cost-effectiveness evaluations in Albania, Argentina, Belarus, Bolivia, Costa Rica, Ecuador, El Salvador, Guatemala, India, Nicaragua, Pakistan, Panama, Paraguay, Peru and Uzbekistan.

In 2011, the PAHO ProVac Initiative received requests from other regions (e.g. Africa, Eastern Mediterranean, Eastern Europe) to use both the TRIVAC model and the ProVac methodology of which the model is just one part. This methodology involves providing practical training at facilitated regional workshops, forming national teams, providing technical assistance, and supporting presentation of results to National Immunization Technical Advisory Groups (NITAGs) and high-level Ministry of Health authorities [5]. In response to these requests, a ProVac International Working Group (IWG) has been established with funding from the Bill and Melinda Gates Foundation [see Toscano C, same Supplement].

One of the challenges of using a standardised model in a diverse set of countries is that the influence of each parameter may vary across settings. A better understanding of this from the outset should allow national teams with limited time and resources to prioritise their data collection efforts and scenario analyses.

This paper aims to: (i) provide a methodological reference document for national teams and partners working with the TRIVAC model; and (ii) identify the TRIVAC parameters likely to have the greatest influence on the cost-effectiveness of Hib vaccine, PCV and RV, in different epidemiological and economic contexts.

2. Methods

The TRIVAC model is a spreadsheet software program that calculates incremental cost-effectiveness ratios (ICERs) and other indicators for three childhood vaccines (Hib, PCV and RV) utilising parameters such as demography, disease burden, vaccine costs, vaccine coverage, vaccine efficacy, health service utilisation and costs. Where more than one vaccine is evaluated, the common model framework provides a consistent basis for comparison.

The model is designed for use in low- and middle-income countries (LMICs) and a small number of countries that have recently graduated to high-income [7]. The 147 countries included in the model can be grouped according to geographical region, and WHO mortality strata B, C, D and E [8]. The model excludes all countries in WHO mortality strata A (very low mortality) and a number of countries with very small populations.

2.1. Rationale for a user friendly model

Many LMICs are constrained by poor data quality and a shortage of technical capacity in economic evaluation. The TRIVAC model can be used at different levels, from the basic or introductory (simple structure, fewer inputs) to the more complex and demanding of data. To increase transparency and accessibility of the model to national teams, it has been developed in Microsoft Excel [9] with a number of additional features in Visual Basic for Applications (VBA). It includes a user-friendly interface with different language options, 'pop-up' parameter definitions, and built-in features for scenario and uncertainty analysis. It is populated with baseline parameter values taken mainly from international databases, and where values are not available at country level (e.g. vaccine efficacy, health care access), estimates for the WHO sub-regional mortality strata are typically used. National teams are encouraged to scrutinise these estimates and suggest improvements if they have better information, or propose alternative scenarios if they are uncertain.

2.2. Outcome indicators

The model calculates a variety of indicators, including numbers of prevented cases, outpatient visits, admissions and deaths, % of under-five mortality prevented, life-years gained, costs of vaccination and prevented health-care costs. However, the primary task for cost-effectiveness analysis is to estimate the incremental cost-effectiveness ratio (ICER). For each scenario, or combination of parameter values, the model calculates the costs and benefits arising over a given period with and without the vaccine in question. TRIVAC generates ICERs for each type of health outcome (cost per death averted, cost per life-year gained, etc.) but the ratio most commonly reported to national authorities, is the cost per DALY averted. This is calculated as:

$$\frac{\text{Costs } \textit{with} \text{ the new vaccine} - \text{Costs } \textit{without} \text{ it}}{\text{DALYs } \textit{without} \text{ the new vaccine} - \text{DALYs } \textit{with} \text{ it}}$$

Costs include both vaccination programme costs and health care costs associated with treating vaccine-preventable diseases. DALYs are healthy years *lost* due to disease mortality and morbidity. Morbidity is included by applying an international standard set of 'weights' to years of ill health, thus providing a more comprehensive basis for comparing different interventions than impact on mortality alone [10].

The model includes the option of discounting future costs and health benefits to the year of vaccine introduction at a rate chosen by the user. Another option allows greater weight to be given to life-years gained during productive working age (DALY age weighting).

2.3. Time horizon and stacked cohorts

Estimates of costs, health benefits and cost-effectiveness are calculated by tracking the experience of annual birth cohorts from 1 to 59 months of age. Vaccination programme costs are assumed to occur in the first year of each cohort, while disease cases, deaths and treatment costs are estimated for the first five years of age. Years of life lost, DALYs and costs of sequelae are estimated over the lifetime of the population in each cohort using current and projected life expectancies.

The model also estimates health benefits and costs arising in each calendar year by 'stacking' the results from each cohort. For the second modelled year, the results from the second year of the first cohort are added to those for the first year of the second cohort, and so on. This has proved to be helpful for policy makers, many of whom find it more natural to think in terms of year-on-year trends than lifetime events in a specific cohort. Also cost-effectiveness can be evaluated over a sustained period of routine vaccination, during which key parameters may be changing. For example: (i) a vaccine can be phased into the programme gradually by steadily increasing coverage; (ii) the proportion of circulating serotypes that are 'vaccine type' can be reduced in future years to simulate serotype replacement; (iii) the vaccine price or co-financing contribution can be varied over time; and (iv) baseline disease mortality can follow long-standing declining trends in the absence of vaccination due to generalised improvement of health conditions. In order to capture the effect of such changes, the model can evaluate up to 20 successive (or 'stacked') annual birth cohorts.

2.4. Model structure

TRIVAC is a static cohort model. This means that effects in unvaccinated children (indirect effects, whether positive through e.g. herd effects, or negative through e.g. type replacement) can only be crudely taken into account, using simple and highly speculative adjustments to the impact of the direct effects.

The structure of the disease burden part of the model is shown in Fig. 1. Life-years lived between 1 and 59 months of age are derived for each successive birth cohort using annual projections of births, neonatal mortality, infant mortality and under-five mortality. To estimate the number of disease cases attributed to each cohort, the projected number of life-years lived between 1 and 59 months is multiplied by the estimated incidence of disease in the same age group.

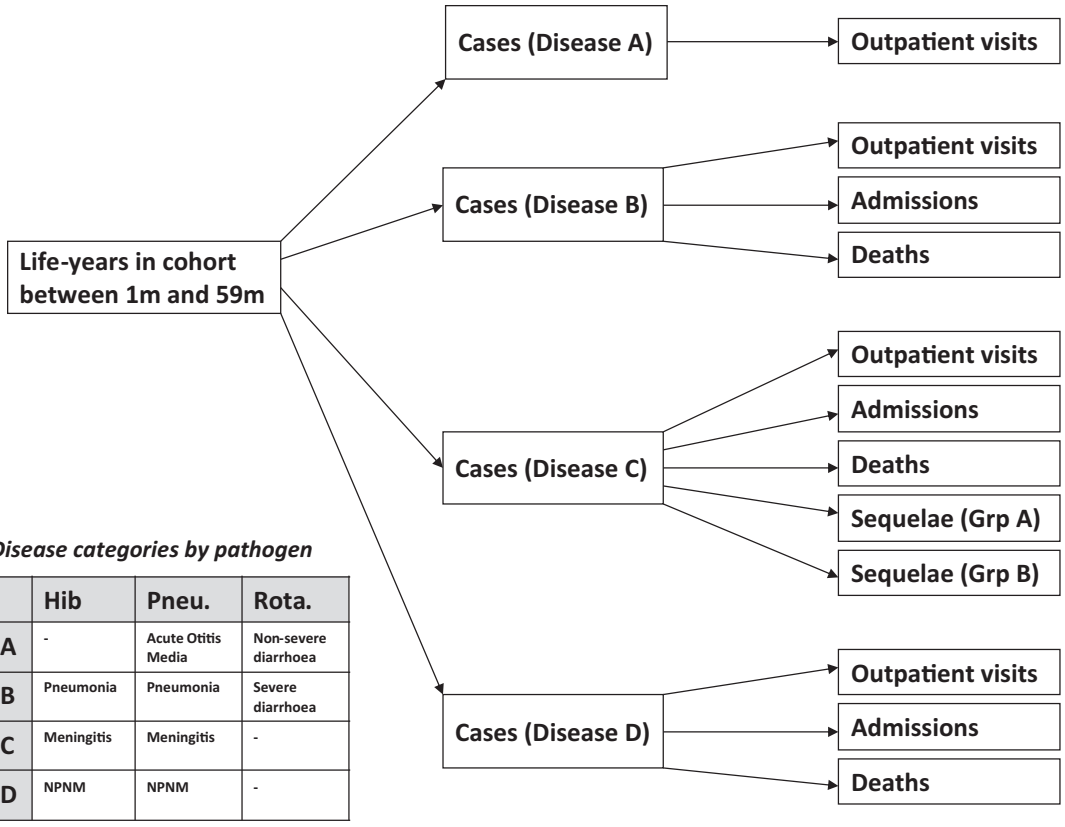
For Hib, disease categories B, C and D correspond respectively to pneumonia, meningitis and all other forms of invasive non-pneumonia and non-meningitis (NPNM), namely epiglottitis, cellulitis, septic arthritis, septicaemia, osteomyelitis and pericarditis [11]. Disease category A (less severe disease, causing no deaths or admissions) is not used. For pneumococcal, disease categories A, B, C and D correspond respectively to cases of acute otitis media, pneumonia, meningitis and other invasive NPNM disease e.g. sepsis and bacteraemia. For rotavirus, disease categories A and B represent *non-severe* and *severe* rotavirus gastroenteritis (RVGE) respectively, as defined by the Vesikari 20-point scale for RV1 [12] and the Clark 24-point scale for RV5 [13]. However, disease categories can be redefined by the user if: (a) there is better local evidence on the incidence and health care costs for a different definition of disease and/or severity and (b) international efficacy estimates are available for this disease category. For example, information about *RVGE admissions* can be used instead of *RVGE severe cases* and *all-cause radiological pneumonia admissions* instead of *pneumococcal pneumonia cases*. When this option is used, case fatality ratios are assumed to be the ratio between e.g. RVGE admissions and RVGE deaths, thus capturing the correct number of deaths in the community.

Total numbers of cases in each disease category are multiplied by their respective case fatality ratios (CFRs) to give total disease-specific deaths up to age 59 m, and total cases and deaths are then distributed across the following age bands: <3 m, 3–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m. Estimates of vaccination coverage for each age band are used to account for delayed vaccination.

A risk of permanent disability is applied to all children who survive an episode of Hib meningitis or pneumococcal meningitis. Sequelae can be divided into two user-defined categories depending on the availability and quality of local data e.g. major and minor, single-syndrome and multiple-syndrome, auditive and neurological, etc.

2.5. Health care use and costs

The numbers of outpatient visits and inpatient admissions are estimated by assuming an average number of visits/admissions per



Disease categories by pathogen

	Hib	Pneu.	Rota.
A	-	Acute Otitis Media	Non-severe diarrhoea
B	Pneumonia	Pneumonia	Severe diarrhoea
C	Meningitis	Meningitis	-
D	NPNM	NPNM	-

NPNM = other non-pneumonia, non-meningitis invasive diseases combined

Outpatient visits and admissions can be divided into ten user-defined categories of healthcare provider e.g. private non-medical (faith healer etc), private pharmacy, private clinic, social security clinic, social security hospital, public clinic, public primary hospital, public secondary hospital, public tertiary hospital.

Sequelae can be divided into two user-defined categories e.g. major and minor, multiple and single, audiological and neurological.

Fig. 1. TRIVAC model structure.

case for each disease. Each outpatient visit and admission can be assigned to the public, social security or private sector by selecting one of up to ten user-defined categories of healthcare provider. Costs per visit and costs per admission can be specified for each type of provider.

The total health care costs avoided in a given cohort are equal to:

$$D * [(O * C_O) + (H * C_H)]$$

where

D, the number of cases of disease avoided among children in the cohort
O, average number of outpatient visits per case
C_O, weighted cost per outpatient visit
H, average number of inpatient admissions (hospitalisations) per case
C_H, weighted cost per inpatient admission

The weighted costs are calculated from the proportions of visits or stays in different types of user-defined provider and their respective costs. Costs borne by governments (e.g. bed day costs, drugs and diagnostics) and costs borne by households (e.g. productivity losses, travel costs and user fees) are treated separately. This allows for analysis from different cost perspectives e.g. one perspective might include all costs, while another may exclude household costs and assume the government bears a % of the Social Security costs. For life-long sequelae an average cost per year is applied from year of onset of meningitis until death.

2.6. Vaccination programme costs

The starting point is the vaccine cost per dose which is calculated as follows:

$$P * \frac{(1 + F + H)}{(1 - W)}$$

where

P, price per dose
F, freight cost (expressed as a % of price per dose)
H, handling cost (expressed as a % of price per dose)
W, % wastage

Costs can also be included for safety boxes and syringes, using the same formula.

To estimate the total numbers of vaccines administered, the model takes into account the differences in coverage for each dose, with surviving infants assumed to be the denominator for each coverage rate. To better represent the true cost, this denominator can also be adjusted to account for doses received by children who die from other causes between 1 and 11 months.

It is assumed that Hib vaccine, PCV and RV are delivered at the same visit as other vaccines in the EPI programme (e.g. DTP, DTP-HepB, etc.). For Hib vaccine, costs are subtracted for any vaccines that would be replaced by the new vaccine, so that if DTP-HepB is replaced by DTP-HepB-Hib the incremental cost is the difference between the cost of the quadrivalent and pentavalent vaccines after accounting for differences in the freight, handling and wastage of the vaccines, syringes and safety boxes.

For all three vaccines, the model can accommodate estimates of the annual incremental costs to the 'health system', expressed per dose. This includes annualised start-up costs (e.g. social mobilisation, training, cold-chain expansion, buffer stock, printing vaccination cards) and any recurrent costs not included in the earlier estimate of vaccination costs per dose (e.g. maintenance of cold chain and surveillance for adverse events). To calculate this, national teams have developed their own costing templates tailored to the nuances of their specific programme.

TRIVAC also provides the option to display charts showing financial costs in each calendar year (i.e. year 1 buffer stock, year 1 capital costs, recurrent non-vaccine costs, and recurrent vaccine costs). This time-profile of financial costs does not inform the cost-effectiveness ratio, and is not intended as a replacement for a detailed budgeting exercise, but can start the process of communicating the financial implications of new vaccine introduction.

Changes in vaccine price can be modelled simply as an initial price with a fixed % change per year. Alternatively a specific price can be given for each year if prices are expected to change in an irregular fashion, or if for example a government is expected to pay only some fraction of a fixed price for a limited period, as in co-payments for the duration of GAVI support.

2.7. Vaccine impact

The key steps for estimating vaccine impact are described in Fig. 2. In summary, the model accounts for dose-specific efficacy, age- and dose-specific coverage, serotype coverage for PCV, age-specific waning protection and relative coverage. In many countries the children most at risk of disease and with poorest access to antibiotics and oral rehydration are also the children least likely to be reached by the vaccination programme; *relative coverage* is the coverage of the children who would have become diseased or, more importantly, died if the population had not been vaccinated, as a % of overall national coverage. Thus overall national coverage can be adjusted downwards by this ratio to better reflect the true impact of the programme. In the model the impact of the programme can be adjusted to account for this, and reasonable proxies can be used to inform its value such as coverage in severely underweight children divided by coverage in the cohort overall.

The user can also investigate some of the potential impact of herd effects by adding a % to the direct vaccination effect, and of serotype replacement, by reducing vaccine type coverage by a fixed % each year. These percentages can be informed by evidence about the possible scale of effects observed in post-licensure studies [14,15].

For a given birth cohort, and age group, the number of cases prevented is equal to:

=	$[B*(1-N_{MR})*(1-PN_{MR})*(11/12)$	life-years 1–11 m for survivors to age 1 year
+	$B*(1-N_{MR})*PN_{MR}*(11/12)*0.5$	life-years for those dying between 1 and 12 m
+	$B*(1-U5_{MR})*4$	life-years 12–59 m for survivors to age 5 years
+	$B*(U5_{MR}-I_{MR})*4*0.5]$	life-years for those dying between 1 and 5 yrs
*	I	% incidence of disease aged 1–59 m per year
*	A	% of disease in age group
*	$[E_b*C_b$	direct protection due to booster
+	$(E_{P3}*(C_{P2}-C_b))$	direct protection due to 3 primary doses
+	$(E_{P2}*(C_{P2}-C_{P3}))$	direct protection due to 2 primary doses
+	$(E_{P1}*(C_{P1}-C_{P2}))]$	direct protection due to 1 primary dose
*	$[T_i*(1-T_r)\hat{}T_n]$	% vaccine serotype coverage in cohort
*	R	% of coverage reaching those at high risk
*	W	% decrease in protection due to waning
*	H	% herd effect multiplier

where

B, live births per year
N_{MR}, neonatal mortality rate (% of live births dying before 1 month of age)
I_{MR}, infant mortality rate (% of live births dying before 1 year of age)
PN_{MR}, post-neonatal mortality rate (% of children dying between 1 and 12 months of age)
$U5_{MR}$, under-five mortality rate (% of live births dying before 5 years of age)
I, incidence of disease aged 1–59 months, per 100,000 per year
A, % of disease in age group
E_b, % efficacy with a booster dose
E_{P1}, % efficacy with 3 doses
E_{P2}, % efficacy with 2 doses
E_{P3}, % efficacy with 1 dose
C_b, % coverage of booster dose in age group
C_{P3}, % coverage of 3 doses in age group
C_{P2}, % coverage of 2 doses in age group
C_{P1}, % coverage of 1 dose in age group
T_i, % vaccine serotype coverage in year of vaccine introduction
T_r, % vaccine serotype replacement per year following vaccine introduction
T_n, number in the sequence of future birth cohorts
R, % of coverage reaching those who would have got the disease with no programme
W, % decrease in protection due to waning
H, % herd effect multiplier (note: maximum possible herd effect = disease elimination)

Standard methods and calculations are used to incorporate discounting, age weighting and DALYs [16]. For cases in disease categories B, C and D, which have the potential to progress to admission and death, vaccine efficacy is assumed to be the same for severe cases, outpatient visits, admissions and deaths. Thus all B, C and D cases are assumed to be relatively severe (e.g. chest X-ray confirmed pneumonia, severe RVGI). For the non-severe disease A cases the same (lower) efficacy is applied to both cases and outpatient visits.

2.8. Uncertainty analysis

The model has a number of built-in facilities for sensitivity and scenario analysis.

1. *Simple (one-way) sensitivity analysis*. On request, the model varies each input parameter in turn by a fixed percentage. Then all the parameters considered are ranked according to the size of the resulting % change in the cost per DALY averted. This can be very helpful in demonstrating what the model does, and that it is working as it should be.
2. *Scenario analysis*. This allows country teams to build up to 20 'what-if' scenarios involving different combinations of parameter values. They may select different combinations of

Step 1	**Vaccine efficacy %:** Vaccine efficacy is estimated for dose 1, dose 2, dose 3 *(if relevant)* and a booster dose *(if relevant)*.
Step 2	**Vaccine type coverage (%):** the % of circulating sero/genotypes that are vaccine type (used for PCV and less commonly for RV). This can vary according to the type of disease e.g. meningitis vs pneumonia. *Note: this can be set (exogenously) to decline by a small fraction each year to represent PCV-related serotype replacement.*
Step 3	**Vaccine coverage (%):** Vaccine coverage in the year of vaccine introduction is estimated for dose 1, dose 2, dose 3 (if relevant) and a booster dose (if relevant) using DTP1, 2, 3 and Measles 1st dose as a proxy. *Note: improvements in vaccine coverage over time are modelled by specifying a long-term target value for coverage (such as 99% over 20 birth cohorts), and reducing the 'distance from target' by a fixed percentage each year. The model includes a final option to adjust manually (override) the trend in coverage if required.*
Step 4	**Vaccine timeliness:** Vaccine coverages for dose 1, dose 2, dose 3 *(if relevant)* and the booster dose *(if relevant)* are converted into age-specific coverage at ages 3m, 6m, 9m, 12m, 24m, 36m, 48m and 59m. Methods for estimating age-specific coverage using survival analysis have been reported elsewhere [22]. This approach involves analysing the reported date of birth and a data of vaccination (DTP1,2,3 and Measles 1st dose) for children represented in household surveys. *Note 1: Disease cases and deaths are also converted into corresponding age bands so the model can account for the expected impact of vaccination delays.* *Note 2: the model includes the option to apply manufacturers recommended age restrictions (Actual, restricted) for RV (1st dose <15weeks; last dose <32weeks)[23]. Alternatively they can choose to evaluate an unrestricted programme with delays similar to DTP1,2,3 and Measles 1st dose (actual, unrestricted) or evaluate what would happen if all vaccines were administered according to the schedule (on -time, unrestricted).*
Step 5	**Relative coverage (%):** the coverage of the children who would have become diseased or, more importantly, died if the population had not been vaccinated, as a % of overall national coverage. *Note: a useful proxy for this can be coverage in children who are severely underweight (e.g. estimated from household surveys) divided by coverage in the cohort overall.*
Step 6	**Waning effect of vaccine per year (%):** Multiply by a fixed % each year using a waning matrix. With age bands (<3m, 4-5m, 6-8m, 9-11m, 12-23m, 24-35m, 36-47m, 48-59m) 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.
Step 7	**Herd effect in cohort evaluated (%):** Rather than endogenous modelling of transmission dynamics, this is specified by the modeller as a simple multiplier of the direct effect i.e. % direct protection * herd effect multiplier. *Note 1: the total impact cannot exceed 100%.* *Note 2: this value can usually be informed by post-licensure studies*

Fig. 2. Steps used to estimate vaccine impact in the TRIVAC model.

'low' or 'high' values for specific parameters, change rates of discounting, waning protection, serotype replacement, relative coverage of deaths, etc., and change the vaccination schedule, the number of cohorts evaluated, the time horizon, etc. Contrasting scenarios combining sets of 'favourable' and sets of 'unfavourable' assumptions can suggest a plausible range of cost-effectiveness values. The model produces graphs to show how each scenario changes the ICER estimated for the base case scenario.

3. *Sub-group analysis*. This allows the cohort to be divided into two groups with different parameter values in each. For example, in the default setup of the model, the cohort is divided into HIV+ and HIV−, and key parameters such as Hib/pneumococcal incidence and vaccine efficacy are varied accordingly. Other possible sub-groups can be chosen by the country team, and might include urban vs. rural, low-risk vs. high-risk, etc.
4. *Probabilistic sensitivity analysis (PSA)*. This requires a plausible range of values (mid, low, high) to be specified by country teams for each uncertain parameter value, generally based on a combination of local evidence, the international literature and expert opinion. These ranges define distributions for each parameter, from which values are sampled to generate a scenario. The

default distribution is triangular, which forms a simple basis for training and understanding of the method. Where data permits, or where better assumptions are required, more advanced users can import other distributions (e.g. gamma, beta, log-normal) from a companion Excel tool developed for TRIVAC. The sampling process is repeated many times, generating a distribution of possible values for health benefit and net cost. These are presented in a scattergram, in which relatively little uncertainty would appear as a small dense cloud of points around the central ICER value, and substantial uncertainty would appear as a larger, more dispersed cloud. This provides a systematic way of eliciting and representing uncertainty about the data and showing the implications for the ICER. Starting seeds can be used for each random number stream to provide reproducible results. The same seeds are used for specific groups of correlated parameters such as case fatality ratios.

2.9. Important drivers of cost-effectiveness for Hib vaccine, PCV and RV

To identify the most influential parameters in the TRIVAC model, we carried out simple one-way sensitivity analyses for each vaccine in each country. For each parameter, we reduced the base case value by 10% and observed the associated change in the discounted cost per DALY averted over a 20 year period (2013–2032), from both a government and a societal perspective.

This desk-based exercise is not designed to provide credible national estimates of cost-effectiveness, and the national ICERs are not presented here. Indeed this would contradict part of the purpose of the model, which is to help promote local data collection and national ownership of the analysis. However, there can be up to around 300 parameters in the TRIVAC model, and a preliminary one-way sensitivity analysis can help to make a start on the question of which parameters are likely to have the greatest influence on the results in each country. National teams can then focus on reviewing the quality of local data on these parameters, seeking better data if possible (e.g. ranges for PSA), and setting the agenda for scenario analysis.

For this exercise we used the standard data used to pre-populate the model. These estimates come from various international sources: (i) demographic projections from the United Nations Population Division (UNPOP) 2010 Revision; (ii) neonatal mortality, timeliness of vaccination and access to health care from Demographic and Health Surveys [DHS]; (iii) vaccination coverage from WHO/UNICEF; (iv) incidence, DALY weights and case fatality ratios used to inform WHO estimates of the Global Burden of Disease [GBD]; (v) vaccine price and supplies data from UNICEF and the PAHO Revolving Fund; (vi) health care costs from WHO-CHOICE [choosing interventions that are cost-effective] and National Health Accounts [NHA]; and (vi) GNI per capita from the World Bank. We used evidence from the global scientific literature to estimate hospitalisation rates, duration of illness and non-severe RVGE incidence. A fuller account of the methods used to support the country-specific assumptions is given in the Appendix.

An initial univariate analysis involved reducing each parameter by −10% and then ranking them in terms of the resulting % change in cost-effectiveness. Subsequent analyses were restricted to parameters with the largest effects, in practice parameters with an effect greater than ~1% across all countries (11 parameters for Hib vaccine, 13 for PCV and 10 for RV). To standardise the presentation of 'key drivers' for each vaccine across a large number of countries, the percentage effect for each parameter was divided by the total of all the effects for the set of influential parameters, so that the total of all these effects for each vaccine in each country was 100%. Scaling factors were generated to allow this *relative influence* to be converted into *absolute influence*. For example, a relative influence of 14% could be scaled by a factor of 1.5 to give the absolute influence (21%) observed for a −10% change.

3. Results

Fig. 3 shows the relative and absolute influence of each key parameter on the cost-effectiveness of Hib vaccine, PCV and RV respectively, from a government perspective, in each WHO subregion. The full country breakdown is available in the Appendix. For all three vaccines, relative coverage and the herd effect multiplier were the most influential parameters. Both factors are important because they have a direct impact on the amount of health and economic benefit without affecting the programme cost. Other influential parameters for all three vaccines were: (i) the baseline disease mortality trend in the absence of vaccination; (ii) vaccine price; and (iii) the % decline in vaccine price per year.

For Hib vaccine, other important parameters were: (i) the incidence and case fatality of Hib pneumonia and Hib meningitis; and, (ii) efficacy of 3 doses against Hib pneumonia and Hib meningitis.

For PCV, other important parameters were: (i) the incidence and case fatality of pneumococcal pneumonia and pneumococcal meningitis; (ii) efficacy of 3 doses against pneumococal pneumonia and pneumococcal meningitis; and (iii) vaccine serotype coverage for pneumococcal pneumonia and meningitis.

For RV, other important parameters were: (i) the incidence and case fatality of severe RVGE; (ii) full-course efficacy against severe RVGE; and (iii) the rate of waning of vaccine protection.

When results were run from a societal perspective, the household costs of meningitis sequelae were influential for both Hib vaccine and PCV i.e. at least as influential as the other meningitis parameters shown in Fig. 3.

For Hib vaccine, the relative influence of most of the 11 parameters did not vary much across the WHO mortality strata. However, in the lower mortality strata, meningitis parameters had a greater influence on ICERs than pneumonia parameters. For PCV, the same effect can be seen but it is less marked. For RV, the inpatient admission rate had a greater influence in lower mortality (and higher income) strata. In higher mortality strata, RVGE mortality and RV waning rates were more influential.

The scaling factors (used to generate the absolute influence for a 10% change) were around 1.0 for all three vaccines. For RV, there was more variation, and in a few countries (e.g. Argentina, Uruguay) the scaling factors were much higher.

4. Discussion

4.1. Strengths and weakness of the model

To date, TRIVAC has been used widely for decision support relating to PCV and RV in Latin America, and mainly for Hib vaccine in a few countries elsewhere. The challenge has been to devise a model that produces results that decision makers can believe in and defend, under sometimes hostile scrutiny, and TRIVAC has a number of advantages in this respect:

1. *Transparency*. National teams led by the Ministry of Health, and ultimately the committees and decision makers they engage with, need to understand what the model does. They cannot be expected to take the validity of a 'black box' model on trust, or to devote much time to studying documentation or deciphering computer code. This suggests using a methodology than can be easily explained to decision makers, and software that allows national teams get 'inside the box' and look round. TRIVAC's

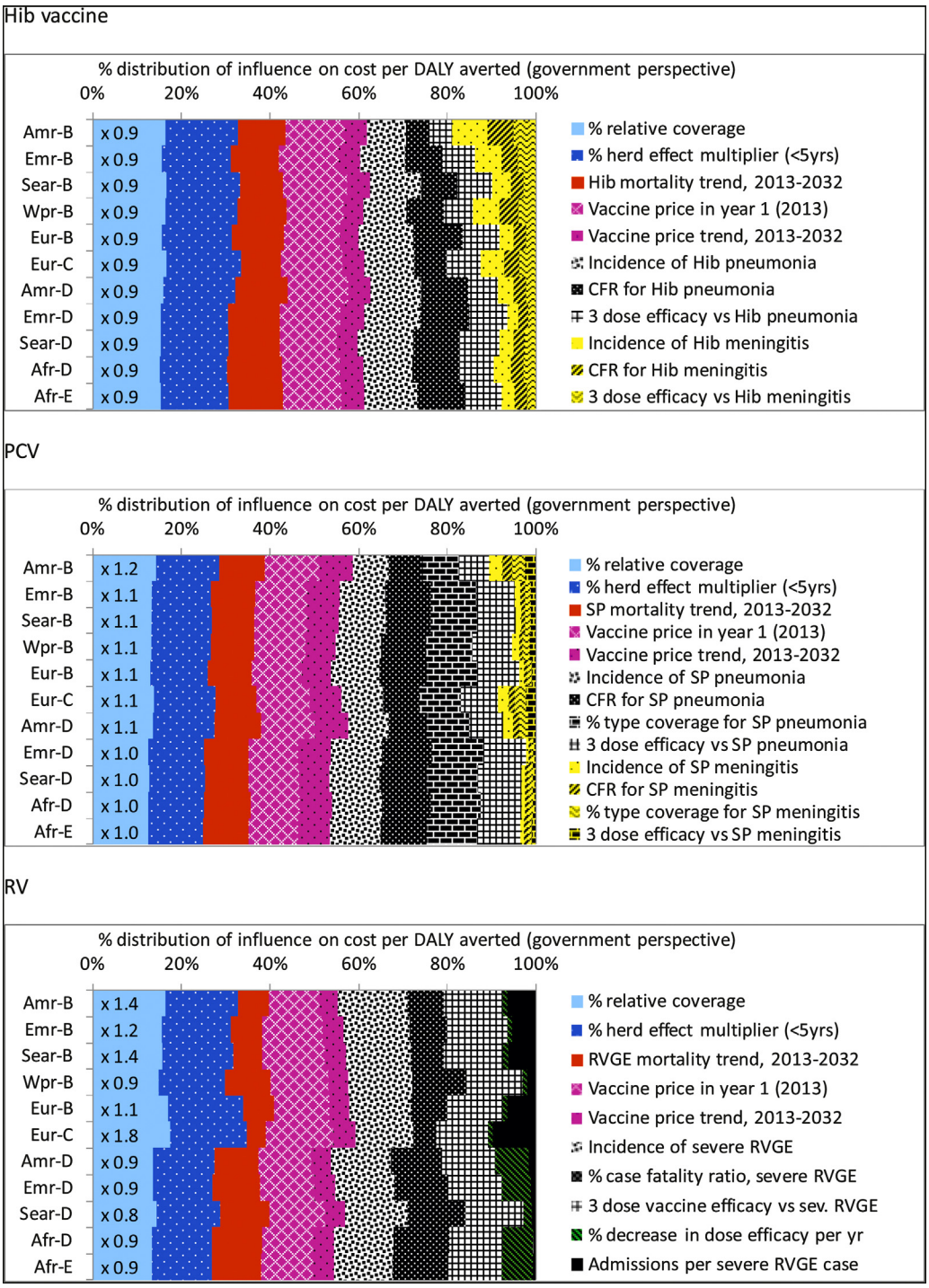


Fig. 3. Relative and absolute influence on ICER for a 10% change in key parameters.

relatively simple structure and Excel platform are advantages in these respects. There is also a stripped down version of the model to get national teams started and additional features that they can engage with as they gain experience and confidence.

2. *Flexibility*. Different decision-makers may have different views about what factors are important, what values are plausible, and even what outcomes are most important. This means that any attempt at producing a single best estimate will be controversial at least, and exploring different scenarios becomes essential. Ideally a model will be able to accommodate all the scenarios that the decision-makers are likely to want to consider. TRIVAC has been under continual development for several years, and new features have been added to accommodate new questions. Now the demand for additional features is perceptibly slowing, but improvements to the facilities for probabilistic sensitivity analysis are in the pipeline.
3. *Speed of response*. Gathering the inputs for the model and getting the right people together to review them can be a challenging and lengthy process. Thus when experts meet to review inputs, there is a critical window of opportunity to review results, explore key drivers, run scenarios and stimulate

thinking about new scenarios. TRIVAC's calculations are fast enough for it to be used interactively and in an exploratory way, allowing national teams to finalise results and present evidence to senior decision makers sooner than would otherwise be possible.

The model does have material shortcomings however (Fig. 4). The most important is its crude way of modelling indirect effects. As a static model it does not directly simulate the changes in disease incidence rates resulting from changes in the risk of infection, or the replacement of sero- or genotypes associated with introduction of a new vaccine. In mitigation, if vaccines are shown to be cost-effective with a static model, then a dynamic model would generally only make them appear more so. However, dynamic models may still be required in situations where: (i) material negative indirect effects (e.g. pneumococcal type replacement) have to be balanced against material positive indirect effects (e.g. herd immunity); or (ii) the issue is a head-to-head comparison of competing vaccines (e.g. PCV10 versus PCV13). To model indirect effects properly would require a dynamic model and enough local epidemiological data to calibrate it [17]. Calibration of dynamic models involves inferring values for generally unobservable parameters such as basic reproductive rates for Hib/pneumococcal colonisation and rotavirus infection, which can be a complex and lengthy process. Such models often seem rather opaque to decision-makers and may not be responsive enough for decision support purposes. The way forward must be to develop static and dynamic models side by side, and validate the former against the latter, and/or to provide enough flexibility for advanced users to change the basic model structure so as to incorporate transmission dynamics while retaining the familiar interface. Where data permits, models such as TRIVAC can help national teams understand the impact of including or excluding specific features, and ideally help stimulate national demand for more advanced modelling techniques.

Another limitation of TRIVAC is that it models each vaccine separately, comparing its impact against the situation with no new vaccines. It thus assumes that the level of benefits from one new vaccine is unaffected by whether the others have been adopted or not. In theory this should only be a problem in countries with very high mortality indeed. Of greater concern is the fact that TRIVAC does not account for the effect of other complimentary health interventions that might be introduced or scaled up at the same time as the new vaccine. For example improving access to oral rehydration will reduce the cost-effectiveness of a rotavirus vaccine in subsequent cohorts, by reducing the burden of mortality from diarrhoea.

In terms of model validation, a lack of good quality pre- and post-introduction surveillance data has generally prevented assessment of the predictive power of the model. However, the default inputs for demography, burden of disease, efficacy, age and dose-specific coverage, waning, etc., were shown to produce results consistent with the real-world impact observed in a case control study of rotavirus vaccination in Nicaragua [18]. In addition, TRIVAC has been shown to produce pneumococcal outcomes consistent with results from other PCV models [19] although meaningful comparisons with transmission dynamic models in LMICs have not been possible to date. Finally, the general structure and methods of the model were presented to WHO's committee for assessing Quantitative Immunization and Vaccine related Research (QUIVER). The experts felt that although further work incorporating temporal dynamics could enhance comparability to other non-vaccine interventions, on the whole TRIVAC was a useful public health tool to build capacity for evidence-based decision making in low and middle income countries [20].

4.2. The most influential parameters

We have identified parameters which influence the cost-effectiveness of Hib vaccine, PCV and RV in each country. This is only part of the story, because the range of plausible values is much greater for some parameters than for others, but this is as far as we can go in a desk-based exercise without extensive consultation on the appropriate ranges of values for each country.

In determining priorities for data collection it does seem important to consider vaccine coverage in children who are most likely to get the disease rather than coverage overall. While vaccine efficacy, herd effects and vaccine price are commonly cited as important drivers of cost-effectiveness, *relative coverage* is rarely considered in models of vaccine impact and cost-effectiveness [21]. In addition, good quality local evidence is needed on the incidence and case fatality of severe RVGE and Hib/pneumococcal pneumonia and meningitis. Other parameters that should be prioritised for local data collection are pneumococcal vaccine type coverage, RVGE admission rates, and meningitis sequelae costs borne by households. Vaccine price and vaccine efficacy are also highly influential and attention should be given to uncertainties in ancillary parameters such as the rates of decline in vaccine price decline and vaccine efficacy.

A one-way univariate analysis highlights the effect of each parameter when varied in isolation. This is a useful check on whether the model is behaving as expected, but as a basis for assessing the relative influence of each parameter it has its limitations. Firstly some parameters, such as costs of health care from specific providers, only affect a minority of cases, and considered in isolation their effects may be small. However, if costs for all the different providers are correlated, taken as a group they may be important. To avoid this problem we could have varied groups of correlated parameters together rather than each in turn, but this would have required data or assumptions about the correlation structure. A univariate analysis has the advantage of being easier to explain, and to some extent the overall influence of a set of finely disaggregated parameters would still be captured by dependencies on other upstream parameters. For example none of the RVGE health care costs for specific types of provider are major drivers, but collectively they can be important, as can be inferred from the influence of the RVGE admission rate.

Second, although parameters are each varied by a constant percentage, their influence may depend on their baseline value. For example, the rate of RV waning had a large influence in Africa and in the high mortality countries in Latin America, but this is driven entirely by the larger but uncertain baseline value assumed in these mortality strata.

More generally, the results are conditional on the whole baseline scenario. If significant changes are made to e.g. the discount rate, the policy regarding RV age restrictions, or the vaccination schedule, then the rankings of parameters may change.

Third, the results will depend on the comparison being made. For example, if the issue is not whether PCV should be introduced but whether it should be PCV10 or PCV13, most factors will be the same for both vaccines, and will balance out. Then the few variables that do discriminate, such as the costs of acute otitis media, will increase in influence.

To conclude, the model provides the motivation and logical framework for a whole process. The first part of this – identifying people and resources within the country concerned, forming institutional collaborations, and collecting and evaluating local data – has often proved at least as valuable as the part that is the concern of this paper – exploring scenarios and interpreting cost-effectiveness results [5]. Experience with TRIVAC to date suggests that cost-effectiveness models have a much better chance of being seen to be relevant to decisions and understood by local

TRIVAC does:	TRIVAC does not:
• Provide estimates of direct vaccine protection among children aged 1-59 months	• Include vaccination benefits for individuals aged over 5 years. This will lead to conservative estimates of vaccination impact, particularly for PCV.
• Include a fixed estimate of the potential influence of herd effects, informed by real-world post-introduction studies.	• Keep track of the number of susceptible, infectious and immune individuals over time, or the likely patterns of transmission between those individuals. • Explicitly model the likely indirect herd effect of a vaccine or the likely changes in the average age of infection.
• Include a fixed estimate of the potential influence of serotype replacement, informed by real-world post-introduction studies.	• Keep track of the number of susceptible, infectious and immune individuals over time. • Differentiate each of the circulating types of a pathogen in terms of their transmissibility, efficacy, and propensity to replace other types.
• Compare the costs and benefits of competing vaccination schedules or brands of a vaccine, by constructing a wide range of plausible scenarios.	• Provide a basis for making decisions between different vaccination schedules or brands of a vaccine when the results from a wide range of plausible simplified 'scenarios' are not persuasive i.e. do not clearly favour one particular schedule or brand of vaccine.
• Allow comparison of cost, impact and cost-effectiveness of alternative vaccines (Hib, PCV, RV) considered separately but on a consistent basis	• Evaluate all three vaccines simultaneously to account for competing risks and subtle demographic effects e.g. preventing early rotavirus deaths, increases the pool of individuals susceptible to PCV.
• Allow for univariate sensitivity analysis, multivariate scenario analysis, and simple probabilistic sensitivity analysis (PSA)	• Provide a correlation structure for parameters varied in sensitivity analysis.

Fig. 4. Summary of situations where the TRIVAC model should be used with caution.

policymakers if they are embedded in such a process, owned and led by national teams.

Conflict of interest

All authors declare no conflict of interest.

Funding

PAHOs ProVac Initiative and GAVIs Hib Initiative.

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.2013.05.045.

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Discussion

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

Anushua Sinha[a,*], Federico Augustovski[b,c], Andrea Alcaraz[b], Sebastián García Martí[b]

[a] New Jersey Medical School – University of Medicine and Dentistry of New Jersey, Newark, NJ, USA
[b] Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina
[c] University of Buenos Aires School of Public Health, Faculty of Medicine, Buenos Aires, Argentina

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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.

* Corresponding author at: Anushua Sinha MD MPH, MSB F506, 185 South Orange Avenue, Newark, NJ 07101, USA. Tel.: +1 973 972 6538; fax: +1 973 972 7625.
E-mail address: sinhaan1@umdnj.edu (A. Sinha).

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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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Review

Establishing a regional network of academic centers to support decision making for new vaccine introduction in Latin America and the Caribbean: The ProVac experience

C.M. Toscano[a,*], B. Jauregui[b], C.B. Janusz[b], A. Sinha[c], A.D. Clark[d], C. Sanderson[d], S. Resch[e], C. Ruiz Matus[f], J.K. Andrus[g], ProVac Network of Centers of Excellence

[a] Department of Community Health, Institute of Tropical Pathology and Public Health, Federal University of Goiás, Goiânia, Goiás, Brazil
[b] ProVac Initiative, Comprehensive Family Immunization Project, Pan American Health Organization, Washington, DC, United States
[c] Department of Preventive Medicine and Community Health, Rutgers University – New Jersey Medical School, Newark, NJ, United States
[d] Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, England, United Kingdom
[e] Center for Health Decision Science, Harvard School of Public Health, Boston, MA, United States
[f] Comprehensive Family Immunization Project, Pan American Health Organization, Washington, DC, United States
[g] Pan American Health Organization, Washington, DC, United States

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ABSTRACT

Background: The Pan American Health Organization's ProVac Initiative, designed to strengthen national decision making regarding the introduction of new vaccines, was initiated in 2004. Central to realizing ProVac's vision of regional capacity building, the ProVac Network of Centers of Excellence (CoEs) was established in 2010 to provide research support to the ProVac Initiative, leveraging existing capacity at Latin American and Caribbean (LAC) universities. We describe the process of establishing the ProVac Network of CoEs and its initial outcomes and challenges.
Methods: A survey was sent to academic, not-for-profit institutions in LAC that had recently published work in the areas of clinical decision sciences and health economic analysis. Centers invited to join the Network were selected by an international committee on the basis of the survey results. Selection criteria included academic productivity in immunization-related work, team size and expertise, successful collaboration with governmental agencies and international organizations, and experience in training and education. The Network currently includes five academic institutions across LAC.
Results: Through open dialog and negotiation, specific projects were assigned to centers according to their areas of expertise. Collaboration among centers was highly encouraged. Faculty from ProVac's technical partners were assigned as focal points for each project. The resulting work led to the development and piloting of tools, methodological guides, and training materials that support countries in assessing existing evidence and generating new evidence on vaccine introduction. The evidence generated is shared with country-level decision makers and the scientific community.
Conclusions: As the ProVac Initiative expands to other regions of the world with support from immunization and public health partners, the establishment of other regional and global networks of CoEs will be critical. The experience of LAC in creating the current network could benefit the formation of similar structures that support evidence-based decisions regarding new public health interventions.

Contents

* Corresponding author. Tel.: +55 62 8199 2229.
E-mail address: ctoscano@terra.com.br (C.M. Toscano).

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1. Introduction

An increasing array of safe and effective vaccines is rapidly emerging for potential global use. Examples include new and previously underutilized vaccines against common causes of invasive bacterial disease and meningitis, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis*, as well as against rotavirus diarrhea and human papillomavirus (HPV). In addition, new vaccines against typhoid fever, dengue, and malaria, among others, are anticipated in the near future. Many of these vaccines should substantially contribute toward achieving Millennium Development Goal 4, to reduce mortality among children <5 years of age by two thirds between 1990 and 2015 [1]. Many of these vaccines have been recommended for inclusion in national expanded programs of immunization [2–6].

2. PAHO's ProVac Initiative

Recognizing the need for an evidence base to support decisions regarding the introduction of new vaccines, the ministers of health from countries in the Region passed a resolution during the 2006 Pan American Health Organization (PAHO) Directing Council meeting calling upon Member States to mobilize additional funding to introduce new vaccines. Both rotavirus vaccine (RV) and pneumococcal conjugate vaccine (PCV) were considered priority new vaccines for the Region [7]. In the same resolution, it was requested that PAHO "support country activities to integrate economic studies into the decision-making process for the introduction of new and underutilized vaccines," as this support was seen as important for the decision-making process. To respond to this request, PAHO accelerated efforts to develop the ProVac Initiative, initiated in 2004 with seed funding from the Global Alliance for Vaccines and Immunization's (GAVI) Pneumococcal vaccines Accelerated Development and Introduction Plan (PneumoADIP) and sustained funding from the Bill and Melinda Gates Foundation.

From its inception, the ProVac Initiative's primary focus has been to promote and strengthen countries' technical capacity to generate evidence to inform decisions on new vaccines, with a special emphasis on health economic analyses. This is achieved through the following objectives: (1) to strengthen infrastructure for decision making; (2) to develop tools for economic analyses and provide training to national multidisciplinary teams; (3) to collect data, conduct analyses, and build decision cases according to technical, financial and operational, and societal criteria; (4) to advocate for evidence-based decisions; and (5) to effectively plan for vaccine introduction when evidence supports it [8].

With ProVac's support, 13 countries in Latin America and the Caribbean (LAC) have conducted or are currently conducting a total of 22 cost-effectiveness studies on the introduction of RV, and/or HPV vaccine. These studies have been conducted by national teams that have led the process of obtaining and evaluating the best available evidence on disease burden, vaccine effectiveness, program costs, and disease costs, among other factors. These data have been used to customize analyses via cost-effectiveness models developed by the ProVac Initiative. ProVac's objectives and rationale, the approach used to achieve its proposed goals, and lessons learned have been reported in detail elsewhere [8–10].

3. ProVac Network of Centers of Excellence

Central to ProVac's vision of South–South and South–North technical cooperation, the ProVac Network of Centers of Excellence (CoEs) was established by PAHO in 2010 to leverage the existing capacity in the Region. The Network comprises a regional group of academic institutions with established expertise in supporting public health decision making in LAC.

In this article, we describe the rationale for establishing the ProVac Network of CoEs. We also describe its operations, challenges, main outcomes, and lessons learned so far. We hope the lessons learned will contribute to the development of networks of academic institutions that provide support to public health programs in other regions of the world.

4. Rationale for establishing the ProVac Network of CoEs

The ProVac Network of CoEs was created with the objective of providing technical support to ProVac activities in LAC, leveraging the existing capacity to perform evidence synthesis and economic evaluations related to immunization policy. Through participation in the Network, it was anticipated that these regional academic institutions would be strengthened and better able to provide training and technical support to, and collaborate with, countries in the Region. The interaction between all actors involved in the ProVac Initiative, including PAHO, country teams, ministries of health (MoH), and CoEs, among others, has been highly useful in fast-tracking necessary studies to generate evidence for decision making regarding the introduction of new vaccines (Fig. 1).

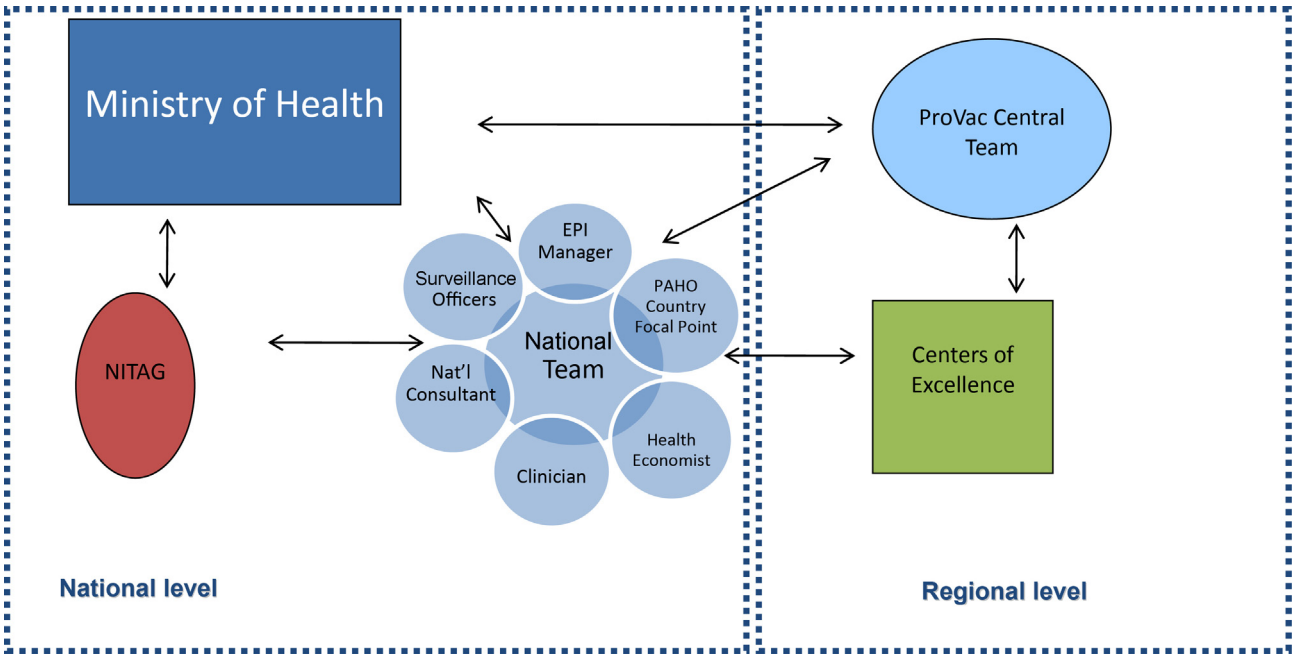

Fig. 1. ProVac Initiative structure, 2012.

5. Structure of the Network

The Network currently includes five academic institutions across LAC (Table 1). Their selection was initiated in 2009, when a survey was sent to eight academic, not-for-profit institutions that had recently published work in the areas of clinical decision sciences and health economic analysis.

Survey results were analyzed by the ProVac technical team, which comprised experts in economic evaluation, epidemiology, and public health. In choosing CoEs, the following criteria were considered: academic productivity in immunization-related work, well-established investigators with track records in relevant fields of investigation, successful collaboration with governmental agencies and international organizations, and experience in training and education on these issues. After this analysis, all six institutions that responded to the survey were invited to join the ProVac Network of CoEs.

In March 2010, the CoEs met for the first time during a regional ProVac training workshop at which the principal investigator and an additional investigator from each CoE acted as workshop

Table 1
Projects assigned to the ProVac Network of Centers of Excellence, May 2010.

Center of excellence	City and country	Project(s)
Department of Internal Medicine and Health Technology Assessment Unit, State University of Rio de Janeiro (UERJ)	Rio de Janeiro, Brazil	• *Acute otitis media incidence*: review of gray literature from LAC and development of a methodology for estimating the incidence of acute otitis media • *Cost of illness and productivity losses*: identification of potential sources of data and development of a methodology for estimating the costs of illness and productivity losses in LAC
Department of Preventative Medicine, School of Medicine, University of Sao Paulo (USP)	São Paulo, Brazil	• *Health service utilization*: development of a methodology for estimating health care service utilization and identification of data sources • *Revision of cervical cancer prevention strategy cost-effectiveness model*: review of and support for the development of a cervical cancer prevention strategy cost-effectiveness model
Epidemiology and Public Health Evaluation Group, Epidemiology Unit, Public Health Department, Universidad Nacional de Colombia (UNAL)	Bogotá, Colombia	• *Vaccination program costs*: development of a tool and a guide for vaccination program costing adapted to the needs of and data availability in the Region
Health Economics Research Group, University of Cartagena (UCart)	Cartagena de indias, Colombia	• *Model parameters and drivers*: identification of model parameters that are key drivers and for which no national-level estimates are available, or for which data do not vary among countries, along with identification of data to prepopulate the above parameters with data available from the Region
Health Economic Evaluations and Technology Assessment, Institute for Clinical Effectiveness and Health Policy (IECS)	Buenos Aires, Argentina	• *Long-distance training*: development of a proposal for long-distance training • *Atlas of data in the Region*: development of a regional "atlas" to facilitate wide, easy, and public access to epidemiological, cost, and health care use information relevant for cost-effectiveness evaluations • *Disease burden*: development of methods for estimating disease burden

Box 1: Terms of reference for the ProVac Network of Centers of Excellence.

- Conduct specific studies and develop specific products for the ProVac Initiative, considering each center's expertise
- Provide training through ProVac workshops and distance learning on economic analyses and evidence-based decision making
- Critically review, validate, and pilot selected ProVac models, tools, and materials, providing critical feedback and updates as needed
- Act as technical subject matter experts in selected issues during the implementation of the ProVac Initiative, as needed and requested by LAC countries through PAHO
- Provide technical support to national multidisciplinary teams in all steps of economic evaluations of new vaccines in various LAC countries, including study design, data collection, data cleaning and critical revision, and analysis and interpretation of results

facilitators. In May 2010, the PAHO team established general terms of reference for the Network (Box 1) on the basis of input received from countries regarding identified gaps in the decision-making process for new vaccine introduction. These terms of reference guided the development of the specific projects to be assigned to each CoE and accompanying plans of action.

The ProVac Network of CoEs was tasked with providing technical support to ongoing activities of the ProVac Initiative, including strengthening capacity in countries, developing methodological guides for performing economic analyses at the national level, and developing, reviewing, or adapting models and tools to support economic analyses and evidence-based decision making. The Network also fosters collaborations among identified CoEs (South–South collaboration) and between CoEs and technical partners and academic institutions outside LAC (South–North collaboration), promoting academic exchange and capacity building. In addition, training of the next generation of technical experts, under the mentorship of CoE investigators, is greatly encouraged.

6. Projects assigned to CoEs

In addition to its main objectives, the ProVac Initiative promotes critical assessments of all factors in the decision-making framework, including technical, logistical and financial, and societal criteria, as described elsewhere [8].

As a result of these assessments, countries identified the following priority issues: lack of information on rotavirus and pneumococcal disease burden in the Region, limited data on the cost of rotavirus and pneumococcal diseases, lack of data regarding the incidence of acute otitis media, challenges in estimating health care service use locally, and underestimation of immunization program costs. Given these priorities, the areas considered for specific project development included the following:

- tools and methods for vaccination program costing;
- tools and methods for budget impact analyses;
- strategies to estimate model parameters for which little or no data are available locally;
- methods for estimating the costs of illness, complications, sequelae, and productivity losses;
- methods to estimate rotavirus and pneumococcal disease burden;
- methods for estimating health care service utilization, given available data sources in the Region;
- impact studies conducted after a vaccine has been introduced.
- continuing education curricula and strategies.

By matching these areas to identified expertise in each of the CoEs, ProVac staff proposed one to three potential projects to each center. These suggested projects were then discussed individually. As a result, consensus was reached about which project the centers were responsible for completing.

After agreement on assigned projects had been reached with the CoEs (Table 1), a detailed plan of action was drafted by each center, including budget needs. Each project was assigned to two CoEs (one responsible for coordination and one for collaboration) with the goal of strengthening South-to-South collaboration. Plans of action and budget proposals were carefully reviewed by the ProVac team (PAHO technical staff and international technical partners, including faculty from Harvard University, the London School of Hygiene and Tropical Medicine, and the New Jersey Medical School, as well as other experts) and revised as needed. On the basis of these plans, one-year contracts were issued by PAHO for each CoE in which intermediate and final deliverables were specified. The final budget for each contract included funding for human resources (based on seniority and expertise), office supplies, and travel and per diems required for project completion. In the first round of contracts, the total amount of funding for Network projects was approximately $300,000.

7. Network coordination and operation

Network members developed and agreed on an internal operating plan describing the overall structure and details of the implementation of the CoE Network. This plan provided specific information about how each CoE would collaborate and coordinate its activities under the ProVac Initiative to ensure that overall objectives were met efficiently. The plan included a structure for coordinating the Network, a series of guiding principles that dictated how CoEs would work together, and an outline of the roles and responsibilities of CoEs, the ProVac team, and collaborators. It also included details on the organizational structures and project personnel for each of the CoEs. Finally, the plan laid out the framework, mechanisms, and tools to facilitate Network communication and monitoring.

The ProVac team oversees the Network, helping to foster the South–North collaboration envisioned. Administrative and technical monitoring mechanisms were established to allow for close follow-up of project development. CoEs were paid against delivery of intermediate and final products after technical approval by the ProVac team. Technical monitoring of projects was performed by assigned focal point personnel.

7.1. Network coordinator

Crucial to the successful implementation of the ProVac Network of CoEs is the appointment of a network coordinator. Selection of the coordinator for the Network was based on the candidate's expertise on economic evaluation and involvement in the early stages of the designing the ProVac Initiative at PAHO. This international consultant, unaffiliated with the CoEs, was hired on a full-time basis and had the following roles: (1) coordinating the committee that selects the CoEs to include in the Network; (2) developing the proposal for the structure of the Network; (3) designing and monitoring the Network's operational plan; (4) coordinating communications between the Network and the ProVac team; (5) reviewing and approving CoE plans of action; (6) negotiating with CoEs on contractual terms; (7) identifying contractual changes that are needed as the project progresses; (8) preventing potential duplication of or gaps in work/activities among groups; (9) supporting the development of the agenda, materials, and reports for Network meetings; (10) monitoring the progress of

plans of action; and (11) coordinating the development of a special journal supplement to disseminate the work performed by the Network.

7.2. Focal points

To facilitate overall Network coordination, ProVac team members were assigned as focal points to each project. Focal points were selected from among the PAHO ProVac team and the ProVac team of international collaborators. They were assigned to projects according to their expertise and areas of interest. Focal points were asked to be considered, to the extent possible, as part of the working group responsible for each of the projects, together with CoE staff.

Specific roles for focal points were identified, including (1) participating in technical discussions related to project development; (2) facilitating collaboration among centers; (3) providing ongoing technical advisory support to CoEs regarding research methods and their implementation; (4) reviewing draft deliverables and providing feedback to verify that work and products meet agreed-on plans of action, resulting in authorization of payments against deliverables; and (5) working with PAHO's ProVac team to align activities and products with ProVac's broader activities and plans. Focal points communicated with CoEs on a regular basis, including conference calls and e-mail exchanges at least once every 2 months.

7.3. Principal investigators

The principal investigator at each CoE was responsible for coordinating the local team of investigators involved in a given project. The contract and the final work and deliverables were the responsibility of the principal investigator. Principal investigators were to participate in all meetings and conference calls with focal points, identifying additional staff from their team to join as needed. Otherwise, the roles of and expectations for principal investigators were similar to those of any principal investigator in terms of executing a funded proposal and carrying out a plan of action.

7.4. Communication

Given the nature of the collaboration, it was critical for all institutions to be committed to clear, transparent communication. This was facilitated by the Network coordinator and tools such as the Network of CoE SharePoint website and regular meeting schedules (in person or through conference calls). The SharePoint website, a mechanism for virtual collaboration, was developed to facilitate communication and exchange of materials among centers.

A conferencing call system was made available by PAHO in which focal points could set up conference calls allowing for free dial-in by CoE and other call participants.

In addition to these virtual communication strategies, Network in-person meetings took place twice a year. The ProVac team, including focal points, two investigators from each CoE, and additional selected PAHO technical staff, participated in these meetings. One biannual meeting was held in Washington, DC, and the other in one of the cities where CoEs are located, rotating among them. Such meetings have proven invaluable in communicating progress, planning next steps, and building team spirit and commitment to effective teamwork.

All reports and deliverables were to be provided in English, allowing for review and constructive comments by all focal points and partner institutions and facilitating publication. Nonetheless, to enhance communication exchanges during face-to-face meetings, trilingual simultaneous translation to and from English, Spanish, and Portuguese was provided. All documents and materials produced by the Network of CoEs are made available in both English and Spanish by PAHO.

Table 2
Products delivered by the ProVac Network of Centers of Excellence, 2012.

Product	Description
Tools	• Tool for vaccination program costing • Tool for budget impact analysis • Review and pilot of a tool for cost-effectiveness analyses of cervical cancer prevention strategies • Review and pilot of a tool for *H. influenzae* type b (Hib), pneumococcal and rotavirus vaccine cost-effectiveness analyses • Regional data repository for LAC including epidemiological, cost, and health care utilization information relevant for cost-effectiveness evaluations
Training materials	• Development of a proposal for long-distance training on decision analyses and economic evaluations relating to new vaccine introduction
Methodological guides	• Guide for use of vaccination program costing tool • Guide for use of a cost-effectiveness tool focusing on cervical cancer prevention strategies • Manual outlining methods for estimating pneumococcal and rotavirus disease burden • Manual outlining methods for estimating incidence of acute otitis media • Manual outlining methods for estimating health care service use considering available data in the Region • Manual outlining methods for estimating costs of illness and productivity losses • Strategies to estimate model parameters for which little or no data are available locally

8. Initial results and outcomes

Since its establishment, the Network has developed and piloted numerous tools, methodological guides, and training materials to support countries in their efforts to assess existing evidence and generate new evidence on vaccine introduction. These products are summarized in Table 2. CoE teams have provided training through workshops and country activities. Examples include the testing and piloting of tools being developed as part of the projects assigned to CoEs, such as an immunization program costing study conducted in Bolivia.

A series of "how-to" guides based on these products is currently under development and will be made available for use by national multidisciplinary teams. In parallel, academic manuscripts presenting the findings from the projects are being published in this special supplement for a broader global audience.

In addition, the Network of CoEs has been effective in fostering collaborative peer work and academic exchanges, strengthening dialogs, and contributing to bridging the gap between academia and policymakers in LAC. Outcomes of the work of the Network of CoEs are being used by various countries in the Region. Country teams led by ministries of health have conducted economic analyses and are now applying methods proposed by CoEs for estimation of disease burden, costs of illness, and health care service utilization. For example, Bolivia has conducted an Expanded Program on Immunization (EPI) costing evaluation using an EPI costing tool developed by one of the CoEs.

9. Lessons learned

Many challenges need to be addressed to ensure equitable access to new vaccines in developing countries, including development of the capacity to make evidence-based decisions in a resource-constrained environment [9]. National governments in

developing countries succeed in promoting health and preventing disease in a more timely manner when they (1) develop the expertise to make the best technical decisions about immunization programs, (2) take responsibility for paying for and distributing vaccines, (3) ensure capacity development of both human and infrastructure resources in order to provide the best possible services for new vaccine administration, and (4) are supported by strong partnerships with international organizations [9].

CoEs are usually established according to criteria such as excellence in a given research area, the structure and capacity to develop research, and past experience in delivering quality results and products. These criteria were also used in establishing the ProVac Network of CoEs. However, the ProVac Network of CoE was developed to operate differently from other funded centers of excellence. In the latter case, academic research groups regarded as leaders in the field usually receive large multiyear grants to fund a combination of investigator-initiated research and training projects after having developed a work plan in response to a request for research proposal issued by the funding institution. Once the work plan is approved and funding is granted to the CoE, limited technical follow-up occurs until the product is delivered.

In the model we used for establishing the ProVac Network of CoEs, we issued per-product contracts with CoEs, which allowed for much closer follow-up and monitoring of each step of the research process. This ensured that the product delivered was relevant to help answer policy questions on new vaccine introduction in LAC in a more timely fashion. Other lessons learned are listed below.

9.1. Project assignment

Academic investigators frequently develop original research protocols and implement study designs themselves. In the case of the Network of CoEs, CoE project proposals were based on needs identified by other decision makers. The products commissioned were guidelines and tools for use by national country teams, although in many circumstances they were piloted by a CoE. From a purely scientific standpoint, working on these "operational" projects may not be of interest to many investigators. Thus, thorough discussions with CoEs and investigators about the products needed, as well as the CoE investigators' understanding of the overall ProVac Initiative work and process, are essential to ensure that the investigators are in full agreement with the work commissioned and, ultimately, that the products of the work can be used in building the capacity of country teams and technical staff at ministries of health.

9.2. Team composition

Local teams with adequate technical capacity should already exist at CoEs, and projects should be assigned on the basis of investigators' previous experience and expertise. In our experience, creating new teams to respond to a specific project request is not efficient and results in unsatisfactory products.

9.3. Close and timely follow-up

Not all CoEs selected to join a network will be able to successfully develop the products included in their contract. Close and periodic monitoring of progress can help to identify and address challenges as they arise and redirect the work as needed. Such situations may include competing demands on investigators' time, changing professional roles for key investigators, and/or lack of institutional support for participation as a CoE.

9.4. Technical oversight and communication

Close communication and interaction between CoE investigators and the ProVac team are essential. The availability of dedicated staff responsible for technical follow-up and discussions with CoEs, in a timely fashion, as well as a clear definition of their roles is crucial. As academic investigators are usually independent and not commonly accustomed to conducting work with close monitoring and feedback throughout the process, strong communication and interpersonal skills are essential for those assigned the task of technical follow-up.

Finally, it is anticipated that as a project is conducted, investigators will often explore ideas and paths that are different from those originally proposed. This is the core of scientific research and is beneficial for the advancement of science. Nonetheless, when operational research is expected to provide results to be used for decision makers in a given time frame, such exploration may distance the final results and the research product from its original intended use. Here again, the role of close technical follow-up is crucial.

9.5. Transverse collaboration among Network members

Transverse collaboration (South-to-South), as sought by the ProVac Network of CoEs, has not been successfully implemented in the Network's current iteration. Although each project was assigned to a coordinating and collaborating center, the collaboration requested was not formally included in contracts, and there was no a priori definition of the roles of collaborating CoEs within each project. When funding is made available and request for project proposals are initiated, collaboration should be clearly indicated, including the roles and responsibilities of each party and a budget item to support the collaboration.

However, the Network was effective in fostering academic exchanges between its members. These exchanges took place mainly during regional ProVac workshops and periodic Network meetings. On such occasions, exchanges between junior and senior researchers, and exposure of junior and mid-career researchers to a broader research community, were successfully promoted.

9.6. Timely dissemination of results to appropriate target groups

National teams led by the ministry of health are the primary audience for the products of the CoEs. It is important that such teams have timely access not only to the materials under development but to the CoE's expertise. To maximize their impact, dissemination of Network results through publication in international peer-reviewed journals as well as national technical manuals and guidelines should be promoted. In addition, regional technical meetings are useful platforms for increasing awareness of online materials that are being made available.

For timely and efficient dissemination of results to technical staff and decision makers at the national level, it is important that regional networks function under the guidance of an organization that has a close technical relationship with national and regional public health decision makers, such as PAHO or other WHO Regional Offices, or under national governments themselves. This will ensure that the Network's plans respond to real-time needs for evidence. Early interaction between the Network of CoEs and national teams can accelerate the dissemination of their work, with the potential to address current data gap issues.

9.7. Management of the potential for conflicts of interest

Investigators and academic institutions often develop research interests and conduct various projects within a given research

area simultaneously, financed by different sources. Slight overlap in work may occur, and to avoid conflicts of interest, particularly regarding funding from government or international organizations and the pharmaceutical industry, all CoEs should clearly declare any perceived or real conflicts.

10. The way forward

As the focus of country ProVac activities continues to expand and evolve according to needs identified at the national level, additional Network projects will continue to be developed. More direct and active involvement of CoEs in country support activities is planned. Expansion of the Network through incorporation of other centers is important with respect to adding breadth and depth of expertise and involving more countries in the Region.

The ProVac Initiative is expanding to other regions of the world with the support of other immunization and public health partners (Agence de Médecine Préventive, PATH, Sabin Vaccine Institute, World Health Organization, Centers for Disease Control and Prevention). The cornerstone of the Network of CoEs is leveraging existing regional capacity. There will be unique challenges in other regions where relevant technical capacity is limited. However, in other regions, the experiences of the PAHO ProVac Network of CoEs within the Region of the Americas should help with the formation of similar structures to support evidence-based decisions on the introduction of new vaccines.

Conflict of interest

None of the authors report a conflict 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.2013.05.033.

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Review

Treatment costs of diarrheal disease and all-cause pneumonia among children under-5 years of age in Colombia

N. Alvis-Guzman[a], J. Orozco-Africano[a], A. Paternina-Caicedo[a,*], W. Coronell-Rodríguez[a], L. Alvis-Estrada[a], D. Jervis-Jálabe[a], F. De la Hoz-Restrepo[b]

[a] Health Economics Research Group, Universidad de Cartagena, Cartagena de Indias, Colombia
[b] Epidemiology and Public Health Evaluation Group, Universidad Nacional de Colombia, Bogotá, Colombia

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ABSTRACT

Objective: We estimate treatment costs associated with diarrheal disease and all-cause pneumonia among children under-5 years of age in Colombia and assess similarities or differences with previous cost estimations in developing countries of the Americas.
Methods: Macro-costing methods were used to carry out an analysis of diarrhea and all-cause pneumonia costs in Colombia in 2010. The perspective of the health care system was taken. Data were extracted from a health insurer database that includes information on health service utilization among 130,800 children from low-income households. Lengths of stay for hospital admissions and frequencies of cases at all levels of care registered in the database were estimated.
Results: There were 1456 diarrheal disease cases among the 130,800 children (aged ≥60 months) included in the study. The median cost per case was $27.10 (interquartile range [IQR]: $15.60–77.40). A total of 1545 all-cause pneumonia cases were reported to the insurer in 2010, resulting in a frequency of 1181 cases per 100,000 children (95% confidence interval [CI] = 1122, 1240). The overall cost of all-cause pneumonia cases was $858,791, and the median cost per case treated was $263 (IQR: $27–546). Comparisons by level of care showed that costs were significantly different for the two diseases ($p < .05$). Costs for the diseases did not differ by age group ($p > .05$).
Conclusions: Diarrhea and all-cause pneumonia constitute a significant economic and health burden in Colombia. The relatively large size of our sample allowed us to provide reliable national estimates of the costs associated with these diseases. Our results for Colombia are similar to previous estimates from developing countries in the Americas. These data provide valid estimates that may be used decision makers in other countries to make appropriate recommendations on the introduction of rotavirus and pneumococcal vaccines.

Contents

* Corresponding author. Tel.: +57 3006370786.
E-mail address: angel.paternina@gmail.com (A. Paternina-Caicedo).

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1. Introduction

Childhood pneumonia is the leading cause of mortality in children under 5 years old worldwide, causing 1.39 million deaths in 2010 [1]. The incidence in this age group is estimated to be 0.29 episodes per child-year in developing countries and 0.05 episodes per child-year in developed countries [2]. In addition, diarrheal disease is one of the most common childhood illnesses in both developing and developed countries [3]. In 2004, there were 10.4 million deaths reported among children under-5 years of age worldwide, and diarrhea caused an estimated 17% of these deaths (1.87 million; uncertainty range: 1.56–2.19) [4]. Rotavirus was estimated to have caused 453,000 deaths in 2008 [5]. Also, diarrheal disease was the third most common cause of death in children and the second most common cause of hospitalizations and outpatient visits [6–8].

Timely case management of diarrheal disease and pneumonia, including the use of oral rehydration therapy and prompt use of antibiotics, can substantially reduce the risk of fatal outcomes. However, the world's poorest populations often have limited access to these basic health services.

Treatment cost analyses of pneumonia and diarrheal disease among children under-5 are scarce in Latin American and Caribbean (LAC) countries. In the published literature on pneumonia treatment costs, data are available for only a limited number of countries [9–15]. In Colombia, for example, only two studies have described pneumonia costs among children [16,17]. These studies were hospital based and involved a relatively small, non-representative sampling of nationwide disease costs. Studies related to disease management costs of diarrhea among children >5 years are also scarce in LAC countries. In Colombia, only one hospital-based study has described the costs of diarrhea among children >2 years in inpatient and outpatient settings [18].

The purpose of the present study was to estimate treatment costs (direct medical costs) of diarrhea and all-cause pneumonia in a hospital-based population of children and to assess similarities with or differences from previous cost estimations in the Americas.

2. Methods

This descriptive cost study of diarrheal disease and all-cause pneumonia in children under 5 was carried out in Colombia. The study was based on a 2010 database of information on health service visits (*Registros Individuals de Prestación de Servicios* [RIPS]) among a hospital-based population of children from low-income households. The perspective of the health care system was taken.

We used a step-down, macro-costing approach, estimating costs for all patients and costs per treated case of all-cause pneumonia and diarrhea [19].

2.1. Population and data collection

All health providers (inpatient and outpatient) in Colombia are required to provide information for the RIPS database; each medical procedure administered to a patient is recorded, along with the total cost charged to the health insurer. The database reports diagnosis data (according to the *International Classification of Diseases* (10th revision; *ICD-10*)) and cost data (medication, diagnostics, personnel, and hospital bed-day costs) for each patient visit or admission. Information is provided by the attending physician in every consultation made within the Colombian health care system, and the database serves as an annex for disbursements made to any health facility within the system.

The Colombian health system covers 96% of the population through two regimes: contributive (covering those who can afford to pay a premium rate) and subsidized (covering those who cannot afford to pay a premium rate and are entitled to subsidized services from the Colombian government) [20]. This study focuses on a database of health service visits from a health insurer in the subsidized regime. This insurer covers approximately 1.25 million people who cannot afford to pay a premium. These individuals are distributed across the country, in 12 states (of a total of 32 states) and 144 municipalities (of a total of 1108), and 130,800 (10.4%) of them are under-5 years of age. Overall, the health insurer covers 2.8% of the Colombian population and 3.1% of the under-5 population.

According to the national poverty line 37.2% of the country's population has an income falling below the national poverty line, and according to the international definition (power purchasing parity of $2 a day) 6.8% of the population is does [21,22].

We used *ICD-10* diagnosis codes to identify all diarrheal disease cases (codes A00–A09) and pneumonia cases (codes J180, J181, J188, J189, J158, J159, P361, A408, and A409) reported to the database. In Colombia, all-cause pneumonia is diagnosed radiologically, usually according to the criteria of the World Health Organization [23]. In addition to costs, we estimated lengths of stay and frequencies of pneumonia health care visits.

The RIPS database reflects the clinical history of a disease in the Colombian health system. As such, several health care encounters may be registered for the same disease in different time periods. As a means of correcting this possible bias, different health care encounters labeled with the same *ICD-10* code were considered as the same pathology if they occurred within a day from the date of discharge to the subsequent admission day.

The data were categorized by age group and level of care. The Colombian health system divides care by level of complexity, depending on the health care service structure available to provide support to patients with severe illness.

2.2. Statistical analysis

Data were extracted and analyzed in Microsoft Excel. We report continuous data as means and medians, depending on the probability distribution of the variable in question. We report parametric variables as means and nonparametric variables as medians. Categorical variables are reported as percentages. We report costs as medians (as an aggregate measure) and interquartile ranges (IQRs; as a measure of dispersion). We converted costs to 2010 US dollars ($) at an exchange rate of 1913.9 Colombian pesos to 1 US dollar. Nonparametric tests (Mann–Whitney) were used in performing cost comparisons. The level of statistical significance was set at $p < .05$.

3. Results

The sample included 130,800 children under-5. Cost comparisons showed no significant differences in median costs for all-cause pneumonia and diarrhea between different age groups ($p > .05$). The results for each disease are outlined below.

3.1. All-cause pneumonia

A total of 1545 inpatient cases of pneumonia were reported in 2010, resulting in a rate of 1181 cases per 100,000 children (95% confidence interval [CI] = 1122, 1240). The overall cost of all cases combined was $858,791, and the median cost per case was $263 (IQR: $27–546) (Table 1).

Case frequencies and costs by age groups and levels of care are shown in Tables 1 and 2. The median length of stay was 2 days (IQR: 1–5), and there were significant differences in lengths of stay

Table 1
Frequency of all-cause pneumonia among children >5 years of age in Colombia.

Age group (months)	No. of children	No. of cases (%)	Total cost (US $)	Median cost per case (US $) (IQR)[a]	Frequency per 100,000 (95% CI)
0–11	17,250	281 (18.2)	184,466	331 (19–693)	1629 (1437–1821)
12–23	41,945	596 (38.6)	370,855	285.5 (29–555.5)	1421 (1306–1535)
24–35	22,099	308 (19.9)	142,267	244 (37.5–506.5)	1394 (1237–1551)
36–47	24,541	178 (11.5)	82,208	185 (29–524)	725 (617–834)
48–60	24,965	182 (11.8)	78,995	226.5 (23–478)	729 (621–837)
Total	130,800	1545 (100)	858,791	263 (27–546)	1181 (1122–1240)

[a] Comparisons of age groups did not show statistically significant differences ($p > .05$).

Table 2
Treatment costs for all-cause pneumonia and diarrhea, by level of care, among children >5 years of age in Colombia.

Level of care	All-cause pneumonia				Diarrhea			
	No. of cases (%)	Length of stay (days) (IQR)	Total cost (US $)	Median cost (US $)[a] (IQR)	No. of cases (%)	Length of stay (days) (IQR)	Total cost (US $)	Median cost (US $)[a] (IQR)
Primary	247 (16)	2 (1–2)	70,474	71 (20–268)	654 (44.9)	1 (1–1)	33,951.4	25.1 (17.8–45.9)
Secondary	1208 (78.2)	4 (1–5)	555,790	283.5 (25–533)	779 (53.5)	1 (1–2)	108,978.4	34.8 (13.3–169.7)
Tertiary	47 (3)	6 (3–9)	40,376	482 (306–1067)	19 (1.3)	1 (1–2)	6120.7	175.6 (55.7–357.8)
Critical care	43 (2.8)	13 (6–14)	192,151	3393 (1358–7164)	4 (0.3)	15 (7–29)	31,885.1	7184.2 (2270.6–13,672)

[a] Comparisons by level of care showed statistically significant differences ($p < .001$).

according to level of care ($p < .001$). Median costs were also significantly different according to level of care (Table 2).

3.2. Diarrhea

In 2010, 1456 children were treated for diarrhea in inpatient and outpatient settings. The total cost of these health services was $180,936. The frequency of diarrhea was 904 cases per 100,000 population (95% CI = 760, 1049). Frequencies were greater in children aged >1 year and in children between 12 and 35 months of age (Table 3). Median costs did not differ according to age group.

The median cost per case was $27.10 (IQR: $15.60–77.40). Costs were significantly different according to level of care ($p < .001$) (Table 2). The median duration of follow-up in primary (outpatient) care was 1 day. Median lengths of stay were 1 day (IQR: 1–2) in secondary and tertiary care hospitals and 15 days (IQR: 7–29) in critical care hospitals. Median costs ranged from $25.10 (IQR: $17.80–45.90) in primary care facilities to $175.60 (IQR: $55.70–357.80) in tertiary care facilities. Although critical care admissions occurred at a low frequency, these admissions involved the highest median cost per stay ($7184.20; IQR: $2270.60–13,672).

4. Discussion

To our knowledge, this is the largest population-based study to measure diarrhea and all-cause pneumonia management costs in a Latin American and Caribbean country. Our data provide reliable statistics on costs, frequencies of inpatient admissions, lengths of stay, and the economic burden of disease in Colombia, an upper-middle-income LAC country.

In cost-effectiveness studies of pneumococcal and rotavirus vaccines in LAC, sensitivity analyses typically show that vaccine price, mortality rate, and treatment costs are key drivers of cost-effectiveness [24–30]. Thus, our estimates are reliable parameters to assess and validate past estimates in Colombia and possibly other LAC countries, and these data can be useful for future cost-effectiveness studies as well.

Research has shown that per-case costs for inpatient all-cause pneumonia range between $440.10 in Brazil [15] and $5547.80 in Argentina (prepaid health system) in complicated pneumonia cases [31]. Our results showed that, in Colombia, the median cost per case for all-cause pneumonia treated at the secondary care level was $482 (IQR: $306–1067). At $859.10 per admission, tertiary care facilities incur roughly two times the cost of secondary-level care (as just noted, $482) and approximately five times the cost of primary-level care ($71; IQR: $20–268). These results are similar to cost data reported in other resource-constrained settings such as India [32], and Pakistan [33], as well as the estimates reported for LAC countries by Constenla et al. [34].

Treatment costs for diarrhea cases attended in tertiary care facilities were similar to those reported in studies conducted in Mexico, Venezuela, Argentina, Brazil, Chile, and Panama [24–26,35]. With the exception of studies from Chile [24,36] and Venezuela [24], the treatment costs we estimated for lower-level care facilities were similar to outpatient visit costs in the studies reviewed.

In 2007, De la Hoz et al. estimated that the annual numbers of diarrhea cases requiring hospitalization in children under 2 years old were 2586 (uncertainty range: 2294–2823) in the absence of a rotavirus vaccination program and 1883 (uncertainty range: 1671–2056) in the presence of such a program [18]. Colombia

Table 3
Frequency of diarrheal disease among children >5 years of age in Colombia.

Age (months)	No. of children	No. of cases (%)	Total cost (US $)	Median cost (US $) (IQR)[a]	Frequency per 100,000 (95% CI)
0–11	17,250	156 (10.7)	35,941.7	28 (14.1–131.3)	904 (760–1049)
12–23	41,945	644 (44.2)	83,016.6	27.9 (15.6–78)	1535 (1416–1654)
24–35	22,099	335 (23)	33,304.5	27.2 (17.2–76.2)	1516 (1353–1679)
36–47	24,541	141 (9.7)	11,219.4	22.3 (14.2–48.2)	575 (478–671)
48–60	24,965	180 (12.4)	17,453.4	30.5 (14.7–87.3)	721 (614–828)
Total	130,800	1456 (100)	180,935.6	27.1 (15.6–77.4)	904 (760–1049)

[a] Comparisons between different age groups showed that median costs were not significantly different ($p > .05$).

introduced the monovalent rotavirus vaccine in 2008 and achieved 82.4% national coverage of the full schedule in 2009 [37].

To extrapolate results on diarrhea and all-cause pneumonia to rotavirus-specific diarrhea and pneumococcal pneumonia, there is a need to consider the possible differences between disease-specific costs and syndrome costs. In the United States, diarrhea costs and rotavirus-specific diarrhea costs are very similar (a median of $3900 for both in 2001–2003), despite slightly longer lengths of stay for rotavirus disease [38]. In addition, a study conducted in eastern China showed that the direct costs of rotavirus diarrhea and non-rotavirus diarrhea were statistically similar ($p = .462$) [39]. We were unable to locate data on the costs of pneumococcal pneumonia in the literature; in most cost-effectiveness analyses, pneumonia costs are used as a proxy for pneumococcal-specific disease costs.

There is a need to consider some limitations of our analysis. We used secondary data from a health insurer, and such information is potentially subject to selection and misclassification bias. Selection bias in this regard can lead to an underestimation of the true incidence of diarrhea, since a portion of the insured population may not have access to hospitalization or health care. However, it is unlikely that selection bias altered our cost results since our estimates were based on a large number of cases. Misclassification of diagnoses may result in both underestimation and overestimation of the incidence of diarrhea. However, for the same reason just described, it is unlikely that misclassification bias led to overestimations in our results. Underestimations are possible if a significant number of cases of diarrhea are classified as other diagnoses or are not classified at all. Another limitation of our study is related to the database we used, which did not allow for identification of specific cost components.

Among the strengths of this investigation is the fact that our sample was relatively large for a cost study, allowing us to make reliable national cost estimates for Colombia. Despite its overall low severity, diarrhea is a significant economic and health burden in Colombia as a result of the frequency of cases. Our findings are similar to previous diarrheal disease estimates from developing countries in the Americas.

Our study adds to the knowledge base regarding the frequency and costs of diarrhea and all-cause pneumonia in a developing country. Our data can assist decision makers in making appropriate recommendations on the introduction of vaccines with the aim of lowering the burden of disease in Colombia.

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Review

Systematic review of pneumococcal disease costs and productivity loss studies in Latin America and the Caribbean

Luciana Bahia[a,*], Cristiana M. Toscano[b], Maíra Libertad Soligo Takemoto[a], Denizar Vianna Araujo[a]

[a] State University of Rio de Janeiro, Rio de Janeiro, Brazil
[b] Federal University of Goiás, Goiânia, Goiás, Brazil

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ABSTRACT

Background: Pneumococcal disease is an important cause of morbidity and mortality associated with significant economic burden for healthcare systems and society.
Objectives: To systematically review pneumococcal disease cost of illness and productivity loss studies in the Latin America and Caribbean (LAC) region.
Methods: A search of relevant databases was performed till November 2011. A broad and sensitive search strategy was used consisting of medical subject headings (MeSH) terms for pneumococcal disease, healthcare costs and productivity loss studies. No language restriction was applied. Only papers from LAC region and child population were analyzed. Additional exclusion criteria included duplicate studies, and insufficient information about methods.
Results: A total of 1241 citations were retrieved. After applying the exclusion criteria, only 16 studies remained for analysis. There were 4 papers from Brazil, 3 from Argentina, 2 from Colombia, 2 from Mexico, 1 from Uruguay, 1 from Chile, and 3 analyzing a group of LAC countries. Only 4 were cost-of-illness studies, 11 were cost-effectiveness studies of pneumococcal vaccine and 1 study of the pneumococcal burden of disease. Methods used for quantifying health resource utilization and costing methods varied significantly among studies, as well as data sources considered. Productivity losses were considered in 8 studies, all of which used the human capital approach method. Pneumococcal disease cost estimates varied significantly depending on the pneumococcal syndromes considered, methods used, study perspective and type of costs included.
Conclusion: This systematic review reinforced the importance of standardization of methods for cost studies that can allow comparison and reproducibility in other settings. These estimates can be useful for future economic analysis conducted to support the decision making process on the introduction of new vaccines in LAC. However, caution must be taken, as methodological aspects of studies will result in estimates with varying levels of accuracy and external validity.

Contents

* Corresponding author at: Internal Medicine Department, State University of Rio de Janeiro, Blv. 28 de Setembro 77-3 andar-sala 329, Vila Isabel, 20551-030 Rio de Janeiro, RJ, Brazil. Tel.: +55 21 28688484/25124350; fax: +55 21 22740856.
E-mail addresses: lucianabahia@gmail.com (L. Bahia), ctoscano@terra.com.br (C.M. Toscano), mliberdad@gmail.com (M.L.S. Takemoto), denizarvianna@gmail.com (D.V. Araujo).

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1. Introduction

Streptococcus pneumonia is a leading cause of bacterial pneumonia, meningitis, and sepsis in children worldwide, and is responsible for approximately 11% of deaths in children under 5 years old [1]. Pneumococcal disease represents a significant economic burden for health care systems and society, constituting a public health priority.

The World Health Organization (WHO) recommends the introduction of pneumococcal conjugate vaccine into national immunization programs, especially in countries with high mortality rates in children under 5 years old [2]. It has been estimated that vaccination could prevent over half of all cases and deaths due to pneumococcal disease annually in the Latin America and Caribbean region (LAC) [3].

The introduction of new vaccines requires significant investment of resources and economic analyses are important to ascertain cost-effectiveness. Such analyses should take into account local epidemiological data; pneumococcal disease incidence; serotype distribution; vaccine efficacy; disease costs including costs of diagnosis, treatment and follow-up of cases; vaccine introduction program costs; and budget impact analysis. National decision makers are frequently constrained by the time and human resources needed to develop such economic analyses.

The Pan American Health Organization (PAHO) provides technical assistance for evidence-based decision making regarding new vaccine introduction in Latin America and the Caribbean, including development of economic analyses. PAHO's ProVac Initiative was launched in 2006 with the objective to promote and strengthen technical capacity in countries to perform economic analyses regarding vaccine introduction, and to make critical assessments of all factors involved in the decision-making process, including technical, logistical, and financial criteria [4].

Cost-of-illness (COI) studies aim to identify and measure the total costs attributable to a particular disease and can include both direct (medical and non-medical) and indirect costs (e.g., productivity losses). Depending on methods used, type of costs included, and syndromes considered, COI estimates can vary significantly.

To date, COI studies assessing pneumococcal diseases have been conducted in several countries, using various methodologies. This article aims to systematically review such studies conducted in the LAC region, assessing the methods used in each of the studies and analyzing results in light of the methodological approach used.

2. Methods

The authors followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and checklist for undertaking and reporting this systematic review [5]. Fig. 1 depicts the flow of information throughout the review, including the number of records identified, articles excluded and the reasons for exclusions, and the final number of articles included in the final review.

2.1. Literature search

As an initial step, published studies, guidelines, and clinical trials were searched in relevant databases. These included the Cochrane Central Register of Controlled Trials (CENTRAL); Embase, a biomedical database; the MEDLINE database of the United States National Medical Library; the Latin American and Caribbean Health Sciences Literature database (LILACS); and the Economic Evaluation Database of the United Kingdom National Health Service (NHS EED). Searches for relevant dissertations and theses available in the database of Brazilian academic dissertations and theses ("Banco de Teses") were also conducted [6]. The date range for searches used November 2011 as the end date; there was no start date. No language restriction was applied. Search strategies were applied in English, Portuguese, and Spanish. The search strategy included a combination of free text terms and standardized terms from the medical subject headings (MeSH) for searches in English-language databases. For searches in LILACS, MeSH synonyms in Portuguese available in the "Descritores em Ciências da Saúde" (DeCS) database were used. MeSH terms used included: "Pneumococcal Infections", "Cost of Illness", "Costs and Cost Analysis", "Absenteeism", "Indirect Costs", "Societal Costs", "Productivity Loss", "Work Impairment", and "Presenteeism".

2.2. Study selection

We considered the following inclusion criteria for studies in this systematic review: studies about economic evaluation or cost of illness, studies conducted in the LAC region, and studies assessing the economic burden of pneumococcal disease or the economic impact of pneumococcal vaccination programs. Studies conducted in countries outside the LAC region and in adult populations (18 years of age and older) were excluded from the analysis. All records retrieved in the literature search were initially screened by title and abstract. When eligibility for inclusion could not be determined after initial title/abstract review, full articles were obtained and independently reviewed by two reviewers. Duplicate studies were excluded. If eligibility was not consensual among reviewers, a third reviewer assessed the paper for final decision on inclusion.

2.3. Data extraction and analysis

Results were analyzed considering each study's methodological aspects. The following information was extracted into standardized data retrieval forms: author; publication year; country; target population; type of study (economic evaluation or cost-of-illness study); type of analysis (cost-effectiveness, cost-utility or cost-benefit analysis, when applicable); study perspective; type of costs included (direct, indirect, or both); sources of unit costs; source of health care resource utilization data (primary data collection, database analysis, expert panel, or modeling); time horizon; and results including currency and year. For productivity loss estimates, methods of cost estimation (human-capital or friction-cost approach) and monetizing method were assessed.

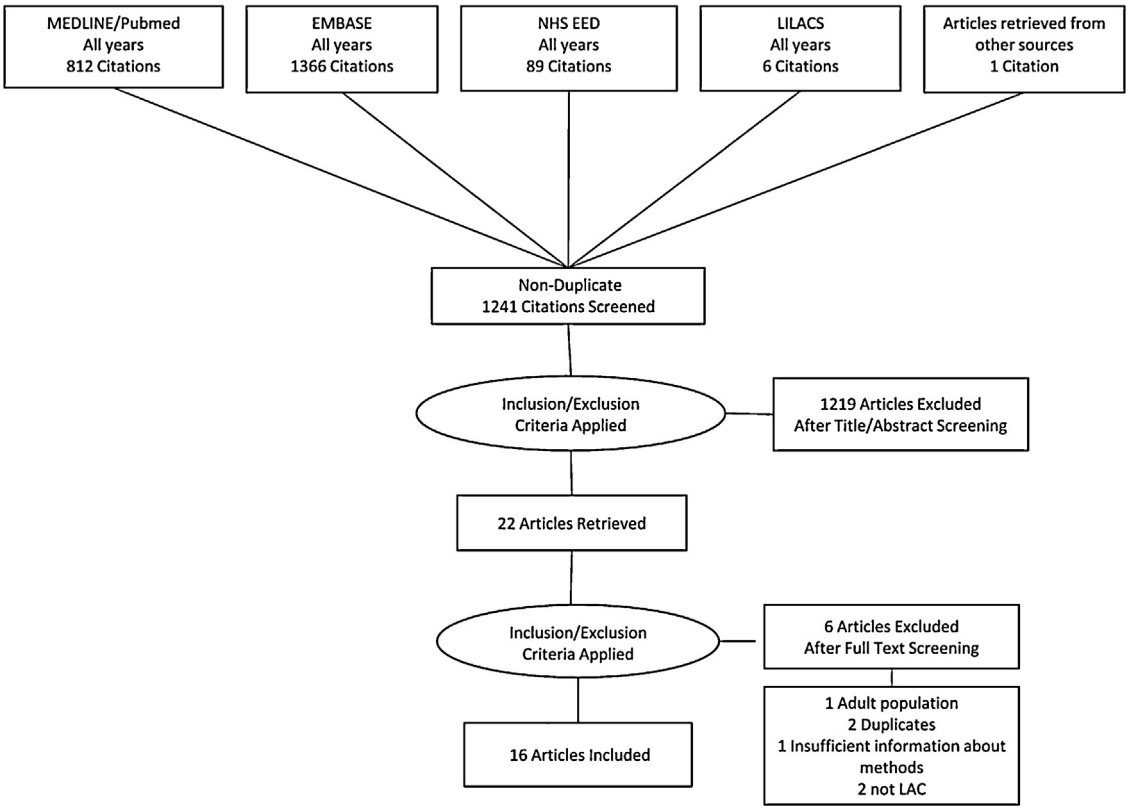


Fig. 1. Systematic review of pneumococcal disease costs and productivity loss studies in Latin America and Caribbean. PRISMA flowchart.

Study perspectives considered included the following: (a) societal perspective, in which all medical and non-medical direct costs, as well as indirect costs incurred by health systems, patients, and their families were included in the analysis; (b) public health system perspective, in which only direct costs incurred by the public health system were included in the analysis; and (c) private health system perspective, in which only costs reimbursed by health insurance companies (usually direct medical costs) were included in the analysis.

Direct medical costs considered in the hospital setting included medications, diagnostic tests, surgeries, health professional fees, physiotherapy, parenteral nutrition, blood products, and ambulance transportation. In the outpatient setting the costs included were medications, diagnostic tests, and health professional fees. Direct medical costs also included the cost of long-term treatment costs, cochlear implants and other procedure-related costs, special education, caregiver time, and rehabilitation.

Non-medical costs included costs of transportation of patients and caregivers to and from the health care facilities. Indirect costs were defined as costs related to productivity losses and were based on the number of days off work (for the parent or caregiver) and income lost due to pneumococcal disease.

Syndromes/outcomes included were acute otitis media (AOM), all-cause pneumonia, pneumococcal pneumonia, meningitis (with or without sequelae), bacteremia, sepsis, and invasive pneumococcal disease (pneumococcal meningitis and sepsis).

2.4. Currency units

Results are presented in both local currencies and US dollars, considering the year of the study. Official inflation rates of each country [7] and exchange rates for local currency to US dollars, considering the 2010 purchasing power parity (PPP), were used [8]. By establishing purchasing power equivalence, where one international dollar purchases the same quantity of goods and services in all countries, PPP conversions allow cross-country comparisons of economic aggregates on the basis of physical levels of output, free of price and exchange rate distortions.

3. Results

A total of 1241 records were initially retrieved from the databases of published studies, guidelines and clinical trials. After initial title/abstract screening, only 22 articles were retrieved to be read in full. An additional 6 articles were further excluded, resulting in 16 papers included in the final analysis (Fig. 1). These studies were published between 2005 and 2011.

There were four papers on Brazil [9–12], three on Argentina [13–15], two on Colombia [16,17], two on Mexico [18,19], one on Uruguay [20], one on Chile [21], and three that analyzed groups of LAC countries [22–24]. The main characteristics of these studies are described in Tables 1 and 2.

In addition, two theses were initially identified from the Brazilian "Banco de Teses" database. One was deleted as it was a narrative review of cost estimation methods for economic evaluation of vaccination programs. One thesis was included in the final analysis [11].

3.1. Study participants

Eight of the 16 studies assessed the economic impact of pneumococcal disease in children up to 5 years of age [9,10,12,15,20–24]. Different target age groups (2, 3, and 10 years old) were used in the remaining studies [11,13,14,16–19,21].

Cost-effectiveness studies ($n = 11$) were conducted considering hypothetical birth cohorts [9,10,12,14,15,17–20,23,24], and

Table 1
Main characteristics of studies on pneumococcal disease costs and productivity loss in LAC.

Author, year	Country	Currency/year of reported results	Study design	Target population	Study perspective	Disease outcomes/syndromes considered	Health resources utilization data sources
Guzmán NA, 2005 [16]	Colombia	2002 US dollars	COI (prospective)	128 pneumonia cases (64 bacterial, 64 viral) 0–2 years old	Public health care system and societal	Pneumonia (bacterial and viral) (only hospitalizations)	Hospital databases (4 hospitals)
Guzmán NA, 2010 [17]	Colombia	2006 US dollars	CEA	Children with low birthweight 0–2 years old	Public health care system	All-cause AOM, all-cause pneumonia, meningitis, and invasive pneumococcal diseases	Sabin Institute report (physician and parent interviews) [3]
Constenla D, 2007 [22]	Brazil, Chile, Uruguay	2004 US dollars	COI Hospital: retrospective (90%) prospective (10%); ambulatory: prospective (100%)	753 children (166 Brazil, 400 Chile. 187 Uruguay) 0–5 years old	Public health care system	All-cause AOM, all-cause pneumonia, pneumococcal pneumonia, and pneumococcal meningitis	Prospective multi-center observational study; secondary databases
Constenla D, 2008 [23]	Brazil, Chile, Uruguay	2004 US dollars	CEA	Annual hypothetical birth cohort, followed up to 5 years	Societal	All-cause AOM, all-cause pneumonia, pneumococcal meningitis, and pneumococcal sepsis	Prospective multi-center observational study[a]; secondary databases
Sinha A, 2008 [24]	All LAC countries	2005 US dollars	CEA	Annual hypothetical birth cohort, followed up to 5 years	Societal	All-cause AOM, all-cause pneumonia, pneumococcal meningitis, and pneumococcal sepsis	Physician interviews (10 LAC countries), interviews with parents of sick children, secondary databases
Vespa G, 2009 [9]	Brazil	2006 US dollars	CEA	Annual hypothetical birth cohort, followed up to 5 years	Public health care system and societal	AOM with and without complications, pneumonia, pneumococcal sepsis, pneumococcal meningitis with or without disabilities	Physician interviews, WHO-CHOICE, Brazilian HMOs and MCOs
De Souza CPR, 2009 [10]	Brazil	2008 Brazilian reais	CEA	Annual hypothetical birth cohort, followed up to 5 years	Public health care system	AOM, pneumonia, and invasive pneumococcal diseases	Medical records of 300 hospitalized patients in Ribeirão Preto city
Lucarevschi BR, 2010 [11][b]	Brazil	2009 Brazilian reais	COI (retrospective)	0–10 years	Public health care system	Pneumococcal meningitis (only hospitalizations)	Medical records, secondary databases
Sartori AM, 2012 [12]	Brazil	2004 Brazilian reais	CEA	Annual hypothetical birth cohort, followed up to 5 years	Public and private health care systems and societal	AOM, pneumonia, pneumococcal sepsis, and pneumococcal meningitis	Secondary databases
Lagos R, 2009 [21]	Chile	2006 US dollars	COI (prospective)	594 children with invasive diseases; 1498 children with pneumonia 0–35 months	Public and private health care systems	Pneumonia and invasive pneumococcal diseases	Medical records and parent interviews
Larraz GG, 2010 [20]	Uruguay	2008 US dollars	CEA	Annual hypothetical birth cohort, followed up to 5 years	Public and private health care systems and societal	AOM, pneumonia, empyema, bacteremia–sepsis, meningitis without and with sequelae (neurologic and auditory)	Medical records of hospitalized patients; expert panel
Augustovski FA, 2009 [13]	Argentina	2006 US dollars	Burden of the disease	Annual hypothetical birth cohort, followed up to 10 years	Societal	AOM, pneumonia, meningitis, bacteremia, and long-term sequelae	Literature review, expert panels, and local health systems

Giglio ND, 2010 [14]	Argentina	2007 US dollars	CEA	Annual hypothetical birth cohort, followed up to 2 years	Public and private health care systems and societal	All-cause AOM, all-cause pneumonia, and invasive pneumococcal disease	Epidemiologic surveillance database, international literature, expert panel, and parent interviews
Urueña A, 2011 [15]	Argentina	2009 US dollars	CEA	Annual hypothetical birth cohort, followed up to 5 years	Public and private health care systems and Society	All-cause AOM, all cause pneumonia, pneumococcal bacteremia/sepsis, and pneumococcal meningitis.	Physician interviews (pediatricians, otolaryngologists and neurologists)
Talbird SE, 2010 [18]	Canada, Germany, Mexico[c], Norway	2008 Mexican pesos	CEA	Annual hypothetical birth cohort, followed up to 10 years	Public health care system	AOM, pneumonia, meningitis, and bacteremia.	Expert panel
Muciño-Ortega E, 2011 [19]	Mexico	2010 US dollars	CEA	Annual hypothetical birth cohort, followed up to 2 years	Public health care system	All-cause AOM, all-cause pneumonia, meningitis, and bacteremia.	Secondary databases, cross-sectional study of nosocomial infection at a tertiary hospital[d]

LAC, Latin America and the Caribbean; COI, cost-of-illness; CEA, cost-effectiveness analysis of anti-pneumococcal vaccine; AOM, acute otitis media; HMO, health maintenance organizations; MCO, managed care organizations.

[a] Based on previous observational study [22].

[b] Academic thesis.

[c] Mexico data only.

[d] Navarrete-Navarro S. Costos secundarios por infecciones nosocomiales en dos unidades pediátricas de cuidados intensivos. Salud Pública Méx 1999;41(Suppl. 1):s51–8.

cost-of-illness studies ($n = 4$) considered actual child population estimates [11,16,21,22].

3.2. Study design

There were 4 cost-of-illness (COI) studies [11,16,21,22], 11 cost-effectiveness analyses (CEA) of pneumococcal vaccine introduction [9,10,12,14,15,17–20,23,24] and 1 burden of disease study [13]. Productivity losses were estimated in eight studies [9,12,14–16,20,23,24] and costs associated with long-term sequelae were included in five studies [9,10,13,14,20].

All COI studies included in this review were observational studies. Two used prospective data collection [16,21], one was a mix of prospective and retrospective data collection [22], and one used retrospective data collection based on the review of medical charts and interviews with parents [11]. Two studies included only inpatient costs [11,16].

All CEAs were based on modeling. None of them was conducted alongside a clinical trial or observational study specifically designed to assess both economic and clinical outcomes.

3.3. Perspectives

Regarding the analytic perspective, four studies considered the societal perspective [13,14,23,24], one considered both societal and public health care system perspectives [9], seven considered only the public health care system perspective [10,11,16–19,22], one considered both the public and private health care systems perspectives [21], and three considered public, private, and societal perspectives [12,15,20].

3.4. Cost estimates

Table 3 describes the direct costs of the pneumococcal infection as originally presented by authors and in 2010 US (international) dollars. The mean cost estimates of all studies is also presented. As expected, costs varied by syndrome (Fig. 2). Acute otitis media (AOM) was the event with lower costs, although in recurrent and/or complicated AOM cases that required surgical procedures and/or hospitalization, cost estimates increased 7–39 times compared to non-complicated cases [10,13]. In one study conducted in selected LAC countries, health care costs (e.g., 10% in Brazil and 84% in Chile) and out-of-pocket expenses (86% in Brazil and 15% in Chile) were factors that contributed to huge differences in AOM costs [22].

Costs for hospitalized pneumonia cases were approximately 6–8 times higher than cases managed as outpatients [13]. The highest costs reported were attributed to pneumococcal meningitis, with the estimated annual costs of long-term meningitis sequelae reaching 3–5 times the costs of acute meningitis [13].

The costs per hospitalization varied by type of health facility, with significantly higher costs in private facilities when compared to public health facilities [12,14,15,20,21]. One study reported that hospitalization costs were 80% higher in private facilities compared to public ones [14].

3.5. Indirect costs

The main methodological characteristics of studies on pneumococcal disease indirect costs are presented in Table 2. All indirect cost studies considered the human-capital approach (HCA), and most (6 out of 8) used average country wages to estimate the cost of each unit of paid work time [9,12,14,20,23,24]. Two studies collected primary data of self-reported wages [15,16]. One study included government benefits for patients with meningitis long-term sequelae (i.e., deafness and/or neuromotor disabilities as a result of meningitis) [9].

Table 2
Methodological characteristics of studies on pneumococcal disease costs and productivity loss in LAC, with indirect cost estimates.

Author/year	Country	Collection of primary data	Absenteeism	Presenteeism	Inclusion of long-term losses	Methodological approach	Wage/income cost estimation	Productivity loss outcome
Guzmán NA, 2005 [16]	Colombia	Yes (n = 100)	Yes	No	No	HCA	Self-reported wage	Lost days of paid work × wage
Constenla D, 2008 [23]	Brazil, Chile, Uruguay	Yes (n = 60)	Yes	No	No	HCA	Country mean wage	Mean hours lost × mean wage
Sinha A, 2008 [24]	LAC region	Yes (n = 60)	Yes	No	No	HCA	Country mean wage	Mean hours lost × mean wage
Vespa G, 2009 [9]	Brazil	Yes; experts	Yes	No	Yes[a]	HCA	Country minimum wage	Lost days of paid work × minimum wage
Sartori AM, 2012 [12]	Brazil	No; assumptions[b]	Yes	No	No	HCA	Country mean wage (women)	Inpatient days × daily wage; outpatients = 5 days for pneumonia and 1 day for AOM × daily wage
Larraz GG, 2010 [20]	Uruguay	No; assumptions[c]	Yes	No	No	HCA	Country mean wage	Inpatient days × daily wage; outpatient visits × 2 × hourly wage
Giglio ND, 2009 [14]	Argentina	No; assumptions	Yes	No	No	HCA	Country mean wage	Inpatient days × 0.5 × daily wage; outpatient visits × 2 × hourly wage
Urueña A, 2011 [15]	Argentina	Yes; secondary reference[d]	Yes	No	No	HCA	Self-reported family income (divided by all the residents of the house)	Lost days of paid work × daily income

LAC, Latin America and Caribbean region; HCA, human-capital approach; AOM, acute otitis media.

[a] Government benefits for disabled patients (sequelae).

[b] Average length of stay in hospital retrieved from government databases and the clinical course of disease treated in an ambulatory setting.

[c] Taking into account unemployment rates.

[d] Based on a previous study of societal costs associated with hospitalizations due to acute respiratory infection in children in different public hospitals in Buenos Aires (Rowensztein H, et al. Carga de enfermedad y costos asociados a las internaciones por infección respiratoria aguda en niños. Arch Argent Pediatr 2007;105(1):5–11.

Table 3
Estimated direct costs by syndrome/disease outcomes, as originally presented and converted to 2010 US dollars.

Author/year	Country	Currency/year of reported results	Study perspective	Acute otitis media (original currency/2010 USD)	All-cause pneumonia (original currency/2010 USD)	Pneumococcal pneumonia (original currency/2010 USD)	Pneumococcal meningitis (original currency/2010 USD)	Bacteremia/sepsis (Original currency/2010 USD)	Sequelae (costs per year) (original currency/2010 USD)
Guzmán NA, 2005 [16]	Colombia	2002 US dollars	Public health care system	NA	NA	Inpatient: 562/1144	NA	NA	NA
Guzmán NA, 2010 [17]	Colombia	2006 US dollars	Health care systems	93/256	NA	885/2417	1303/3557	NA	NA
Constenla D, 2007 [22] * Constenla D, 2008 [23]†	Brazil, Chile, Uruguay	2004 US dollars	Public health care system	Brazil: 20/22[a] 194/222[b] Chile: 217/248[a] 250/286[b] Uruguay: 90/103[a] 103/118[b]	Oupatient: Brazil: 75/85[a] 88/101[b] Chile: 220/252[a] 255/292[b] Uruguay: 45/51[a] 88/101[b]	Inpatient Brazil: 372/426[a] 387/443[b] Chile: 3483/3991[a] 3572/4093[b] Uruguay: 1147/1314[a] 1444/1654[b]	Brazil: 1134/1299[a] 1240/1421[b] Chile: 5436/6229[a] 5589/6404[b] Uruguay: 2271/2602[a] 2497/2861[b]	Brazil: 1080/1237[a] 1178/1349[b] Chile: 5120/5867[a] 5226/5988[b] Uruguay: 2100/2406[a] 2235/2561[b]	–
Sinha A, 2008 [24]	All LAC countries	2005 US dollars	Societal	82/92	Outpatient: 98/110 Inpatient: 940/1054	NA	1792/2009	1256/1409	NA
Vespa G, 2009 [9]	Brazil	2006 US dollars	Societal	19/39 Complicated: 85/177	Outpatient: 26/55 Inpatient: 511/1060	NA	982/2037	1718/3562	Auditory sequelae: 7189/14,904 Motor sequelae: 8052/16693
De Souza CRP, 2009 [10]	Brazil	2008 Brazilian reais	Public health care system	19/12 Complicated: 715/469 to 1488/976[c]	NA	Outpatient: 58/38	14143/9278	3048/2000	Auditory sequelae: 77/50[d] Motor sequelae: 1540/1010
Lucarevschi BR, 2010 [11]	Brazil	2009 Brazilian reais	Public health care system	NA	NA	NA	5666/3518	NA	NA
Sartori AM, 2012 [12]	Brazil	2004 Brazilian reais	Public and private health care systems and societal	17/13 Complicated: 257/201	NA	Outpatient: 25/20 Inpatient: 526/412	1135/889[e]	1135/889[e]	NA
Lagos R, 2009 [21]	Chile	2006 US dollars	Public health care system	NA	NA	Outpatient: 87.4/137 Inpatient: 740.8/1161[f] Complicated: 1995/3128[g]	2590/4061	Outpatient: 67/106 Inpatient: 429/673	NA
Larraz GG, 2010 [20]	Uruguay	2008 US dollars	Public and private health care systems	11/16	NA	Outpatient: 21/30 Inpatient: 777/1104 Complicated: 7406/10,524	1457/2071 Complicated: 3152/4479	Outpatient: 43/61 Inpatient: 233/332 Sepsis: 1405/1997	Auditory sequelae: 1860/3755 Neurologic sequelae: 5568/7913

Table 3 (*Continued*)

Author/year	Country	Currency/year of reported results	Study perspective	Acute otitis media (original currency/2010 USD)	All-cause pneumonia (original currency/2010 USD)	Pneumococcal pneumonia (original currency/2010 USD)	Pneumococcal meningitis (original currency/2010 USD)	Bacteremia/sepsis (Original currency/2010 USD)	Sequelae (costs per year) (original currency/2010 USD)
Augustovski FA, [13] 2009	Argentina	2006 US dollars	Societal	40/73 With surgery: 278/511	NA	883/1624[h]	1351/2485	Outpatient: 73/134 Inpatient: 1052/1935	Auditory sequelae: 2706/4979 Motor sequelae: 6374/11728 Epileptic sequelae: 4558/8386
Giglio ND, 2010 [14]	Argentina	2007 US dollars	Public and private health care systems and societal	24/41	NA	104/180	1592/2740	173/298	Neurologic sequelae: 21,645/37,251
Urueña A, 2011 [15]	Argentina	2009 US dollars	Public and private health care systems	13/26 Recurrent: 85/171	NA	Outpatient: 36/72 Inpatient: 644/1301 Complicated: 2500/5658	1299/2625 Complicated: 4216/8502	Outpatient: 126/259 Inpatient: 624/1261	NA
Talbird SE, 2010 [18] g	Mexico	2008 Mexican pesos	Public health care system	3826/531 With myringotomy: 5315/738	NA	Outpatient: 4819/669 Inpatient: 49636/6899	172,849/24,026	71,932/9998	NA
Muciño-Ortega E, 2011 [19] [i]	Mexico	2010 US dollars	Public health care system	831	Inpatient: 1560 Complicated: 16541	NA	5651	14946	NA
All studies[j]	–	–	–	116 [12–531] Complicated or recurrent: 480 [171–831]	Outpatient: 122 [55–252] Inpatient: 1057 [1054–1060]	Outpatient: 164 [20–669] Inpatient: 2062 [412–6899] Complicated: 4393 [3128–5658]	4692 [889–24026] Complicated: 6490 [4479–8502]	Outpatient: 140 [61–259] Inpatient: 3578[332–14,946]	Auditory sequelae: 7879 [3755–14904] Neurologic sequelae: 13,830 [1010–37,251]

This Table displays only public costs of all studies (private cost data not shown). Decimal values for currencies were rounded to the nearest integer. NA–not available

[*] Costs of pneumococcal disease in Latin America countries

[†] Economic impact of pneumococcal conjugate vaccination in Brazil, Chile and Uruguay

[a] Medical costs per child.

[b] Total direct cost per child including medical and non-medical costs.

[c] With or without adenoidectomy or placement of tympanostomy tubes.

[d] De Souza et al. [10] estimate for auditory sequelae costs considered only the cost of hearing aid and was not included in the calculation of average total costs.

[e] Pneumonia meningitis and pneumococcal sepsis considered together as invasive pneumococcal disease.

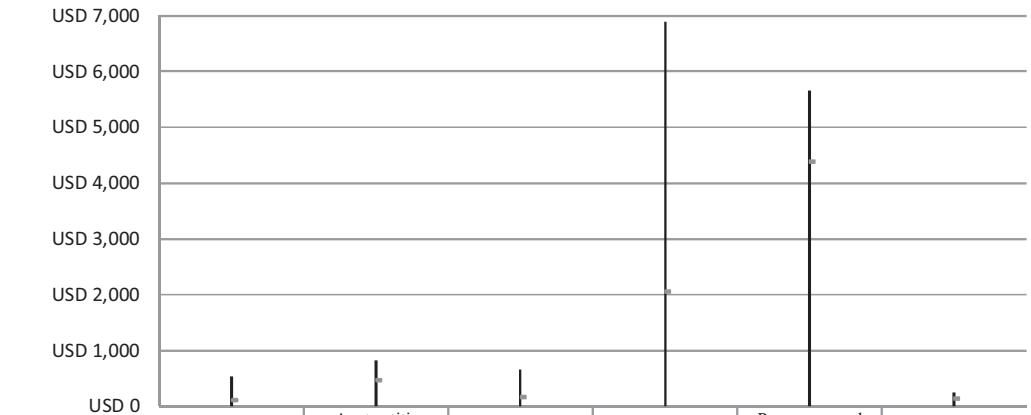
[f] Pneumonia with bacteremia.

[g] Pneumonia with pleural effusion or empyema.

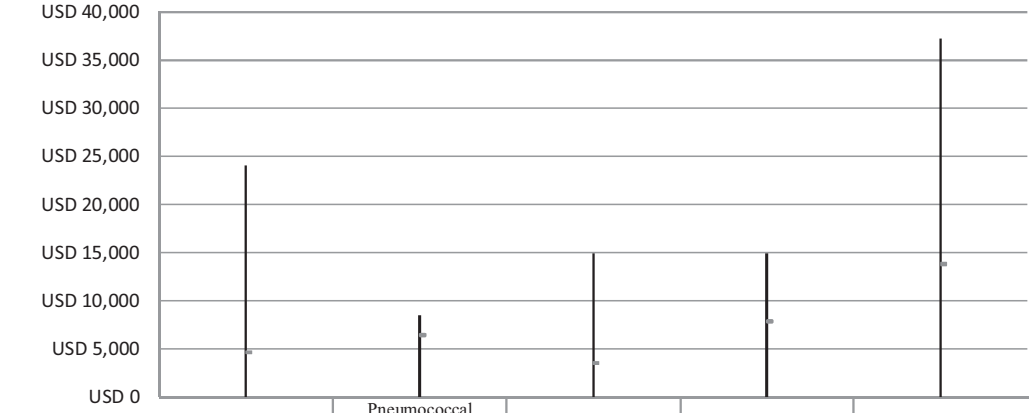
[h] Based on unpublished estimates of resource use from a Delphi panel.

[i] Direct medical costs of bacteremia and pneumonia were estimated based on 37 pneumonia and 20 bacteremia/sepsis cases in two intensive care units of a tertiary hospital without mention of pneumococcal etiology – Navarrete-Navarro S. Costos secundarios por infecciones nosocomiales en dos unidades pediátricas de cuidados intensivos. Salud Pública Méx 1999;41(Suppl. 1):s51–8. Costs of meningitis, AOM and outpatient pneumonia were obtained from an IMSS report – Instituto Mexicano del Seguro Social, Dirección de Planeación y Finanzas, Coordinación de Presupuestos, Contabilidad y Evaluación Financiera. Costs by diagnosis-related group for hospitalized cases. Mexico, D.F. IMSS; 2003.

[j] Cost values are expressed only in 2010 USD and as a mean [min – max]. When the costs per event were not specified as out- or inpatient care, they were excluded from the mean calculation.



	Acute otitis media (US$)	Acute otitis media-complicated (US$)	Pneumococcal pneumonia-outpatient (US$)	Pneumococcal pneumonia-inpatient (US$)	Pneumococcal pneumonia-complicated (US$)	Bacteremia-oupatient (US$)
Min	12	177	20	412	3,128	61
Max	531	831	669	6,899	5,658	259
Mean	113	480	164	2,062	4,393	140
number of studies	12	6	6	7	3	4



	Pneumococcal meningitis (US$)	Pneumococcal meningitis-complicated (US$)	Bacteremia / Sepsis-inpatient (US$)	Auditive sequelae (US$)	Neurologic sequelae (US$)
Min	889	4,479	332	3,755	1,010
Max	24,026	8502	14,946	14,904	37,251
Mean	4,692	6,490	3,578	7,879	13,830
number of studies	13	2	9	3	5

Fig. 2. Variation in unit costs for pneumococcal syndromes across studies.

Two studies conducted in Brazil differ in these estimates because national country wages were obtained with a four-year interval. One did primary data collection [9], while the other adopted an assumption based on length of hospital stay of a sick child with an employed caregiver [12].

In the majority of studies the inclusion of productivity losses contributed to a smaller proportion of the total costs compared to direct costs with a wide variability (1.9–78.3%) [14,24]. In outpatient AOM and pneumonia cases, three studies reported indirect costs that were higher than direct costs due to productivity losses of the caregiver [9,12,20].

Estimated costs for productivity loss related to pneumococcal diseases are presented in Table 4 as originally described by the authors and in 2010 US dollars.

4. Discussion

This systematic review analyzed pneumococcal disease cost-of-illness and productivity loss studies in the LAC region. The methodology for collecting data about health resource utilization and their costs varied broadly among studies (retrospective and prospective primary data collection, government and hospital databases, international literature adaptation, physician and parent interviews, expert panels). Varying methods and data sources were used in the same studies, making it difficult to compare results between studies conducted in different countries and to extrapolate cost results from one setting to another.

Although there is no method that is the gold standard for cost-of-illness studies, those using micro-costing methodology, collecting primary data prospectively, and considering the societal perspective are considered to generate more accurate cost estimates [25]. Secondary databases were commonly used as data sources for health resource utilization and costs [9,11–14,19,24]. These included vital registries, census, population and household surveys, and administrative records. Many countries in LAC have health information systems that managers and policy makers use to plan and evaluate both performance and costs of health care programs and interventions. Although most of these databases are

Table 4
Estimated indirect costs by syndrome/disease outcomes, as originally presented in studies and converted to 2010 US dollars.

Author/year	Currency/year of reported results	Acute otitis media (original currency/2010 USD)	Pneumonia (original currency/2010 USD)	Invasive pneumococcal disease[a] (Original currency/2010 USD)	Bacteremia (original currency/2010 USD)	Sepsis (original currency/2010 USD)	Meningitis (original currency/2010 USD)	Meningitis with sequelae[b] (original currency/2010 USD)	Lower respiratory tract infection (original currency/2010 USD)
Guzmán NA, 2005 [16]	2002 US dollars	–	Inpatient: 67/136	–	–	–	–	–	–
Constenla D, 2008 [23]	2004 US dollars	Brazil 9/10 Chile 9/10 Uruguay 9/10	Outpatient: Brazil 9/10 Chile 9/10 Uruguay 9/10 Inpatient: Brazil 61/69 Chile 61/69 Uruguay 61/69			Brazil 72/82 Chile 72/82 Uruguay 72/82	Brazil 35/40 Chile 35/40 Uruguay 35/40	–	–
Sinha A, 2008 [24]	2004 US dollars	9/10	Outpatient: 9/10 Inpatient: 61/69	–	–	72/81	35/40	–	–
Vespa G, 2009 [9]	2006 US dollars	34/71 Complicated: 43/89	Outpatient: 51/107 Inpatient: 139/289	–	–	241/501	186/386	Auditory sequelae: 829/1,718 Neurologic sequelae: 829/1720	–
Sartori AM, 2012 [12]	2004 US dollars	15/12 Complicated: 62/49	Outpatient: 162/127 Inpatient: 78/61	202/159	–	–	–	–	–
Larraz GG, 2010 [20]	2008 US dollars	9/12 Complicated: 49/70	Outpatient: 7/10 Inpatient: 67/96 Complicated: 151/215	–	Outpatient: 13/19 Inpatient: 54/76	216/309	163/232	Auditory sequelae: 396/567 Neurologic sequelae: 1323/1879	–
Giglio ND, 2009 [14]	2007 US dollars	15/27	82/141[c]	–	75/129[c]	–	893/1538	Auditory sequelae: 782/1,347 Neurologic sequelae: 2642/4547	–
Urueña A, 2011 [15]	2009 US dollars	–	–	–	–	–	–	–	Tertiary level center 158/319[d] Primary level center 124/252[d]
All studies[e]	–	20 [10–71] Complicated: 69 [49–89	Outpatient: 41 [10–127] Inpatient: 111 [61–289]	–	–	189 [81–501]	331 [40–1532]	Auditory sequelae: 1210 [567–1718] Neurologic sequelae: 2715 [1720–4547]	–

Decimal values for currencies were rounded to the nearest integer.

[a] Invasive pneumococcal disease (IPD) includes pneumococcal meningitis and pneumococcal sepsis.

[b] Costs per year.

[c] Pneumonia and bacteremia costs not divided by out- and inpatient costs.

[d] Based on a previous study of societal costs associated with hospitalizations due to acute respiratory infection in children in different public hospitals in Buenos Aires (Rowensztein H et al. Arch Argent Pediatr 2007;105(1):5–11).

[e] Cost values are expressed only in 2010 USD and as a mean [min – max].

developed and used for administrative and reimbursement purposes, they are valuable sources of information on health care resource utilization and costs. A potential limitation of using such data sources is the quality of data input. Another limitation is that an estimated cost of illness may be an underestimate of true costs.

In addition to primary or secondary data collection, health care resource utilization estimates can be obtained using a "per protocol" or a guideline-oriented approach, in which a typical treatment course is developed by expert panels, and costs of each treatment component are then estimated using appropriate data sources to determine unit costs. This approach was used in many of the studies reviewed [9,13–15,18,20,24], indicating the lack of secondary data sources in many countries. This method relies on expert judgment for determining the average treatment, length, and proportion of patients receiving it. As such, it may represent either an over- or under-estimate of resource utilization.

In most studies conducted in LAC, pneumococcal meningitis is associated with higher costs compared to other pneumococcal syndromes requiring hospitalizations (pneumonia, bacteremia, sepsis). Some studies showed a huge variation in costs when they separated complicated cases from uncomplicated ones [11,15,20]. The cost estimates generated from primary data collection [10,11,20] and specialist opinions [15,18] were higher than those obtained from secondary databases [9,12–14,17,22–24].

Similar results were found for pneumococcal pneumonia and AOM episodes, with clear differences in cost estimates if complications occurred and/or hospitalization was needed. Most studies have separated the costs of a single AOM episode from recurrent and/or complicated cases, but without a clear definition of diagnosis criteria. Likewise, the highest cost estimates came from the two Mexican studies and were generated using information from an expert panel [18] and diagnosis-related group payment for hospitalized patients [19]. This latter study showed much higher cost estimates than the average. These values may have included all cases together (simple and complicated), but this cannot be confirmed.

Long term sequelae costs were indirectly estimated in five studies and there was a wide difference among them [9,10,13,14,20]. The occurrence of auditory and/or other neurologic sequelae increased the long-term costs for health systems and society. The comparison of these estimates is difficult, however, because some studies do not clearly describe the methodology for estimating costs related to sequelae [9,10]. One study based estimates on interviews conducted with five parents [14], another study used local expert opinion [20], and a third based its estimates on the authors' assumption [13]. Furthermore there was no uniformity in the characterization of auditory sequelae (unilateral versus bilateral hearing impairment, severe hearing sequelae needing special education and cochlear implants, partial hearing loss versus deafness) and neurologic sequelae (neuromotor disabilities, seizure disorder).

All studies adopted the human-capital approach to estimate productivity loss based on work time lost (hours or days) multiplied by its costs. Some differences in indirect costs could be attributed to the methods used for assessing the value attributed to paid work time. The majority of studies obtained this information predominantly from average national wages [12,14,20,23,24]. By using the societal perspective, the inclusion of productivity loss costs contributed to a smaller proportion of the total costs compared to direct costs, although this percentage varied greatly from one study to another, and sometimes, in uncomplicated cases of AOM and pneumonia, indirect costs were higher than direct costs.

Even after adjusting for inflation and taking PPP into account, cost estimates presented in different studies are difficult to compare and there is not a single explanation for the broad variation. In some cases the variation could be explained by the type of data source used (higher values for values obtained from expert panels and microcosting), inclusion of different types of costs (medical, non-medical, and societal costs), the perspective considered, and differences in the value of payments for health resources among countries. All studies were done in countries grouped as upper-middle-income (based on World Bank classifications [26]), so there is no reason to suggest that cost estimates differ because of income differences among countries.

The generalization of cost estimates from the published literature is difficult due to the important differences already described. In the absence of accurate cost estimates there are two reports that are available to the general public that can be used as a proxy for cost estimates in regional analysis. The first is the World Health Organization's project "Choosing Interventions that are Cost Effective" (WHO-CHOICE) which provides estimates of the per diem cost of public hospitals, outpatient visits, and health center visits for 14 epidemiological categories based on geographical region and mortality stratum [27]. The second is a report by the Sabin Vaccine Institute (in collaboration with PAHO, US Centers for Disease Control and Prevention [CDC] and the Global Alliance for Vaccines and Immunizations [GAVI]) which estimated the burden and costs of pneumococcal disease in Latin America and the Caribbean for 2007 [3]. This report demonstrates the average regional costs due to treatment (in- and outpatient care) for pneumonia, meningitis, acute otitis media, and sepsis, and provides insight into the cost of pneumococcal disease by country income group (low income, lower-middle income, and upper-middle income).

5. Conclusion

This systematic review reinforces the need to standardize methodology for cost-of-illness studies in order to compare results and duplicate them in different settings. Estimates from standardized approaches will be useful for future economic analysis conducted to support the decision-making process on the introduction of new vaccines in countries where local pneumococcal epidemiologic and costing data are limited or not readily available. However, caution must be taken when reproducing these results in other settings, as methodological aspects of any given study will result in estimates with varying levels of accuracy.

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Review

Systematic review of studies on rotavirus disease cost-of-illness and productivity loss in Latin America and the Caribbean

Maíra Libertad Soligo Takemoto[a], Luciana Bahia[a], Cristiana M. Toscano[b], Denizar Vianna Araujo[a,*]

[a] State University of Rio de Janeiro, Rio de Janeiro, Brazil
[b] Federal University of Goiás, Goiânia, Goiás, Brazil

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ABSTRACT

Background: Rotavirus is the most common cause of severe acute diarrhea among children in both developed and developing countries. Vaccination can reduce the disease burden and its incorporation into health care systems should consider future costs and benefits.
Objectives: To systematically review studies on costs due to rotavirus infection in Latin America and Caribbean (LAC) region, considering their methods and results.
Methods: A search of relevant databases including the Cochrane Central Register of Controlled Trials, Embase, MEDLINE via PubMed, the Latin American and Caribbean Health Sciences Literature database (LILACS), and the Brazilian Thesis Databank was performed. Inclusion criteria for studies were: (a) economic evaluation or cost-of-illness studies; (b) conducted in the LAC region; (c) assess economic burden of rotavirus disease or the economic impact of rotavirus vaccination programs. Two authors independently screened the studies for eligibility.
Results: Of 444 studies initially retrieved, 21 met the eligibility criteria and were included (14 cost-effectiveness analyses of vaccination programs and 7 cost-of-illness studies). Direct medical costs were assessed in all 21 studies, but only 10 also investigated indirect and non-medical direct costs. The most commonly observed methods for cost estimation were retrospective database analysis and hospital-based surveillance study. Only one study was a household-based survey.A wide cost range was identified (e.g., inpatient care US$79.91 to US$858.40 and outpatient care US$13.06 to US$64.10), depending on the methods, study perspective, and type of costs included.
Conclusion: Rotavirus-associated costs were assessed in 21 studies across the Latin America and Caribbean region. The majority of studies were made alongside economic evaluations of vaccination programs. Methods are broadly different among studies but administrative databases seem to be the most employed source of data.

Contents

* Corresponding author at: Internal Medicine Department, State University of Rio de Janeiro, Blv. 28 de Setembro 77–3 andar–sala 329, Vila Isabel, ZIP 20551-030, Rio de Janeiro/RJ Brazil. Tel.: +55 21 28688484/25124350.
E-mail addresses: mlibertad@gmail.com (M.L.S. Takemoto), lucianabahia@gmail.com (L. Bahia), ctoscano@terra.com.br (C.M. Toscano), denizarvianna@gmail.com (D.V. Araujo).

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1. Introduction

Diarrhea is one of the main causes of morbidity and death among children worldwide. A World Health Organization (WHO) review of surveillance studies conducted before 1980 estimated that 4.6 million children died from diarrhea each year [1] numbers that dropped to approximately 3.3 million annually in the 1980s [2]. Rotaviruses are the most common cause of severe acute diarrhea among children in both developed and developing countries. A global study designed to assess the rotavirus-related morbidity and mortality estimated that rotavirus causes close to 111 million episodes of mild gastroenteritis, 25 million moderate episodes (requiring only outpatient care), and 2 million severe cases requiring hospitalizations each year. Of these, around 82% of cases occurs in the poorest countries of the world [3]. A recent systematic review showed that 68% of all deaths in children under 5 years old worldwide are due to infectious disease, and that diarrhea is responsible for 15% of those deaths (ranging from 0.8 million and 2.0 million) [4]. Estimates of worldwide rotavirus-associated mortality in children younger than 5 years old in 2008 indicate that diarrhea attributable to rotavirus infection accounted for 453,000 deaths (37% of all diarrhea-related deaths and 5% of all deaths in children younger than 5 years) [5,6].

To help the decision-making process on the inclusion of a vaccine into a health care system, a critical evaluation of its future costs and benefits is highly recommended. This is usually done by a formal, country-specific cost-effectiveness analysis. The Pan American Health Organization (PAHO) provides technical assistance for evidence-based decisions particularly in the use of cost-effectiveness analysis and economic evaluations of interventions in Latin America and the Caribbean. The ProVac Initiative was launched by PAHO in 2006 to strengthen the technical capacity of countries to perform economic analyses regarding vaccine introduction. This takes into account critical assessments of all factors in the decision-making process, including technical, logistical, and financial criteria [7]. Those economic evaluations are designed to estimate the epidemiological and economic disease burden, and the expected value of vaccine introduction [8]. Among the required steps involved in these assessments is the measurement of costs related to a particular health condition, usually done through cost-of-illness (COI) studies [9].

In this context, this paper carries out a systematic review of studies assessing costs related to rotavirus disease in the Latin America and Caribbean (LAC) region.

2. Methods

The authors followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and checklist for undertaking and reporting this systematic review [10]. The diagram presented in Fig. 1 depicts the flow of information throughout the review, including the number of records identified, articles excluded and the reasons for exclusion, and the number of articles included in the final review.

2.1. Literature search

A search was made of published studies, guidelines, and clinical trials in relevant databases. These included the Cochrane Central Register of Controlled Trials (CENTRAL); Embase, a biomedical database; the MEDLINE database of the United States National Medical Library; the Economic Evaluation Database of the United Kingdom National Health Service (NHS EED); the Latin American and Caribbean Health Sciences Literature database (LILACS); and the Brazilian Thesis Databank. The reference lists of identified studies were also searched. No language restriction was applied for studies but searches were made in English, Portuguese, and Spanish. The date range for searches used November 2011 as the end date; there was no start date.

Two authors independently searched these databases using the subject headings for rotavirus infection, health care costs, and productivity loss studies, combined with a variety of free text words in order to build a broad and sensitive search strategy. The medical subject headings (MeSH) and key words used for thePubMed database search (which were adapted to search other databases) are described in Table 1.

2.2. Inclusion criteria for studies

Inclusion criteria for studies were: (*a*) economic evaluation or cost-of-illness studies; (*b*) conducted in the LAC region; (*c*) assess the economic burden of rotavirus disease or the economic impact of rotavirus vaccination programs. Exclusion criteria were: (*a*) duplicate papers or documents referring to the same study; (*b*) studies

Table 1
Medical subject headings [MeSH] and text words used in literature search for costs related to rotavirus disease in Latin America and the Caribbean.

Component	Search terms
Diseases	Rotavirus [MeSh] OR "Rotaviruses" OR "Rotavirus Infections" [MeSh] OR "Infection, Rotavirus" OR "Infections, Rotavirus" OR "Rotavirus Infection"
Outcomes	Cost of Illness [MeSh] OR "Illness Cost" OR "Illness Costs" OR "Cost of Disease" OR "Sickness Cost" OR "Cost, Sickness" OR "Costs, Sickness" OR "Costs of Disease" OR "Disease Cost" OR "Cost, Disease" OR "Costs, Disease" OR "Disease Costs" OR "Burden of Illness" OR "Illness Burden" OR "Illness Burdens" OR "Cost of Sickness" OR "Sickness Costs" OR "Costs and Cost Analysis" [MeSh] OR "Costs and Cost Analyses" OR "Costs, Cost Analysis" OR "Cost, Cost Analysis" OR "Cost Measures" OR "Cost Measure" OR "Measure, Cost" OR "Measures, Cost" OR "Pricing" OR "Cost Analysis" OR "Analysis, Cost" OR "Analyses, Cost" OR "Cost Analyses" OR "Cost" OR "Costs" OR Absenteeism [MeSh] OR "Workload" [MeSh] OR "Workloads" OR "Work Load" OR "Work Loads" OR "Employee Workload" OR "Employee Workloads" OR "Workload, Employee" OR "Workloads, Employee" OR "Employee Work Load" OR "Employee Work Loads" OR "Work Load, Employee" OR "Work Loads, Employee" OR "Staff Workload" OR "Staff Workloads" OR "Workload, Staff" OR "Workloads, Staff" OR "Staff Work Load" OR "Staff Work Loads" OR "Work Load, Staff" OR "Work Loads, Staff" OR "Indirect Costs" OR "Societal Costs" OR "Productivity Loss" OR "Work Impairment" OR "Absenteeism" OR "Presenteeism"

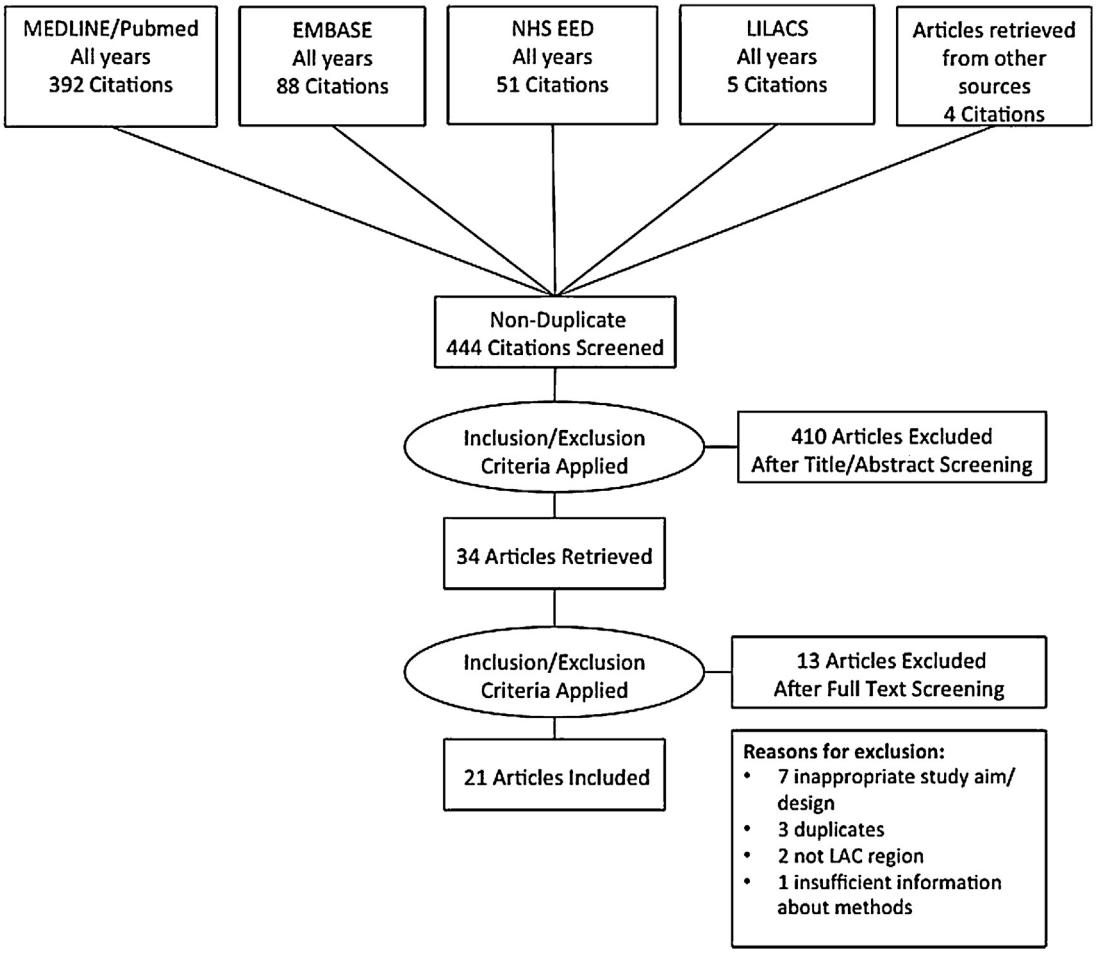

Fig. 1. PRISMA flowchart.

conducted outside the LAC region; (*c*) papers without sufficient information to clearly identify methods, sources, and unit costs. All records retrieved in the literature search were initially screened by title and abstract. For records where eligibility for inclusion could not be determined, and records selected for inclusion after initial title/abstract review, full articles were obtained and independently reviewed by two reviewers. Duplicate studies were excluded. If eligibility was not consensual among reviewers, a third reviewer assessed the paper for final decision on inclusion.

2.3. Data extraction

T The following information was extracted into standardized data retrieval forms: author; publication year; country; population; type of study (economic evaluation or cost-of-illness study); type of analysis (cost-effectiveness, cost-utility, or cost-benefit analysis, where applicable); study perspective; type of costs included (direct medical, non-medical, or indirect); method of cost estimation (primary data collection, database analysis, expert panel, or modeling); sources of unit costs; sources of data for health care resource utilization; and results. When indirect costs were included in the study, the authors assessed the method used to determine productivity loss (human-capital versus friction-cost approach) and the monetizing method (self-reported wage or national/local average wage).

The study perspectives were separated into: (*a*) societal (all direct medical, non-medical, and indirect costs provided by health systems, patients, and their families); (*b*) the health care system (only direct costs), (*c*) the health care provider or hospital (only direct medical costs), (*d*) the household (both direct medical and non-medical costs), or some combination of these.

2.4. Currency units

Study results are presented both in local currencies and U.S. dollars. To allow for comparison of results among the various studies, all results were converted into 2010 U.S. dollars. Official inflation rates of each country [11] and exchange rates for local currency to U.S. dollars were used, considering 2010 purchasing power parity (PPP) [12]. By establishing purchasing power equivalence, where 1 dollar purchases the same quantity of goods and services in all countries, PPP conversions allow cross-country comparisons of economic aggregates on the basis of physical output levels, free of price and exchange rate distortions [12].

3. Results

The broad search strategy resulted in the retrieval of 444 non-duplicate articles. Most of the studies excluded at this phase were conducted outside the LAC region. After title and abstract screening, only 34 articles were retrieved to be read in full. Thirteen of these studies were excluded after full text screening for the following reasons: seven had an inappropriate design to answer the research question [13–19]; three were duplicate publications from studies already included in the systematic review [20–22]; two were conducted outside the LAC region; [23,24] one did not provide sufficient information about methods and results.[25]

Two reviewers reached consensus that 21 studies on the economic impact of rotavirus infection met the inclusion criteria and were selected for analysis. The studies' publication dates ranged from 2001 to 2011. There were four studies from Mexico [26–29]; four from Brazil [30,31]; three from Peru [34–36]; two from Chile, [37,38]; and one study from each of the following countries: Venezuela [39], Honduras [40], Panama [41], Colombia [42], and Bolivia [43]. Three studies [44–46] assessed the economic impact of rotavirus infection and/or rotavirus vaccine in groups of countries in the Latin American and Caribbean region.

3.1. Study participants

Most of the studies (17 out of 21) assessed economic and/or clinical impact of rotavirus infections in children up to 5 years of age. Different cut-offs for age (2 or 3 years of age) were adopted by cost-of-illness studies and one cost-effectiveness analysis conducted in Colombia followed three hypothetical birth cohorts from birth to 2 years [42]. All cost-effectiveness studies ($n = 14$) [26,29,31,32,36,38–46] and three cost-of-illness studies [28,33,34] were conducted considering hypothetical birth cohorts; the remaining four cost-of-illness studies collected data from a sample of rotavirus patients [27,30,35,37].

3.2. Study design

Table 2 presents the main characteristics of included studies. Fourteen of the 21 studies were cost-effectiveness analysis of vaccination programs for rotavirus infections. Ten of the 21 studies assessed both direct and indirect costs (only one of them was a cost-of-illness study).

All cost-effectiveness analyses (CEAs) were based on modeling; none of them was conducted alongside clinical trials or observational studies specifically designed to assess economic and clinical outcomes simultaneously. Most (12 out of 14) of the CEA adopted the cost averted per disability-adjusted life years (DALYs) as the primary outcome. However, other outcomes were found in vaccine CEA studies, such as averted cases, deaths, hospitalizations, and life years gained (LYG). Health resource utilization and cost estimates were obtained from different sources, as described in Table 2.

Among the seven COI studies included in this review, four were designed to collect primary data on resource utilization and costs (one was a medical chart retrospective review and three conducted interviews with family caregivers) [27,30,35,37]. The three remaining COI studies were based on hypothetical scenarios built using literature review and retrospective database analysis (secondary data) [28,33,34]. Only one study was a household-based survey [35] (Table 2).

3.3. Study perspective and included costs

As illustrated in Table 2, the selected studies adopted the following perspectives: societal ($n = 8$), health care system ($n = 7$), health care provider ($n = 3$), and both health care system and household ($n = 3$). Ten of the 21 studies considered indirect costs due to productivity loss in the cost estimation (Table 3). Of these, nine studies also evaluated direct non-medical costs, such as transportation and food. Ten studies considered non-medical costs, including the nine studies which also reported indirect costs and one study which did not [30]. The studies assessing non-medical costs mainly considered information obtained from family and/or caregiver surveys.

3.4. Cost estimates

The unit costs reported in each study are presented in Table 4, grouped by country. Whenever possible, unit costs were abstracted for the following categories: per dose, per inpatient day, per outpatient consultation, per emergency department visit, hourly wage (for productivity loss monetizing), and cost per travel (transportation costs). Since some studies reported only cost per case or per episode, these data were presented as described in the publication (overall cost per case, inpatient case cost, or outpatient case cost). Four studies did not report country-specific and/or currency year information [30,34,43,45] so their cost data were not converted into 2010 U.S. dollars. For the remaining 17 studies, Table 4, presents 2010 U.S. dollar values for each cost category.

Cost data for seven countries were reported in individual studies, so comparative analyses were not possible. For three countries (Bolivia, Chile, and Peru), more than one estimation was available, but the study perspectives were different across them, making it difficult to derive conclusions about comparability. Cost estimations for Venezuela [39,45], Panama [41,45], and two out of three estimation conducted for Honduras [40,45] used the same perspective and source of data (for both resource utilization and unit costs), so cost estimates are similar (see Table 4).

Even among studies conducted in the same country and adopting the same perspective, the costs significantly varied, as in the three Brazilian studies conducted under the societal perspective [31,32,45] and the three Mexican studies which adopted the health care system perspective [26,28,29]. For example, in Brazil, the inpatient and outpatient societal cost per case varied from US$ 267.57 to US$ 576.91 and from US$ 30.04 to US$ 62.21, respectively, while in Mexico the cost per inpatient day for the health care system ranged from US$ 98.92 to US$ 345.73.

The productivity loss assessment and monetizing methods employed to convert paid work time lost due to rotavirus infection into indirect costs are presented in Table 3. All studies assessed only absenteeism in their estimation of productivity loss – neither presenteeism nor long-term productivity losses (premature death, early retirement, disability-related government subsidies, etc.) were included. All indirect cost assessments adopted a human-capital approach and most (7 out of 10) used average wages (primarily female wages) to estimate the cost of each unit of paid work time. The human-capital approach is one of the simplest ways to monetize productivity losses (based on self-evaluation of work time losses and decreased productivity) and work time losses (hours or days) are multiplied by its costs [47,48]. Only three studies conducted primary data collection and the remaining eight used data from previously published or unpublished studies

Considering the variation in cost estimates identified within the systematic review, alternative grouping criteria (besides individual country) were adopted (see Table 5). These included: country income according to World Bank classifications (lower-middle-income and upper–middle-income countries, with the exception of Haiti, which is not included in any categories but was assumed to be a lower-middle-income country for the purpose of this analysis); study perspective (societal, health care system, and hospital), and type of data source.

Most of the studies employed several different sources of data, as described in Table 2. For the purpose of exploring if costs are systematically different depending on the type of data source even when different types were used within the same study, three comprehensive categories were proposed: predominantly primary data sources, predominantly secondary data sources, and mixed data sources (used to classify studies for which it was not possible to recognize a clear predominance of type of source). Additionally, each unit cost estimation was mapped to its original source in order to identify only unique individual estimates of cost, excluding those derived from unit costs previously accounted for in other estimates. The number of independent sources of data is also described in Table 5.

Table 2
Characteristics of studies on costs related to rotavirus disease in Latin America and the Caribbean.

Reference	Country	Type of study	Study design	Population	Perspective	Type of costs	Main outcomes	Source of data
Ehrenkranz P et al., 2001 [34]	Peru	Cost-of-illness study	Simulation analysis based on systematic review	Hypothetical birth cohort, followed up to 5 years	Health care system	Direct medical costs	Inpatient, outpatient and death-related costs	Local published and unpublished studies, national administrative database, and hospital-based COI study [a]
Vera JCA, et al. 2005 [35]	Peru	Cost-of-illness study	Household-based cross-sectional study and expert interviews	Children < 3 years old with acute diarrhea in the previous 15 days	Local government and household	Direct medical, direct nonmedical, and indirect costs	Total costs per episode	Family caregiver and managers of primary care services
Constenla D, et al. 2006a [38]	Chile	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Health care system	Direct medical costs	Averted DALYs, averted deaths, cost per averted DALY, cost per averted death	Hospital administrative database and a hospital-based rotavirus surveillance study
Constenla D, et al. 2006b [39]	Venezuela	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Societal	Direct medical, direct nonmedical, and indirect costs	Averted DALYs, averted deaths, cost per averted DALY, cost per averted death	Administrative database (hospital and regional health department) and a hospital-based rotavirus surveillance study
Constenla D, et al. 2006c [40]	Honduras	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Societal	Direct medical, direct nonmedical, and indirect costs	Averted DALYs, averted deaths, cost per averted DALY, cost per averted death	Hospital administrative database and a hospital-based rotavirus surveillance study
Delpiano M, et al. 2006 [37]	Chile	Cost-of-illness study	Hospital-based prospective cohort study	Children < 2 years admitted to hospital due to acute rotavirus diarrhea	Hospital	Direct medical costs	Inpatient costs, resource utilization	Prospectively collected from patients and hospital records [a]
Rheingans R, et al. 2007 [45]	LAC countries: Argentina, Brazil, Chile, Dominican Republic, Honduras, Mexico, Panama, and Venezuela	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Societal	Direct medical, direct non-medical, and indirect costs	Averted DALYs, cost per averted DALY	WHO-CHOICE, physician interviews, local COI studies, and a hospital-based rotavirus surveillance study
de Soárez PC, et al. 2008 [32]	Brazil	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Societal	Direct medical, direct non-medical, and indirect costs	Averted case, averted deaths, LYG, cost per averted case, cost per averted death, cost per LYG	National administrative database and local COI study
Valencia-Mendoza A, et al. 2008 [29]	Mexico	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Health care system	Direct medical costs	Averted case, averted deaths, LYG, cost per averted case, cost per averted death, cost per LYG	Local COI study
Constenla D, et al. 2008a [31]	Brazil	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Societal	Direct medical, direct non-medical, and indirect costs	Averted DALYs, averted deaths, cost per averted DALY, cost per averted death	WHO-CHOICE, physician interviews, local COI study, and a hospital-based rotavirus surveillance study
Constenla D, et al. 2008b [41]	Panama	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Societal	Direct medical, direct non-medical, and indirect costs	Averted DALYs, averted deaths, cost per averted DALY, cost per averted death	Hospital administrative database and a hospital-based rotavirus surveillance study
Atherly D, et al. 2009 [46]	GAVI-eligible countries in LAC region: Cuba, Guyana, Honduras, Bolivia, Haiti, Nicaragua	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Successive annual hypothetical birth cohorts, followed up to 5 years	Health care system	Direct medical costs	Averted DALYs, cost per averted DALY	WHO-CHOICE

Table 2 (*Continued*)

Reference	Country	Type of study	Study design	Population	Perspective	Type of costs	Main outcomes	Source of data
Clark AD, et al. 2009 [36]	Peru	Economic evaluation of 3 scenarios for the timing of vaccination	Cost-effectiveness analysis based on modeling	Successive annual hypothetical birth cohorts, followed up to 5 years	Health care system and household	Direct medical, direct non-medical costs and indirect costs	Averted DALYs, averted deaths and cost per averted DALY	Hospital-based cost survey (unclear methods), physician interviews, medical chart reviews, and structured interviews with families (n = 33)
Constenla D, et al. 2009 [26]	Mexico	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Health care system	Direct medical costs	Averted DALYs, averted deaths, LYG, cost per averted DALY cost per averted death, cost per LYG	WHO-CHOICE, physician interviews, hospital administrative database and a hospital-based rotavirus surveillance study
Granados-García V, et al. 2009 [27]	Mexico	Cost-of-illness study	Hospital-based prospective cohort study	Children < 5 years admitted to hospital due to acute rotavirus diarrhea	Hospital	Direct medical costs	Inpatient costs, outpatient costs, resource utilization	Medical records
Souza CPR, et al. 2009 [33]	Brazil	Cost-of-illness study (comparison of inpatient children receiving nitazoxanide or standard of care)	Simulation analysis based on systematic review and expert opinion	Hypothetical cohorts of children < 5 years admitted to hospital due to acute severe rotavirus diarrhea	Hospital	Direct medical costs	Inpatient costs	Expert opinion and one pediatric hospital guideline in the management of severe diarrhea
Centenari C, et al. 2010 [30]	Brazil	Cost-of-illness study (comparison before and after vaccine introduction)	Database retrospective analysis and parents interview-based cross-sectional study	Children < 2 years old with acute diarrhea	Health care system and household	Direct medical and non-medical costs (including out-of-pocket expenses)	Health system costs, out-of pocket costs, resource utilization	Family caregivers, national administrative database and local administrative data obtained from the health department
De la Hoz F, et al. 2010 [42]	Colombia	Economic evaluation of introduction of two different vaccines	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 2 years	Societal	Direct medical, direct non-medical, and indirect costs	Averted DALYs, averted deaths, cost per averted DALY, cost per averted death	National administrative database and survey with parents (n = 45) designed to collect both indirect and direct non-medical costs
Granados- García V, et al. 2011 [27]	Mexico	Burden of disease and cost-of-illness study	Simulation analysis based on systematic review	Successive annual hypothetical birth cohorts, followed up to 5 years	Health care system	Direct medical costs	DALYs, deaths, inpatient and outpatient costs	Hospital-based published COI studies, national administrative database, and hospital administrative data obtained from the local health department
Kim SY, et al. 2010 [44]	GAVI-eligible countries in LAC region: Cuba, Guyana, Honduras, Bolivia, Haiti, Nicaragua	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Societal and local government	Direct medical and indirect costs	Averted DALYs, cost per averted DALY	WHO-CHOICE and assumptions based on resource utilization to estimate productivity loss
Smith ER, et al. 2011 [43]	Bolivia	Economic evaluation of vaccine introduction	Cost-effectiveness analysis based on modeling	Annual hypothetical birth cohort, followed up to 5 years	Health care system	Direct medical costs	Averted DALYs, cost per averted DALY	Medical chart retrospective review for resource utilization; WHO estimates and official price lists for unit cost

LYG: life years gained; DALY: disability-adjusted life year; COI: cost-of-illness.

[a] Detailed information not provided in the published article.

Data from 35 different countries and settings were identified in the review, but four of them were not included in the subgroup analysis for the following reasons: three lacked sufficient information to allow conversion into 2010 U.S. dollars [34,35,43] and in one study the cost data were presented only as cost per case without segmentation into the components used in the other studies [35]. One study [33] was not included in the analysis for type of data source once it was determined to be the sole study that derived cost

Table 3
Methodological characteristics of indirect cost assessment in studies on rotavirus disease in Latin America and the Caribbean.

Reference	Primary data collection for productivity loss	Monetizing method	Indirect cost calculation
Vera JCA et al., 2005 [35]	Yes	Average local wage	Paid work time lost × average wage
Constenla D, et al. 2006b [39]	No; previously published data	National average female wage	Paid work time lost × average wage
Constenla D, et al. 2006c [40]	No; previously published data	National average female wage	Paid work time lost × average wage
Rheingans R, et al. 2007 [45]	No; unpublished data of an ongoing study	National average female wage	Paid work time lost × average wage
Constenla D, et al. 2008a [31]	No; previously published data	National average female wage	Paid work time lost × average wage
Constenla D, et al. 2008b [41]	No; previously published data	National average female wage	Paid work time lost × average wage
de Soárez PC, et al.2008 [32]	No; previously published data	Self-reported wage	Paid work time lost × self-reported wage
Clark AD, et al. 2009 [36]	Yes	Not stated	Outpatient-related indirect costs were collected and inpatient-related were calculated assuming a 2.5 ratio
De la Hoz F, et al. 2010 [42]	Yes	Self-reported wage	Paid work time lost × self-reported wage
Kim SY, et al. 2010 [44]	No; assumptions based on resource use	National average wages	Assumed paid work time lost × average wage

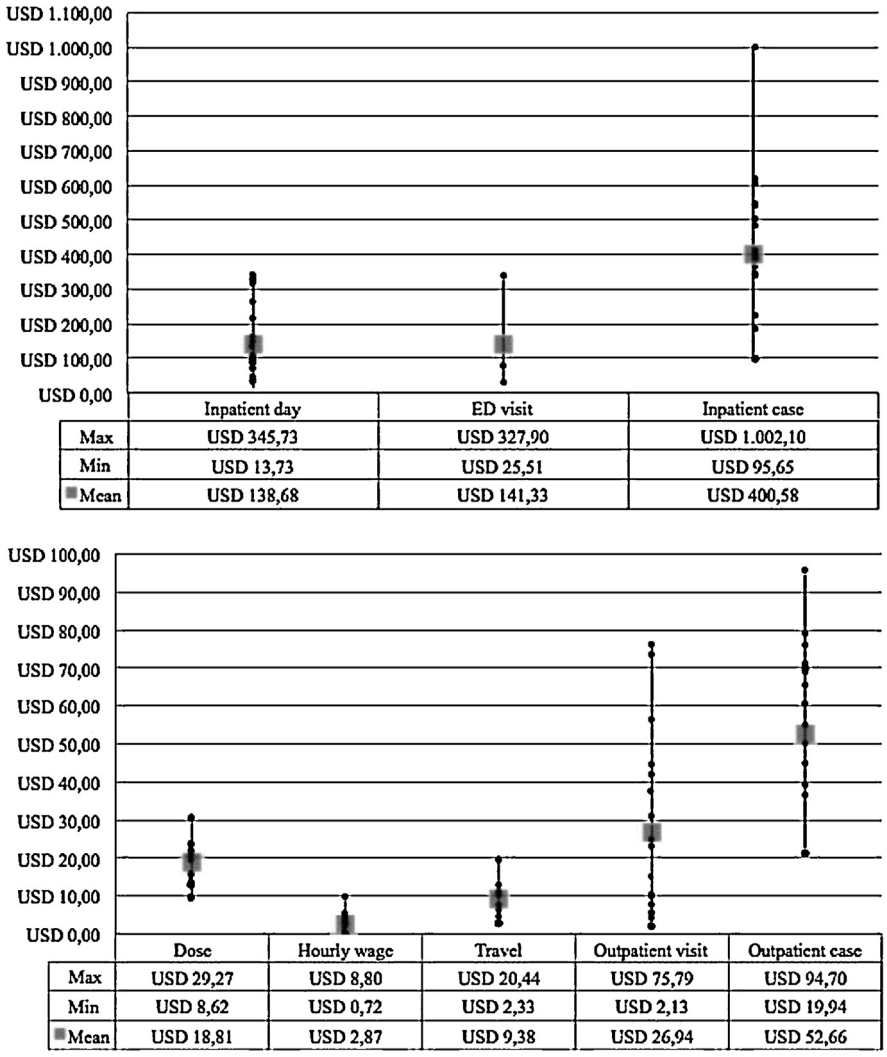

Fig. 2. Variation in unit costs for each cost category across studies of costs related to rotavirus disease in Latin America and the Caribbean ($n = 17$).

Table 4
Reported unit costs in studies on rotavirus disease in Latin America; original currency adjusted for inflation and converted to 2010 U.S. dollars.

Country (GDP per capita; 2010 PPP)	Study perspective	Reference	Currency/Year	Cost per dose[a]	Cost per inpatient day[a]	Cost per outpatient visit[a]	Cost per ED visit[a,b]	Hourly wage[a]	Cost per travel[a]	Cost per case[a]	
										Inpatient	Outpatient
Argentina (15,550)	Societal	Rheingans R et al., 2007 [45]	2003 US dollars	12.5 [29.27]	39.67[c] [92.88]	5.62 [13.16]	N/A	0.87 [2.04]	N/R	181.89 [425.84]	15.85 [37.11]
Bolivia (4560)	Health care system	Smith ER et al. 2011 [43]	US dollars (year not stated)	3.5–24.5[d]	260.57[d]	N/R	16.88[d]	N/A	N/A	N/R	N/R
	Societal and local government	Kim SY et al. 2010 [44]	2005 International dollars	3.33–8.33[e]	N/R	N/R	N/A	2.82 [8.80]	3.96 [12.36]	N/R	N/R
Brazil (10,920)	Societal	Rheingans R et al. 2007 [45]	2003 US dollars	12.5 [19.55]	35.07[c] [54.86]	5.39 [8.43]	N/A	1.58 [2.47]	N/R	171.04 [267.57]	19.20 [30.04]
	Societal	de Soárez PC et al. 2008 [32]	2004 Brazilian reals	18.6 [14.57]	N/R	N/A	N/R	N/R	N/R	736.36 [576.91]	64.10 [50.22]
	Societal	Constenla D et al. 2008a [31]	2003 US dollars	7.5 [11.73]	N/R	5.39 [8.43]	N/A	1.45 [2.27]	1.49 [2.33]	205.65 [321.71]	39.71 [62.12]
	Hospital	Souza CPR et al. 2009 [33]	2008 Brazilian reals	N/A	214.6[c] [140.17]	N/A	N/A	N/A	N/A	858.4 [560.69]	N/A
	Health care system and household	Centenari C et al. 2010 [30]	US dollars (year not stated)	N/A	271.10–323.65[d]	1.05[d]	N/A	N/A	N/A	N/R	N/R
Chile (13,890)	Health care system	Constenla D et al. 2006 [38] (Public sector)	2003 US dollars	12.5 [20.71]	55.13 [91.36]	14.01 [23.21]	N/A	N/A	N/A	165.37 [273.98]	33.99 [56.31]
		Constenla D et al. 2006 [38] (Private sector)		12.5 [20.71]	201.61 [334.09]	24.56 [40.69]	N/A	N/A	N/A	604.84 [1002.10]	44.54 [73.79]
	Hospital	Delpiano M et al. 2006 [37]	2005 US dollars	N/A	46.0[c] [74.76]	N/A	15.7 [25.51]	N/A	N/A	276.0 [448.54]	N/A
	Societal	Rheingans R et al. 2007 [45]	2003 US dollars	12.5 [20.71]	41.70[c] [69.10]	14.01 [23.22]	N/A	2.11 [3.50]	N/R	196.36 [325.39]	42.29 [70.08]
Colombia (9000)	Societal	De la Hoz F et al. 2010 [42]	2003 US dollars	5.0–7.5 [11.84–17.76]	N/R	12.5 [29.60]	29.8 [70.57]	N/R	N/R	N/R	N/R
Cuba (not available)	Societal and local government	Kim SY et al. 2010 [44]	2005 International dollars	3.33–8.33[e]	N/R	N/R	N/A	1.83 [2.17]	3.96 [4.70]	N/R	N/R

Dominican Republic (8700)	Societal	Rheingans R et al. 2007 [45]	2003 US dollars	12.5 [21.97]	16.64[c] [29.24]	4.49 [7.89]	N/A	0.71 [1.25]	N/R	79.91 [140.43]	13.06 [22.95]
Guyana (3530)	Societal and local government	Kim SY et al. 2010 [44]	2005 International dollars	3.33–8.33[e]	N/R	N/R	N/A	1.07 [1.66]	3.96 [6.14]	N/R	N/R
Haiti (1100)	Societal and local government	Kim SY et al. 2010 [44]	2005 International dollars	3.33–8.33[e]	N/R	N/R	N/A	1.14 [2.02]	11.51 [20.44]	N/R	N/R
Honduras (3730)	Societal	Constenla D et al. 2006 [40]	2003 US dollars	12.5 [29.27]	30.70 [71.88]	5.81 [13.60]	N/A	0.53 [1.24]	N/R	125.18 [293.02]	25.97 [60.81]
	Societal	Rheingans R et al. 2007 [45]	2003 US dollars	12.5 [29.27]	24.36[c] [57.04]	5.81 [13.60]	N/A	0.53 [1.24]	N/R	125.18 [293.09]	25.97 [60.81]
	Societal and local government	Kim SY et al. 2010 [44]	2005 International dollars	3.33–8.33[e]	N/R	N/R	N/A	1.26 [2.94]	3.96 [9.23]	N/R	N/R
Mexico (15,010)	Societal	Rheingans R et al. 2007 [45]	2003 US dollars	12.5 [20.23]	50.98[c] [82.49]	13.30 [21.52]	N/A	1.86 [3.01]	N/R	215.88 [349.32]	39.28 [63.56]
	Health care system	Valencia-Mendoza A et al. 2008 [29]	2006 US dollars	14.59 [22.67]	222.55 [345.73]	35.85 [55.69]	N/A	N/A	N/A	N/R	N/R
	Health care system	Constenla D et al. 2009 [26]	2007 US dollars	8.0 [12.74]	62.13 [98.92]	27.23 [43.35]	N/A	N/A	N/A	211.0 [335.94]	27.00 [42.99]
	Hospital	Granados-García V et al. 2009 [27]	2004 US dollars	N/A	212 [327.90]	49 [75.79]	212 [327.90]	N/A	N/A	936 [1447.71]	
	Health care system	Granados-García V et al. 2011 [28]	2006 US dollars	N/A	167.94 [260.90]	47.0 [73.02]	N/A	N/R	N/R	N/R	N/R
Nicaragua (2610)	Societal and local government	Kim SY et al. 2010 [44]	2005 International dollars	3.33–8.33[e]	N/R	N/R	N/A	1.54 [4.08]	3.96 [10.49]	N/R	N/R
Panama (12,940)	Societal	Rheingans R et al. 2007 [45]	2003 US dollars	12.5 [28.65]	53.00[c] [121.47]	15.88 [36.40]	N/A	2.10 [4.81]	N/R	214.92 [492.59]	41.32 [94.70]
	Societal	Constenla D et al. 2008 [41]	2003 US dollars	8.0 [18.34]	66.61 [152.67]	15.88 [36.40]	N/A	2.10 [4.81]	N/R	217.95 [499.53]	41.32 [94.70]

Table 4 (*Continued*)

Country (GDP per capita; 2010 PPP)	Study perspective	Reference	Currency/Year	Cost per dose[a]	Cost per inpatient day[a]	Cost per outpatient visit[a]	Cost per ED visit[a,b]	Hourly wage[a]	Cost per travel[a]	Cost per case[a]	
										Inpatient	Outpatient
Peru (8940)	Health care system	Ehrenkranz P et al. 2001 [34]	US dollars (year not stated)	N/R	53.51[c]	12.03[c]	N/A	N/A	N/A	N/R	N/R
	Local government and household	Vera JCA et al. 2005 [35]	2002 Peruvian Nuevos Soles	N/A	N/R	N/R	N/R	N/R	N/R	17.8 [7.57]	
	Health care system and household	Clark AD et al. 2009 (primary hospital) [36]	2006 US dollars	8.0 [9.00]	70.99 [79.88]	3.27 [3.68]	N/A	N/A	N/A	N/R	N/R
		Clark AD et al. 2009 (secondary hospital) [36]			187.72 [211.23]	1.89 [2.13]	N/A	N/A	N/A	N/R	N/R
		Clark AD et al. 2009 (tertiary hospital) [36]			284.08 [319.66]	5.30 [5.96]	N/A	N/A	N/A	N/R	N/R
Venezuela (11,950)	Societal	Constenla D et al. 2006 [39]	2003 US dollars	12.5 [8.62]	30.47 [21.01]	5.48 [3.78]	N/A	1.05 [0.72]	N/R	138.7 [95.65]	28.92 [19.94]
	Societal	Rheingans R et al. 2007 [45]	2003 US dollars	12.5 [8.62]	19.91[c] [13.73]	5.48 [3.78]	N/A	1.05 [0.72]	N/R	138.7 [95.65]	28.92 [19.94]
Bolivia, Cuba, Guyana, Haiti, Honduras, Nicaragua (N/A)	Health care system	Atherly D et al. 2009 [46]	2007 US dollars	1.25–7.00[e]	30.60[e]	8.03[e]	N/A	N/A	N/A	N/R	N/R

N/R: not reported; N/A: not applicable; ER: emergency room.

[a] Top figure is original currency, converted value (to 2010 PPP) is in brackets.

[b] When emergency department/room setting was clearly mentioned, the costs were aggregated in this category.

[c] Tests not included in the reported daily fee.

[d] Costs were not converted into 2010 PPP due to the lack of currency year data.

[e] Costs were not converted into 2010 PPP due to the lack of country-specific unit costs (only aggregated for the groups of countries).

Table 5
Comparative analysis of unit cost estimation provided in the included studies on rotavirus disease in Latin America and the Caribbean, according to selected criteria for study grouping.

Grouping criteria	Categories	*n*	Vaccine dose [a]		Inpatient day [a]		Outpatient visit [a]		ED visit [a]		Hourly wage [a]		Travel [a]		Cost per case [a]			
			Cost	*n*	Cost	*n*	Cost	*n*	Cost	*n*	Cost	*n*	Cost	*n*	Inpatient		Outpatient	
															Cost	*n*	Cost	*n*
All studies	N/A	31	18.8 [8.6–29.3]	15	138.7 [13.7–345.7]	22	26.9 [2.1–75.8]	17	141.3 [25.5–327.9]	3	2.9 [0.7–8.8]	15	9.4 [2.3–20.4]	7	400.6 [95.6–1002.1]	16	52.7 [19.9–94.7]	13
Country income	UMI	24	18.1 [8.6–29.3]	14	146.1 [13.7–345.7]	20	27.8 [2.1–75.8]	16	141.3 [25.5–327.9]	3	2.5 [0.7–4.8]	9	3.5 [2.3–4.7]	2	407.7 [95.6–1002.1]	15	52 [19.9–94.7]	12
	LMI	7	N/A [29.3–29.3]	1	64.5 [57.0–71.9]	2	N/A [13.6–13.6]	1	N/A	0	3.5 [1.2–8.8]	6	11.7 [6.1–20.4]	5	N/A [293.0–293.0]	1	N/A [60.8–60.8]	1
Study perspective	Societal	20	19.7 [8.6–29.3]	11	69.7 [13.7–152.7]	11	16.8 [3.8–36.4]	8	N/A [70.5–70.5]	1	2.9 [0.7–8.8]	15	9.4 [2.3–20.4]	7	344.4 [95.6–576.9]	11	51.2 [19.9–94.7]	10
	Health care system	8	16.3 [9–22.7]	4	217.7 [79.9–345.7]	8	31 [2.1–73.0]	8	N/A	0	N/A	0	N/A	0	537.3 [273.9–1002.1]	3	57.7 [42.9–73.8]	3
	Hospital	3	N/A	0	180.9 [74.7–327.9]	3	75.8 [75.8–75.8]	1	176.7 [25.5–327.9]	2	N/A	0	N/A	0	504.6 [448.5–560.7]	2	N/A	0
Type of data source	Primary	4	15.8 [9–22.7]	2	226.5 [74.7–345.7]	6	28.7 [2.1–75.8]	5	176.7 [25.5–327.9]	2	N/A	0	N/A	0	448.5 [448.5–448.5]	1	N/A	0
	Secondary	12	19.2 [8.6–29.3]	4	155.3 [21.0–334.0]	6	30.9 [3.8–73.0]	5	N/A	0	3 [0.7–8.8]	8	10.6 [4.7–20.4]	6	432.9 [95.6–1002.1]	5	52.7 [19.9–73.8]	4
	Both	12	19.3 [11.7–29.3]	9	68.9 [13.7–121.5]	9	22.9 [7.9–43.3]	7	70.6 [70.5–70.5]	1	2.8 [1.2–4.8]	7	2.3 [2.3–2.3]	1	359.5 [140.4–576.9]	9	52.6 [22.9–94.7]	9

[a] Top figure is average unit cost among studies reporting each particular component, minimum and maximum values is in brackets.

estimates based primarily on expert opinion. The cost components for which most data were available were cost per inpatient day (22 estimates) and outpatient visits (17 estimates). Emergency department visits were underrepresented, with only three estimates. The magnitude of the variation observed in each cost category is presented in Fig. 2. Six outliers (defined as any estimate that is more than two standard deviations away from the mean) were identified: cost per travel of US$ 20.44 in Haiti [44]; hourly wage of US$ 8.80 in Bolivia [44]; cost per inpatient case of US$ 1002.10 in the private sector in Chile [38]; cost per emergency department visit and outpatient visit of US$ 327.90 and US$ 75.79, respectively, in Mexico [27]; and cost per outpatient visit of US$ 75.79 in Mexico [28].

The data presented in Table 5, based on selected criteria for study type, do not reveal strong trends or provide an explanation for the variation in cost categories observed. For some cost categories in the country income group there were not sufficient data to allow more reliable inferences. Even so, it is interesting to note that the available estimates of health care system related costs (such as vaccine dose, inpatient day, outpatient visits, etc.) are generally higher for upper-middle-income countries while for hourly wage and travel expenses the estimates for lower-middle-income countries are markedly higher. The analysis regarding study perspective did not show a consistent trend across cost categories, but it draws attention to the fact that both the costs per inpatient and outpatient case were higher in the health care system perspective as compared to the societal perspective, which is an unexpected finding. No particular insight could be derived from the analysis of cost categories according to the type of data source.

4. Discussion

High quality cost estimation is essential to ensure the validity of cost-effectiveness analysis of health technologies. The rigorous selection of data sources for both resource utilization and unit costs is mandatory to provide an adequate overview of future costs associated with the adoption of health interventions. This systematic review sought to find studies conducting cost estimation for rotavirus-related events and interventions within the Latin America and Caribbean region, and identified 21 individual studies that met certain criteria for description of methods and sources.

The methods employed in each study varied broadly but most were based on retrospective administrative database analysis, hospital-based surveillance studies, physician and parent interviews, and local/regional literature review (for resource utilization data). The combination of multiple methods and sources was a common finding in this review. One source of cost data identified in multiple studies ($n = 6$) was the World Health Organization's "Choosing Interventions that Are Cost Effective" (WHO-CHOICE), which provides resource consumption and cost and price estimates to be used in cost-effectiveness analysis of interventions targeting 21 different diseases and their risk factors [8].

In general, the cost-effectiveness analyses in this review employed epidemiological data to calculate the number of rotavirus-related events (hospitalizations, outpatient visits, and deaths). They then used different sources of unit costs to calculate the overall disease burden by multiplying the number of events by their costs (both direct and indirect). The same method is used by the three COI studies which estimated costs based on literature review [28,33,34]. The other four COI studies collected data directly from patients and/or caregivers, usually in a hospital-based approach (patients were selected during their inpatient stay). Only one of the studies used a household-based survey, a data collection method that can capture data from the full spectrum of disease severity (including mild cases that do not seek medical care), since

hospital-based studies usually enroll only more severe patients [35].

All studies assessing productivity loss adopted the human-capital approach, which calculates indirect costs by multiplying the self-evaluated work time losses and monetizes them using self-reported or setting-specific average wages. Among the 21 studies included in this systematic review, only two of them [32,42] used self-reported wages to monetize the loss of paid work time. This underscores our conclusion that national or regional average wages are the most common source of data used to monetize the productivity loss due to rotavirus infections in the LAC region.

Among rotavirus indirect cost studies, most investigators assumed local female average wages as reference values for indirect costs (assuming that rotavirus patients are usually cared for by female caregivers). It was not possible to find any study that included long-term productivity losses (due to death or permanent disability of the sick child). A potential explanation for this finding is that most cost-of-illness estimations are conducted in conjunction with cost-effectiveness analysis using DALYs as primary outcomes for effectiveness. Since long-term disabilities and deaths (potentially leading to long-term productivity losses) are already accounted for in DALYs, including those events in the cost estimation could lead to double counting the same events accounted for in both the numerator and denominator of the incremental cost-effectiveness ratio, as discussed by Johannesson [49] and Brouwer et al. [50] for the cost per quality-adjusted life year (QALY) analysis which includes indirect costs in the cost estimation.

Although all studies were conducted in the same geographic region between 2001 and 2011, they cannot be considered comparable because of significant differences in terms of methods, data sources, and study perspectives. Even when similar methods are employed, country-specific characteristics (particularly health care system organization and funding) could raise important concerns about comparability among costs reported for each country. Some studies were conducted in the same country in different time periods and found quite diverse costs per event (as previously mentioned for Brazil and Mexico, for example). For this reason, unit costs were extracted from the original studies and summarized to provide an overview of the studies' findings. This allowed an assessment of, and possible explanation for, the observed variation in these estimates. This review did not reveal any strong trends in the difference in costs across similar studies, and it is possible to affirm that country income, study perspective, and type of data source were not consistently linked to the variation in unit costs. There were some unexpected findings, particularly the higher hourly wage and travel-related expenses found in lower-middle-income countries and the lower cost per case (both inpatient and outpatient) in studies conducted under the societal perspective. In a similar manner, outliers were not systematically found in any particular subgroup of studies.

The findings of this review could not indicate a particular method of cost estimation that is predominantly employed in rotavirus cost-of-illness studies within the LAC region. However, it seems reasonable to assert that the most commonly used methods are based on retrospective analysis of administrative databases, hospital-based surveillance studies (usually employed to collect data on direct medical costs), and small studies designed to collect data about indirect and direct non-medical costs using patients and their relatives as the primary source of data. A marked diversity in methods and data sources was observed and a particular tendency in the selection of methods was difficult to identify. The literature regarding cost-of-illness studies commonly proposes that micro-costing methodology and prospective primary data collection under the societal perspective generate more accurate and comprehensive cost estimates [51]. If these aspects are considered best practice in cost-of-illness studies, none of the studies included in this review could fulfill simultaneously all the quality criteria. Most of the studies collecting primary cost data were conducted under the health care system perspective and/or were cross-sectional or retrospective.

Future research might address the use of similar protocols for cost estimation (study design, perspective, source of data, etc.) concurrently in Latin American and Caribbean countries (or even different settings within the same country), in order to systematically assess the comparability and transferability of disease-related costs across the region.

5. Conclusion

Rotavirus-associated costs were assessed in 21 studies across Latin American and Caribbean countries, the majority of them in conjunction with economic evaluations of vaccination programs. Methods are broadly different among the studies but administrative databases seem to be the most employed source of data. Primary data collection is a common strategy for indirect and direct non-medical costs assessment. The results of cost estimations performed in COI studies vary but it was not possible to provide a reasonable explanation for the observed variation. These findings reinforce the need for rigorous selection of the sources of resource consumption and cost data to be employed in local cost-effectiveness analysis. Furthermore, the standardization of methods employed in COI studies can favorably affect the comparability and transferability of cost data across countries and even within different local settings.

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Review

Using standardized tools to improve immunization costing data for program planning: The cost of the Colombian Expanded Program on Immunization

Carlos Castañeda-Orjuela[a,*], Martin Romero[b], Patricia Arce[c], Stephen Resch[d], Cara B. Janusz[e], Cristiana M. Toscano[f], Fernando De la Hoz-Restrepo[a]

[a] Epidemiology and Public Health Evaluation Group, Universidad Nacional de Colombia, Bogotá, Colombia
[b] Salutia Foundation, Bogotá, Colombia
[c] Expanded Program on Immunization, Secretaría Distrital de Salud, Bogotá, Colombia
[d] Center for Health Decision Science, Harvard School of Public Health, Boston, MA, United States
[e] ProVac Initiative, Comprehensive Family Immunization Project, Pan American Health Organization, c/o PAHO, Washington, DC, United States
[f] Federal University of Goiás, Goiânia, Goiás, Brazil

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ABSTRACT

Introduction: The cost of Expanded Programs on Immunization (EPI) is an important aspect of the economic and financial analysis needed for planning purposes. Costs also are needed for cost-effectiveness analysis of introducing new vaccines. We describe a costing tool that improves the speed, accuracy, and availability of EPI costs and that was piloted in Colombia.
Methods: The ProVac CostVac Tool is a spreadsheet-based tool that estimates overall EPI costs considering program inputs (personnel, cold chain, vaccines, supplies, etc.) at three administrative levels (central, departmental, and municipal) and one service delivery level (health facilities). It uses various costing methods. The tool was evaluated through a pilot exercise in Colombia. In addition to the costs obtained from the central and intermediate administrative levels, a survey of 112 local health facilities was conducted to collect vaccination costs. Total cost of the EPI, cost per dose of vaccine delivered, and cost per fully vaccinated child with the recommended immunization schedule in Colombia in 2009 were estimated.
Results: The ProVac CostVac Tool is a novel, user-friendly tool, which allows users to conduct an EPI costing study following guidelines for cost studies. The total costs of the Colombian EPI were estimated at US$ 107.8 million in 2009. The cost for a fully immunized child with the recommended schedule was estimated at US$ 153.62. Vaccines and vaccination supplies accounted for 58% of total costs, personnel for 21%, cold chain for 18%, and transportation for 2%. Most EPI costs are incurred at the central level (62%). The major cost driver at the department and municipal levels is personnel costs.
Conclusion: The ProVac CostVac Tool proved to be a comprehensive and useful tool that will allow researchers and health officials to estimate the actual cost for national immunization programs. The present analysis shows that personnel, cold chain, and transportation are important components of EPI and should be carefully estimated in the cost analysis, particularly when evaluating new vaccine introduction.

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* Corresponding author at: Department of Public Health, Faculty of Medicine, Universidad Nacional de Colombia, Carrera 30 #45-03, Office 150, Bogotá, DC, Colombia. Tel.: +57 3165000x15086; fax: +57 3165175.
E-mail addresses: cacastanedao@unal.edu.co, carloscastanedao@gmail.com (C. Castañeda-Orjuela), januszc@paho.org (C.B. Janusz).

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1. Introduction

The ProVac Initiative of the Pan American Health Organization (PAHO) aims to strengthen evidence-based decision making regarding new vaccine introduction at national and sub-regional levels in Latin America and the Caribbean. One need identified and addressed by ProVac is that of developing tools for costing and cost-effectiveness modeling that can improve accessibility of these methods and strengthen capacity at the local level [1,2].

The Expanded Program on Immunization (EPI) in developing countries is responsible for two tasks: improving access to traditional EPI antigens and introducing new vaccines. Over the last three decades, several new vaccines have been developed and many have been incorporated into the EPI. While this expansion has increased the impact of EPI, universal introduction of new vaccines has substantial planning and budgetary implications. This is due, in part, to the expensive technology involved in producing new vaccines, such as those against pneumococcal disease, rotavirus diarrhea, and human papillomavirus (HPV) [3]. As more expensive vaccines become available, decisions about their universal adoption at the national level will inevitably need to address the economic and health benefit tradeoffs of introducing a vaccine versus maintaining current disease control strategies. Determining the costs and cost-effectiveness of national immunization programs may help countries prepare and plan for new vaccine introduction as well as to support a case for investment that ensures sustainability of the new vaccine program over time [4].

The World Health Organization (WHO) recognizes the importance of determining the costs of health programs, and has made efforts to develop standardized costing procedures [5] to generate information on the cost of national EPIs [6]. WHO recommends that not only the cost of procuring vaccine but all costs related to the introduction of a new vaccine be considered [7,8]. One of the limitations in cost-effectiveness studies of new vaccines is how little attention is paid to the calculation of actual costs of delivering immunization services, which are in addition to the cost of procuring the new vaccine.

Despite the importance of estimating accurate incremental new Vaccine Introduction Costs for a cost-effectiveness analysis [7]. WHO costing guidelines are difficult to implement, and as a result many published cost-effectiveness analyses do not consider incremental program costs or they use weak assumptions [9]. Often, crude assumptions are made for incremental vaccine delivery costs (for example, US$ 1 per dose). Available tools such as the Vaccine Introduction Costing tool (VIC) [10] and comprehensive multi-year planning tool (cMYP) [11] were designed for planning and budgeting purposes rather than for comprehensive EPI costing exercises.

The development of standardized methods for estimating immunization program costs will improve the quality of available data needed to estimate the cost-effectiveness of new vaccines and the incremental costs of expanding the EPI. The methodology will serve to identify cost drivers and inefficiencies in current resource allocation policies, to analyze programmatic changes to delivery strategy, and to establish a baseline EPI cost against which the financial impact of adding new vaccines to the EPI can be quantified.

In response to the need for standardized EPI costing tools to improve the speed, consistency, and availability of cost data for national immunization program managers and decision makers, researchers at the National University of Colombia, in collaboration with the PAHO ProVac Initiative, undertook the development of a vaccine program costing tool: the ProVac CostVac Tool.

This article describes the ProVac CostVac Tool and presents results from a pilot exercise with the tool to estimate the total costs of the EPI in Colombia. The tool described here is intended to help countries carry out immunization program costing consistent with WHO guidelines, and to provide a transparent framework for collecting and analyzing the cost data. The tool is particularly useful for measuring costs that generally are not visualized in EPI budgets at the central level, for example shared labor costs across public health programs at the service provision level. In addition, it will help countries develop standardized program costing estimates for the WHO-UNICEF Joint Reporting Form on Immunization, among other reporting purposes. Finally, the tool aims to provide countries with up-to-date costing data by allowing updates for part of the data in subsequent years while carrying over other data.

2. Methods

The ProVac CostVac Tool ("CostVac") encompasses a package of guidance materials for country use, including a study protocol, generalized data collection instruments, a spreadsheet tool for cost analysis, a comprehensive guide for using the tool, and a technical appendix explaining the underlying methodology. While its primary purpose is to estimate the actual costs of national EPI from the public sector perspective, the tool can account for the delivery costs of vaccines in the private sector that were procured by the government (as occurs in the Colombian EPI). It also aims to fill a conceptual and operational gap existing in the field of immunization program costing since there are very few guidelines on how to do this properly and even fewer tools readily available for collecting and analyzing cost data at the national level.

2.1. Description of the ProVac CostVac Tool

The core of "CostVac" is a set of spreadsheets in a Microsoft Excel® workbook used to store and analyze costing data. These spreadsheets are described below.

2.1.1. Set-up worksheet

This worksheet allows users to define the tool's general structure by specifying the year of evaluation and the country-relevant labels for all standard parameters, for example the names of administrative levels, health facility types and currency units. In this worksheet, users select the appropriate method for extrapolating results from lower administrative levels to the national level and define the type of cost (financial versus economic) to be included in the analysis. Vaccines and other central level data for cost's estimation are included here.

2.1.2. Survey worksheets

Five worksheets are used to store the data collected in surveys carried out at the local level or health facilities. Each worksheet contains a survey instrument to collect data at the health facility, municipality and department level on the following items: (1) basic contact information and production of services, i.e. number of doses applied and ambulatory visits in a year, (2) labor, (3) cold chain, (4) vehicles, and (5) buildings.

2.1.3. Calculations worksheet

This "backend" worksheet shows calculations performed in "CostVac". In an effort to ensure transparency, this sheet is not hidden, and care is taken to document calculation steps and to present the results of alternative assumptions. For cost data gathered from surveys, the worksheet provides mean, median, maximum, and minimum values obtained from the sample.

2.1.4. Outputs worksheet

This worksheet displays numeric and graphic results of the costing analysis. The overall cost structure of the EPI is presented by cost input and by administrative level or geographic area.

2.1.5. Worksheets with default and validated data

There are several worksheets with pre-populated default data on demographics and vaccine, supply and cold chain equipment prices. The source for the price data, demographic data and exchange rates from local currency to US dollars is the PAHO Revolving Fund, the United Nations World Population Projections and the World Bank, respectively. These worksheets are hidden from users in order to avoid inadvertent user changes to defaults. While these worksheets are intended to help users quickly populate their costing model with internationally available data, the user always has the option to overwrite these "pre-populated" values.

2.2. Data collection for the ProVac CostVac Tool

The survey instruments in "CostVac" provide users with standard data collection questionnaires to define resource use information at the different levels of the EPI: central level, intermediate administrative levels (department and municipality), and service delivery level, or rather health facilities. Costs at each level are divided into six major cost categories: vaccines and supplies (only captured at the central level), personnel, cold chain, vehicles, buildings, and other costs (only captured at the central level). Data are typically collected using paper-based surveys, and then entered into the costing tool spreadsheets. Vaccine, syringes, and other immunization supplies are identified using procurement records at the central level or by using vaccination schedules and reported coverage of each applied vaccine in a particular setting. Personnel, cold chain, vehicles, and building costs are identified using a bottom-up approach for each level. That is, surveys at the intermediate administrative levels and service delivery levels gather information from the sampled entities. The cost estimate obtained from the sample is then extrapolated with appropriate weighting to obtain an estimate of the national EPI cost for the year of evaluation. In the 'other costs' section of the tool, users can allocate EPI costs to EPI components or activities, including surveillance and laboratory, training, social mobilization, other operational costs, supervision, evaluation, research, and program management costs. The methodological guide assists the user in distributing the total EPI cost structure across these components using a step-down approach to allocation.

2.3. Sampling strategy for ProVac CostVac Tool

The sample design and strategy is dependent on the level of resources available for data collection. The methodological guide for "CostVac" reviews general guidance for sampling such as the tradeoffs between number of facilities sampled and accuracy of results. Much of this guidance is drawn from previous experience with a similar costing exercise in Bolivia and alternative approaches that stratify estimates by specific sub-national levels or by urban and rural settings. The guide also describes how to use the tool with common sampling designs.

2.4. Cost analysis in ProVac CostVac Tool

Estimating the total national EPI costs requires a cost rollup at each level of the program. When lower levels are sampled to obtain data on the delivery of the routine EPI at these levels, they must be extrapolated to the national level using an appropriate method. To do this, the tool offers four built-in methods for extrapolation to accommodate a wide range of country-specific situations. These methods are further reviewed in Section 2.5.

Results of the costing analysis are presented in standard tables and charts that are produced automatically. The tool generates the following cost indicators: total costs, cost by item (vaccine and supplies, personnel, cold chain, vehicle, facility, and other), costs by program level (central level, intermediate administrative level, and service delivery level), and costs per dose applied and per fully immunized individual (FII). When only the under 1 population is considered, this output is the fully immunized children (FIC). Additionally, the tool can estimate multiple scenarios, for example, costs of the routine EPI compared to costs of the routine EPI plus supplemental immunization activities (SIAs).

Estimated costs per FII include the vaccine-related costs (vaccine and supply costs per dose applied, adjusted for wastage) and the non-vaccine costs, for example delivery costs, in each population of interest. For non-vaccine costs in the cost per FII, the proportion of the population of interest receiving vaccine doses is applied to the total cost of items such as personnel and buildings whereas in the case of cold chain and transport, the proportion of physical volume of doses being consumed in the population of interest is applied to the total cost of these items. For example, if 20% of total doses were applied in the under-1 population, only 20% of the total personnel and building costs are considered. By contrast, if 20% of doses applied correspond to 30% of the physical volume of all doses applied, we would consider 30% of total cold chain and vehicle costs in the cost per FIC calculation.

The number of fully immunized individuals in each target group is estimated as the ratio between the total number of doses applied in the target group (e.g. under-1 population, for the FIC) and the total number of doses in the complete schedule for the particular target group. A second definition of FII is used to create a lower limit. According to this second definition, FII is the number of individuals that have received the last dose of the vaccine that has the lowest administrative coverage in the national schedule. For example, in a given country with a reported rotavirus vaccination coverage of 60%, which represents the lowest coverage level among all coverage

levels of vaccines in the recommended schedule, the number of FIC in this country would be 60% of the under-1 population.

2.5. Extrapolation of sampled costs to a national cost estimate

All central level costs (the first administrative level) can be captured directly with "CostVac" and it also allows users to extrapolate the data collected at the sampled lower levels to the national level. Several methods of extrapolation are provided for the user. The choice of method will depend on the sampling method used and users' assumptions.

2.5.1. General weighted method

This method adjusts costs by size of surveyed units (e.g. catchment-area or number of doses applied). Adjustment depends on weighting administrative or facility level data. Administrative level data are weighted according to under-1 population size. Facility level data are weighted using total diphtheria–tetanus–pertussis (DTP) doses applied annually.

2.5.2. Simple average method

When a representative (random) sample of health facilities is surveyed, a simple average across unit costs at the health facilities can be used. That is, the average cost of the EPI per health facility is applied directly to all health facilities delivering immunization services in the country and then summed to reach a national service delivery level cost.

2.5.3. Categorical weighted method

The categorical weighted average method groups all health facilities (in-sample and out-of-sample) by their size (small, medium, and large). The cutoff thresholds that define the size category are described in the set-up worksheet. This method allows the user to calculate different simple averages by size, which will be weighted by the percentage of total numbers of health facilities of each size. This estimation is performed at each of the lower levels, first for health facilities and then for the other intermediate administrative levels (department and municipality).

2.5.4. Average cost-per-dose method

A fourth method computes the cost per dose delivered at each sampled facility and, adjusting for facility size, applies this cost to the doses delivered in non-sampled facilities. In the case of other sampled lower administrative levels, the average cost per child in the under-1 population is multiplied by the total number of children under-1 who are potentially reached by immunization services in each size category.

2.6. Application of the ProVac CostVac Tool: Colombian costing exercise

In 2011, "CostVac" was used to estimate total routine immunization costs for 2009 in Colombia. Using the data collected at different levels, the tool estimated the overall cost of the Colombian EPI and the cost per FIC. A costing survey was carried out at four levels (national, departmental, municipality, and health facility) to identify which cost items are partially shared with other public health programs. The municipalities and health facilities were selected using a stratified random sampling strategy. First, municipalities were stratified by population size within each department. Then, health facilities identified in each selected municipality were stratified by health sector (public or private) and by the number of ambulatory visits and a simple random sample of 112 health facilities were selected. The following cost items were computed for each level (department, municipality, or health facility) selected for the study: vaccines and supplies, personnel, cold chain, vehicles, buildings, and other costs.

Costs were defined at each level using two approaches. First, EPI staff were interviewed and asked to provide inputs on the EPI costs. Second, where information from EPI staff was not available, financial information from the Ministry of Health was reviewed in order to estimate the cost per input. Paper-based surveys were used to collect this data. Once the process of reviewing and cleaning the data was completed, the data were entered into the respective "CostVac" worksheets previously described. All costs are expressed in 2009 US dollars.

The Colombian cost estimates encompass costs to deliver BCG (1 dose), pentavalent (3 doses), hepatitis B virus (HBV, 1 dose), oral polio (3 doses), rotavirus (2 doses), and pneumococcal (3 doses) vaccines, as indicated by the national vaccination schedule for 2009 (Table 1). Additionally, the total cost structure estimates include vaccines administered after the age of one such as influenza, measles–mumps–rubella (MMR), yellow fever (YF), and booster doses for DTP, polio, and MMR in children, and influenza, diphtheria–tetanus, and measles–rubella in adults (Table 1). Only the costs of routine EPI were estimated because no SIAs were carried out in 2009.

Data gathered from the central level included number of vaccine doses applied, reported coverage, wastage rates, and the Colombian EPI budget execution for 2009. Additional information on costs for the four most relevant items (i.e. personnel, cold chain, vehicles, and buildings) was collected from the 112 health facilities sampled for this study, additionally a sample of 6 municipalities and 3 departments was selected to estimate the cost at these two levels.

Since results from a previous costing exercise in Colombia indicated that costs vary by volume of patients attended per facility, we used a stratified random sample of the health facilities for this study and we chose the average cost-per-dose extrapolation approach for estimating the Colombian EPI costs. Based on the sampling strategy used for this costing study, all other extrapolation methods reviewed would have introduced bias into the total cost estimates, either over or under-estimating the real costs. Facilities with less than 1000 doses applied annually were considered "low volume", facilities with 1000–5000 doses applied annually were considered "medium volume", and facilities with more than 5000 doses applied were considered "high volume". Departments with less than 15,000 children under-1, 15,000–30,000 children under-1, and more than 30,000 children under-1 were considered low-, medium- and high-volume, respectively. Municipalities considered "low volume" had less than 1000 children under-1, "medium volume" had between 1000 and 5000, and "high volume" had more than 5000 in this age group (Table 2). At the departmental level 7.7% of children under-1 were in the catchment-area of low-volume facilities, 30.7% in the catchment-area of medium-volume, and 61.6% in the catchment-area of high-volume facilities. At the municipal level, 35.4% of children under-1 were covered by low-volume facilities, 24.1% by medium-volume, and 40.5% by high-volume facilities. Finally, at health facilities, 0.4% of doses were delivered at the low-volume facilities, 6.6% at medium-volume, and 93.0% at high-volume facilities.

3. Results

The total cost of the Colombian EPI in 2009 was estimated to be US$ 107.8 million. Vaccines and vaccination supplies represented the largest share of costs, amounting to 58% of total EPI costs. Personnel, cold chain, and vehicles represented 21%, 18%, and 2% of total costs, respectively (Table 3). Since vaccines and vaccination supplies are typically procured at the central level, it was assumed that a smaller proportion of total costs would occur at the lower

Table 1
Summary of number of doses of vaccines applied in Colombian EPI, 2009.

Type of vaccine	Doses per schedule	Price per dose (US$ 2009)	Target population	Doses applied	Coverage (%)	Wastage (%)
BCG	1	0.11	Newborns	774,040	90.2	64.6
Hepatitis B recombinant (pediatric)	1	0.27	Newborns	2,373,607	92.2	10.1
DTP-HepB-Hib	3	3.55	Newborns	2,373,607	92.2	4.7
Oral polio	3	0.17	Newborns	2,371,032	92.1	30.0
Rotavirus vaccine	2	7.90	Newborns	1,414,210	82.4	6.1
Pneumococcal conjugate vaccine	3	21.75	Newborns	419,629	16.3	2.0
Southern hemisphere influenza (pediatric)	2	1.40	Children under 1 year	1,582,405	92.2	25.7
Measles–mumps–rubella	1	1.55	Children under 1 year	816,946	95.2	0.0
Yellow fever	1	0.63	Children under 1 year	819,521	95.5	57.1
Diphtheria–tetanus–pertussis	2	0.16	Children under 5 years	1,258,029	73.3	51.1
Oral polio	2	0.17	Children under 5 years	1,347,275	78.5	74.7
Measles–mumps–rubella	1	1.55	Children under 5 years	638,454	74.4	4.9
Diphtheria–tetanus (adult)	2	0.08	Women of childbearing age	9,590,362	40.0	30.7
Measles–rubella (adult)	1	1.35	Pregnant women	645,193	92.2	0.0
Southern hemisphere influenza (adult)	1	2.65	Over 65 years	2,454,838	83.0	3.8

Table 2
Number of total and surveyed intermediate administrative levels and health facilities in the 2009 Colombian EPI costing pilot.

Level	Unit	Function	Total units (no.)	Units selected to survey (no.)	Cut-off points
First	Central	Administrative	1	1	NA
Second	Department	Administrative	33	6	15,000 and 30,000 under 1 year population
Third	Municipality	Administrative	1121	3	1000 and 5000 under 1 year population
Fourth	Health facility	Operational	3181	112	1000 and 5000 vaccine doses delivered

Table 3
Total Colombian EPI costs by cost item and type of cost, 2009.

	Capital costs (US$ 2009)	Recurrent costs (US$ 2009)	Total cost (US$ 2009)	Percentage of total costs
1. Total vaccine and vaccination supplies cost	–	62,113,988	62,113,988	57.6
1.1. Vaccine cost	–	54,874,981	54,874,981	50.9
1.2. Syringe cost	–	1,313,871	1,313,871	1.2
1.3. Other vaccination supplies cost	–	5,925,135	5,925,135	5.5
2. Total personnel	–	22,375,620	22,375,620	20.8
3. Total cold chain	514,306	19,022,605	19,536,911	18.1
4. Total vehicles and transport	17,432	2,409,455	2,426,887	2.3
5. Total buildings	7478	134,462	141,940	0.1
6. Other costs	–	1,207,409	1,207,409	1.1
6.1. Total surveillance and laboratory	–	–	–	0.0
6.2. Total training	–	–	–	0.0
6.3. Total social mobilization	–	1,206,604	1,206,604	1.1
6.4. Total operating cost	–	588	588	0.0
6.5. Total supervision	–	218	218	0.0
6.6. Total evaluation	–	–	–	0.0
6.7. Total research	–	–	–	0.0
6.8. Total wastage management	–	–	–	0.0
Total costs of EPI	539,216	107,263,539	107,802,755	100.0

Dashes (–) correspond to US$ 0.

levels. In our analysis, we estimate that 62% of costs occurred at the central level and 30% at local or health facility level. The costs collected in the 112 service delivery facilities extrapolated to the national level are reported in Table 4. The department and municipality levels accounted for 3% and 4% of total cost, respectively (Table 5).

More than 27.2 million doses were delivered in 2009 through the Colombian EPI. The cost per dose delivered was, on average, US$ 3.95 including the vaccine price. Considering only the vaccine delivery costs (excluding the vaccine price), the average cost of the program per dose applied was US$ 1.93, almost double the $1.00 per dose assumption generally applied in cost-effectiveness studies [9].

Table 4
Comparison between the extrapolated estimates calculated by the ProVac CostVac Tool for 3181 health facilities and the survey data for112 health facilities in Colombia; Cost in US$ 2009.

Item	From extrapolation (average per fourth level unit) (US$)	From survey data					
		Average (US$)	Median (US$)	Max (US$)	Min (US$)	95% CI (US$)	
Personnel	12,649,718	10,106,517	3,613,243	166,426,200	–	6,427,046	13,785,987
Cold chain	18,059,780	10,564,433	460,767	229,094,138	–	4,324,748	16,804,119
Transport	2,052,640	1,508,065	–	15,373,735	–	651,542	2,364,588

Dashes (–) correspond to US$ 0. Some facilities reported US$ 0 in its costs by component and therefore, the minimum reported in this table is US$0; Building costs were not captured in the health facility survey.

Table 5
Total Colombian EPI costs by cost item and administrative level.

	Central level		Departmental level		Municipal level		Health facility level	
	US$ 2009	%	US$ 2009	%	US$ 2009	%	US$ 2009	%
1. Total vaccine and vaccination supplies cost	62,113,988	92.3	–	0.0	–	0.0	–	0.0
1.1. Vaccines cost	54,874,981	81.6	–	0.0	–	0.0	–	0.0
1.2. Syringe cost	1,313,871	2.0	–	0.0	–	0.0	–	0.0
1.3. Other vaccination supplies cost	5,925,135	8.8	–	0.0	–	0.0	–	0.0
2. Total personnel	3,704,589	5.5	2,754,529	89.1	3,266,785	70.1	12,649,718	38.6
3. Total cold chain	31,420	0.0	96,917	3.1	1,348,793	28.9	18,059,780	55.1
4. Total vehicles and transport	221,672	0.3	130,711	4.2	21,863	0.5	2,052,640	6.3
5. Total buildings	9130	0.0	108,607	3.5	24,203	0.5	–	0.0
6. Other	1,207,409	1.8	–	0.0	–	0.0	–	0.0
6.1. Total surveillance and laboratory	–	0.0	–	0.0	–	0.0	–	0.0
6.2. Total training	–	0.0	–	0.0	–	0.0	–	0.0
6.3. Total social mobilization	1,206,604	1.8	–	0.0	–	0.0	–	0.0
6.4. Total operating cost	588	0.0	–	0.0	–	0.0	–	0.0
6.5. Total supervision	218	0.0	–	0.0	–	0.0	–	0.0
6.6. Total evaluation	–	0.0	–	0.0	–	0.0	–	0.0
6.7. Total research	–	0.0	–	0.0	–	0.0	–	0.0
6.8. Total wastage management	–	0.0	–	0.0	–	0.0	–	0.0
Total costs of EPI	67,288,208	100.0	3,090,764.35	100.0	4,661,644	100.0	32,762,138	100.0
% by level		62.42		2.87		4.32		30.39

The actual cost per FIC in the population under 1 year of age ranged between US$ 93.96 and US$ 420.80, with an average cost of US$ 153.62. Such a wide range is due to two different sets of assumptions in the calculation for FIC. The number of FIC for upper limit of the range was obtained by dividing all doses administered to the under-1 population by the total number of doses required by the national immunization schedule by the age of one (i.e. 13 doses for infants under 1 year old in Colombia, excluding influenza vaccine). The number of FIC for the lower limit of the range was obtained by applying the coverage level of the vaccine with the lowest coverage among all coverage levels in the under-one population by vaccine in the Colombian immunization schedule (i.e. coverage levels of a completed rotavirus schedule). When we took into account the two vaccines (one of MMR and one of YF) given to children at 1 year of age and two doses of influenza vaccine given at 6 and 7 months, the additional cost per FIC ranges between US$ 15.26 and US$ 15.52. For the population under 2 years old, the cost per FIC ranged from US$ 111.19 to US$ 436.32.

4. Discussion

This article addresses two important issues that may have an impact on future economic evaluations of vaccination programs. We have presented a new economic tool to generate detailed estimates for the economic costs associated with national immunization program activities. The tool captures both vaccine purchase costs and other operational costs, such as personnel, cold chain, supplies, vehicles, and building costs. It is also useful for estimating costs at different administrative levels of the immunization program (central, departmental, and municipal).

There are several planning and budgeting tools currently being used to estimate costs and resource use from the central level perspective. The limitation of these tools is that they do not provide comprehensive cost estimates for the entire EPI by excluding lower administrative and service delivery levels. For example, the Vaccine Introduction Costing (VIC) tool [10], has a relatively simple structure but only assesses the incremental cost of EPI for four new vaccines. The comprehensive multi-year planning tool (cMYP) [11] provides a more complete framework for collecting EPI data, but the tool is data hungry and its user-friendliness could be improved.

The Vaccine Forecasting Tool [12], and PAHO form 173 evaluate vaccine items for a forecasting exercise, which limits their use for estimating costs of the current national EPI. The Immunization Supply Chain Planning Tool [13], Effective Vaccine Management (EVM) Initiative [14], and Cold Chain Equipment Manager (CCEM) Tool [15] present a useful approach to approximate cold chain inventory that could be used in a micro-costing (bottom-up) exercise, but are not costing tools. None of these tools take into account personnel costs, which differ sharply between countries and health system models. Inadequate costing of personnel may introduce distortions because at local and lower administrative levels labor is often shared across several health programs and requires a detailed accounting of the time health workers devote to EPI activities. In the Colombian exercise, personnel accounted for about 20% of the total cost of the EPI.

Most EPI costing exercises in the published literature do not consider costs incurred at lower administrative levels and mainly concentrate on the costs of vaccine and supplies, with limited consideration of other costs. In addition, the effort to collect data on vaccination costs is concentrated only on financial information at the central level, ignoring the significant economic contribution to vaccination activities that local and district levels make. This gap is in part due to a lack of tools with clear instructions on how to carry out such costing exercises, on how to collect vaccination costs, on which costs should be collected, on how to identify sources of financial or economic information to retrieve vaccination costs and on how health facilities should be sampled in order to evaluate costs. The newly developed ProVac CostVac Tool is a valuable tool for collecting and estimating economic costs at different administrative levels of the EPI. It provides users with a detailed list of cost items that should be evaluated to generate precise total cost estimates of the EPI and includes a handbook that provides guidance to users on how to define the number of health facilities that should be sampled to conduct the exercise at local or lower administrative levels.

The ProVac CostVac Tool was tested using data from an EPI costing exercise carried out in Colombia in 2009. This exercise demonstrates the importance of estimating vaccination costs incurred by lower administrative levels in a decentralized and partially privatized health system, as is the case in Colombia. The pilot study showed that most of the costs of the Colombian EPI, estimated at more than US$ 107 million, were incurred at the central level (63%) whereas the departmental and municipal levels accounted for only 7% of total costs. However, health facilities accounted for 30% of the total program costs, mainly due to the lower level labor costs. At the time this study was carried out, no other Colombian cost analysis had been published so the results cannot be compared

against other costing exercises. The total cost of the EPI in 2009 represented 0.04% of Colombian GDP, and a cost per capita of US$ 2.40.

There is an important link between the sampling strategy used and the extrapolation method and the relationship between the two should be kept in mind in order to develop unbiased estimates at the national level. Given the importance of developing a robust sampling design, this issue will continue to be explored in future pilots of the ProVac costing tool. The choice of applying the average cost-per-dose method in the Colombian setting, based on the empirical evidence from the data, allowed us to extrapolate the costs for the items captured in the lower level survey and generate reliable national-level estimates (Table 4) despite the heterogeneity in the unit cost per health facility.

A costing tool with a valid and transparent methodology will be a useful instrument to generate EPI costs. Cost analysis of the routine EPI is an important input for cost-effectiveness analysis. However, the lack of transparent and standardized methodologies to generate estimates on EPI costs is a limitation of published cost-effectiveness analyses of new vaccines. The variation in EPI cost inputs and the availability of cost data by country result in published EPI cost estimates that vary substantially between studies [16]. In the Colombian EPI costing exercise, had we only considered financial reports we would have only identified about 70% of the overall total EPI cost, and the costs identified at lower administrative levels would have been neglected.

Our estimates for cost per FIC of US$ 153.62 (Ranging US$ 93.96–US$ 420.80) are substantially higher (fivefold) than those previously reported by other countries; however, we included the cost of new, more expensive vaccines (pneumococcal and rotavirus). Including new vaccines in the analysis may influence the cost per FIC. The Global Alliance for Vaccines and Immunization (GAVI) reported a FIC value of US$ 20.00 including only a basic schedule with six traditional antigens [17]. In addition, our estimates may represent the actual costs of delivering immunization services because we accounted for inefficiencies such as incomplete and out-of-schedule vaccination among children. There is a wide disparity in EPI costs reported from low- and middle-income countries in the literature. In general, studies conducted in the 1980s [18–21] showed a lower cost per FIC than those conducted in the 1990s [22] and 2000s [23]. The cost per FIC in the earlier studies ranges from US$ 2.86 to US$ 10.73 [24], while in the latest studies it ranges from US$ 4.39 to US$ 59.90 [25]. Most of those cost estimates are not corrected for inflation, possible changes in immunization schedules, or for the variable cost of inputs across countries.

Although the ProVac CostVac Tool is designed to carry out a comprehensive EPI cost estimation based on a detailed costing methodology, there are some limitations to the tool. The quality and accuracy of the analyses depend on the users' ability to access the necessary information at central, district and local levels and the precision with which data collection instruments collect accurate information. There is a detailed user's guide, but the process of defining the sampling strategy can be difficult for users that do not have basic training in statistics, and time may be needed for user training on the tool and in Excel. Data collection in the field requires time and resources. However, these limitations are minor compared to those present in other available tools.

The Colombian pilot exercise presented certain limitations because we included fewer institutions at the departmental and municipal levels than would be desired. However, due to the organizational structure of the Colombian immunization program, EPI financing occurs primarily at the central and operational levels, which were exhaustively evaluated. Additionally, building costs were not included because data were not available at health facilities, implying an underestimate of the total cost of the EPI. Also, "other costs" were not disaggregated but that only affects incremental costs. In the Colombian estimation only the cost of routine EPI was included, but the ProVac costing tool is able to differentiate between the routine program and supplementary immunization activities (SIAs), and can estimate the cost for FIC in both scenarios.

In conclusion, "CostVac" promises to be a comprehensive and valuable tool for providing immunization program cost. The information provided could facilitate decision making on the financing of national EPI, introduction of new vaccines, and identification of ways to improve resource allocation and program efficiency. The first pilot of the ProVac CostVac Tool demonstrated the robustness of the tool's methods. Further piloting of this instrument will help refine the proposed methodology and the tool's structure.

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Review

Systematic review of incremental non-vaccine cost estimates used in cost-effectiveness analysis on the introduction of rotavirus and pneumococcal vaccines

Fernando De la Hoz-Restrepo[a], Carlos Castañeda-Orjuela[a,*], Angel Paternina[b], Nelson Alvis-Guzman[b]

[a] Epidemiology and Public Health Evaluation Group, Universidad Nacional de Colombia, Bogotá, Colombia
[b] Health Economics Research Group, Universidad de Cartagena, Cartagena de Indias, Colombia

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ABSTRACT

Objective: To review the approaches used in the cost-effectiveness analysis (CEAs) literature to estimate the cost of expanded program on immunization (EPI) activities, other than vaccine purchase, for rotavirus and pneumococcal vaccines.
Methods: A systematic review in PubMed and NHS EED databases of rotavirus and pneumococcal vaccines CEAs was done. Selected articles were read and information on how EPI costs were calculated was extracted. EPI costing approaches were classified according to the method or assumption used for estimation.
Results: Seventy-nine studies that evaluated cost effectiveness of rotavirus ($n=43$) or pneumococcal ($n=36$) vaccines were identified. In general, there are few details on how EPI costs other than vaccine procurement were estimated. While 30 studies used some measurement of that cost, only one study on pneumococcal vaccine used a primary cost evaluation (bottom-up costing analysis) and one study used a costing tool. Twenty-seven studies (17 on rotavirus and 10 on pneumococcal vaccine) assumed the non-vaccine costs. Five studies made no reference to additional costs. Fourteen studies (9 rotavirus and 5 pneumococcal) did not consider any additional EPI cost beyond vaccine procurement. For rotavirus studies, the median for non-vaccine cost per dose was US$0.74 in developing countries and US$6.39 in developed countries. For pneumococcal vaccines, the median for non-vaccine cost per dose was US$1.27 in developing countries and US$8.71 in developed countries.
Conclusions: Many pneumococcal (52.8%) and rotavirus (60.4%) cost-effectiveness analyses did not consider additional EPI costs or used poorly supported assumptions. Ignoring EPI costs in addition to those for vaccine procurement in CEA analysis of new vaccines may lead to significant errors in the estimations of ICERs since several factors like personnel, cold chain, or social mobilization can be substantially affected by the introduction of new vaccines.

Contents

* Corresponding author at: Department of Public Health, Faculty of Medicine, Universidad Nacional de Colombia, Carrera 30 #45-03, office 150, Bogotá, DC, Colombia. Tel.: +57 3165000x15086; fax: +57 3165175.
E-mail addresses: fpdelahozr@unal.edu.co (F. De la Hoz-Restrepo), cacastanedao@unal.edu.co, carloscastanedao@gmail.com (C. Castañeda-Orjuela), angel.paternina@gmail.com (A. Paternina), nalvis@yahoo.com (N. Alvis-Guzman).

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1. Introduction

Immunization services are one of the most cost-effective interventions to reduce child mortality [1]. However, new vaccines are more expensive than traditional ones which has an important financial impact on vaccination programs costs. For example, the current vaccine dose prices provided by the Pan American Health Organization (PAHO) Revolving Fund for Vaccine Procurement in 2011 were US$14.85 for pneumococcal vaccine, and US$5.25 and US$7.50 for rotavirus mono- and penta-valent vaccine, respectively. This is many times the cost of traditional vaccines like polio, measles, and DPT, whose cost per dose is below US$0.50.

The World Health Organization (WHO) proposes that countries carry out studies on the potential cost-effectiveness of new vaccines before making the decision to introduce them. A recent systematic literature review showed that cost-effectiveness analysis (CEA) has become an increasingly important factor for stakeholders who need to make decisions about adding new vaccines into national immunization programs versus alternative uses of resources [2]. Capacity strengthening in this area at the local level is a critical step in promoting the rational use of these evaluations and tools [3,4].

WHO has developed guidelines recommending that economic evaluation of immunization programs consider all costs related to the introduction of a new vaccine and not the vaccine procurement cost alone [5,6]. The guidelines present comprehensive methods to estimate the additional non-vaccine costs incurred when introducing new vaccines. Including those incremental non-vaccine costs in CEAs is strongly recommended in the WHO guidelines [7].

There is little published evidence on whether researchers estimating cost-effectiveness of introducing new vaccines follow the WHO guidelines, especially regarding the inclusion of all potential costs to be incurred when new vaccines are introduced in the expanded program on immunization (EPI). This analysis reviews the approaches used in the CEA literature to estimate the incremental cost of EPI activities, other than vaccine procurement, for rotavirus and pneumococcal vaccines.

2. Methods

A systematic review was made of studies on rotavirus and pneumococcal vaccines CEAs published from 1995 to December 2010. Selected articles were read and information on how EPI costs were calculated was extracted. EPI costing approaches were classified according to the method or assumption used for estimation.

2.1. Search strategies

Two databases (PubMed of the United States National Medical Library and the Economic Evaluation Database of the United Kingdom National Health Service [NHS EED]) were reviewed, using different combinations of the search terms listed in Table 1.

2.2. Type of studies

Studies included in the review were those containing data from cost-effectiveness analysis where the observation unit was an individual country. Multi-country studies were included when it was possible to obtain cost assumptions or estimations disaggregated by country. Cost-effectiveness studies of small cohorts of patients (e.g., clinical trials) or a portion of a country were excluded, as well as those from multi-country analysis where all data were aggregated and no individual country values could be determined. Review articles were not included.

2.3. Type of intervention

The rotavirus vaccine cost-effectiveness review considered intervention with vaccination with monovalent or pentavalent rotavirus vaccine compared with no intervention. Likewise, the pneumococcal vaccine cost-effectiveness review considered vaccination with pneumococcal conjugate vaccines PCV7 and/or PCV10 and/or PCV13 compared with no intervention.

2.4. Data collection and analysis

One author (AP) independently reviewed each study retrieved for inclusion. A database was created with studies collected by one researcher (CC). The procedure was supervised by two other researchers (FDLH, NA). Data on vaccination cost assessment were extracted to a database from every paper included in the review. Specifically, information was entered on how authors measured costs that were in addition to those of vaccine purchase, and whether freight and insurance costs were included in the procurement cost. Wastage rates were recorded separately.

Approaches used by authors to estimate incremental non-vaccine costs of vaccination were classified in two broad categories: assumed costs or measured costs. Assumed costs were classified as those in which authors clearly stated that they used a fixed value or a portion of the dose cost as a surrogate for additional vaccination costs. Measured costs were classified as those in which authors followed a methodology, developed on their own or taken from former studies, to compute the incremental non-vaccine costs (for example, estimating the person time spent applying a dose, or estimating expansion of the cold chain as a result of introducing a new vaccine).

The main characteristics of each article were tabulated, including the year of publication, the country origin of the data, whether incremental non-vaccine costs were taken into account, how

Table 1
Search terms used in PubMed and NHS EED databases.

Rotavirus	Pneumococcal
MEDLINE (PubMed): ((vaccine) AND rotavirus) AND cost	MEDLINE (PubMed): ((pneumococcal) AND vaccine) AND cost
NHS EED: 'rotavirus'	NHS EED: 'pneumococcal'

Table 2
Studies with cost-effectiveness analysis of rotavirus vaccine reporting additional costs.

First author	Year	Reference	Vaccine	Country studied	Additional costs assumed or measured	Additional cost per dose in 2010 US$
Smith	1995	[8]	Not defined	U.S.	Not included	–
Huet	2007	[13]	Pentavalent	France	Not included	–
Melliez	2008	[24]	Not defined	France	Not included	–
Standaert	2008	[25]	Monovalent	France	Not included	–
Giammanco	2009	[32]	Mono- and pentavalent	Italy	Not included	–
Milne	2009	[35]	Pentavalent	New Zealand	Not included	–
Wu	2009	[44]	Mono- and pentavalent	Republic of China (Taiwan)	Not included	–
de la Hoz-Restrepo	2010	[46]	Mono- and pentavalent	Colombia	Not included	–
Mangen	2010	[49]	Mono- and pentavalent	Germany	Not included	–
Ortega	2009	[36]	Not defined	Egypt	Not specified	–
Panatto	2009	[37]	Not defined	Italy	Not specified	–
Lorgelly	2008	[23]	Mono- and pentavalent	U.K.	Assumed	–
Carlin	1999	[11]	RRV-TV	Australia	Assumed	$4.22
Podewils	2005	[12]	Monovalent	Asia	Assumed	$3.55
Isakbaeva	2007	[14]	Monovalent	Uzbekistan	Assumed	$0.27
Rheingans	2007	[17]	Monovalent	Latin America and the Caribbean	Assumed	$0.82
Widdowson	2007	[18]	Pentavalent	U.S.	Assumed	$10.52
Constenla	2008	[21]	Not defined	Brazil	Assumed	$0.72
Valencia-Mendoza	2008	[20]	Pentavalent	Mexico	Assumed	$5.50
Bilcke	2009	[27]	Mono- and pentavalent	Belgium	Assumed	$7.17
Clark	2009	[29]	Monovalent	Peru	Assumed	$0.56
Constenla	2009	[30]	Not defined	Mexico	Assumed	$0.58
Jit	2009	[45]	Mono- and pentavalent	Belgium, England, Wales, Finland, France, the Netherlands	Assumed	$6.28
Rose	2009	[38]	Monovalent	India	Assumed	$0.67
Shim	2009	[39]	Pentavalent	U.S.	Assumed	$10.52
Wilopo	2009	[43]	Not defined	Indonesia	Assumed	$0.60
Chotivitayatarakorn	2010	[48]	Monovalent	Thailand	Assumed	$0.54
Kim	2010	[50]	Mono- and pentavalent	GAVI- eligible countries	Assumed	$3.02
Tucker	1998	[9]	Monovalent	U.S.	Measured (previous study)	$13.84
de Soaĭrez	2008	[19]	Not defined	Brazil	Measured (previous study)	$1.34
Goossens	2008	[22]	Monovalent	Netherlands	Measured (previous study)	$6.39
Martin	2009	[34]	Monovalent	U.K.	Measured (previous study)	$4.38
Tate	2009	[40]	Monovalent	Kenya	Measured (previous study)	$0.76
Wang	2009	[41]	Mono- and pentavalent	China	Measured (previous study)	$2.47
Berry	2010	[47]	Monovalent	Malawi	Measured (previous study)	$0.41
Takala	1998	[10]	RRV-TV	Finland	Measured	$3.59
Jit	2007	[15]	Mono- and pentavalent	U.K.	Measured	$11.25
Newall	2007	[16]	Mono- and pentavalent	Australia	Measured	$1.97
Kim	2009	[33]	Monovalent	Vietnam	Measured	$1.26
Atherly	2009	[26]	Monovalent	GAVI-eligible countries	Measured	$0.77
Chodick	2009	[28]	Mono- and pentavalent	Israel	Measured	$3.26
Flem	2009	[31]	Not defined	Kyrgyzstan	Measured	$0.58
Weycker	2009	[42]	Mono- and pentavalent	U.S.	Measured	$10.52

Note: Dash in table indicates US$0 when additional costs are not included or that information was not available.

incremental non-vaccine costs were determined (i.e., assumed or measured), and finally, the monetary value of the incremental non-vaccine costs (see Tables 2 and 3). All costs data were converted to 2010 U.S. dollars since articles covered an extended period of time and different national currencies were used.

2.5. Classification of countries

The analysis was stratified by income level of the countries. They were classified as developed or developing economies using criteria from the International Monetary Fund. Median cost analysis was carried out for both groups.

Table 3
Studies with cost-effectiveness analysis of pneumococcal vaccine reporting additional costs.

First author	Year	Reference	Vaccines	Country studied	Additional costs assumed or measured	Additional cost per dose in 2010 US$
Marchetti	2005	[62]	PCV-7	Italy	Not included	–
Wisløff	2006	[66]	PCV-7	Norway	Not included	–
Bergman	2008	[68]	PCV-7	Sweden	Not included	–
Vespa	2009	[80]	PCV-7	Brazil	Not included	–
Sohn	2010	[83]	PCV-7	Korea	Not included	–
Lebel	2003	[57]	PCV-7	Canada	Not specified	–
Asensi	2004	[59]	PCV-7	Spain	Not specified	–
Silfverdal	2009	[79]	PCV-7	Sweden	Not specified	–
Giachetto	2010	[81]	PCV-7	Uruguay	Not available	–
Poirier	2009	[77]	PCV-7	Canada	Measured (previous study)	–
Tilson	2008	[72]	PCV-7	Ireland	Not available	$19.06
Lee	2009	[75]	PCV-7	Hong Kong SAR, China	Not available	$1.60
Weycker	2000	[51]	PCV-7	U.S.	Assumed	$6.47
Claes	2003	[55]	PCV-7	Germany	Assumed	$3.37
McIntosh	2003	[58]	PCV-7	U.K.	Assumed	$4.41
Ess	2003	[56]	PCV-7	Switzerland	Assumed	$8.58
Butler	2004	[60]	PCV-7	Australia	Assumed	$4.22
McIntosh	2005	[63]	PCV-7	U.K.	Assumed	$4.81
Salo	2005	[64]	PCV-7	Finland	Assumed	$2.41
Constenla	2008	[69]	PCV-7	Brazil, Chile, Uruguay	Assumed	$1.42
Sinha	2008	[71]	PCV-7	Latin America and the Caribbean	Assumed	$1.35
Rubin	2010	[86]	PCV-7, -13	United States	Assumed	$11.14
De Wals	2003	[53]	PCV-7	Canada	Measured	$5.23
Bos	2003	[54]	PCV-7	Netherlands	Measured	$5.40
Melegaro	2004	[61]	PCV-7	U.K.	Measured	$19.25
Sinha	2007	[67]	PCV-7	72 GAVI-eligible countries	Measured	$1.18
Lloyd	2008	[70]	PCV-7	Germany	Measured	$10.21
Kim	2010	[82]	PCV-7, -9, -10, -13	Gambia	Measured	$0.42
Lieu	2000	[52]	PCV-7	U.S.	Measured (previous study)	$13.45
Ray	2006	[65]	PCV-7	U.S.	Measured (previous study)	$9.90
Claes	2009	[73]	PCV-7	Germany	Measured (previous study)	$8.79
O'Brien	2009	[76]	PCV-7	U.S.	Measured (previous study)	$13.04
Ray	2009	[78]	PCV-7	U.S.	Measured (previous study)	$11.97
Rozenbaum	2010	[84]	PCV-7, -10, -13	Netherlands	Measured (previous study)	$8.64
Rubin	2010	[85]	PCV-7	U.S.	Measured (previous study)	$10.73
Giorgi-Rossi	2009	[74]	PCV-7	Italy	Assumed and measured[a]	$9.06

Note: Dash in table indicates US$0 when additional costs are not included or that information was not available.
[a] For aggregate calculations, this was applied as "measured" costs.

2.6. Currency conversion

All costs were converted to 2010 U.S. dollars using two adjusting factors: exchange rate of local currency (LCU) to U.S. dollars at 31 December of the year of the cost report (available in OANDA[1]), and the consumer price index constructed from the annual inflation database of the World Bank for each country. When the study included a group of countries, an average consumer price index per year was estimated to adjust the price to 2010 US$.

3. Results

Fig. 1 shows the number of articles identified at each step of the review process. Most articles were found through the PubMed (MEDLINE) database. In the first stage of the process, 246 articles on rotavirus and 485 on pneumococcal vaccine evaluation were identified, but in subsequent steps that number was reduced to 79 studies evaluating the cost-effectiveness of rotavirus ($n = 43$ (8–50)) or pneumococcal ($n = 36$, (51–86)) vaccines.

3.1. Rotavirus vaccine

Forty-three studies were included in this analysis (Table 2). Publication dates ranged from 1995 to 2010 but most studies ($n = 38$) were published between 2007 and 2010. Over half of the articles analyzed cost-effectiveness of rotavirus vaccine in developed economies ($n = 23$) and analysis from developing or less-developed economies amounted to 20 papers. For several countries more than one study reported on CEAs for rotavirus vaccine introduction: there were five studies for the United States (published in 1995, 1998, 2007, and 2009) [8,9,18,39,42]; three studies for the United Kingdom (2007, 2008, 2009) [15,23,34]; three

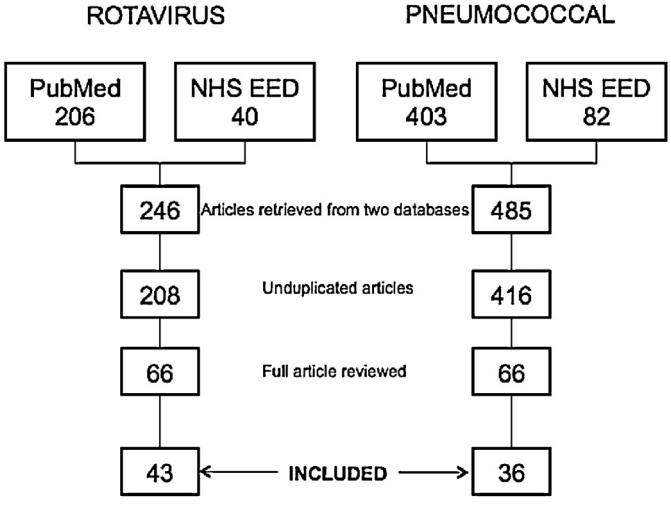

Fig. 1. Review process of articles on cost-effective analysis of rotavirus and pneumococcal vaccines using PubMed and NHS EED databases.

[1] http://www.oanda.com/currency/converter/.

studies for France (2007, 2008) [13,24,25]; two studies for Italy (2009) [32,37], two studies for Australia (1999, 2007) [11,16]; two studies for Brazil (2008) [19,21]; and two studies for Mexico (2008, 2009) [20,30].

Fourteen of the 43 studies focused on economic analysis for the monovalent vaccine, 13 considered both monovalent and pentavalent vaccines, 5 analyzed only pentavalent, and 2 were on the rhesus rotavirus tetravalent (RRV-TV) vaccine. Nine studies did not define the type of rotavirus vaccine evaluated.

Most studies ($n = 32$) considered incremental non-vaccine costs, while nine did not. Two studies did not specify which costs were analyzed. Seventeen papers (40%) assumed an incremental non-vaccine cost per dose of between US$0.27 and US$10.52 (one of them did not specify the value). Of 15 studies that measured incremental non-vaccine costs, 7 used estimates from previous studies, and only 1 used a bottom-up costing approach.

For studies on developed economies (Australia, Belgium, Finland, France, Israel, Netherlands, Republic of China [Taiwan], the United Kingdom, and United States) the average additional rotavirus vaccination costs were US$7.22 (median US$6.39). For studies on individual developing economies (Brazil, China, India, Indonesia, Kenya, Kyrgyzstan, Malawi, Mexico, Peru, Thailand, Uzbekistan, and Vietnam) and groups of developing economies (Asia, Latin America and the Caribbean, and Global Alliance for Vaccines and Immunization [GAVI]-eligible countries) the mean non-vaccine cost was US$1.36 (median US$0.74) (see Table 4).

Among those studies using assumed non-vaccine costs, the median cost was US$0.67 for developing countries and US$7.17 for developed countries, while for studies using measured costs it was US$0.77 and US$5.39, respectively (Table 4).

3.2. Pneumococcal vaccine

Thirty-six studies were included in the analysis of pneumococcal vaccine (Table 3). Publication dates ranged from 2000 to 2010, but more than half ($n = 20$) were published between 2007 and 2010. Thirty of the 36 papers presented data from pneumococcal vaccine evaluations carried out in developed economies. Developing economies were represented by six papers including two that combined results from GAVI-eligible or Latin American countries. Several developed countries had more than one paper with CEA on pneumococcal vaccines: seven papers discussed CEA in the United States (published in 2000, 2006, 2009, and 2010) [51,52,65,76,78,85,86]; three studies were CEA for the United Kingdom (2003, 2004, 2005) [58,61,63]; three for Germany (2003, 2008, 2009) [55,70,73], three for Canada (2003, 2009) (53, 57, 77), two for Italy (2005, 2009) [62,74]; two studies for the Netherlands (2003, 2010) (54, 84); and two studies for Sweden (2008, 2009) [68,79].

Fourteen studies (39%) presented some kind of incremental non-vaccine costs estimation; seven of these (19% of total) used estimations from previous studies. Ten studies (28%) assumed incremental non-vaccine costs between US$1.35 and US$11.14. Five studies (14%) did not consider additional vaccination costs, and three (8%) did not specify which vaccination costs were included. For developed economies (Australia, Canada, Finland, Germany, Hong Kong SAR, Ireland, Italy, Netherlands, Switzerland, United Kingdom, and United States) the average non-vaccine cost was US$8.72 (median US$8.71). In developing economies (including groups of GAVI-eligible and Latin American and Caribbean countries and Brazil, Chile, Gambia, and Uruguay) the mean non-vaccine cost was US$1.09 (median US$1.27).

Among those studies using assumed costs for additional non-vaccine cost, the median cost was US$1.39 for developing economies and US$4.61 for developed ones, while for studies that used measured costs the figures were US$0.80 and US$10.05, respectively (Table 4).

4. Discussion

This study focused on the approaches used by researchers to estimate the incremental non-vaccine costs of introducing new vaccines. Incremental non-vaccine costs refer to those aside from vaccine cost and include personnel, cold chain expansion, vaccine wastage, staff training, social mobilization, monitoring, surveillance, and others. Our results show that most studies consider some incremental non-vaccine costs in addition to vaccine procurement but the approaches to estimate them vary widely and as a result the incremental cost and cost-effectiveness results also vary. Only one study [77] performed a formal micro-costing evaluation of non-vaccines costs, but these costs were not reported separately. In addition, the Gambia pneumococcal CEA [82] used results from a costing/financing tool (comprehensive multi-year plan, or cMYP) to consider the non-vaccine cost. Only one study [50], included international freight or insurance as part of the vaccine procurement cost, and only two articles on pneumococcal vaccine [51,55] included vaccine taxes within the vaccine acquisition cost.

We found differences in the measured values depending on the approach used by researchers, but we also found differences between developed and developing countries. Costs tended to be lower where researchers assumed a fixed portion of the vaccine price as an estimation of the incremental non-vaccine costs for introduction compared with studies that used measured costs. However, most of the cost measurement methods only considered personnel time and ignored other cost items. Moreover, the incremental non-vaccine costs tend to be higher in developed than in developing countries. For example, the cost of rotavirus vaccine introduction in developed countries was estimated on average to be almost eight times higher than in developing countries. When we further stratified developing countries by income level, according to the World Bank classification (low-, lower-middle-, and upper-middle-income), the incremental non-vaccine cost considered for rotavirus vaccine were similar (see Supplemental Tables 1 and 2), while for pneumococcal there are

Table 4
Medians and IQRs of non-vaccine costs included in studies with cost-effectiveness analysis of rotavirus and pneumococcal vaccines (2010 U.S. dollars).

Vaccine	Median costs [IQR] in developing economies		Median costs [IQR] in developed economies	
Rotavirus	Median costs [IQR] $0.74 (IQR: $0.58–1.32; $n = 18$)		Median costs [IQR] $6.39 (IQR: $4.22–10.52; $n = 13$)	
	Assumed costs: $0.67 (IQR: $0.57–1.92; $n = 11$)	Measured costs: $0.77 (IQR: $0.67–1.30 $n = 7$)	Assumed costs: $7.17 (IQR: $6.28–10.52; $n = 5$)	Measured costs: $5.39 (IQR: $3.50–10.70; $n = 8$)
Pneumococcal	Median costs [IQR] $1.27 (IQR: $0.99–1.37; $n = 4$)		Median costs [IQR] $8.71 (IQR: $4.92–11.04; $n = 22$[a])	
	Assumed costs: $1.39 (IQR: $1.37–1.40; $n = 2$)	Measured costs: $0.80 (IQR: $0.61–0.99; $n = 2$)	Assumed costs: $4.61 (IQR: $4.01–7.00; $n = 8$)	Measured costs: $10.05 (IQR: $8.75–12.24; $n = 12$)

IQR: interquartile range; n: number of studies.

[a] Two papers reported non-vaccine costs but did not specify the calculation method.

not enough studies for comparison between low-, lower-middle-, and upper-middle-income countries.

In general, the approach used to estimate additional vaccination cost seems to be perfunctory. For several countries where more than one study on the same vaccine has been published, it was observed that the value assumed for non-vaccine costs remains unchanged across several years. For instance, there are four studies on rotavirus vaccine in the United States [9,18,39,42] that use the same non-vaccine value of US$10 per dose for different years between 1998 and 2009 without taking into account that the purchasing power per dollar would change over a 11-year period. We extrapolated those values to 2010 U.S. dollars, finding that for the earliest study (1998) [9] US$10 would mean a much higher cost than for the latest one (US$13.84 vs. $10.52 in 2010 dollars). In other cases, different values for the same item were used for CEA carried out for the same country. In the United Kingdom, one study on rotavirus vaccine published in 2007 assigned a £5.00 value to the nurse time for applying a dose of vaccine while a second study, published in 2009, valued the time at £2.00 [15,34].

There were also examples of differences between estimations for developing economies. In Mexico, a CEA study on rotavirus vaccine published in 2008 [20] included an overall estimation of US$0.50 per dose for non-vaccine costs while a second study in 2009 [30] valued the incremental non-vaccine costs at US$2.30 per dose.

We reviewed how authors addressed vaccine wastage, another factor that increases the cost of the immunization program and that has a negative impact on the cost-effectiveness of the intervention. Of 79 articles only 20 considered some degree of wastage: 15 CEAs on rotavirus vaccine and 5 on pneumococcal conjugate vaccine (PCV). In only one of those 20 studies the authors did not consider incremental non-vaccine costs of the vaccine [80]. The cost due to wastage was impossible to isolate from the incremental non-vaccine costs in two cases [26,29], and in both cases the incremental non-vaccine cost considered was less than US$1 per dose. The wastage rate assumed in 14 of 20 studies was 10% of the vaccine. More accurate wastage rates should be included in the model to correctly estimate cost-effectiveness, and a costing tool of the EPI should also include these rates.

Most studies showed that rotavirus or pneumococcal immunizations are cost-effective strategies and probably the best interventions to prevent mortality from diarrheal disease or pneumonia in children. However, these vaccines are expensive and whether to introduce them into countries' immunization schedules is a challenging issue for decision-makers, particularly where there are severe constraints on financing. Ignoring additional EPI costs in cost-effectiveness analysis of new vaccines may lead to significant errors in the estimations of the incremental cost-effectiveness ratio (ICER), probably overestimating the value of introducing a vaccine. The real costs of vaccine introduction will be underestimated if aspects like taxes, freight, cargo insurance, cold chain expansion, promotion activities, or personnel are not properly measured.

An example of the differences arising when considering non-vaccine costs is found in two independent studies carried out in Mexico to assess the cost-effectiveness of rotavirus vaccine. One of them, conducted by a governmental institution, assumed incremental non-vaccine costs of US$15.00 per complete schedule (almost 50% of the vaccine cost) while the second one, sponsored by a multinational pharmaceutical company, assumed only US$1.0 per complete schedule in incremental non-vaccine costs. There was also a wide difference between the ICER reported by both studies: the government study reported US$4233 per life-year saved, while the company study was US$1100 per DALY averted. It is worth noting that, even though cost per life-year saved and cost per DALY represent different outcome measures, since rotavirus is an acute illness with no sequelae, these two measures can be compared, and the difference is relevant in this case. Though the studies also differed in the number of hospitalizations and medical consultations averted, with the industry-sponsored study reporting a substantially higher decrease in both indicators, we estimated that at least 25% of the difference between ICERs was the result of differences in incremental non-vaccine cost assumptions.

Several cost-effectiveness analyses on pneumococcal and rotavirus vaccines have been published since we finished the review for the present study. Their results are not included here, but their calculations for costs other than vaccine procurement are similar to those in our review. Four new studies reported results for rotavirus vaccines. A study in Ireland estimated a higher incremental non-vaccine "assumed" cost of US$9.16 (USD$2010) [87] while for developing countries incremental non-vaccine costs were US$0.08 for Vietnam [88], US$0.29 for Uganda [89], and US$0.34 for India [90]. For pneumococcal vaccines there were five recent studies, all of them from developing countries. They show similar figures to those presented in our results with the highest value for incremental non-vaccine costs measured in Argentina (2009 US$1.40 per dose) [91]. This was in contrast to two papers in Colombia where non-vaccine costs were "assumed" (less than US$1 for PPV23 in adults and US$1.07 per PCV dose in children) [92,93]. A study on Uganda assumed an incremental non-vaccine cost of US$0.29 [89], while a study on Malaysia did not consider incremental non-vaccine costs [94].

WHO has made specific recommendations on how to evaluate costs of immunization programs when countries are planning the introduction of new vaccines. According to those guidelines, economic costs of vaccination activities should be considered when performing a CEA to assess the benefits of new vaccines. However, the present review shows that vaccination costs considered in the studies are usually financial costs, only including prices, and not considering economic costs such as the opportunity cost, resulting in an underestimation of the incremental non-vaccine costs. Recently, Hutubessy et al. [95] made an appeal to improve the quality of the CEA tools used to support decisions for introducing new vaccines. The authors, however, focused on the structure of the models but not on the quality of the economic information related to EPI activities.

The failure to carefully consider incremental non-vaccine costs is probably a consequence of the scarcity of valid information on the costs of running a national, regional, or local immunization program. Our search for studies on this issue in the international literature yielded few results, which indicates that estimating real economic costs of EPI is a neglected issue in public health. The development of new tools and methodologies to assess real costs of EPI in developed and developing countries, as proposed by PAHO's ProVac Initiative and others, should be a priority among the efforts to improve the quality of CEA, especially in countries where resource constraints are apparent. Ultimately, ignoring the EPI costs may result in miscalculation of financing requirements for the introduction of new vaccines.

Conflict of interest statement

The authors affirm that there is no conflict of interest in the publication of this study.

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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.2013.05.064.

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Review

Estimating health service utilization for treatment of pneumococcal disease: The case of Brazil

A.M.C. Sartori[a,*], C.G. Novaes[a], P.C. de Soárez[b], C.M. Toscano[c,1], H.M.D. Novaes[b]

[a] Clínica de Moléstias Infecciosas e Parasitárias, Hospital das Clínicas, São Paulo, Brazil
[b] Departamento de Medicina Preventiva, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[c] Departamento de Saúde Comunitária, Instituto de Patologia Tropical e Saúde Pública, Universidade Federal de Goiás, Goiânia, Brazil

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ABSTRACT

Background: Health service utilization (HSU) is an essential component of economic evaluations of health initiatives. Defining HSU for cases of pneumococcal disease (PD) is particularly complex considering the varying clinical manifestations and diverse severity.
Objective: We describe the process of developing estimates of HSU for PD as part of an economic evaluation of the introduction of pneumococcal conjugate vaccine in Brazil.
Methods: Nationwide inpatient and outpatient HSU by children under-5 years with meningitis (PM), sepsis (PS), non-meningitis non-sepsis invasive PD (NMNS), pneumonia, and acute otitis media (AOM) was estimated. We assumed that all cases of invasive PD (PM, PS, and NMNS) required hospitalization. The study perspective was the health system, including both the public and private sectors. Data sources were obtained from national health information systems, including the Hospital Information System (SIH/SUS) and the Notifiable Diseases Information System (SINAN); surveys; and community-based and health care facility-based studies.
Results: We estimated hospitalization rates of 7.69 per 100,000 children under-5 years for PM (21.4 for children <1 years of age and 4.3 for children aged 1–4 years), 5.89 for PS (20.94 and 2.17), and 4.01 for NMNS (5.5 and 3.64) in 2004, with an overall hospitalization rate of 17.59 for all invasive PD (47.27 and 10.11). The estimated incidence rate of all-cause pneumonia was 93.4 per 1000 children under-5 (142.8 for children <1 years of age and 81.2 for children aged 1–4 years), considering both hospital and outpatient care.
Discussion: Secondary data derived from health information systems and the available literature enabled the development of national HSU estimates for PD in Brazil. Estimating HSU for noninvasive disease was challenging, particularly in the case of outpatient care, for which secondary data are scarce. Information for the private sector is lacking in Brazil, but estimates were possible with data from the public sector and national population surveys.

Contents

* Corresponding author at: Rua Jose Maria, Lisboa, 695/91, São Paulo, SP 01423-001, Brazil. Tel.: +55 11 2661 7517; fax: +55 11 2661 7517.
E-mail addresses: ana.sartori@hc.fm.usp.br, anasartori@gmail.com (A.M.C. Sartori).
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1. Introduction

Estimating health service utilization (HSU) is an essential part of economic evaluations of health initiatives. Developing HSU estimates that capture the variability in clinical practice and health service access in the population is a challenge for countries performing economic analyses relating to vaccine introduction decisions. The methods used to identify, collect, and quantify HSU may have a significant impact on the results of an economic evaluation and the usefulness of economic evaluations in the decision-making process [1].

Estimating HSU for cases of pneumococcal disease (PD) provides a good example of the challenges faced in arriving at accurate and representative estimates. *Streptococcus pneumoniae* is implicated in several clinical syndromes also caused by other pathogens. Clinical manifestations of pneumococcal infection include more serious and less frequent invasive pneumococcal diseases (IPDs); these life-threatening diseases, such as meningitis, sepsis, pneumonia with bacteremia or pleural effusion, peritonitis, and bone and joint infection, are mostly treated in hospitals. Pneumococcus may also cause less serious and more frequent noninvasive diseases, such as pneumonia without bacteremia, bronchitis, sinusitis, and otitis media, usually treated in outpatient care [2].

Taking Brazil as a case study, we describe the process of estimating nationwide HSU due to PD in children under-5. We present methods for estimating HSU; discuss the concepts, strategies, sources, calculations, and results obtained; and describe the main challenges and decisions as well as their consequences. The estimates presented here were originally developed as part of an economic evaluation of the introduction of pneumococcal conjugate vaccine (PCV) into the Brazilian National Immunization Program [3].

2. Brazil and its health care system

Brazil covers 8.5 million km^2 (47% of South America) and is the world's fifth most populous country, with an estimated 2010 population of 190,732,694 and 15,687,927 children under-5. The country is divided into five geographical regions with differing demographic, economic, social, cultural, and health conditions [4].

The Brazilian health care system has two sectors: the public sector (*Sistema Único de Saúde* [SUS]), with health services financed by the government at the federal, state and municipal levels, and the private sector, with services financed by public or private funds. The public and private health sectors are distinct but interconnected, and private health care services may also provide care for SUS enrollees [4,5]. Access to SUS services is universal; approximately 20–25% of the population is also covered by private insurance plans. SUS and private-sector participation in health care varies according to age, education, income, region of the country, type of care setting, and type of treatment [6,7]. In parallel with the expansion of SUS in the past 20 years, national health information systems have been developed and continuously improved [8,9].

3. Methods

3.1. Clinical syndromes and etiologies of interest

We estimated HSU associated with pneumococcal meningitis (PM), pneumococcal sepsis (PS), non-meningitis non-sepsis IPD (NMNS), pneumonia, and acute otitis media (AOM). All-cause "radiologically confirmed pneumonia" (RCP) and all-cause AOM were considered the clinical syndromes of interest. In the case of invasive diseases, for which etiology can be established in clinical practice, we considered pneumococcal-specific disease.

3.2. Indicators of health service utilization

The HSU indicators identified as useful for an economic evaluation of PCV programs and considered in this study are presented in Table 1.

3.3. Target population and study period

In 2004, an estimated total of approximately 16.3 million children aged <5 resided in Brazil (3,276,676 children <1 year of age and 13,083,991 children aged 1–4 years) [10].

3.4. Unit of study

The unit of study was the health care system, including both the public (SUS) and private sectors. Morbidity characteristics were assumed to be similar in the two sectors [7].

3.5. Data sources

The main sources of data used in this study, including their characteristics, coverage, and the information available, are presented in Table 2 [10–15].

3.6. Codes used in health information system database searches

Our search of the Hospital Information System (*Sistema de Informações Hospitalares* [SIH/SUS]) and Notifiable Diseases

Information System (*Sistema de Informação de Agravos de Notificação* [SINAN]) databases was based on *International Classification of Diseases* (10th revision; *ICD-10*) codes [16]: pneumococcal meningitis (G00.1), pneumococcal sepsis (A40.3), *S. pneumoniae* as the cause of disease (B95.3), all-cause pneumonia (J12–J18), and otitis media and mastoiditis (H65–H67, H70–H71).

Etiology is not confirmed in all bacterial meningitis (BM) cases, and data on meningococcal meningitis (A39.0), *Haemophilus* meningitis (G00.0), streptococcal meningitis (G00.2), staphylococcal meningitis (G00.3), other BM (G00.8), and unspecified BM (G00.9) were also collected to estimate the proportions of BM with identified pathogens and assess the need of modeling unspecified BM data to recalculate PM case estimates. Data on unspecified streptococcal sepsis (A40.9) and unspecified sepsis (A41.9) were also collected.

Diagnostic and therapeutic procedures are coded in the SIH/SUS according to the Table of Procedures, Medications, Orthoses, Prostheses and Special Materials (*Tabela Unificada de Procedimentos, Medicamentos, Órteses, Próteses e Materiais Especiais do SUS*), a reference table used in payment for delivered patient care. Data on otoscopic microsurgery/myringotomy with equalization tube placement were collected by the authors in SIH/SUS, complementing data on HSU for treatment of complicated AOM.

3.7. Ethical approval

This study was approved by the Ethical Committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. The data extracted from the SIH and SINAN databases had no identifiers.

Table 1
Health service utilization indicators that can be useful for economic evaluations of pneumococcal vaccines.

HSU indicators used in complete economic evaluation analyses
- Numbers/proportions of hospital admissions per episode of clinical syndrome[a], per provider[b], and, if appropriate, by level of care[c]
- Numbers/proportions of cases treated in outpatient settings per episode of clinical syndrome[a], per provider[b] and, if appropriate, by level of care[d]

HSU indicators used in cost-of-illness studies
- Length of stay in hospital per clinical syndrome[a], per provider[b], and, if appropriate, by level of care[c]
- Numbers of medical visits in outpatient facilities per episode of disease per clinical syndrome[a], per provider[b], and, if appropriate, by level of care[c]
- Type and number of diagnostic tests (chest radiographies, lumbar punctures, blood cultures, other) per clinical syndrome[a], per provider[b], and, if appropriate, by level of care[c,d]
- Type and number of therapeutic procedures (surgical procedures for complicated acute otitis media, such as tympanostomy and aspiration or Eustachian tube inflation, tympanostomy with pressure-equalizing tube insertion; surgical procedures for complicated pneumonia, such as thoracocentesis, chest tube drainage, thoracoscopy, decortication; mechanical ventilation use; oxygen use) per clinical syndrome[a], per provider[b], and, if appropriate, by level of care[c,d]
- Pharmacy: numbers/proportions of antibiotic prescriptions, numbers/proportions of cases for which antibiotic change was needed (treatment failure), and other drugs, such as antipyretics, per clinical syndrome[a] per provider[b], and, if appropriate, by level of care[c,d]
- HSU due to long-term sequelae (neurological, hearing loss): numbers of medical visits, numbers and types of other health professional visits (physiotherapist, speech therapist, nurse), and numbers of diagnostic tests and therapeutic procedures, such as cochlear implant, per provider[b], and, if appropriate, by level of care[d]

[a] Clinical syndrome: meningitis, sepsis, pneumonia, and acute otitis media.
[b] Provider: public, private, social security, and other.
[c] Levels of care: primary, secondary, and tertiary.
[d] Type of outpatient facility: emergency room, outpatient specialized clinic, primary care, etc.

4. Results

4.1. Hospitalizations

The numbers of hospital admissions due to PD and related syndromes and the number of all-cause hospitalizations among children under - 5 who were registered in the SIH/SUS in 2004 are presented in Table 3.

4.2. Pneumococcal meningitis

Etiology was confirmed in only 40% of BM cases among children under-5 hospitalized in the public sector (Table 3). *S. pneumoniae* was responsible for 34.1% (209/613) and 27.4% (180/657) of BM cases with identified pathogens in infants (<1 year) and children aged 1–4 years, respectively. Assuming the same proportion of PM among cases of "unspecified BM," we estimated that pneumococcus was responsible for another 325 (34.1% of 954 cases) meningitis cases in infants and 254 (27.4% of 929) cases in children aged 1–4 years, resulting in a total of 534 infants and 434 children aged 1–4 years hospitalized for PM in the public sector.

Seventy-seven percent of hospitalizations of children under-5 years occurred in the public sector [17]. Thus, these numbers underestimate total PM admissions nationwide. To represent the participation of the private sector (23%), we estimated that there were an additional 159 hospitalizations for PM in infants and 129 cases in children aged 1–4 years, totaling 1256 episodes (Table 4).

The numbers of meningitis cases registered in SINAN were used to double-check the estimates derived from SIH/SUS. The estimated number of PM cases according to SINAN was 15% greater than the SIH-based estimates. Since data on other clinical syndromes are not available in SINAN, we chose to base our PM estimates on SIH data.

4.3. Pneumococcal sepsis

Etiology was confirmed for most cases of sepsis in SUS-hospitalized children under-5 years (Table 3), and no correction for unspecified sepsis was made. Among children under-5 hospitalized for sepsis, 4.74% were hospitalized for pneumococcal sepsis (4.5% of children under-5 and 5.39% of children aged 1–4 years). Considering the private sector, there were an additional 156 hospitalizations of infants and 65 hospitalizations of children aged 1–4 years, totaling 962 hospitalizations for PS (Table 4).

4.4. Non-meningitis non-sepsis invasive pneumococcal disease

The numbers of SUS hospitalizations of children under-5 years of age with *S. pneumoniae* as the cause (*ICD-10* code B95.3) are presented in Table 3. An additional 41 hospitalizations of infants and 109 hospitalizations of children aged 1–4 years were estimated in the private sector, resulting in a total of 654 hospitalizations for NMNS (Table 4).

On the basis of the estimated total number of public- and private-sector hospitalizations for each clinical syndrome and Brazil's population figures for 2004, we calculated annual age group-specific hospitalization rates for PM, PS, NMNS, and all IPD (Table 4).

4.5. All-cause pneumonia

All-cause pneumonia (*ICD-10* codes J12–J18) accounted for 21.8% and 24.8% of SUS hospitalizations among children <1 and 1–4 years of age, respectively (Table 3). Pneumococcus was identified as the causal pathogen in only 1.3% of children under-5 hospitalized for pneumonia (Table 3). There were another 106,060 estimated

Table 2
Main sources of data on health service utilization for treatment of pneumococcal disease used in this study.

Variable of interest	Source of data	Data coverage	Characteristics of data source	Available data
Hospital admissions and procedures (myringotomy with equalization tube placement)	Hospital Information System (SIH/SUS, *Sistema de Informações Hospitalares*) [11]	Public system (SUS) based	This nationwide administrative database was established for analysis and payment of services provided by public and private hospitals contracted by SUS. More than 11 million admissions at primary, secondary, and tertiary hospitals are recorded in SIH annually. Medical records are the primary source of data. Data are collected through a hospital admission form filled in by the hospital and sent monthly to the local health authority, which is responsible for certifying the accuracy of the information before transmitting it to the regional and national levels. At the national level, data are processed and consolidated by SUS' Department of Informatics (DATASUS). The database is continuously updated. SIH covers approximately 70% of all hospitalizations in the country, with variations by age group and region of the country. The SIH database without identifiers is open and free for use in the public domain [8,9,12]	• Hospital identification • Patients' demographic characteristics • *ICD* discharge diagnoses • Duration of admission (in days) • Admission to intensive care unit • Diagnostic and therapeutic procedures • Outcomes (discharge, death) • Costs (reimbursement paid by the government to the contracted hospitals, including all diagnostic tests, procedures, and treatments performed during hospitalization)
Meningitis cases	Notifiable Diseases Information System (SINAN, *Sistema de Informação de Agravos de Notificação*) [13]	Population based	The national epidemiologic surveillance system covers the entire country. Data are collected through an individual notification form filled in by health professionals or specialized units in health services when a patient has a suspected clinical condition included in the national list of reportable diseases. All levels of health care services in both the public and private sectors report cases to the epidemiologic surveillance system. This information is registered in SINAN and monitored by local, state, and national health authorities. The Health Surveillance Secretariat (*Secretaria de Vigilância em Saúde*, SVS) of the Ministry of Health processes and consolidates data sent continuously by the other levels. The SINAN database without identifiers is open and free for use in the public domain [8,9,12]	• Patients' demographic characteristics • Epidemiological, clinical, and laboratorial data • Diagnoses • Etiology • Outcomes
Cases treated in outpatient facilities	Review of national peer-reviewed and gray literature	Health care service-based and community-based studies	The search was performed in the PubMed and LILACS databases using the keywords "pneumococcal disease" or "pneumococcal meningitis" or "pneumococcal sepsis" or "pneumonia" or "acute otitis media" and "Brazil." Unpublished research was obtained from a Brazilian thesis database	• Hospitalization rates among children under-5 with pneumonia diagnosed in public emergency rooms, by age • Proportion of children under-5 seen in emergency rooms with clinical suspicion of pneumonia who undergo chest radiography • Rates of radiographic confirmation of pneumonia among children who undergo radiography • Health service utilization by children with neurological sequelae
Public- and private-sector participation in health care	National Survey of Household Samples (PNAD, *Pesquisa Nacional por Amostras de Domicilio*) [17]	Population based	The annual PNAD is conducted by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*, IBGE) in a nationally representative sample of Brazilian households. More detailed data on health are periodically collected (health supplements were included in the 2003 and 2008 surveys) [7,14]	• Demographic and socioeconomic characteristics of the population (education, employment, income, housing, social security, migration, fertility, nutrition) • Access to health care, utilization of health services, health insurance plans, medication use and access, financing of health care (health supplements)
Demographic data	National census, mapping of urbanized areas [15]	Population based	Censuses are conducted every 10 years by IBGE. Yearly population estimates are calculated by IBGE based on fertility, mortality, and migration rates.	• Brazilian population figures, by age • Proportion of the Brazilian population living in urban areas and proportion of the urban population living in medium and large cities (100,000 or more inhabitants)

Table 3
Numbers of hospital admissions of children under-5 due to pneumococcal disease and related syndromes in the public health system, according to clinical presentation, etiology, and age group: Brazil, 2004.

Clinical presentation (*ICD-10*)	Age (years)		
	<1	1–4	<5
Pneumococcal meningitis (G00.1)	209	180	389
Meningococcal meningitis (A39.0)	121	236	357
Haemophilus meningitis (G00.0)	95	63	158
Meningitis due to other bacteria (G00.2, G00.3, G00.8)	188	178	366
Bacterial meningitis, unspecified (G00.9)	954	929	1883
Pneumococcal sepsis (A40.3)	522	219	741
Streptococcus sepsis, unspecified (A40.9)	4	3	7
Sepsis, unspecified (A41.9)	58	11	69
All-cause sepsis (A40–A41)	11,574	4061	15,635
S. pneumoniae as cause of disease (B95.3)	137	367	504
Pneumococcal pneumonia (J13)	2048	2690	4738
All-cause pneumonia (J12–J18)	145,424	209,072	355,072
All-cause otitis media and mastoiditis (H65–H67, H70–H71)	11	1581	1592
Myringotomy with equalization tube placement	NA	NA	414
All-cause hospitalizations	667,227	843,984	1,511,211

Source: SIH/SUS, 2004.
Note: NA = not available.

Table 4
Estimated numbers and rates of hospitalizations of children under-5 for invasive pneumococcal diseases (pneumococcal meningitis, pneumococcal sepsis, non-meningitis nonsepsis IPD, and all IPD) in the public and private health systems: Brazil, 2004.

Clinical syndrome	Health care sector	Age (years)		
		<1	1–4	<5
Pneumococcal meningitis	Public[a]	534	434	968
	Private[b]	159	129	288
	Both	693	563	1256
Pneumococcal meningitis hospitalization rate (per 100,000)	Both	21.40	4.30	7.69
Pneumococcal sepsis	Public[c]	522	219	741
	Private[b]	156	65	221
	Both	678	284	962
Pneumococcal sepsis hospitalization rate (per 100,000)	Both	20.94	2.17	5.89
Nonmeningitis nonsepsis IPD	Public[c]	137	367	504
	Private[b]	41	109	150
	Both	178	476	654
Nonmeningitis nonsepsis IPD hospitalization rate (per 100,000)	Both	5.50	3.64	4.01
All IPD	Public	1193	1020	2213
	Private	356	303	659
	Both	1549	1323	2872
IPD hospitalization rate (per 100,000)	Both	47.27	10.11	17.59

[a] *Source*: SIH/SUS. Estimated numbers including unspecified bacterial meningitis attributable to pneumococcus.
[b] Estimates based on the 2003 National Household Sample Survey, which showed that 77% of all-cause hospitalizations among children under-5 occurred in the public health sector.
[c] *Source*: SIH/SUS.

private-sector admissions of children under-5 for all-cause pneumonia, totaling 461,132 hospitalizations (Table 5).

4.6. Radiologically confirmed pneumonia in hospital settings

Estimates of RCP were based on the estimated number of hospitalizations for all-cause pneumonia (retrieved from SIH/SUS and expanded to include patients cared for in the private sector), the proportion of children under-5 with clinical suspicion of pneumonia who underwent a chest X-ray, and the proportion of RCP among children who underwent an X-ray; these data were obtained from the national literature. Brazilian health service-based studies conducted in public emergency rooms in medium and large cities in different regions have shown that 89–100% of children under-5 with clinical suspicion of pneumonia have undergone chest X-rays [18–21] and that pneumonia has been confirmed in 74–98% of these children [18–21].

We assumed that chest radiographies would be performed for 95% of children under-5 hospitalized for pneumonia and that the diagnosis would be confirmed in 85%. Therefore, 80% of children under-5 hospitalized for all-cause pneumonia would have RCP and the other 20% would have clinically diagnosed pneumonia. Considering the estimated numbers of hospitalizations for all-cause pneumonia in the public and private health sectors, we estimated that there would be 368,905 hospital admissions for RCP (Table 5); the remaining 92,227 admissions were assumed to be clinically diagnosed pneumonia.

4.7. Acute otitis media

The numbers of SUS hospitalizations of children under-5 for all-cause AOM and mastoiditis are presented in Table 3. Another 475 episodes were estimated in the private sector (3 infants and 472 children aged 1–4 years), totaling 2067 hospitalizations for AOM and mastoiditis (14 among infants and 2053 among children aged 1–4 years).

4.8. Myringotomy with equalization tube placement

We identified 414 otoscopic microsurgery procedures (myringotomy with equalization tube placement) in children under-5 in SIH/SUS. Data from the National Household Sample Survey (*Pesquisa Nacional por Amostra de Domicilios* [PNAD]) show that 52% of ambulatory surgeries among children under-5 of age occur in the public sector [17]. An additional 382 ear tube surgeries were estimated in the private sector, resulting in a total of 796 procedures.

Data on mean length of SUS hospitalization per clinical syndrome were also retrieved from the SIH database and are shown in Table 6.

4.9. Outpatient care

All meningitis, sepsis, and NMNS cases were assumed to require hospitalization. On the basis of expert opinion, two outpatient medical visits per illness episode were assumed.

4.10. All-cause pneumonia

Estimates of the numbers of all-cause pneumonia cases treated in outpatient facilities were based on the numbers of hospitalizations for all-cause pneumonia and the proportions of

Table 5
Estimated numbers of all-cause pneumonia and radiologically confirmed pneumonia cases among children under-5 treated in hospitals and outpatient health care facilities in the public and private sectors: Brazil, 2004.

Pneumonia type and health care setting	Health care sector	Age (years)		
		<1	1–4	<5
All-cause pneumonia				
Hospitals	Public[a]	145,424	209,648	355,072
	Private[b]	43,438	62,622	106,060
	Both	188,862	272,270	461,132
Outpatient facilities	Public[c]	218,136	628,944	847,080
	Private[d]	55,284	161,028	216,312
	Both	273,420	789,972	1,063,392
All	Public[c]	363,560	838,592	1,202,152
	Private[d]	98,722	223,650	322,372
	Both	462,282	1,062,242	1,524,524
Incidence rate (per 1000)	Both	142.8	81.2	93.4
Radiologically confirmed pneumonia[e]				
Hospitals	Both	151,089	217,816	368,905
Outpatient facilities	Both	82,026	236,992	319,018
All	Both	233,115	454,808	687,923
Incidence rates (/1000)	Both	71.1	34.8	42.2

[a] *Source*: SIH/SUS.
[b] Estimates of hospitalizations in the private sector were based on the 2003 National Household Sample Survey, which showed that 77% of all-cause hospitalizations among children under-5 occurred in the public health sector.
[c] Estimates of pneumonia cases treated in public-sector outpatient facilities were based on hospitalization rates of children diagnosed with pneumonia in public emergency rooms derived from health care facility-based studies: 40% among infants and 25% among children aged 1–4 years.
[d] Estimates of pneumonia cases treated in private-sector outpatient facilities were derived from a survey that showed that rates of hospitalization among children <5 years of age were higher in the private sector than in the public sector. Thus, hospitalization rates in the private sector were assumed to be 44% for infants and 28% for children aged 1–4 years.
[e] Radiologically confirmed pneumonia was estimated as a subset of all-cause pneumonia cases, considering the proportions of children under-5 with clinical suspicion of pneumonia who undergo a chest X-ray and the proportions of radiologically confirmed pneumonia among children with an X-ray.

Table 6
Mean hospitalization duration per episode among children under-5 years of age resulting from invasive pneumococcal diseases in the public health system, according to clinical syndrome and age: Brazil, 2004.

Clinical syndrome	Mean duration (days)		
	Children <1 year	Children 1–4 years	Children <5 years
Pneumococcal meningitis	13.3	10.4	11.9
Pneumococcal sepsis	14.7	12.7	14.1
Non-meningitis non-sepsis IPD	5.9	5.5	5.6
All-cause pneumonia (J12–J18)	6.0	4.9	5.4
Otitis media and mastoiditis (H65–H67, H70–H71)	NA	NA	3.5
Myringotomy with tube placement	NA	NA	1.0

Source: SIH/SUS, 2004.
Note: NA = not available.

hospitalization among children under-5 diagnosed with pneumonia in public emergency rooms; these data were found in the Brazilian literature. In Salvador, Bahia, 44% of infants and 28.2% of children aged 1–4 years with pneumonia were hospitalized [18]; in Campinas, São Paulo, 40.2% of infants and 18.3% of children aged 1–4 years were hospitalized [22]; and in Recife, Pernambuco, 54.9% of children aged 6–59 months were hospitalized. This latter study was conducted in a low-income community, and social factors influence the decision of health care workers to hospitalize children. Social disadvantage may result in hospital admissions of less severely ill children in order to guarantee treatment, which may explain the higher hospitalization rates observed in this study [19]. Considering these studies, we assumed that, in the public sector, 40% of infants and 25% of children aged 1–4 years with pneumonia were hospitalized.

Although no data were available on the proportions of children with pneumonia who were hospitalized in the private sector, a household survey conducted in São Luiz, Maranhão (northeastern Brazil), showed that rates of hospitalization among children under-5 were higher in the private sector than in the public sector [23]. PNAD data also showed a higher frequency of hospitalization among children in the private system [6]. Thus, the maximum proportions of hospitalization reported in public emergency rooms were assumed for the private sector: 44% for infants and 28% for children aged 1–4 years.

On the basis of the assumptions described above, the numbers of cases of all-cause pneumonia treated in outpatient public- and private-sector settings were calculated independently for infants and for children aged 1–4 years using the following formula: N outpatient = N hospitalization $\times (1 - pH)/pH$, where N outpatient = number of episodes of all-cause pneumonia treated in outpatient settings, N hospitalization = number of hospitalizations for all-cause pneumonia, and pH = proportion of hospitalizations among children diagnosed with pneumonia in emergency rooms.

The numbers of all-cause pneumonia episodes treated in outpatient settings, in both the public and private sector, and the annual incidence rates of all-cause pneumonia (inpatients and outpatients) are presented in Table 5.

4.11. Radiologically confirmed pneumonia in outpatient settings

Data on rates of chest X-ray performance and radiographic confirmation in children with clinically suspected pneumonia treated in primary health care services are not available in Brazil. Health service-based studies that have analyzed rates of chest radiography and radiographic confirmation of pneumonia have been conducted in medium to large Brazilian cities where access to health care services is relatively good [18,19,22]. In this study we assumed that, in medium and large cities, children under-5 with clinically suspected pneumonia who had been seen in outpatient settings would be referred for a chest X-ray (81% of the Brazilian population lives in urban areas, and 59% of the urban population lives in cities with 100,000 or more inhabitants) [15]. We assumed that 47% (81% × 59%) of children under-5 with clinically suspected pneumonia treated in outpatient settings would undergo chest X-rays. In the Recife study mentioned earlier, confirmatory chest radiography results were more frequently found among hospitalized children (92.7%) than among all children (both inpatients and outpatients) treated for pneumonia (86.1%) [19].

We assumed that radiologically confirmed pneumonia would be diagnosed less frequently (65%) among children seen in outpatient settings than among hospitalized children. Therefore, we assumed that 30% (47% × 65%) of children with pneumonia treated in outpatient settings would have RCP. Considering the estimated total numbers of all-cause pneumonia episodes treated in both public and private outpatient facilities (Table 5), we estimated 319,018

episodes of RCP. The remaining 744,374 cases were assumed to be clinically diagnosed pneumonia. Annual RCP incidence rates are presented in Table 5.

We assumed that all children with RCP would have two medical visits, undergo a chest X-ray, and receive antibiotic therapy, following the Brazilian Society of Pediatrics' guidelines for the treatment of community-acquired pneumonia [24].

4.12. Acute otitis media

There was no available information from the Brazilian health information system or the literature that allowed reliable estimates of HSU for treatment of acute otitis media (AOM) in outpatient facilities. The alternative was to estimate HSU according to the cumulative incidence of all-cause AOM in children under-5. We based our estimates on a Mexican study (the socioeconomic conditions of the Mexican population were considered similar to those of the Brazilian population) that showed a cumulative incidence of 2.34 episodes of AOM per child in the first 5 years of life (1.26 episodes among infants (<1 year of age) and 1.08 episodes among children aged 1–4 years) [25].

We assumed that children with AOM would have two medical visits and would be treated according to the guidelines for AOM treatment of the Brazilian Society of Pediatrics [26].

4.13. Health care utilization for treatment of pneumococcal disease sequelae

The frequency of HSU for treatment of hearing loss and the neurological sequelae of meningitis is largely unknown in Brazil. In this study, HSU for treatment of neurological sequelae of meningitis was estimated on the basis of data on children with cerebral palsy derived from the Disabled Children Assistance Association (*Associação de Assistência à Criança Deficiente*), a Brazilian private nonprofit organization that provides rehabilitation therapy for physically disabled children and adolescents. One medical visit per month; weekly visits to a physiotherapist, speech therapist, occupational therapist, and psychologist; and one orthotic device per year were estimated (personal communication, L.R. Batistella, School of Medicine, Hospital das Clínicas).

No Brazilian data on HSU among children for treatment of hearing loss secondary to meningitis or recurrent AOM were available, and thus HSU for this condition was not considered.

5. Discussion

Estimating HSU for bacterial diseases requires a syndromic approach. The first challenge is to decide which clinical syndromes to include in the analysis. Including all syndromes associated with PD is too burdensome. Analyses should include the most serious but less frequent illnesses (meningitis and sepsis) that require intense HSU for relatively few patients with high costs per case. They should also include less serious but very frequent diseases (pneumonias and AOM) involving lower costs per patient but large population costs.

Another challenge is to determine whether pneumococcal-specific disease or nonspecific disease will be considered for each syndrome. Pneumonia etiology is not usually established in clinical practice. It is accepted that the proportion of pneumonia caused by pneumococcus increases with increasing disease severity. A case definition that incorporates the more severe cases has greater specificity with respect to pneumococcal pneumonia. Chest X-rays are considered the gold standard for diagnosing pneumonia, despite the variability in their interpretation even when standard guidelines are used [27,28]. The efficacy of PCV in protecting against RCP has been established in clinical trials and has been used in economic evaluations of PCV [29–35]. The etiology of AOM is also not usually established in clinical practice, and given that data on the efficacy of PCV against all-cause AOM are available, all-cause AOM can be used in economic evaluations of PCV [30–36].

Our assumption that all patients with IPDs are hospitalized may have led to an underestimation of the number of cases, in that some severe cases may evolve to death in emergency rooms and are not recorded by SIH/SUS. In addition, in Brazil, blood cultures are not routinely collected in feverish children, and the use of antibiotics is very frequent and may compromise the culture results.

As etiology was not identified in most cases of BM, SIH data were modeled to include cases of unspecified BM that could be attributable to pneumococcus. Events in the private sector were estimated according to the distribution of all SUS and private-sector hospitalizations of children younger than 5 years. However, hospitalization rates in the public and private systems may differ by cause of admission [6]. Hospitalizations for severe acute infectious diseases, such as meningitis, may be more frequent in the public sector, and we may have overestimated IPD hospitalizations in the private sector.

Data retrieved from the SINAN database, which covers both the public and private sectors, showed estimates that were 15% greater than the SIH/SUS-based estimates. As a result of ethical issues, neither of the information system databases used in this study contained patient identifiers, and we were not able to directly compare the data reported in the two databases. A study evaluating the meningitis surveillance system in Belo Horizonte, Minas Gerais, showed that both the SIH/SUS and SINAN databases were incomplete [37]. The estimated sensitivities of the two databases with respect to all-cause meningitis were 51% and 66%, respectively [37]. In studies conducted in other countries, the proportion of unreported cases has been show to vary according to etiology, being smaller in the case of meningococcus and larger in the case of viral meningitis [37,38]. These data suggest that HSU for treatment of PM may have been underestimated in this study, even after modeling data to include cases of unspecified BM attributable to pneumococcus and hospitalizations in the private sector. The major problem regarding reliability of diagnosis data in SIH/SUS is the limited information found in medical records, the primary source of information for this database [9]. In addition, errors in *ICD* codification may occur [9]. Particularly in the case of PD, another problem is that only meningitis is recorded in SINAN. Cases recorded as meningitis in SINAN may have been registered as sepsis in SIH; however, because the database did not include identifiers, we were not able to assess this issue.

NMNS was the cause of a significant number of SUS hospitalizations. Although SIH/SUS does not provide detailed information on the illnesses referred to by this code, the shorter length of hospitalization (Table 6) and the lower case-fatality rates registered by that database (0.7% of children under-5 hospitalized for NMNS, compared to 33.9% for PM and 19% for PS) suggest that it includes less severe illnesses. As a less severe disease, it is possible that cases of NMNS were treated in outpatient care; however, these data were not estimated because of a lack of available information.

Information on invasive pneumococcal disease other than meningitis and sepsis (in this study, NMNS) has not been included in any of the economic evaluations of PCV in Latin American and Caribbean countries [3,32,34–36]. Models used in cost-effectiveness analyses of PCV generally include four syndromes: pneumonia, AOM, meningitis, and non-pneumonia non-meningitis disease (NPNM) [35]. Meningitis and sepsis are the most serious and frequent IPDs and must be included in economic analyses of PCV, but strategies that also include NMNS in the analyses should be considered. As an example, data on meningitis and sepsis cases data can be entered together in the model, as they involve

similar patterns of HSU (Table 6) and allow entrance of NMNS data separately (as NPNM).

As a result of methodological differences, comparisons of the annual IPD incidence rates estimated in this study (47.27 among children <1 year and 10.11 among children aged 1–4 years; Table 4) with data from other sources are difficult. In a population-based surveillance study of PD in Goiânia conducted from 2007 to 2009, the estimated IPD incidence rate of among children aged 28 days to 36 months was 54.9 per 100,000 (30.9 among infants aged 28 days to 6 months, 114.6 among those aged 6–12 months, 69.8 in the second year of life, and 20.6 in the third year of life) [39]. However, in Goiânia, "an extensive effort was made to capture all outpatients and inpatients with suspicion of IPD or pneumonia" (p. 1902) [39].

HSU for cases of pneumonia and AOM may have a great impact in economic evaluations of PCV due to the high frequency of these diseases among children [40]. However, estimating HSU for treatment of noninvasive disease proved to be challenging, particularly in outpatient settings, for which secondary data are scarce. Furthermore, the definitions and criteria used to diagnosis pneumonia and AOM vary widely in practice.

Data on the proportions of hospitalization of children with all-cause pneumonia found in the national literature allowed us to estimate outpatient HSU from numbers of hospital admissions. The annual incidence rates of all-cause pneumonia (93.4/1000) and RCP (42.1/1000) in children under-5 estimated through this approach (Table 5) are comparable to the data from the Goiânia population-based study (overall incidence rates of 95.98/1000 and 34.28/1000 for clinical pneumonia and RCP, respectively, among children under 3 years of age) [39].

Estimating HSU for AOM cases was the major challenge. Data on AOM in Latin American and Caribbean (LAC) countries are very scarce [41]. National data that would have allowed reliable estimates of HSU due to AOM in children under-5 in Brazil were not available. We chose to use international data on AOM incidence, as in most economic evaluations of PCV conducted in LAC countries [32–36]. HSU for AOM cases was estimated according to Brazilian guidelines on AOM treatment. In developing countries, the management and treatment approach proposed by panels of experts and guidelines for treatment of specific diseases may be quite different from routine clinical practice. Considering that, we may have overestimated HSU for treatment of AOM. However, not including AOM in our analyses would have limited the estimated economic and epidemiological impact of PCV [40].

It is important to differentiate uncomplicated AOM, easily treated and cured without sequelae, from recurrent otitis that requires more medical visits, results in greater use of diagnostic and therapeutic technologies, and may lead to long-term sequelae. In this study, HSU due to complicated AOM included hospitalization for AOM and mastoiditis as well as myringotomy with equalization tube placement, and this may have led to an underestimation of complicated AOM given that most recurrent cases are also treated in outpatient settings.

Estimating HSU in terms of long-term treatment of sequelae due to PD was also a challenge. In this study, estimates of HSU for treatment of neurological sequelae considered the only available data (data on treatment of cerebral palsy). Treatment of hearing loss secondary to meningitis or recurrent/chronic otitis media was not included due to a lack of data. In most economic studies of PCV conducted in LAC countries, the only available information on PM sequelae is their frequency [34]. Some studies have estimated the costs associated with PM sequelae, but it is unclear how these data were obtained [32,33]. Detailed data on HSU for treatment of sequelae are not usually reported.

HSU estimates are important in economic evaluations before a vaccine is introduced into national immunization programs, as well as in evaluations of program impact after vaccine introduction. They also contribute to the development of burden of disease estimates. Data that allow quantification of individual components of health care, such as diagnostic tests, medical visits, hospital stays, medications, other therapeutic procedures, and rehabilitation services, are useful in cost of illness studies. HSU estimates are considered to have low transferability, as they are very context specific, and most economic evaluation guidelines emphasize the importance of using HSU data based on the local context [1,42,43]. The methods and estimates discussed here were used in a cost-effectiveness study and have been useful in impact studies conducted in Brazil [44], and the resulting publications have been well accepted internationally.

Identifying the strengths and limitations of available data and potential data sources is critical for developing reliable HSU estimates. National health information systems are relevant sources of data for HSU estimation, particularly in countries where they include a large proportion of services provided to the population, they are updated continuously, and data quality has been demonstrated as acceptable. Strengthening health information systems is now recognized as an essential element of health care system policies and management. In addition, these systems are essential when evaluating and monitoring the effects of specific interventions on health care utilization and quality and on population health. International efforts to improve global health, such as the Millennium Development Goals, have stimulated the production and utilization of health information systems in evaluations of program impact [45].

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Review

Systematic documentation of new vaccine introduction in selected countries of the Latin American Region

Lúcia H. de Oliveira[a,*], Cristiana M. Toscano[b], N. Jennifer Sanwogou[a], Cuauhtémoc Ruiz-Matus[a], Gina Tambini[c], Mirta Roses-Periago[d], Jon K. Andrus[e]

[a] Comprehensive Family Immunization Project, Pan American Health Organization, Washington, DC, USA
[b] Department of Community Health, Institute of Tropical Pathology and Public Health, Federal University of Goiás, Goiânia, Goiás, Brazil
[c] Family and Community Health, Pan American Health Organization, Washington, DC, USA
[d] Director, Pan American Health Organization, Washington, DC, USA
[e] Deputy Director, Pan American Health Organization, Washington, DC, USA

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ABSTRACT

Background: Countries in Latin America were among the first developing countries to introduce new vaccines, particularly rotavirus (RV) and pneumococcal conjugate vaccines (PCVs), into their national immunization schedules. Experiences and lessons learned from these countries are valuable to donors, immunization partners, and policy makers in other countries wishing to make informed decisions on vaccine introduction.
Objectives: In order to enhance knowledge and promote understanding of the process of new vaccine introduction in the Latin American Region, with particular focus on RV and PCV, we conducted a systematic qualitative assessment. We evaluated the decision-making process, documented the structure in place, and reviewed key factors pertaining to new vaccine introduction. These include country morbidity and mortality data available prior to vaccine introduction, funding sources and mechanisms for vaccine introduction, challenges of implementation, and assessment of vaccine impact.
Methods: From March 2010 to April 2011, we evaluated a subset of countries that had introduced RV and/or PCV in the past five years through interviews with key informants at the country level and through a systematic review of published data, gray literature, official technical documents, and country-specific health indicators. Countries evaluated were Bolivia, Brazil, Nicaragua, Peru, and Venezuela.
Results: In all countries, the potential of new vaccines to reduce mortality, as established by Millennium Development Goal 4, was an important consideration leading to vaccine introduction. Several factors—the availability of funds, the existence of sufficient evidence for vaccine introduction, and the feasibility of sustainable financing—were identified as crucial components of the decision-making process in the countries evaluated.
Conclusions: The decision making process regarding new vaccine introduction in the countries evaluated does not follow a systematic approach. Nonetheless, existing evidence on efficacy, potential impact, and cost-effectiveness of vaccine introduction, even if not local data, was important in the decision making process for vaccine introduction.

Contents

* Corresponding author at: c/o PAHO, 525 23rd Street NW, Washington, DC 20037, USA. Tel.: +1 202 974 3753; fax: +1 202 974 3635.
E-mail address: oliveirl@paho.org (L.H. de Oliveira).

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1. Introduction

One hallmark of the twenty-first century is the development and availability of new vaccines. In January 2006, two new human oral vaccines against rotavirus (RV) were licensed and made available [1,2]. The World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) has recommended RV introduction in all National Expanded Programs on Immunization (EPI) where diarrheal deaths account for more than 10% of mortality among children aged less than 5 years (<5 y). In 2000, a heptavalent pneumococcal conjugate vaccine (PCV7) was licensed, with 10-valent (PCV10) and 13-valent (PCV13) PCVs made available in 2009 and 2010. SAGE has also recommended the introduction of PCVs, especially in countries with high child mortality [3,4].

Countries in the Latin American and the Caribbean (LAC) Region were among the first developing countries to introduce RV and PCV into their EPIs. In 2006, LAC Ministries of Health passed a resolution at the Pan American Organization (PAHO) calling upon Member States to mobilize additional resources to introduce new vaccines, while requiring PAHO to support countries in obtaining the evidence necessary to make informed decisions on vaccine introduction. Both RV and PCV were considered priority new vaccines for the Region [5].

As of June 2012, 15 countries and one territory in LAC had introduced RV and 21 countries and five territories had introduced PCV into their immunization schedules [6].

These vaccines are important for achieving Millennium Development Goal 4 (MDG4), which aims for a two-thirds reduction in mortality for children <5 y by 2015 [7]. Thus, countries must make informed decisions regarding the introduction of new vaccines [8].

2. Objectives

We conducted an evaluation of the process of new vaccine introduction in the Latin American (LA) Region focusing on RV and PCV. Our objectives were to enhance the understanding of the process of new vaccine introduction and to share lessons learned with other countries considering the introduction of new vaccines. Below, we provide a summary of lessons learned and offer recommendations for donors, immunization partners, and policy makers in countries wishing to make informed decisions on vaccine introduction.

3. Methods

We conducted an observational qualitative study, based on a systematic assessment of the process of new vaccine introduction in five countries (Bolivia, Brazil, Nicaragua, Peru, and Venezuela).

Criteria for making decisions on new vaccine introduction include political, technical, and programmatic aspects associated with the introduction (Fig. 1) [9,10]. The following criteria were assessed: EPI structure, morbidity and mortality data available

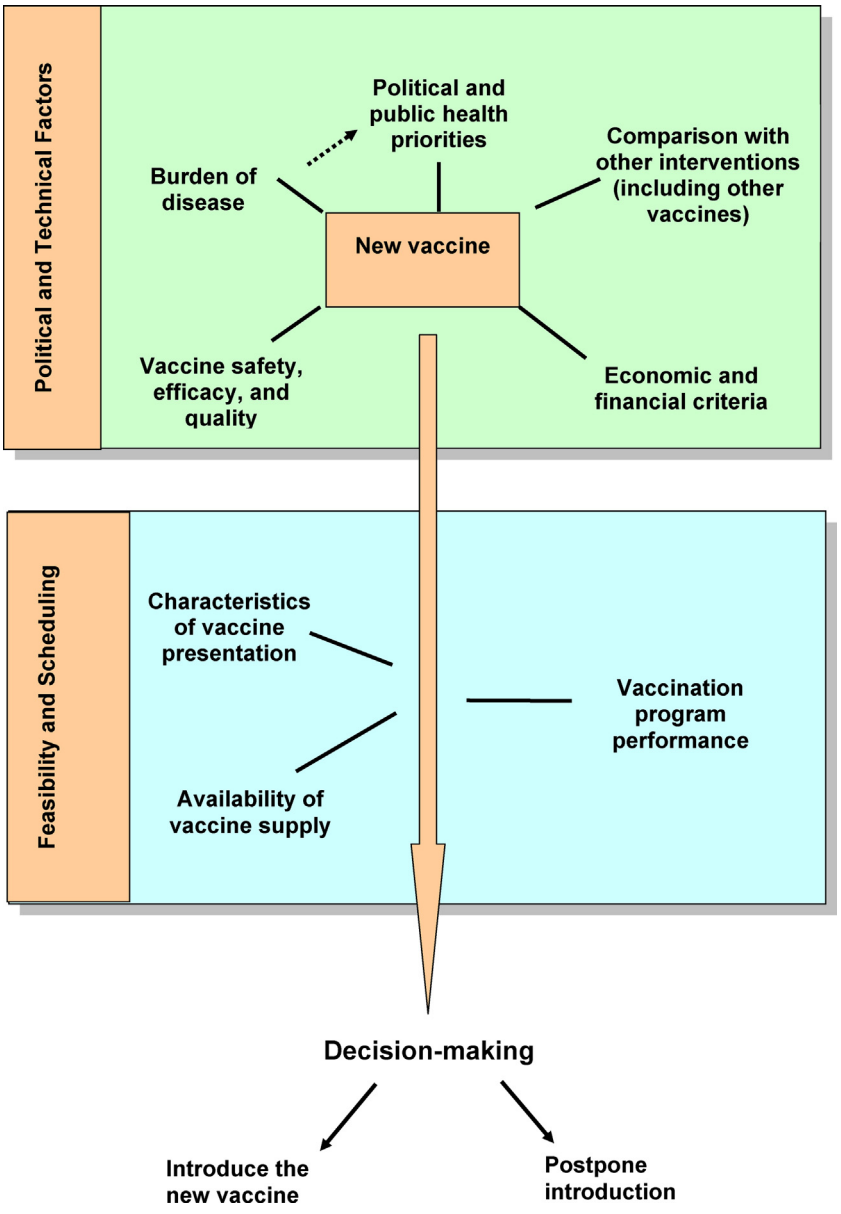

Fig. 1. Decision-making criteria for new vaccine introduction.

prior to vaccine introduction, introduction process, funding, challenges of implementation, and impact assessment.

To highlight the diversity of experiences in the LA Region, we selected five countries that had introduced RV and/or PCV as case studies. Countries were chosen based on select variables (Table 1). All countries agreed to participate in the assessment providing official government authorization.

Demographic and socioeconomic indicators of countries assessed are presented in Table 2.

The study was conducted from March 2010 to February 2011. We first reviewed published data, gray literature, and official country-specific health indicators (Table 3). We then conducted interviews with key informants at the country level, using standardized piloted questionnaires (*online annex*).

In each country, we conducted an average of 10 interviews addressing select issues (Table 4).

Two investigators reviewed and summarized all data. Findings were compiled for each country, aggregated for the Region, and

Table 1
Vaccine introduced, year of introduction and criteria for country selection. Assessment of new vaccine introduction in the Americas, 2010–2011.

Country	Vaccine introduced, year	Variable considered for country selection
Bolivia	Rotavirus vaccine, August 2008	GAVI country Surveillance in place prior to vaccine introduction
Brazil	Rotavirus vaccine, March 2006	Technology transfer agreements in place for vaccine introduction
Nicaragua	Rotavirus vaccine, October 2006	Surveillance in place prior to vaccine introduction
Peru	Rotavirus vaccine and 7-valent conjugate pneumococcal vaccine, 2009	Joint introduction of two new vaccines
Venezuela	Rotavirus vaccine, April 2006	Surveillance in place prior to vaccine

Table 2
Selected country demographic and socioeconomic indicators for Bolivia, Brazil, Nicaragua, Peru, and Venezuela.

	Bolivia 2007	Brazil 2005	Nicaragua 2005	Peru 2007	Venezuela 2005
Basic demographic indicators					
Total population (thousands)	9524	186,075	5455	28,508	26,726
Population < 5 years (thousands)	986	13,967	535	2373	2280
Population < 1 year (thousands)	254	3343	134	600	584
Proportion of urban population (%)	65	84	56	76	92
Proportion of rural population (%)	35	16	44	24	8
Life expectancy at birth (years)	65	72	72	73	73
Total fertility rate (child/woman)	4	2	3	3	3
Crude birth rate (per 1000 pop)	28	18	25	21	22
Ethnic distribution (%)	Quechua: 31% Aymara: 25% Guarani: 6% Euro/mixed: 38%	Mulattos & Blacks: 49.6% White: 49.4%	Indigenous/Afro descendants: 15% Mestizos: 85%	Amerindian: 45% Mestizo: 35% African decent: between 6 and 10% Japanese/Chinese/other: 3%	Indigenous: 2.3% Mestizos/Mulattos/Zambo: 75%
Basic socioeconomic indicators					
Current GNI[a] per capita (US$)	1190	3970	890	3340	
GDP[b] per capita (international PPP adjusted US$)	4015	8505	2314	7676	4950
Annual GDP growth rate (%)	0	3	4	9	9924
Annual Public National Health Expenditure as a proportion of GDP (%)	2	4	4	2	10
Annual Private National Health Expenditure as a proportion of GDP (%)	3	2	4	2	4
HDI[c] Index	Medium	Medium	Medium	High	High
Annual death average (thousands)	72.81	136	26	154	136
Crude death rate (per 1000 pop)	8	5	5	5	5
Under 5 mortality estimated (per 1000 live births)	62	23	28	24	23

[a] Gross National Income.
[b] Gross National Product.
[c] Human Development Index.

discussed among a group of economists, immunization experts, epidemiologists, and national EPI managers.

4. Results

The main issues identified are summarized in Table 5.

4.1. Bolivia

4.1.1. EPI structure

Established in 1979, the EPI in Bolivia is funded by the government treasury, with additional support from international and non-governmental organizations (NGOs), and bilateral cooperation agencies. A vaccine law ensuring specific EPI budgetary funding line from the national treasury was recently issued.

4.1.2. Disease burden data pre-introduction

Acute diarrheal disease in children <5 y is a notifiable disease and the main cause of death and hospitalization in this age group. In 2004, the WHO estimated that diarrhea caused 4% of the total 18,117 deaths in children <5 y in Bolivia [11].

Bolivia was among the first countries in the Region to initiate sentinel surveillance for diarrheal disease in 2005. The country estimated rotavirus disease burden based on data from acute diarrheal disease and rotavirus sentinel surveillance systems, and on estimates of rotavirus in non-hospitalized diarrhea cases from the international literature.

Prior to RV introduction, cost-of-illness [12,13] and cost-effectiveness studies [14] were conducted. The country used local data to make the case for vaccine introduction. The process was transparent and technical. Discussions began in 2003 and reached high political levels after 2006.

4.1.3. Vaccine introduction

Making national authorities aware of new vaccine introduction was a crucial process that involved various partners, including officials from academia, the Immunization Interagency Coordinating Committee (ICC), and the Bolivian National Immunization Technical Advisory Group (NITAG).

RV was introduced in August 2008. Several challenges were encountered. Staff turnover at all EPI levels consumed resources and posed operational and training difficulties. Vaccine

Table 3
Country, regional, and global documents reviewed. Assessment of new vaccine introduction in the Americas, 2010–2011.

Regional/global level data
World Health Organization (WHO) disease burden estimates for rotavirus and pneumococcal invasive disease
Regional, Pan American Health Organization (PAHO) Technical Advisory Group on Vaccine-preventable Diseases (TAG), reports addressing new vaccines and their introduction
International Expanded Immunization Program (EPI) country evaluations conducted in last 10 years
Information from the PAHO's Revolving Fund regarding vaccine procurement and cost and doses purchased by country
Immunization coverage reported annually by countries to PAHO, from 2005–2009
Rotavirus and pneumococcal disease sentinel surveillance data and indicators reported to PAHO from 2004–2009 and regional surveillance reports
Published literature on epidemiology, disease burden, surveillance, and economic evaluations of pneumococcal and rotavirus vaccines in the select countries
Country level data
Flowchart of the current structure of country's Ministry of Health (MoH)
Vaccine laws available in country
New vaccine introduction plans
Five-year EPI plans for the period of 2005–2009
Annual EPI Plan of Action from year of vaccine introduction till 2009
Rotavirus and pneumococcal disease surveillance protocols/guidelines/manuals
Burden of disease, cost-effectiveness, economic analyses, and other relevant estimates or studies conducted at the ministerial level and/or commissioned by the MoH
Reports of the National Immunization Technical Advisory Group Meetings (NITAGs) in which new vaccines were addressed and discussed
Reports of the Immunization Interagency Committee (ICC) reports in which new vaccines were addressed and discussed
Country-level data on vaccine coverage for rotavirus/pneumococcal vaccines, including intermediate level data, from the year of vaccine introduction to 2009
Country level surveillance data including:
Sentinel surveillance for rotavirus and pneumococcal disease
Mandatory surveillance of acute diarrheal, meningitis, and respiratory diseases available in countries for the period of 2005–2009
Annual budgets for the Ministry of Health, EPI program, and new vaccines for 2005–2010
GAVI plan for new vaccine introduction
Any other relevant document specific to a given country, such as an assessment conducted by the MoH, Non-Governmental Organizations (NGOs) or international organizations

distribution was difficult in hard-to-reach areas. In October 2008, vaccine delivery was interrupted for three months, resulting in shortages in many parts of the country.

4.1.4. Financing and purchase

GAVI provided financial support for RV introduction for the period 2008–2011 [15].Bolivia's government co-financed the vaccine, providing the highest level of co-financing among GAVI countries to date.

4.1.5. Implementation challenges

Second dose of RV (RV2) vaccine coverage (40%) was lower than expected in 2008. Possible causes include vaccine stock-out and age restrictions for RV administration [16].

4.1.6. Vaccine impact evaluation

A case-control study is being conducted to assess the effectiveness of RV. Trends in the incidence of severe rotavirus and all-cause gastroenteritis among children are also being evaluated. These studies will help Bolivia estimate the impact of vaccination against rotavirus.

Table 4
Key informants interviewed and issues addressed in country-level interviews. Assessment of new vaccine introduction in the Americas, 2010–2011.

	Key informant	Key issues addressed
1	EPI[a] PAHO[b] consultant in the country	Political and technical environment, PAHO's role, overall information on the decision-making process and participating institutions
2	EPI coordinator at time of new vaccine introduction	Decision-making process, data used to generate evidence, key institutions and staff involved in the process, planning and introduction of the vaccine, critical assessment of the introduction process
3	Expert investigator involved in studies and projects on surveillance, disease burden, or cost effectiveness of new vaccines	Country-level data on new vaccine disease burden, communication of data and its uses during the decision-making process, assessment of impact of vaccine introduction
4	Coordinator of the department overseeing EPI in the MoH, at time of new vaccine introduction	Political and technical environment, overview of the decision-making process and key challenges
5	President or coordinator of the NITAG[c] at the time when new vaccine was introduced	Role of the NITAG, content of technical discussions, sources of information considered, main recommendations from NITAG
6	UNICEF[d] technical officer responsible for immunization activities	Partnerships with international organizations
7	Institution or Agency participating in the Immunization Interagency Coordinating Committee (ICC)	Partnerships with other global partners and donors and their roles in the decision-making process and vaccine introduction
8	National authority responsible for assigning financial resources and budget to immunization activities, particularly to new vaccines	Process of assignment of funds for EPI, funding for new vaccines, sustainability of the program and plans for additional vaccine introduction
9	National regulatory agency	Regulatory process, roles and responsibilities of regulatory agency, quality-control procedures in place
10	Current EPI coordinator and new vaccine surveillance technical office (if different than at time of vaccine introduction)	Vaccine coverage over time following vaccine introduction, main challenges in routine immunization program, impact of vaccine introduction, operational challenges
11	Current coordinator of the department overseeing EPI in the MoH	Current political and technical environment, overview of the current decision-making process and plans for future vaccine introduction
12	National vaccine manufacturers receiving technology transfer for new vaccines	Technology transfer processes, installed manufacturing capacity
13	Coordinator of the department overseeing or negotiating technology transfer agreements in the government	National policy for vaccine production and self-sufficiency of vaccine production. Process of decision making and negotiation for technology transfer, priority issues in tech transfer agreements

[a] Expanded Immunization Program.
[b] Pan American Health Organization.
[c] National Immunization Technical Advisory Group.
[d] United Nations Children's Fund.

Table 5
Regional overviews: main issues identified in the assessment of case-study countries. Assessment of new vaccine introduction in the Americas, 2010–2011.

Issues	Bolivia	Brazil	Peru	Nicaragua	Venezuela
Availability of vaccines	GAVI funding	National funds available and technology transfer agreement	National funds available	Donation for three years followed by GAVI funding	National funds available
Decision making trigger	Technical	Political/technology transfer	Technical and Political	Political/donation	Political
PAHO[a]/WHO[b] recommendations and vaccine pre-qualification	Major factor for initiating technical discussions and for driving decision on which vaccine should be introduced	Not relevant	– Major factor for initiating technical discussion – Not significant factor for driving decision on which vaccine should be introduced	Major factor for technical discussion and for driving decision regarding which vaccine to be introduced	– Major factor for initiating technical discussion – Not significant factor for driving decision on which vaccine should be introduced
NITAGs[c] role	Important	Minimal	Non-existent	Important	Non-existent
ICC[d] and international cooperation	+++	Minimal	+	++	Minimal
Local vaccine-preventable disease research capacity and production of evidence	Significant	Significant	Significant	Significant	Significant
Local evidence from surveillance or disease burden estimates from national data	Significant, Surveillance from 2005–2008	Data from local studies and outbreak in 2005. No surveillance data or disease burden estimates available	No surveillance data available. Disease estimates and DALYs[f] from secondary data	Data from diarrheal diseases surveillance and outbreak in 2005. No disease burden estimates available	Significant, Surveillance data available
Political transit of EPI[e] staff	Significant	Minimal	Significant	Minimal	Significant

[a] Pan American Health Organization.
[b] World Health Organization.
[c] National Immunization Technical Advisory Group.
[d] Immunization Interagency Coordinating Committee.
[e] Expanded Immunization Program.
[f] Disability adjusted life-years.

4.2. Nicaragua

4.2.1. EPI structure

The Nicaraguan EPI was created in 1980. Nicaragua has neither a national vaccine law nor a specific budget line for vaccine purchases. In addition to funding from the National Treasury, the country receives significant support from international agencies.

4.2.2. Disease burden data pre-introduction

Acute diarrhea in children <5 y is a notifiable disease, being the main cause of morbidity and one of the main causes of mortality in this age group. The WHO estimated the rotavirus disease burden for 2004 to be 220 child deaths, with a mortality rate of 30 deaths per 100,000 children <5 y [17]. Rotavirus sentinel surveillance began after RV introduction in October 2006.

Research on pediatric diarrheal diseases has been conducted in Nicaragua since 1983 with studies on various disease aspects [18,19], including vaccine clinical trials [1,20]. Taking into account local morbidity data and published studies in LA [21], Nicaragua's MoH estimated the prevalence of rotavirus among children and the potential impact of RV on rotavirus economic burden [22].

During an outbreak of acute diarrhea (February–April 2005), a total of 47,470 cases and 52 deaths were reported. Rotavirus was identified in 42% of children hospitalized with diarrhea [23].

4.2.3. Vaccine introduction

The Decision making process for RV introduction was initiated in high political levels and later discussed at the EPI. In 2006, the MoH was offered a three-year donation of RV from one of the vaccine manufacturers. This donation, local disease burden estimates, and the outbreak of rotavirus were the principal considerations of the country's decision-making process.

Based on this evidence, Nicaragua's NITAG and the National Committee for Health Research and Ethics (CONIS) recommended RV introduction [24]. Many organizations provided technical support in the process, including the Pediatric Society, The American University, NicaSalud, the Japan International Cooperation Agency (JICA); PATH; UNICEF; and PAHO.

4.2.4. Financing and purchase

To ensure financial sustainability after the donation period (2006–2009), the MoH requested GAVI support for RV vaccine for 2009–2015 [25]. In 2015, the country will assume full funding of rotavirus vaccines.

4.2.5. Implementation challenges

Challenges encountered during RV introduction include insufficient capacity of the regulatory agency to perform lot-by-lot quality control, difficulties vaccinating populations in hard-to-reach areas, and lack of resources for training and social mobilization activities.

Vaccine coverage for RV third dose (RV3) was 79% in 2007 and increased to 98% in 2010.

The country implemented rotavirus sentinel surveillance in October 2006.

4.2.6. Vaccine impact evaluation

Several studies have evaluated the vaccine's impact and effectiveness [26,27]. Results indicated 58% effectiveness of three doses against severe rotavirus disease [26]. In addition, assessments using

secondary hospitalization data in the country demonstrated RV initial impact [28].

4.3. Brazil

4.3.1. EPI structure

Brazil's EPI was established in 1973. In 1975, the country passed a vaccine law requiring federal health institutions to purchase and distribute vaccines. EPI funding is provided in full by the Government treasury. New vaccine sustainability has been strengthened by a new vaccine budget law passed in 2010, which prevents Congress from rejecting vaccination budget lines prepared by the MoH and approved by Ministry of Planning and Budget.

4.3.2. Disease burden data pre-introduction

Research groups had generated some evidence in selected hospitals in the country [29], but limited data on rotavirus specific disease burden was available when the country decided to introduce RV. Although acute diarrhea is a notifiable disease in the country, rotavirus sentinel surveillance was not established.

In 2005, a large rotavirus outbreak of occurred in Brazil's Amazon region [30], which substantially stimulated discussion regarding RV introduction.

4.3.3. Vaccine introduction

The decision making process for RV introduction was initiated in 2005 in high political levels stimulated by a potential technology transfer agreement, and later brought for discussion at the EPI. After the decision had been made, discussion took place at a NITAG's special meeting in 2005.

The decision making process for new health technology policy decisions, including new vaccines, was further structured in Brazil as of 2008, with the establishment of a secretariat charged for decision making for the public health care system considering all evidence and information available [31].

4.3.4. Vaccine production and technology transfer

Over the past 20 years, Brazil has developed a strong infrastructure for local vaccine manufacturing. As part of the National Program for Sufficiency for Vaccine and Biologicals established by the MoH in 1985, the country has made investments to improve quality and enhance the capacity for internal supply [32]. Today, Brazil is an important potential source of vaccines for the developing world [33].

4.3.5. Financing and purchase

When RVs were made available in early 2006, the MoH initiated discussions on a technology transfer agreement with vaccine manufacturers and Biomanguinhos/Fiocruz, a national public vaccine producer.

Shortly thereafter, in March 2006, the country introduced RV. In 2007, an agreement was established, with an expected timeline of 5 years for full technology transfer.

4.3.6. Implementation challenges

Challenges encountered during implementation include insufficient cold chain capacity, limited training received by healthcare staff, and lack of time to prepare for vaccine introduction.

RV3 coverage in Brazil reached 77% in 2007 and 81% in 2010. Rotavirus sentinel surveillance system began in 2007.

4.3.7. Vaccine impact evaluation

Several studies have assessed rotavirus vaccine effectiveness [34,35]. An impact assessment study, using secondary hospitalization data, showed an initial RV impact [36–40]. Most of these studies have been conducted independently by research groups [34–37], a few by the vaccine manufacturer [38,39], and one by the MoH with support from PAHO and the Centers for Disease Control and Prevention (CDC) [40].

Time series analysis of diarrhea hospitalization using secondary data from the National Hospitalization Information System demonstrated significant reductions in morbidity and mortality following RV introduction [37,40].

4.4. Peru

4.4.1. EPI structure

The Peruvian EPI was created in 1979. In June 1993, the country enacted a vaccine law assuring government funding for most immunization activities.

4.4.2. Disease burden data pre-introduction

Rotavirus is the most common cause of severe diarrhea in Peruvian children. The WHO estimated the 2004 rotavirus disease burden to be 691 child deaths, with a mortality rate of 23 deaths per 100,000 children <5 y [41].

Before introduction, Peru lacked national estimates of pneumococcal disease burden, but, given regional data, the country acknowledged the cause for concern [42].

In 2008, the MoH commissioned a study that demonstrated that pneumonia was the second leading cause of loss of healthy life years [43]. At the time of RV and PCV introduction, sentinel surveillance of rotavirus and pneumococcal disease had not been established.

4.4.3. Vaccine introduction

In 2006, Peru's EPI began discussing the introduction of new vaccines. In 2008, with support from the *Comité Consultivo* (committee resembling NITAG), the Minister of Health decided to include rotavirus, pneumococcal, and influenza vaccines in the country's EPI.

International partners reported having had limited participation in the decision-making process. Research groups generated substantial evidence on RV development, epidemiology, economic burden and cost-effectiveness. However, few studies on pneumococcal disease were generated in Peru. Therefore, the country considered regional evidence, specifically a study assessing the cost-effectiveness of PCV, in deciding to introduce PCV [44]. RV and PCV were introduced in 2009.

4.4.4. Financing and purchase

Health funding in Peru has increased significantly from 2000–2007, with immunization funding increasing from 6.5% of the MoH budget in 2000 to 44% in 2006 [45]. Since 2008, Peru has purchased RV and PCV through PAHO's Revolving Fund.

4.4.5. Implementation challenges

Challenges identified during vaccine introduction include lack of a specific social mobilization plan for RV and PCV introduction, insufficient staff training prior to vaccine introduction, limited cold chain capacity, and introduction of PCV at three and five months of age rather than at two and four months as recommended.

RV3 coverage was 41% in 2009 and increased to 75% in 2010. PCV3 coverage was 8.8% in 2009 and increased to 83.2% in 2010. Possible reasons for lower-than-expected coverage include the age restriction for RV and PCV vaccine schedule used in Peru, which, in turn, may have led to missed vaccination opportunities [16]. Additionally, issues with vaccine distribution and vaccine registration presented challenges to the introduction of the vaccines.

In 2009, Peru began reporting rotavirus diarrhea and bacterial pneumonia and meningitis.

4.4.6. Vaccine impact evaluation

To our knowledge, few studies assessing the impact of vaccine introduction have been conducted. Recently, Peru requested PAHO's support in evaluating the impact of PCV introduction in the country.

4.5. Venezuela

4.5.1. EPI structure

Established in 1997, the Venezuelan EPI receives regular budget funds from the government and has benefited from extrabudgetary funding since september 2005. The country also possesses a vaccine law that declares immunization a public good but does not provide information on vaccine funding.

4.5.2. Disease burden data pre-introduction

Diarrhea is the third leading cause of child death in Venezuela, representing 7% of child deaths <1 y, and the main cause of death and hospitalization in children <5 y. The WHO estimated the disease burden for Venezuela in 2004 to be 428 child deaths due to rotavirus, with a mortality rate of 15 deaths per 100,000 children <5 y [46].

Research groups have produced studies on RV development, efficacy, and safety and on the disease's epidemiology, genotype distribution, and economic burden. In Venezuela, acute diarrhea is a notifiable disease. Rotavirus sentinel surveillance began in 2004.

4.5.3. Vaccine introduction

Substantial local evidence was available when the decision to introduce RV was made. Following technical discussions, the decision was made at the vice-minister level.

International partners were not involved in the decision-making process. There is no functioning ICC, nor a technical advisory committee or NITAG equivalent in Venezuela. RV was introduced into the EPI in April 2006.

4.5.4. Financing and purchase

Though MoH and immunization budgets increased significantly from 2000–2009, there was a sharp reduction in immunization expenditures in 2009–2010. Since 2006, Venezuela has purchased RV through PAHO's Revolving Fund.

4.5.5. Implementation challenges

Challenges during vaccine introduction include limitations in cold chain capacity and limited communication and social mobilization activities.

Very low RV2 coverages have been reported: 26% in 2006, 19% in 2007, 47% in 2008, 54% in 2009, and 48% in 2010. Potential reasons include missed vaccination opportunities, age restrictions for the second dose of the vaccine, lack of routine supervision activities, an inadequate information system and population estimates used for vaccine coverage estimation [16].

4.5.6. Vaccine impact evaluation

To our knowledge, few studies assessing the impact of vaccine introduction have been conducted.

5. Discussion

The decision making process regarding new vaccine introduction in the countries evaluated does not follow a systematic approach. In most countries, the process was initiated as a political decision, later supported by technical aspects. Nonetheless, existing evidence on efficacy, potential impact, and cost-effectiveness of vaccine introduction, even if not local data, was important in the decision making process for vaccine introduction in all countries.

Reaching MDG4 and society's perception of vaccines as a public good were also important motivators in governmental decisions to introduce new vaccines. The availability of vaccines and funds for vaccine introduction either through donation, co-funding by GAVI, or national funds for vaccine purchase was essential in the process. In countries funding the EPI program, vaccine laws have proven essential for supporting the decision-making process on vaccine introduction and sustainability.

Although few countries possessed surveillance and local disease burden data prior to new vaccine introduction, all countries studied implemented surveillance during or following vaccine introduction and are planning to conduct impact assessments.

Limited evidence is available in the literature on the process of new vaccine introduction. The issues identified in this study are being addressed by PAHO through the ProVac Initiative, which has been working in the LAC Region since 2004 to strengthen the decision making process for new vaccine introduction [47].

6. Conclusion

Despite the fact that the countries assessed do not represent the Region as a whole, the results are useful for each respective country, and lessons learned valuable for other countries and Regions.

Political commitment is crucial in the decision making process, but coordination with technical sectors for evidence based decision making is of utmost importance.

Mechanisms for sharing the scientific evidence with decision makers need to be enhanced.

Countries should capitalize on NITAG's role in providing technical support during the decision-making process and on the participation of other technical agencies and institutions supporting immunization.

Lastly, prior to vaccine introduction countries must conduct cold-chain assessments at all levels and more accurately forecast vaccine demand and financial needs in order to avoid lack of resources during the implementation period.

Conflict of interest

None of the authors has reported a conflict of interest.

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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.2013.05.032.

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Review

Temporal trends in diarrhea-related hospitalizations and deaths in children under age 5 before and after the introduction of the rotavirus vaccine in four Latin American countries

L.H. De Oliveira[a,d,*], N. Giglio[b,d], A. Ciapponi[c,d], S. García Martí[c,d], M. Kuperman[e,d], N.J. Sanwogou[a,d], C. Ruiz-Matus[a,d], M.F. Marinho de Sousa[a,d]

[a] Pan American Health Organization, Washington D.C., United States
[b] El Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina
[c] Instituto de Efectividad Clínica y Sanitaria, Buenos Aires, Argentina
[d] Instituto Balseiro, Universidad Nacional de Cuyo, Bariloche, Argentina
[e] Grupo de Física Estadística e Interdisciplinaria, Centro Atómico Bariloche, Argentina

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ABSTRACT

Introduction: Rotavirus infection mainly affects children under 5 years of age and causes 453,000 deaths annually throughout the world. Several countries in Latin America have introduced the rotavirus vaccine and the majority have epidemiological data to measure impact following vaccine introduction.
Objective: To assess the impact of rotavirus immunization on the number of all-cause diarrhea-related deaths and hospitalizations in children under 1 and 5 years of age in Bolivia, El Salvador, Honduras and Venezuela.
Methods: Interrupted time-series analyzed with the integral method and the projection method to evaluate the pre and post-vaccine introduction trend in diarrheal disease compared to Argentina as the control country. The analysis period was from 2002 to 2010, including 2 to 4 post-vaccine years depending on the country. Information sources included records from PAHO, the Ministry of Health, public hospitals, social security, the private health system, the Expanded Programme on Immunization and UNPop 2008.
Results: Over the period studied, reductions were observed in trends of diarrhea-related deaths and hospitalizations in children under five. In diarrhea-related deaths, under the integral method, the range of reduction was between 15.7% (13.5–17.9) and 56.8% (56.0–57.5) while with the projection method was between 19.9% (4.9–34.8) and 63.7%(56.1–71.4). In diarrhea-related hospitalizations, under the integral method was 5.6% (4.1–6.7) and 17.9% (16.7–19.1)) while with the projection method was between 5.1%(1.7–8.7) and 11.1% (5.8–16.3)
Conclusions: A decrease was observed in the number of diarrhea related deaths and hospitalizations in all countries under study following introduction of the rotavirus vaccine as opposed to the control country. The impact on reduction of deaths was greater than hospitalization.

Contents

* Corresponding author at: Pan American Health Organization, 525 23rd Street NW; Washington, DC 20037, United States.
E-mail address: oliveirl@paho.org (L.H. De Oliveira).

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1. Introduction

Rotavirus infection mainly affects children under 5 years of age, causing 453,000 deaths annually throughout the world [1,2], 80% of which occur in developing countries [3]. It has been estimated that in the Americas rotavirus infection causes 5000 deaths annually in children under age 5 after the introduction of the vaccine in many countries. [1].

Currently, there are two attenuated oral rotavirus vaccines licensed and prequalified by the World Health Organization (WHO). The first is the monovalent human vaccine (Rotarix®), derived from the G1 P1 human virus strain and administered in two doses, usually at 2 and 4 months of age [4]. The second is a pentavalent vaccine (RotaTeq®) made with a human-bovine reassortant virus that contains G1, G2, G3, G4, and P1 strains of human serotypes, and usually administered in three doses at 2, 4, and 6 months of age [5,6].

In 2006 and 2007, respectively, the Directing Council of the Pan American Health Organization (PAHO) [7] and the World Health Organization's Strategic Advisory Group of Experts (SAGE) [8] declared that the introduction of the rotavirus vaccine in the Americas was a priority, with the goal of preventing deaths and hospitalizations caused by this virus. This decision was based on the results of clinical trials on both vaccines, which showed 85% to 98% efficacy in the prevention of severe rotaviral diarrhea in Europe and Latin America [4–6].

Six Latin American countries introduced the vaccine in their immunization programs in 2006 (Brazil, El Salvador, Mexico, Nicaragua, Panama, and Venezuela); Ecuador introduced it in 2007; Bolivia in 2008; Colombia, Honduras, Peru, and the territories of the Cayman Islands in 2009; and Guatemala, Guyana, and Paraguay in 2010 [9].

Aspects related to the impact of vaccination such as mortality, morbidity, coverage rates, seasonality, serotype replacement, and the indirect benefits for people who have not been vaccinated justify monitoring the rotavirus vaccine following its introduction into Expanded Programs on Immunization (EPI) in the Latin American region, in spite of the results of randomized clinical trials [10].

To date, impact studies in Latin America pre- and post-introduction of the rotavirus vaccine have shown a reduction in disease burden. A 22% to 50% decrease in deaths from all-cause diarrhea has been observed [11–14]. For hospitalizations related to all-cause diarrhea, the decrease ranged from 17% to 51% [12,15–18] and specifically for rotavirus, hospitalizations decreased between 59% and 81% [19,20].

Based on these reported data, and due to the need to continue assessing the impact of these vaccines in Latin America, the objective of this study was to evaluate the trend in diarrhea-related deaths and hospitalizations before and after introduction of the rotavirus vaccine in Bolivia, El Salvador, Honduras, and Venezuela.

2. Methods

2.1. Design

An interrupted time-series analysis was used to assess the impact of rotavirus immunization on the number of deaths and hospitalizations related to all-cause diarrhea in children under 1 year and under 5 years of age. The study considered data from four Latin American countries that met the following criteria: rotavirus vaccine introduction in the country's national routine EPI schedule in the 2006–2009 period; national records on diarrhea-related deaths and hospitalizations for at least three years prior to the introduction of the vaccine; reliable vaccine coverage records; and no significant changes in the method for registering hospitalizations and deaths or in the health care system during the pre- and post-vaccine introduction period.

Argentina has relatively good surveillance data to serve as a control country. In addition some areas of Argentina, specifically the northwest and northeast regions, present similar sanitation conditions to the countries selected for this study. Because Argentina had not introduced the rotavirus vaccine to its EPI during the study period, it was selected as a control country in order to evaluate possible secular changes in diarrhea morbidity and mortality in the region. Table 1 shows the general characteristics of the countries selected and the periods pre- and post-vaccine introduction analyzed.

2.2. Sources and data collection

The impact of rotavirus vaccine introduction was assessed through monthly hospitalizations and mortality reports received from the Ministries of Health for at least three years prior to implementation of the vaccination program and every subsequent year available through December 2010. The time series window of the countries is detailed in Table 1. We used databases on epidemiological surveillance of rotaviral diarrhea from the PAHO recommended sentinel surveillance network and records on hospitalizations and deaths at the Ministries of Health of the countries selected for this study [21,22].

Hospitalizations and deaths from diarrhea-related causes corresponding to the following codes from the tenth version of the International Classification of Diseases (ICD-10) [23] were considered: A00–A03, A04, A05, A06.0–A06.3, A06.9, A07.0–A07.2, and A08–A09The Venezuelan surveillance systems report aggregated data for all diarrhea-related hospitalizations. Therefore, data on hospitalizations from that country were excluded from the regional analysis because that data could not be stratified.

Monthly national rotavirus vaccine coverage data reported to PAHO was used for this study. Demographic data were obtained from the United Nations World Population Prospects database for 2008 [24].

The proportion of all diarrhea cases caused by rotavirus was taken from sentinel surveillance data on hospitalized children from 0 to 5 years of age through the year 2009. This proportion was applied to all-cause diarrhea reported cases in order to estimate those attributable to rotavirus. Due to the predictable seasonality of hospitalizations and deaths and the stable proportion of all cause diarrhea caused by rotavirus over time, the proportions corresponding to 2010 were modeled by means of an exponential smoothing method [25]. The relative reduction in deaths and hospitalizations attributed to rotavirus infection and corresponding 95% confidence intervals were estimated for each analysis proposed.

2.3. Statistical time-series analysis

For the time-series analysis, two different methods were used: the integral method and the projection method. Time-series data were adjusted for changes in the population size of the target age groups. The absolute number of estimated cases took into account the age-specific rate of natural increase [24].

Table 1
Population characteristics of selected countries and the periods analyzed pre- and post-introduction of rotavirus vaccine.

Countries	Population 0–5 years of age[a,b]	All-cause deaths in children under age 5 for every 1000 live births in 2005[b]	Introduction of the vaccine	Start of TIME SERIES	Completion of the TIME SERIES
Bolivia	1,242,000	66.00	Yes (August 2008)	January 2003 (Hospitalizations) January 2004 (Deaths)	December 2010
El Salvador	710,000	27.73	Yes (April 2006)	January 2002 (Hospitalizations) January 2002 (Deaths)	December 2010
Honduras	905,000	41.59	Yes (February 2009)	January 2004 (Hospitalizations) January 2004 (Deaths)	December 2010
Venezuela	2,850,000	23.00	Yes (April 2006)	January 1998 (Cases) January 2002 (Deaths)	December 2009
Argentina	3,355,000	16.00	No (Control country)	January 2005 (Hospitalizations) January 2004 (Deaths)	December 2009

[a] Averages for the period following vaccine introduction.
[b] Based on United Nations, Department of Economic and Social Affairs, Population Division (2009). World Population Prospects: the 2008 Revision. (CD-ROM Edition) New York: United Nations.

2.3.1. Integral method

This methodology uses the cumulative case distribution calculated based on the integral over the course of the time series and makes possible a quantitative and qualitative (visual) analysis of changes [26].

Based on the date of vaccine introduction into each country's National Immunization Program, an estimate was obtained using the least-squares linear regression of the integral curve pre- and post-introduction of the vaccine, using the following formulae:

$$C_o(t) = \int_{t_0}^{t} N_o(t)\,dt$$

$$C_e(t) = C_o(t_v) + r(t - t_v)$$

where $C_o(t)$ is the integrated value of the cases observed following introduction of the vaccine and $C_e(t)$ is the integrated value of cases adjusted by regression that would be expected in the absence of the vaccine. The number of cases expected in the absence of vaccine is obtained by projecting the linear regression line prior to introduction of the vaccine.

In estimating the net effect of vaccination using quantitative analysis, the cumulative number of actual cases (number of cases observed: N_o) were compared following introduction of the vaccine (t_v) with the projection of cases that would have occurred if the vaccine had not been introduced (t_f) (number of cases expected: N_e), using the following formula:

Number of cases averted $= \int_{t_v}^{t_f} (N_e(t) - N_o(t))\,dt$, where the difference between the cumulative values of expected cases and observed cases during the post-vaccination period is calculated. Expected cases are estimated based on the slope of the integral curve during the pre-vaccination period.

For qualitative analysis, the slopes of the integral curves associated with the incidence of events were compared. A potential impact can thus be inferred for each country pre- and post-vaccination if there is an observed change in slope when compared to the control country.

In order to facilitate visual comparison of the qualitative behavior of the time series in each country, the maximum values corresponding to the last value available in the time series were standardized in integral curves, acquiring values between 0 and 1.

Data were analyzed by means of linear regression by using the best adjustments for each series, comparing the differences between intervention countries and the control country.

2.3.2. Projection method

This method was used to obtain a more detailed analysis of the time series, eliminating the stochastic noise and seasonality components of the global trend from the original monthly data curve.

First, least-squares non-linear regression was applied to the data curve. Subsequently, using the Levenberg–Marquardt algorithm [27] and the Hodrick–Prescott filter [28] for trend analysis, the impact of change compared the actual trend of the time series (N_o) with what could be expected without vaccination (N_e). In this way, similar to the regression method, the cases averted through vaccination were quantified using the formula: $N_e - N_o$.

3. Results

The number of cases observed over the post-vaccination study period was less than the number of expected cases modeled in the absence of vaccination programs, suggesting a reduction in diarrhea-related deaths and events in all the countries studied. Fig. 1 shows the number of diarrhea-related deaths and hospitalizations reported by the different countries during the study time period. It also shows the results of the best adjustments for each series, comparing the intervention countries and the control country.

In the post-introduction period, a total of 2231 diarrhea-related deaths were observed in contrast with the 4430 (integral method) to 5337 (projection method) expected in children under age 5 in Bolivia, El Salvador, Honduras, and Venezuela) (Table 2). 110,227 diarrhea-related hospitalizations were observed in contrast with 120,146 (projection method) to 120,518 (integral method) expected in Bolivia El Salvador, and Honduras. In Venezuela, 1,582,480 cases of diarrhea were registered in the under 5 age group (hospital discharges and outpatient cases) compared to the 1,858,700 (integral method) to 1,887,080 (projection method) expected for the same period (Table 3).

Using the integral method, mortality trends due to all-cause diarrhea in children under age 5 during pre- and post-vaccination showed that mortality reduction ranged from 15.7% (CI95%: 13.5%–17.9%) in Honduras to 56.8% (CI95%: 56.0%–57.5%) in Venezuela. Using the projection method, reduction in mortality ranged from 19.9% (CI95%: 4.9%–34.8%) in Honduras to 63.7% (CI95%: 56.1%–71.4%) in Venezuela (Table 2).

The assessment of impact on diarrhea-related hospitalizations for Bolivia, El Salvador, and Honduras revealed a decrease in the number of hospitalizations following vaccine introduction,

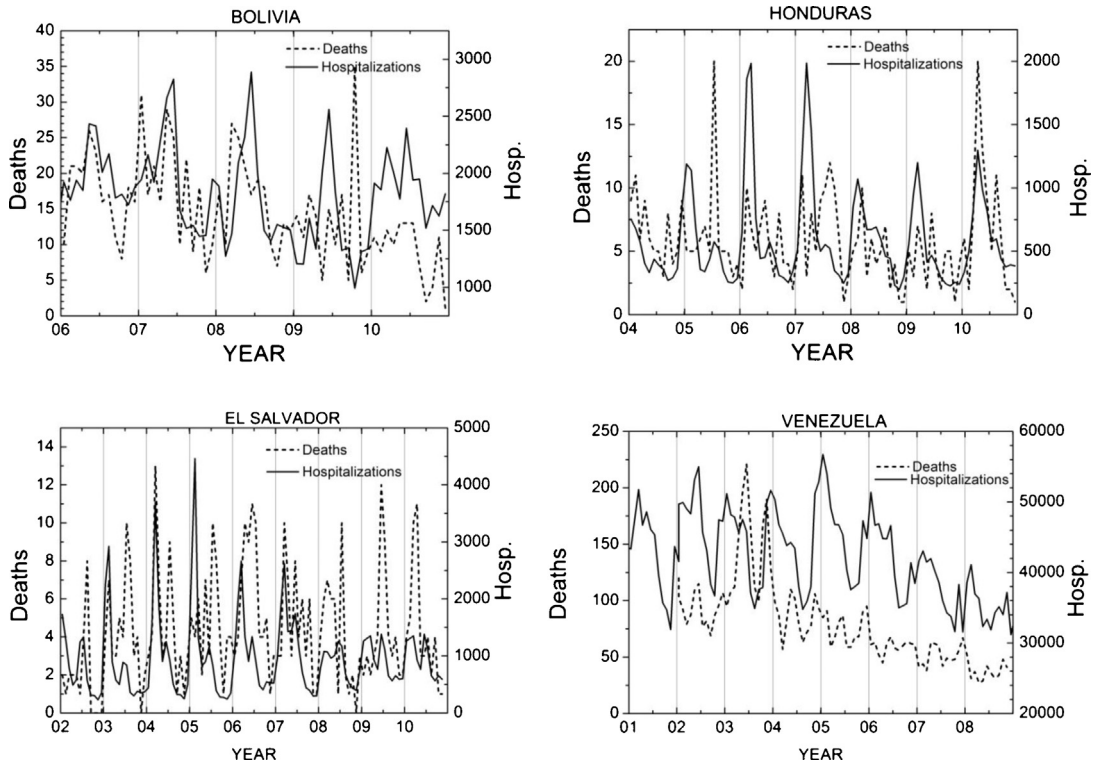

Fig. 1. Number of deaths and hospitalizations for the countries included during the entire study period. All causes. The graphs show the number of deaths (dashed line) and hospitalizations (solid line) for the countries included during the entire study period. The *y* axis shows the absolute number of events, hospitalizations are shown on the left, deaths are shown on the right and the years are shown on the *x* axis.

ranging from 5.6% (CI95%: 4.1%–6.7%) in El Salvador to 17.9% (CI95%: 16.7%–19.1%) in Honduras using the integral method, and 5.1% (CI95%: 1.7%–8.7%) in El Salvador to 11.1% (CI95%: 5.8%–16.3%) in Honduras using the projection method (Table 3).

The reduction in the proportion of deaths attributed to all-cause diarrhea did not vary considerably in the 0 to 1 year age group compared with the 0 to 5 year group (Table 2), but the reduction in hospitalizations was greater in the 0 to 1 year age group (Table 3). Of the total number of deaths in the 0 to 5 year age group, the majority occurred in the 0 to 1 age group, accounting for 96% of deaths in Bolivia, 96%, 75% in El Salvador, 66% in Honduras, and 66% in Venezuela.

Trends in diarrhea-related deaths and hospitalizations in children under age 5 in countries where the vaccine was introduced were different than the control country (Argentina). In the control country, the cumulative number of deaths and hospitalizations maintained the same slope over time, while the study countries showed a drop in the slope following introduction of the vaccine

Table 2
Number of observed and expected deaths related to all-cause diarrhea following rotavirus vaccine introduction in children, by age group, in selected countries.

Country	Age range	Integral method				Projection method			
		Observed deaths	Expected deaths	Difference	Δ% (CI 95%)	Observed deaths	Expected deaths	Difference	Δ% (CI 95%)
Bolivia	0–1 year	303	430 ± 4	127 ± 4	29.5% (28.2%–30.8%)	303	376 ± 40	73 ± 40	19.4% (2.3%–36.5%)
	0–5 years	314	487 ± 5	173 ± 5	35.5% (34.1%–36.9%)	314	546 ± 50	232 ± 50	42.5% (32.0%–53.0%)
El Salvador	0–1 year	188	178 ± 2	−10 ± 2	−5.6% (−8.0%–−3.2%)	188	211 ± 20	23 ± 20	10.9% (0–27.8%)
	0–5 years	253	240 ± 3	−13 ± 3	−5.4% (−8.3%–−2.8%)	253	395 ± 60	142 ± 60	35.9% (16.5%–55.4%)
Honduras	0–1 year	85	99 ± 4	14 ± 4	14.1% (7.2%–21.1%)	85	85	0	0% (0–0.0)
	0–5 years	129	153 ± 2	24 ± 2	15.7% (13.5%–17.9%)	129	161 ± 15	32 ± 15	19.9% (4.9%–34.8%)
Venezuela	0–1 year	1010	2510 ± 10	1500 ± 10	59.8% (59.4%–60.1%)	1010	2770 ± 300	1760 ± 300	63.5% (55.6%–71.4%)
	0–5 years	1535	3550 ± 32	2015 ± 32	56.8% (56.0%–57.5%)	1535	4235 ± 450	2700 ± 450	63.7% (56.1%–71.4%)
Argentina	0–5 years	423	425 ± 1	–	0.4% (0.3%–0%)	–	–	–	–
Total[a]	0–1 year	1586	3217 ± 20	1631 ± 20	50.7% (50.1%–51.3%)	1586	3442 ± 360	1856 ± 360	53.9% (44.3%–63.6%)
Total[a]	0–5 years	2231	4430 ± 42	2199 ± 42	49.6% (48.7%–50.6%)	2231	5337 ± 575	3106 ± 575	58.2% (49.2%–67.2%)

Note: Deaths for the entire period, from the introduction of rotavirus vaccination through the last information available, adjusted for population growth.

[a] The total does not include Argentina.

Table 3
Number of observed and expected hospitalizations due to all-cause diarrhea following rotavirus vaccine introduction in children, by age group, in selected countries.

Country	Age range	Integral method				Projection method			
		Observed hospitalizations	Expected hospitalizations	Difference	Δ% (CI 95%)	Observed hospitalizations	Expected hospitalizations	Difference	Δ% (CI 95%)
Bolivia	0–1 year	21,772	24,987 ± 80	3215 ± 80	12.9% (12.3%–13.4%)	21,772	25,281 ± 520	3509 ± 520	13.8% (10.3%–17.7%)
	0–5 years	46,646	51,220 ± 420	4574 ± 420	8.9% (7.4%–10.4%)	46,646	52,288 ± 650	5642 ± 650	10.8% (9.0%–12.6%)
El Salvador	0–1 year	20,790	22,464 ± 250	1674 ± 250	7.5% (5.4%–9.5%)	20,790	21,930 ± 400	1140 ± 400	5.2% (1.7%–8.7%)
	0–5 years	51,229	54,250 ± 410	3021 ± 410	5.6% (4.1%–6.7%)	51,229	53,965 ± 920	2736 ± 920	5.1% (1.8%–8.3%)
Honduras	0–1 year	4948	6780 ± 60	1832 ± 60	27.0% (25.7%–28.3%)	4948	6190 ± 190	1242 ± 190	20.1% (15.1%–25.0%)
	0–5 years	12,352	15,048 ± 110	2696 ± 110	17.9% (16.7%–19.1%)	12,352	13,893 ± 410	1541 ± 410	11.1% (5.8%–16.3%)
Venezuela[a]	0–1 year	58,4910	786,260 ± 7500	201,350 ± 7500	25.6% (24.2%–27.0%)	584,910	722,610 ± 14,200	137,700 ± 14,200	19.1% (15.9%–22.2%)
	0–5 years	1,582,480	1,858,700 ± 11000	276,220 ± 11,000	14.9% (13.9%–15.8%)	1,582,480	1887,080 ± 21,000	304,600 ± 21,000	16.1% (14.2%–18.0%)
Argentina	0–5 years	1,974,266	1,975,000	734 ± 10	0.03% (0.25%–0.32%)	–	–	–	–
Total[b]	0–1 year	47,510	54,231 ± 390	6721 ± 390	12.4% (11.1%–13.6%)	47,510	53,401 ± 1110	5891 ± 1110	11.1% (7.3%–14.7%)
Total[b]	0–5 years	110,227	120,518 ± 940	10,291 ± 940	8.5% (7.1%–9.9%)	110,227	120146 ± 1980	9919 ± 1980	8.3% (5.2%–11.3%)

Note: Hospitalizations for the entire period, from vaccine introduction through the last information available, adjusted for population growth.

[a] In Venezuela, outpatient and inpatient cases combined were reported since no disaggregated data were available.

[b] Venezuela and Argentina are excluded from this result.

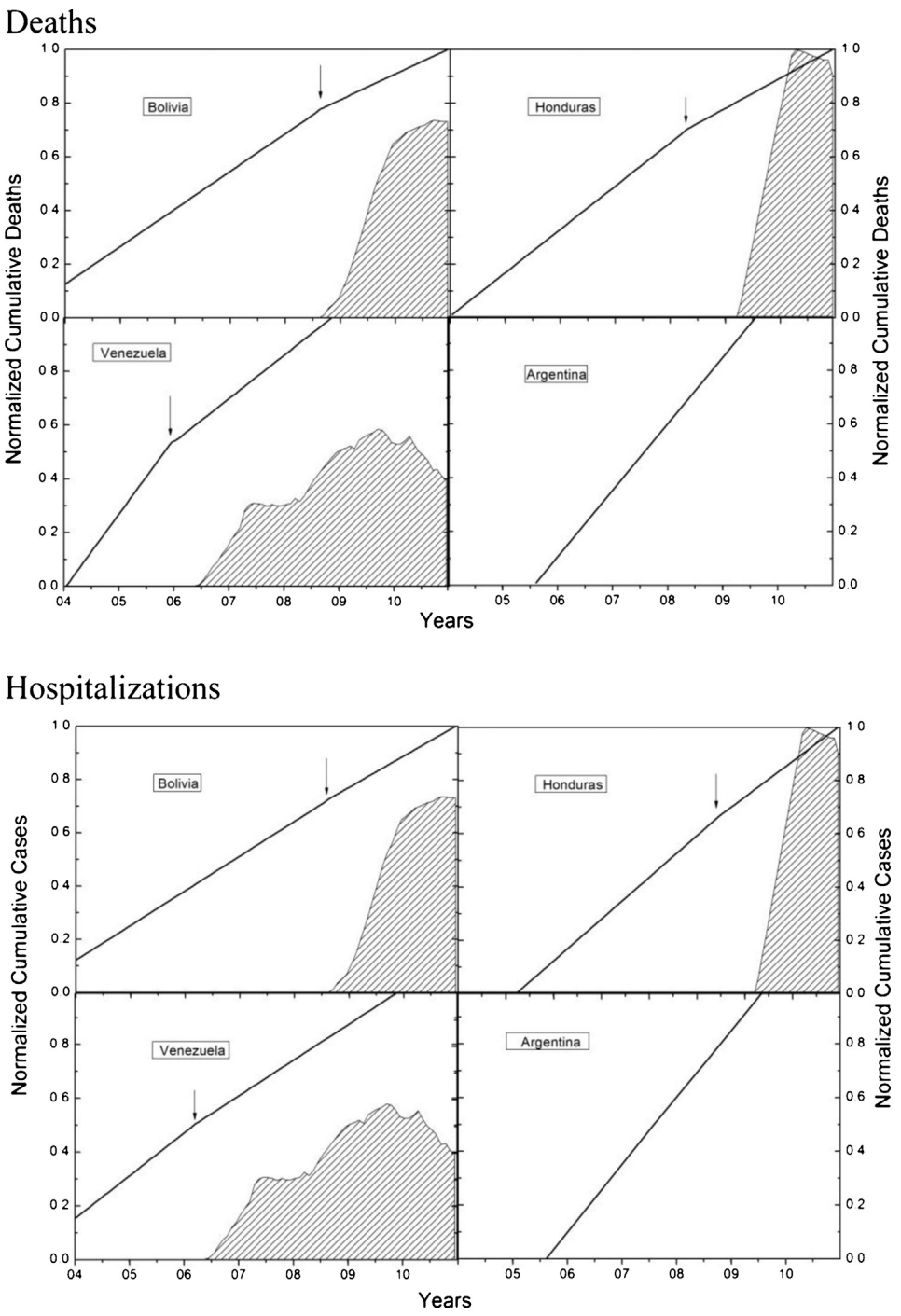

Fig. 2. All-cause diarrhea-related deaths and hospitalizations of children under five in countries where the vaccine has been introduced and in the control country (Argentina). Cumulative number of all-cause diarrhea-related deaths (top) and hospitalizations (bottom) observed in children under five, normalized to the total number of cases during the analyzed period. The arrow indicates when the vaccine was introduced and the shaded area shows cumulative vaccine coverage. It can be noted that in the control country (Argentina), there was no change in the slope, whereas this did occur in other countries where the vaccine was introduced. The *Y* axis indicates the cumulative number of cases, normalized to the total number of cases during the whole period. The quality of the data corresponding to El Salvador deaths was not good enough to be studied with the integral method, as can be observed in Table 2.

(Fig. 2). Due to the high degree of variability observed in the number of events over time in El Salvador, it could not be included in this graph.

Fig. 3 shows a decrease of mean value in the number deaths and hospitalizations in children under 5 years old using the projection method. The shaded areas in Figs. 2 and 3 represent the percentage of cumulative vaccine coverage following vaccine introduction.

The proportion of all-cause diarrhea attributed to rotavirus and the seasonality of cases are shown for each country in Fig. 4.

4. Discussion

Unlike the majority of rotavirus impact studies conducted in Latin America, this analysis evaluates several countries concurrently, using the same design, and comparing them with a control country. This makes it possible to estimate a decreasing trend in rotavirus disease burden regionally following vaccine introduction, so that possible secular changes can be evaluated.

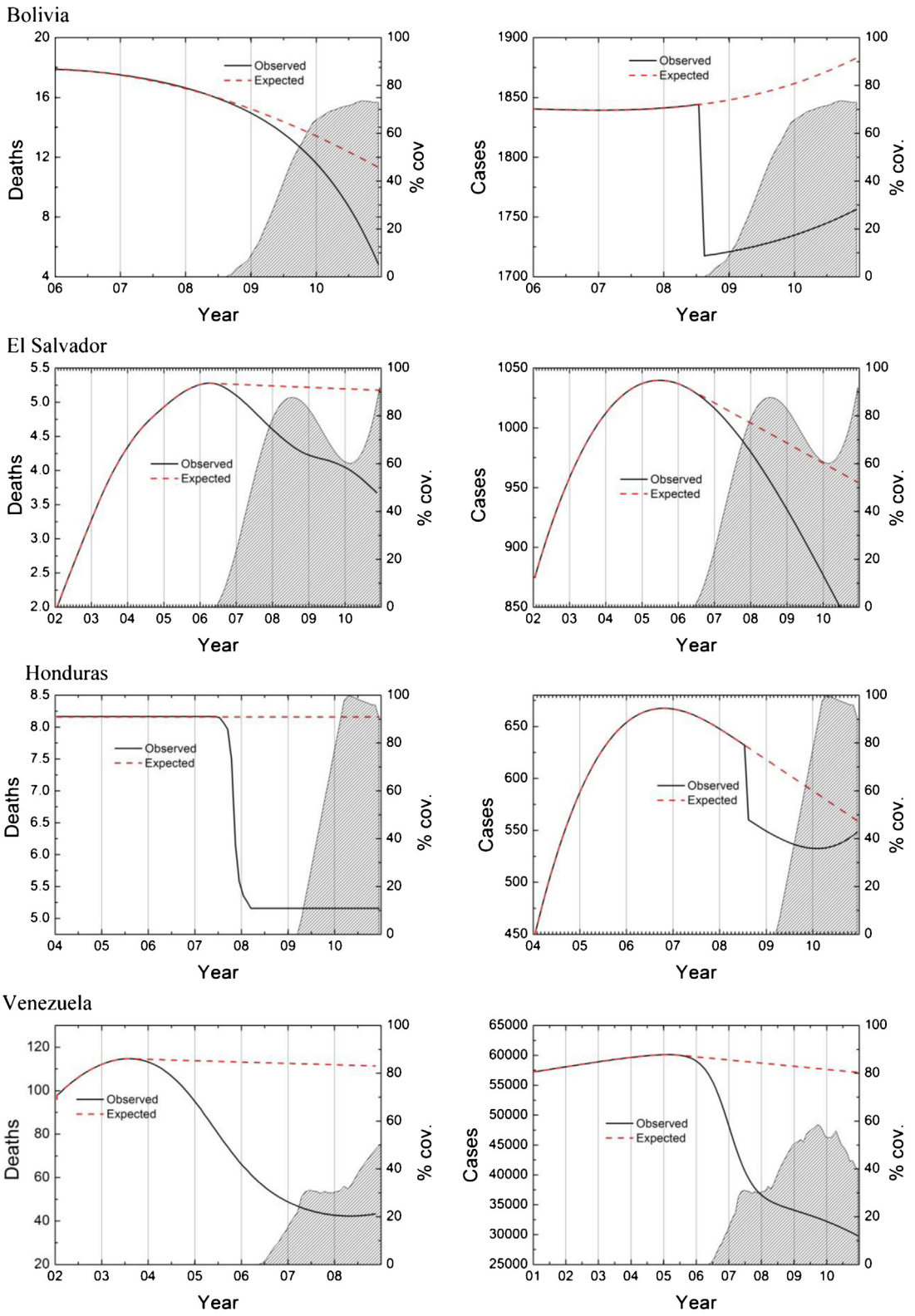

Fig. 3. All-cause diarrhea-related deaths and hospitalizations observed vs. expected
The graphs show deaths (right) and hospitalizations (left) observed and expected for the different countries. The solid line shows the trend observed and the dotted line corresponds to the projection of the trend in the absolute number of deaths (adjusted for population growth based on time series behavior prior to vaccine introduction). The shaded area represents cumulative coverage percentage since introduction of the vaccine, on a scale of 0–100% shown on the right ordinates.

The results show an absolute decrease of approximately 10,000 hospitalizations and between 2000 and 3000 fewer diarrhea-related deaths in children under 5 years old for all of the countries studied following introduction of the rotavirus vaccine as mentioned previously. Venezuela did not have disaggregated data on inpatient and outpatient cases and has therefore not been included in calculations on the reduction of the estimated number of hospitalizations.

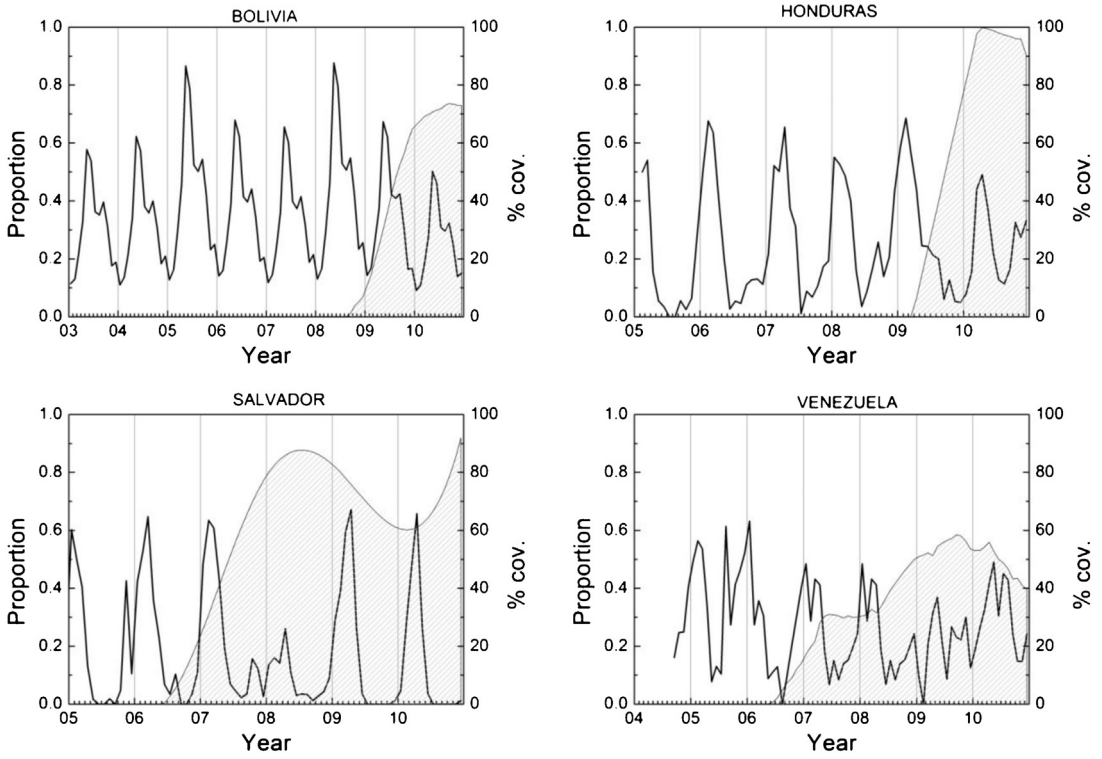

Fig. 4. Monthly ratio of rotavirus diarrhea to total diarrhea cases
On the *y* axis, the proportion of rotavirus diarrhea cases is shown for the different follow-up years shown on the *x* axis.

The data revealed a substantial drop in deaths and hospital admissions occurring after the vaccine had been introduced in Bolivia, Honduras and Venezuela, as shown in Fig. 2. The change in trend appears to happen before the introduction of the vaccine, but this is an artifact of the mathematical method. Regardless of when this change in trend happens, its sole presence suggests impact of the vaccine. If vaccination had no effect, all the curves would be similar to that of the control country (Argentina), which showed a constant slope throughout the whole period.

In the case of Honduras, a decrease was observed in rotaviral disease prior to introduction of the vaccine. This discrepancy in the temporal association may be due to an artificial increase in the number of cases during 2004–2006 as a result of improvements in the surveillance system that resulted in an increase in number of reported cases. However, this observed decrease in rotaviral disease could also be due to the introduction of the vaccine in neighboring countries (Nicaragua and El Salvador in 2006 and Guatemala in 2008) with which Honduras has a continuous population exchange due to inter-regional migration.

The observed reduction in the number of deaths is consistent with the results of studies conducted in Brazil [12,14,29], Panama [11], and Mexico [13]. As in the studies conducted previously in Brazil [12,15], Panama [16], Mexico [17] and El Salvador [18], a decreasing trend was also observed in the number of hospitalizations related to all-cause diarrhea in children under age 5.

Generally, a greater reduction was observed in the number of deaths than in hospitalizations, although this was not as apparent in Honduras and El Salvador. In the case of Honduras, the reduction in deaths and hospitalizations was similar. This may be due to a lack of statistical power given the low absolute number of cases, which makes it difficult to observe differences between events.

In the case of El Salvador, a more pronounced decreasing trend can be observed in the number of deaths than in hospitalizations using the projection method, although this was not observed using the integral method. This may be due to the low number of cases, as well as their high temporal variability.

The greater reduction observed in the number of deaths compared to the reduction in hospitalizations could be due to the fact that the vaccine is particularly effective in preventing severe diarrhea. This is consistent with studies conducted in El Salvador and Nicaragua, where the drop in mortality was more pronounced than the drop in hospitalizations following vaccine introduction [18,23,30]. It is possible that many of the deaths during the pre-rotavirus vaccination period occurred in children who had not been hospitalized due to poor access to health care, which may contribute to this difference. In addition, the majority of deaths or serious cases are found in children under 1 year of age, which is the group that would obtain the greatest protection from the vaccine [31].

The cumulative number of deaths and hospitalizations sustained the same trend over time in the control country (Argentina). In contrast, a decrease could be observed in the four countries that introduced the vaccine, reinforcing the validity of the results obtained, in addition to suggesting certain stability in the health care systems in the region. While it is possible that some structural differences exist, the better quality of water supply and sanitation services found in the control country are not important factors that influence the transmission of rotavirus disease [32,33]. Moreover, some areas of Argentina, specifically the northwest and northeast regions, present similar water and sanitary conditions to the countries selected for this study. Beyond these considerations, situations such as changes in social and health conditions, improvement in access to health care systems, and variations in the reporting patterns of surveillance systems may influence the results.

The results were robust given two different analysis methods used; a difference in disease burden reduction was observed in relation with the control country, and both methods were consistent with previously published studies. The impact of the vaccine would be even more evident had under-reporting in the pre-vaccine introduction period been considered.

In all of the countries, over 65% of total deaths among children 0 to 5 years ocurred in children under 1 year old. This result reinforces the reliability of the reports obtained, since the most serious cases of diarrhea generally occur in children under 1 year old.

Due to the lack of disaggregated information in the 0 to 5 age group, it was not possible to develop an analysis by age sub-groups. It was only possible to report results with a breakdown for 0 to 5 years of age and 0 to 1 year of age, which makes it difficult to prove in all the scenarios proposed that there is a greater impact in children 0 to1 year of age in relation with the 2 to 5 year age group in each scenario proposed.

It was not possible to categorize cases of diarrhea by severity because of study design. Our only indicator of severity of cases was the number of deaths.

The reduction in rotavirus disease burden correlated with vaccine introduction in the countries selected for this study, even though the post-vaccine introduction time series were limited (two to four years) and increase in coverage has been gradual. Although it has not been observed that greater vaccine coverage is associated with greater reduction in morbidity and mortality, it is clear that coverage and morbidity/mortality curves follow an inverse pattern in each study country.

Unresolved questions include impact of vaccination in the medium- and long-term, serotype replacement, and changes in the disease profile. Additional research based on epidemiological surveillance studies of rotavirus will be needed to answer these questions.

This study shows results consistent with other studies conducted on the impact of the rotavirus vaccine in reducing diarrhea-related hospitalizations and deaths in Latin American countries. Furthermore, the study provides evidence of disease burden reduction following the introduction of rotavirus vaccine, especially in diarrhea-related deaths in four countries of Latin America, using two different methods. These findings have important global health policy implications to help decision makers considering the introduction of rotavirus vaccine to their national immunization schedules.

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Review

Critical issues in implementing a national integrated all-vaccine preventable disease surveillance system☆

Terri B. Hyde[a,*], Jon K. Andrus[b], Vance J. Dietz[a], The Integrated All-VPD Surveillance Working Group, Jon K. Andrus[c], Terri B. Hyde[d], Carla E. Lee[d], Marc-Alain Widdowson[d], Jennifer R. Verani[d], Cindy Friedman[d], Eduardo Azziz-Baumgartner[d], Adriana S. Lopez[d], Aisha Jumaan[d], Vance J. Dietz[d]

[a] Global Immunization Division, US Centers for Disease Control and Prevention (CDC), 1600 Clifton Road NE, Atlanta, GA 30333, USA
[b] Comprehensive Family Immunization Project, Pan American Health Organization (PAHO), 525, 23rd Street, N.W., Washington, DC 20037, USA
[c] Pan American Health Organization (PAHO), USA
[d] U.S. Centers for Diseases Prevention and Control (CDC), USA

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ABSTRACT

In 2007, the World Health Organization published the Global Framework for Immunization Monitoring and Surveillance (GFIMS) outlining measures to enhance national surveillance for vaccine preventable diseases (VPDs). The GFIMS emphasized that VPD surveillance should be integrated and placed in a 'unified framework' building upon the strengths of existing surveillance systems to prevent duplication of activities common to all surveillance systems and to minimize human resource and supply expenditures. Unfortunately, there was little experience in actually developing integrated VPD surveillance. We describe the process of developing operational guidance for ministries of health to implement such an integrated surveillance system for multiple VPDs.

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Contents

1. Introduction

Surveillance is the foundation of sound public health practice; however, disease surveillance systems are often fragmented and vertical, based on the characteristics of the targeted disease or syndrome, and the characteristics of the existing public health infrastructure. To address the need for surveillance for vaccine preventable diseases (VPDs), in 2007, the World Health Organization published the Global Framework for Immunization Monitoring and Surveillance (GFIMS), which outlines measures that ministries of health may take to enhance national VPD surveillance [1]. The GFIMs emphasizes that VPD surveillance should be integrated and placed in a 'unified framework' that builds upon the strengths of existing surveillance systems rather than being implemented as new disease-specific and vertical systems. The main goal of an integrated VPD (iVPD) surveillance system is to prevent duplication of activities that are common to all surveillance systems and at the same time to minimize human resource and supply expenditures. Global immunization partners viewed the GFIMS as a welcome framework, at a time when multiple new and underutilized vaccines were entering developing world markets. These new products are costly compared with existing Expanded Programme on Immunization vaccines, and their introduction must be

☆ The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author at: Global Immunization Division, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS-A04, Atlanta, GA 30333, USA. Tel.: +1 404 639 8764; fax: +1 404 235 3566.
E-mail addresses: thyde@cdc.gov, terri.hyde@cdc.hhs.gov (T.B. Hyde), andrusjo@paho.org (J.K. Andrus), vdietz@cdc.gov (V.J. Dietz).

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prioritized among other health interventions. In addition to providing routine vaccination program monitoring information, iVPD surveillance data may demonstrate disease impact through a streamlined system that minimizes redundancy and is beneficial and efficient. Enhanced integrated surveillance systems could potentially assist in reaching multiple disease surveillance objectives while providing quality data for decision makers at national and international levels. Building these systems upon the existing national communicable disease network will ideally strengthen surveillance for all communicable diseases of public health importance.

Despite the recommendation from the World Health Organization (WHO) and major partners for expansion of VPD surveillance and immunization program monitoring, countries continued to struggle to implement efficient iVPD surveillance systems even after the GFIMS had been developed and widely distributed, as it did not provide operational guidance for implementation. Few countries had experience in iVPD surveillance systems apart from febrile rash illness surveillance to detect measles and rubella in the Americas [2,3]. The most developed VPD surveillance system globally is the acute flaccid paralysis network, a highly sensitive, but vertical, single disease surveillance system for the detection of poliomyelitis [4]. Examples of other stand-alone systems include regional, sub-regional or national surveillance for influenza-like illness, sentinel site surveillance for meningitis in Africa (Pediatric Bacterial Meningitis [PBM] surveillance) [5], sentinel surveillance for invasive bacterial disease in the Americas (Sistema Regional de Vacunas [SIREVA]) [6], and the global rotavirus surveillance network [7]. Thus, while public health experts believed that iVPD surveillance was a more economic and efficient system, little was known about how to develop and implement a practical and relevant iVPD surveillance system, which surveillance components could feasibly be integrated, and what the programmatic and financial benefits of integrating surveillance for multiple VPDs would be.

The GFIMS' call for the development of iVPD surveillance was timely, given the increasing availability of vaccines for diseases caused by Streptococcus *pneumoniae* (pneumococcus), rotavirus, influenza virus, and human papilloma virus (HPV) in the developing world. Furthermore, the increased uptake of underutilized vaccines such as Haemophilus *influenzae* type b (Hib) vaccine and regionally important vaccines such as Japanese Encephalitis (JE) and Yellow Fever (YF) vaccines further highlighted the need for strengthened or new surveillance to estimate the local burden of disease and monitor the impact of vaccine introduction [8].

New vaccine introduction generally involves significant expense [9]. For example, in addition to the purchase of new vaccines for the routine immunization program, expansion of existing cold chain capacity and enhancement of other vaccine delivery logistics typically require substantial investments. What was less clear; however, was how to develop quality surveillance necessary for diseases targeted by new vaccines, how to link it with existing vertical disease surveillance systems, and how much additional investment will be required for the system. In 2007, immunization experts at the US Centers for Disease Control and Prevention (CDC), WHO Headquarters and the Pan American Health Organization (PAHO) began to discuss the feasibility of integrating surveillance for multiple diseases. Critical issues related to the potential benefits and limitations of integration were addressed, including which diseases were candidates for integration, which surveillance components could feasibly be integrated, and ways to integrate laboratory and data management activities. We present the process that went into developing operational guidance for ministries of health and the lessons learned in consideration of preparing generic guidelines for integrated "all-VPD surveillance" for countries to adapt to their national circumstances. This is the first time that this process has been undertaken for the integration of VPD surveillance, and while we do not present data from an in-country implementation, our experience may be helpful to countries considering embarking on this type of work. This CDC and PAHO collaboration has led to opportunities to pilot the generic protocol in the Americas.

2. Conceptual development of integrated surveillance

At the onset of the process, it was not known how an integrated product for surveillance would be structured or whether it was a realistic goal within a national context. Before identifying the critical issues to be addressed and the requirements for developing an all-VPD surveillance system, it was important to reach consensus about the definition of the word "integration" in the context of VPD surveillance. "Integrate" is defined as "to form, coordinate, or blend into a functioning or unified whole", or "to unite with something else" [10]. Thus, while integration denotes a process for combining, it does not in itself refer to the impact of such an action, and nothing inherent in the definition suggests a positive or negative outcome. The term "synergy", on the other hand, refers to the "interaction of discrete agents such that the total effect is greater than the sum of the individual effects" [11]. The "integrated" surveillance system envisioned was one that would result in synergy, with improved efficiency of resource use, and surveillance performance greater than that of the individual single-disease systems, recognizing that a universal fully integrated surveillance system will not fit all diseases, and it is unlikely that one can be fully achieved. This is partially due to fundamental differences in objectives and methods of surveillance for certain diseases, which do not allow a complete integration.

The integration of surveillance for VPDs may be approached in several ways. Our approach focused on the syndromes associated with diseases prevented by vaccines already in the EPI program as well as by vaccines soon to be added. While global or regional surveillance goals have been established for most of these 'EPI diseases', the objectives for surveillance for a particular disease will define the structure of the surveillance system and the type of surveillance conducted (e.g. sentinel or population-based, target age-group, clinical only or lab-based). For some diseases, for example, it may be important to detect every case in order to reach a goal to eradicate or eliminate the etiologic agent, (e.g. polio globally, measles, and rubella in selected Regions); however, for other diseases detection of disease trends is sufficient (e.g. rotavirus gastroenteritis). An alternative approach may be to conduct surveillance for syndromes that can result from both VPDs and non-VPDs. In the case of acute gastroenteritis, this might include testing stool specimens for other common diarrheal pathogens, such as salmonella and shigella. While a stool specimen is needed for laboratory identification of all these pathogens, the disease surveillance goals for each disease may differ, and surveillance may target different populations. For example, the goal of rotavirus surveillance in the context of vaccine introduction is to provide information on vaccine impact, whereas surveillance for salmonella and shigella is primarily targeted at monitoring disease trends and detecting outbreaks and may therefore include a broader target age group. These differing surveillance goals overlap in the population less than five years of age, where the majority of rotavirus disease occurs and which is targeted by the rotavirus vaccination program, however, this group represents only a small subset of the total population that needs to be followed to identify disease caused by the other diarrheal pathogens.

The integrated VPD surveillance protocol focused on clinical syndromes associated with VPDs that already had established global surveillance goals. These syndromes (and the diseases or

disease agents that cause them) included acute flaccid paralysis (AFP [polio]), acute fever and rash (AFR [measles, rubella, varicella]), influenza-like illness (ILI [influenza, pertussis]), meningitis (Hib, pneumococcus, meningococcus), Severe Acute Respiratory Infection (SARI [influenza, pertussis, pneumococcus, Hib]), and acute gastroenteritis (AGE [rotavirus]). We did not include certain VPDs of regional importance such as Yellow Fever and focused on the VPDs for which vaccines either are being introduced or are currently in use globally. We recognize that many other pathogens may cause the syndromes under surveillance, but as the focus of the protocol was collection of information about vaccine impact, we elected not to consider non-VPD pathogens. As a first step, immunization partners identified key surveillance system characteristics that were necessary to begin the process of integrating VPD surveillance. We understood that some surveillance systems may not easily be integrated, particularly if different government departments outside the immunization program were responsible for the different VPD surveillance systems. Hence, one critical requirement for a successful iVPD surveillance system is high level government support that can bring together stakeholders from different departments, including epidemiologists, virologists, and other key groups.

We next identified ten major attributes of a VPD surveillance system (Table 1). These include (1) the existence and use of case definitions, (2) a case detection system, (3) a process for case notification, (4) procedures for case investigation, including standardized data variables, (5) data management procedures, including data analysis and information reporting, (6) outbreak response guidelines, (7) laboratory algorithms and standard procedures, (8) final classification procedures, (9) feedback to partners and (10) clear program management and supervision. We then created a matrix that mapped these surveillance system attributes for each VPD, and grouped individual diseases by syndrome when possible, to facilitate integrated case detection and investigation (Table 2). Through group discussions and analysis, we identified synergies among different disease surveillance system attributes, and used these to determine which attributes within a surveillance system for a given VPD could be combined with those for another VPD.

We further refined the initial matrix and analysis within the context of WHO-recommended regional and country level VPD surveillance activities, based on currently recommended vaccines. We considered as possible sites for implementation of a pilot project to develop an iVPD surveillance system those countries whose VPD surveillance systems included the above-mentioned attributes. Immunization experts from PAHO in Washington, DC wished to identify a country to pilot the integrated system in order to gain practical experience.

2.1. Development of generic protocol for integrated VPD surveillance

We recognized that remodeling established stand-alone systems may be more challenging than merging new systems into an existing VPD disease surveillance infrastructure. For example, data information systems developed for specific VPD surveillance and existing surveillance data information systems may not be compatible with one another, and this may prevent integration of some system components, thereby limiting the integration of information flow and use. In addition, the priorities and funding streams for single and separate disease initiatives may limit the ability to combine activities or purchases required to combine tasks for different syndromes, including purchasing laboratory equipment or hiring personnel. Bearing these constraints in mind, we developed guidelines using an approach to help characterize the structure of an integrated VPD surveillance system, with the understanding that there may be different national, regional, and global objectives. Ideally, a surveillance system should be sufficiently flexible to meet the needs of all administrative levels, taking into consideration global and regional disease elimination (measles, rubella) and eradication (polio) goals, as well as overall disease control and strain monitoring (influenza, Hib, pneumococcus, and rotavirus) goals. We included the VPDs that required laboratory confirmation for case classification, and considered each disease individually in terms of the type of surveillance that was needed, based on national control objectives (e.g. population-based vs. sentinel surveillance), as well as whether surveillance needed to be conducted in hospitals, clinics or in all health-care facilities. We further considered each component of a surveillance structure needed for a particular disease, including the type of case detection required (active or passive), patient volume needed to detect trends for each disease, the type of investigation (aggregate case counts or case-based investigation), type of laboratory specimen and testing needs, and the type (aggregate or individual case/lab data) and frequency (monthly or weekly) of reporting. For instance, in order to identify every measles case and meet elimination goals, every administrative level of the health care system conducts measles surveillance. On the other hand, the aim of rotavirus disease surveillance is identification of a sample of case-patients with the most severe presentations, in order to assess vaccine impact and identify circulating genotypes that are causing disease. The most appropriate structure for this is hospital-based sentinel surveillance for children under age five years hospitalized for treatment of acute diarrhea. After reviewing the unique surveillance needs of the target diseases, we compared the surveillance objectives for each disease to determine how to integrate new and existing elements within existing systems, keeping in mind the necessary surveillance type, structure, and investigation; the need for laboratory testing; and the type and frequency of reporting.

We selected a surveillance structure that consisted of a combination of population-based and sentinel site surveillance. We grouped diseases by both syndromes and age-groups under surveillance, and then integrated activities or surveillance components for the target diseases when appropriate and feasible. For example, we combined surveillance activities for diseases that shared similar case-finding and investigation procedures, and repeated this process for issues related to laboratory samples, data management, analysis, and feed-back. We developed a generic protocol that included clinical, laboratory, and reporting procedures (Figs. 1 and 2) and surveillance algorithms for national use and adaptation, and identified key variables for case investigation forms and issues to consider in both sentinel site and population-based surveillance forms. The goal was to align the procedures with existing national and regional surveillance guidelines for each disease included.

3. Requirements for pilot project

To identify a country to pilot the surveillance integration, we identified key requirements (Fig. 1). As previously noted, clear interest and agreement by the national ministry of health, with a commitment to sustainability with national funds and only modest donor support was critical. Since the system was to include surveillance for diseases prevented by new vaccines, a pilot country needed to have early adoption of one or more new vaccines as well as existing laboratory capacity. In addition, the national Ministry of Health needed to agree to partner with the private sector as well as with international agencies. Finally, since it would be a pilot project, we requested that the site for the initial implementation of the iVPD surveillance system agree to share lessons learned and economic costing information with the international community. Following discussions with PAHO and with the agreement and

Table 1
Attributes of disease-specific surveillance systems that could feasibly be integrated with at least one other disease-specific surveillance system.

	Polio	Measles	Rubella	Haemophilus influenza type b	Pneumococcus	Influenza	Rotavirus	Varicella	Pertussis
System of notification									
Case definition	–	+	+	+	+	+	–	+	+
Case detection	+	+	+	+	+	+	+	+	+
Case notification	+	+	+	+	+	+	+	+	+
Case investigation	+	+	+	+	+	+	+	+	+
Data management									
Analysis	+	+	+	+	+	+	+	+	+
Feedback	+	+	+	+	+	+	+	+	+
Case classification[a]	+	+	+	+	+	+	+	+	+
Outbreak response	–	–	–	–	–	–	–	–	–
Laboratory aspects									
Quality control	+	+	+	+	+	+	+	+	+
Training	+	+	+	+	+	+	+	+	+
Specimen processing	–	–	–	+	+	–	–	–	–
Management coordination	+	+	+	+	+	+	+	+	+

+ = amenable to integration, – = not amenable to integration.
Feasibility for integration – whether this surveillance element of the VPD could be combined/integrated with the same element of another VPD.
[a] Case classification dependent on specific laboratory testing for each disease.

Table 2
Proposed integrated surveillance by health care site, syndromes, and diseases.

Location	Syndrome	Diseases/infections
All health care sites (entire population)	Acute flaccid paralysis	Polio
	Fever/rash	Measles, rubella
Sentinel clinic(s)	Moderate acute gastroenteritis[a]	Rotavirus
	Fever/rash (non-measles/rubella)	Varicella
	Influenza-like illness	Influenza, pertussis
Sentinel hospital	Severe gastroenteritis[b]	Rotavirus
	Meningitis	*Haemophilus influenzae*, pneumococcus, meningococcus
	Severe acute respiratory illness	*Haemophilus influenzae*, pneumococcus, influenza, pertussis

[a] Moderate gastroenteritis – not requiring hospitalization; may be considered if resources are available and countries would like more information on baseline and rotavirus vaccine impact on moderate gastroenteritis caused by rotavirus.
[b] Severe gastroenteritis – requiring hospitalization.

interest of the government of Costa Rica, the iVPD surveillance was pilot-tested in Costa Rica.

4. Implementation and the way forward

The next step in the integration process was to implement the protocol at a national level to learn the extent to which the integration could be achieved within an established system. With technical assistance from CDC and PAHO, the Costa Rica Ministry of Health began the implementation process in 2008 [12]. Toscano and colleagues have detailed the incremental costing of the implementation of the project [13], and lessons learned by Costa Rica's experience will provide key information on the practical application and sustainability of an iVPD surveillance system.

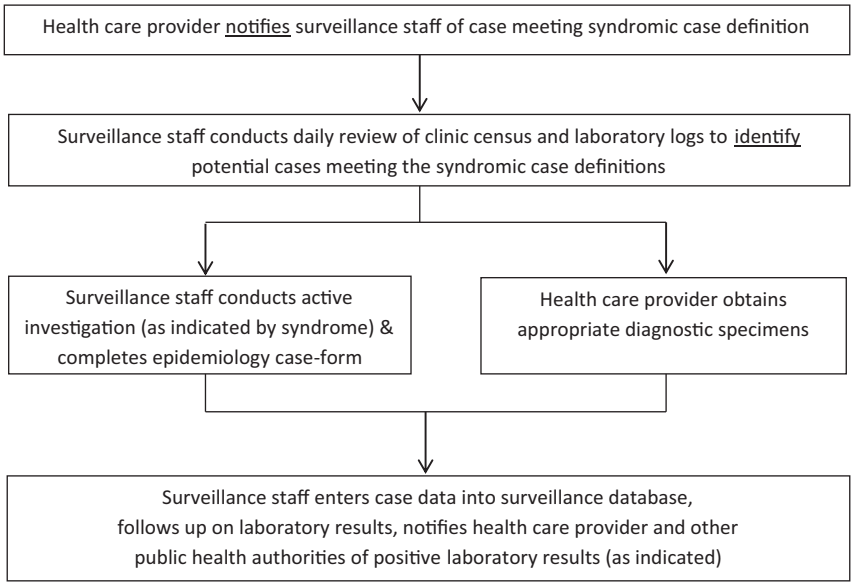

Fig. 1. Syndromes and diseases under surveillance, age groups, laboratory specimen for collection; clinical surveillance algorithm.

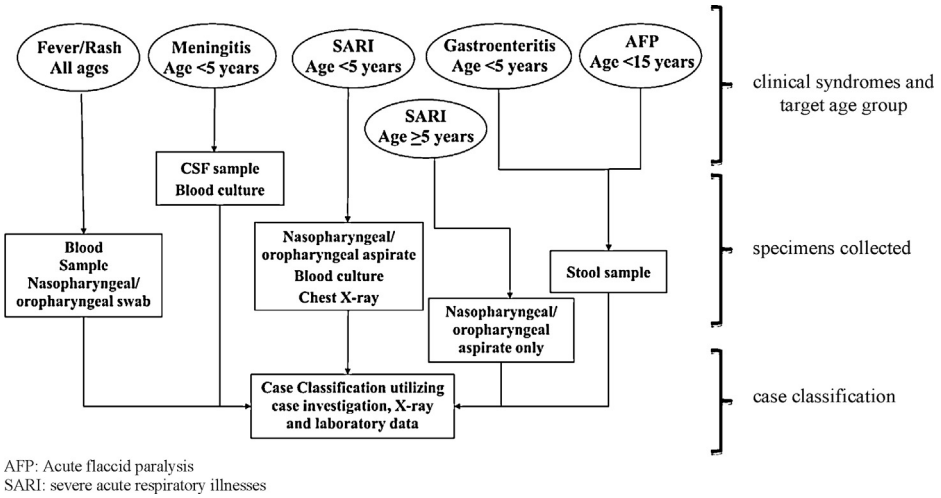

Fig. 2. Syndromes and age groups targeted for surveillance, samples collected for each syndrome and process of case-classification – integrated vaccine-preventable diseases surveillance.

This integration process focused on building upon existing measles, rubella, and polio surveillance networks and expanding to include diseases whose vaccines have been prioritized by WHO such as Hib, pneumococcus, and rotavirus. The addition of other diseases, such as influenza and pertussis demonstrated the flexibility that an integrated surveillance system should possess in order to be able to include additional diseases in the network and then to be adapted to the country or regional priorities.

Ministries of health choosing to implement an integrated all-VPD surveillance system should identify and prioritize attributes within the existing national disease surveillance system that can be feasibly integrated. However, it must be recognized that a universal fully integrated surveillance system will not fit all diseases and likely cannot be achieved. This is partially due to fundamental differences in objectives and methods of surveillance for certain diseases, which may not allow a complete integration. Nonetheless, there are many components of a surveillance system that can be integrated, thereby improving efficiency and optimizing limited resources. The protocol developed and implemented as a field guide in Costa Rica continues to evolve. An important lesson learned is that any approach to iVPD surveillance must be flexible and must be able to respond to local conditions. Accordingly, the field guide continues to be modified and evaluated. Once finalized, this guide will be distributed for use in other countries and regions of the world. Our experience demonstrates that expectations from the start have always been high, but those expectations need to be balanced and adjusted appropriately with the realities of the field. Sustaining the commitment to do so will be a challenge in any country.

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Review

Effectiveness of the 7-valent pneumococcal conjugate vaccine against vaccine-type invasive disease among children in Uruguay: An evaluation using existing data

Teresa Picón[a], Lucía Alonso[b], Gabriela García Gabarrot[c], Noelia Speranza[a], Mariana Casas[d], Fernando Arrieta[e], Teresa Camou[c], Raquel Rosa[b], Lucia Helena De Oliveira[f], Jennifer Rabke Verani[g,*]

[a] Immunization Unit, Epidemiology Division, Ministry of Public Health, Montevideo, Uruguay
[b] Epidemiology Division, Ministry of Public Health, Montevideo, Uruguay
[c] National Reference Laboratory, Ministry of Public Health, Montevideo, Uruguay
[d] Surveillance Department, Epidemiology Division, Ministry of Public Health, Montevideo, Uruguay
[e] Immunization Department, Honorary Commission for the Fight Against Tuberculosis and other Prevalent Diseases, Montevideo, Uruguay
[f] Pan American Health Organization, Washington, DC, USA
[g] Respiratory Diseases Branch, Division of Bacterial Diseases, Centers for Disease Control and Prevention, Atlanta, USA

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ABSTRACT

The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the routine immunization program in Uruguay in March 2008 with a 2-dose primary series (given at 2 and 4 months) plus a booster (at 12 months) and a catch-up campaign (two doses given at 15 and 17 months). We used a case–control methodology and existing laboratory surveillance and immunization registry data from Uruguay to evaluate PCV7 effectiveness against vaccine-type invasive pneumococcal disease (VT-IPD). Cases of VT-IPD (with pneumococcus obtained from a normally sterile site) were identified through the National Reference Laboratory. Age- and neighborhood-matched controls were obtained through a national immunization registry in which all children are enrolled at birth regardless of vaccine receipt; all eligible controls were included. Immunization status of cases and controls was assessed through the immunization registry, and conditional logistic regression was used to calculate PCV7 effectiveness. Between April 2008 and February 2010, 44 cases of VT-IPD among children < 5 years were identified; 43 (98%) of those children were located in the registry. Among located case patients, 7 (16.3%) were age-eligible to have received at least one dose of PCV7. A total of 637 matched controls were included. Vaccine effectiveness was 91.3% (95% CI: 46.4, 98.6) for ≥1 PCV7 doses and 94.8% (95% CI: 43.1, 99.5) for ≥2 PCV7 doses. Using existing data we demonstrated high effectiveness of PCV7 against VT-IPD in Uruguay–a middle-income country using a 2-dose primary series plus a booster dose and a limited catch-up campaign. These data also highlight the utility of surveillance and high-quality immunization registries for evaluating the effectiveness of vaccines.

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* Corresponding author. Tel.: +1 404 639 8652.
E-mail address: jverani@cdc.gov (J.R. Verani).

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1. Introduction

Streptococcus pneumoniae is an important cause of childhood morbidity and mortality worldwide, causing an estimated 826,000 deaths per year, with the vast majority of those deaths occurring in low- and middle-income countries [1]. In Uruguay, a middle-income country in South America, *S. pneumoniae* was shown to be the most common bacterial cause of community-acquired pneumonia [2–6] and the leading cause of bacterial meningitis [6]. As in other areas of the world, the greatest burden of pneumococcal disease in Uruguay is among children < 5 years – particularly those less than 2 years old [1,6].

The 7-valent pneumococcal conjugate (PCV7), which includes serotypes 14, 4, 6B, 9V, 18C, 19F, 23F, was introduced into the routine immunization program in Uruguay in March 2008. Prior to PCV7 introduction, approximately 50% invasive pneumococcal disease episodes among children < 5 years in Uruguay were caused by PCV7 serotypes [7,8]. The dosing schedule in Uruguay included a 2-dose primary series given at 2 and 4 months of age and a booster dose given at 12 months (2 + 1 schedule). A two-dose catch-up series was also offered to the 2007 birth cohort (who were aged 3–15 months at the time of introduction), with doses given at ages 15 and 17 months during visits for routine health care. Routine infant immunizations in Uruguay are free for all children. PCV7 coverage with three doses among 1–2 year olds during 2008 and 2009 was 93 and 91% respectively. In March 2010, PCV7 was replaced by the 13-valent pneumococcal conjugate vaccine (PCV13).

While the efficacy of PCV7 and PCV9 (a similarly formulated vaccine that also included serotypes 1 and 5) have been studied in a variety of settings [9–12], and the effectiveness of PCV7 has been measured in high-income countries [13–19], there is paucity of data on PCV effectiveness in low- and middle-income countries. In addition, while data has become available on the effectiveness of 2 + 1 PCV dosing schedules in high-income countries [16,20,21], the effectiveness of such a schedule in a middle-income country is unknown. In Uruguay, a stable laboratory-based surveillance system for invasive pneumococcal disease (IPD) and a national immunization registry provided a unique opportunity to evaluate PCV7 effectiveness against IPD using existing data sources.

2. Methods

We used a matched case–control methodology and existing laboratory surveillance data from the Ministry of Public Health to measure the effectiveness of PCV7 against vaccine-type IPD (VT-IPD) among children during the period in which PCV7 was in use in Uruguay.

2.1. Cases

Cases were defined as IPD (*S. pneumoniae* isolated from a normally sterile site such as blood or cerebrospinal fluid) due to a PCV7 serotype in a child who was age-eligible for at least one dose of PCV7 at the time of illness. Age-eligibility for PCV7 was based on the dosing schedules for different birth cohorts, and we assumed that it would take 2 weeks for a PCV7 dose to have a protective effect. Thus, children born on or after January 1, 2008 had to be at least 2 months and 2 weeks old on their culture date (or on the date their isolate was received at NRL if no culture date was available); children born in 2007 had to be at least 15 months and 2 weeks old. Children with cultures received between April 2008 and February 2010 were eligible.

Cases were identified through on-going passive laboratory-based surveillance for IPD. Surveillance has been conducted by the National Reference Laboratory (NRL) since 1994. Participation in the surveillance system is voluntary and open to microbiologists throughout the country. *S. pneumoniae* isolates from normally sterile sites of patients of all ages are sent to NRL, along with patient identifiers, clinical diagnosis, date and source of sample. At NRL the isolates undergo testing to confirm identification of *S. pneumoniae*, assess antimicrobial susceptibilities, and determine serotype (using the Quellung reaction, with antisera from Serum Staten Institute, Denmark). Laboratory procedures are subject to external quality control carried out by the SIREVA II Network [22], coordinated by the Pan American Health Organization via a regional center at the Adolfo Lutz Institute in Brazil. NRL is the only laboratory in Uruguay that serotypes *S. pneumoniae* isolates.

2.2. Controls

Controls were identified through a national immunization registry. All children are entered at (or soon after) birth and the registry is considered to be the most complete listing of children in the country. The accuracy of the listing of children in the registry compared with other official data sources (including the national civil registry, census projections and the newborn screening program) has been estimated to be 100% (95% confidence interval of 98.8–100%) [23]. The registry includes vaccinated and non-vaccinated children. Routine infant immunizations in Uruguay are procured only through the Ministry of Public Health, and administered doses must be recorded in the registry. All providers (in the public or private sector) fill a paper form for each routine infant immunization administered, including the vaccine, date given, and identifying information for the child who received the vaccine. Data are entered centrally into an electronic data base that is used to generate reports on vaccine coverage and reminders for health centers about under-immunized children. Data in the registry include: name, sex, place of birth, date of birth, identification document number, place of immunization, vaccine(s) received, mother's name, police precinct, telephone number and alternate address. An independent external evaluation of the registry found the data to be highly reliable and valid, with an estimated 100% accuracy for both doses administered and denominator [23].

Controls were matched by date of birth (±1 month) to cases and also had to be age-eligible for at least one PCV7 dose (as described above for cases) on their corresponding case's culture date. Controls were also matched by police precinct – a relatively small geographic zone. We aimed to enroll a minimum of 5 controls per case, however there was no upper limit of controls; all eligible controls identified in the registry for each case were included. If controls were eligible to be matched to more than one case, they were matched to the case with the closer date of birth. Potential controls were excluded if known to be IPD cases during the study period.

2.3. Data collection and analysis

Parents of case patients and controls were not contacted; data were obtained only from the immunization registry. Case patients were identified in the registry using name, date of birth and geographic location. Case patients that could not be located in the registry were excluded. A list of matched controls was generated from the registry database. Vaccination history (including all vaccines received and dates of receipt), date of birth, and sex were obtained for both case patients and controls from the registry.

A de-identified dataset was exported into Excel (Microsoft Corporation, Redmond, WA, USA). Analysis was conducted in SAS v.9.2 (SAS Institute, Cary, NC, USA). Doses of vaccine received at least 2 weeks prior to the culture date for case patients (and the corresponding case patient's culture date for controls) were considered in the analysis. Conditional logistic regression was used

Table 1
Case characteristics, vaccination status, and number of matched controls.

ID#	Case year	Sex	Birth cohort	Age at culture (months)	Serotype	PCV7doses eligible	PCV7doses received	Up-to-date for age for PCV7	Number of controls
1	2008	F	2007	16.2	14	1	0	No	235
2	2009	F	2007	28.1	14	2	1	No	100
3	2009	M	2007	30.7	6B	2	0	No	91
4	2009	M	2007	15.8	14	1	0	No	24
5	2009	M	2008	5.8	14	2	0	No	41
6	2009	F	2008	16.3	23F	3	3	Yes	72
7	2009	F	2008	11.0	6B	2	0	No	74

to estimate PCV7 effectiveness against VT-IPD using the following formula: effectiveness = (1 − matched odds ratio for PCV7 vaccination) × 100. We examined the effectiveness of 1 dose, ≥1 dose, ≥2 doses, and up-to-date for age. For children born in 2008–2009 (eligible for full schedule), up-to-date was defined as: ≥1 dose among those age <4 months and 2 weeks, ≥2doses among those age ≥4 months and 2 weeks to <12 months and 2 weeks, and ≥ 3 doses for those age ≥12 months and 2 weeks. For those born in 2007 (eligible for catch-up doses), up-to-date was defined as ≥1 dose among those age <17 months and 2 weeks, and ≥2 doses among those age 17 months and 2 weeks. Sex was assessed as a potential confounder; data were not available for other potential confounders.

2.4. Human subjects

This evaluation utilized existing data and was deemed to be a public health evaluation and not human subjects research. The protocol was reviewed and approved by the Uruguayan Ministry of Public Health.

3. Results

Between April 15, 2008 and February 28, 2010, a total of 131 cases of IPD among children < 5 years had isolates tested at NRL. Among those cases, 44 (34%) were caused by serotypes included in the 7-valent vaccine; 43 (98%) of those had sufficient information to locate the case patient in the vaccine registry. Among the case patients located in the registry, 28 (65%) were born in birth cohorts that were eligible to receive vaccine (2007 and 2008); of those, 7 (25%) were age-eligible to have received at least one dose of PCV7 at least 2 weeks prior to their culture date.

The characteristics of the 7 eligible VT-IPD case patients are presented in Table 1. The median age of case patients was 16.2 months, with a mean of 17.7 months and a range from 5.8 to 30.7 months. One case occurred in 2008 and the remainder in 2009. Of the 7 cases, 4 were in children born in 2007, and therefore eligible to receive PCV7 catch up doses, and 3 were in children born in 2008 and eligible for a primary series and potentially a booster dose.

A total of 637 controls were identified in the immunizations registry. The number of age- and police precinct–matched controls for each case ranged from 24 to 235. No children were listed as a potential control for more than one case and none were identified as having IPD by NRL; therefore all potential controls were included. The demographic characteristics and vaccination status of case patients and controls are detailed in Table 2. Cases and controls were similar with respect to age and sex. Among the 7 case patients, 5 (71.4%) had received no PCV7 doses, compared with 232 (36.4%) of controls. Among controls, 330 (51.8%) were up-to-date for age with respect to PCV7 doses at least 2 weeks prior to the culture date of their corresponding cases; among case patients, only 1 (14.3%) was up-to-date.

Table 2
Sex, age and number of PCV7 doses received for case patients and controls.

	Cases $n = 7$ n (%)	Controls $n = 637$ n (%)
Male	3 (43)	339 (53)
Age (months)		
Range	5.8–30.7	4.8–31.6
Mean	17.7	19.0
Median	16.2	16.6
Number of PCV7 doses		
0	5 (71.4)	232 (36.4)
1	1 (14.3)	136 (21.4)
2	0 (0)	221 (34.7)
3	1 (14.3)	48 (7.5)
1 or more	2 (28.6)	405 (63.6)
2 or more	1 (14.3)	269 (42.2)
Up-to-date for age	1 (14.3)	330 (51.8)

The results of conditional logistic regression to estimate vaccine effectiveness are presented in Table 3. One dose of PCV7 had an estimated effectiveness of 82.7% against VT-IPD, although with confidence intervals that included no effectiveness. One or more doses was 91.3% (95% CI: 46.4, 98.6) effective while the effectiveness of two or more doses was 94.8% (95% CI: 43.1, 99.5). Having a PCV7 vaccination status that was up-to-date for age was 88.8% effective against VT-IPD, with non-significant confidence intervals. Adjusting for sex did not substantially alter PCV effectiveness estimates.

4. Discussion

This study provides evidence of high PCV7 effectiveness against VT-IPD in the context of the routine immunization program in Uruguay by using existing laboratory surveillance and immunization registry data. To our knowledge these are the first post-marketing data estimating PCV7 effectiveness against IPD in a middle-income country. While the confidence intervals are wide because of the small number of cases, the point estimates are similar to those of efficacy trials and effectiveness studies in other settings. Clinical trials of PCV7 conducted in the United States found

Table 3
7-valent pneumococcal conjugate vaccine (PCV7) effectiveness against vaccine-type invasive pneumococcal disease (VT-IPD) among children in Uruguay.

Number of PCV7doses	VT-IPD Cases $n = 7$ n (%)	Controls $n = 637$ n (%)	Matched odds ratio (95% CI)	PCV7 effectiveness
1[a]	1 (14.3)	136 (21.4)	0.173 (0.017, 1.703)	82.7 (−70.3, 98.3)
1 or more[a]	2 (28.6)	405 (63.6)	0.086 (0.014, 0.536)	91.3 (46.4, 98.6)
2 or more[a]	1 (14.3)	269 (42.2)	0.052 (0.005, 0.569)	94.8 (43.1, 99.5)
Up-to date for age	1 (14.3)	330 (51.8)	0.112 (0.012, 1.008)	88.8 (−0.01, 98.8)

[a] Reference was 0 doses.

the vaccine to be 94% effective against VT- IPD among children in Northern California [9], and 83% effective among American Indian children [10], who are at particularly high risk for pneumococcal disease. Subsequent observational studies of PCV7 conducted in North America and Europe have demonstrated an effectiveness of one or more PCV7 doses against VT-IPD to be in the range of 88–96% [13,15–17] – findings very consistent with ours.

Uruguay introduced PCV7 using a schedule of 2 primary doses plus a booster, 2 + 1 schedule, as well as a limited catch-up campaign. Although PCV7 was initially licensed for a 3-dose primary series followed by a booster, because of the high cost of the vaccine, there is much interest in reduced-dosing schedules – either 2+1 or 3 primary doses with no booster. Available immunogenicity data suggest that immune responses to 2-dose primary series are less robust than the response to 3-dose primary series, particularly for serotypes 6B and 23F [24]; however differences in responses are minimal following a booster dose [25,26]. Both the Pan American Health Organization [27] and the World Health Organization [28] have recommended that policy makers consider the age distribution of the pneumococcal disease burden in determining whether to introduce PCV using a 2- or 3-dose primary series. While further research is needed to determine the optimal PCV7 dosing schedule for different epidemiologic contexts, our findings in Uruguay are consistent with those of countries or regions that have seen declines in pneumococcal disease with a 2 + 1 PCV7 schedule [20,21,29]. A case–control study in the context of a 2 + 1 PCV7 schedule in Quebec, Canada found that the effectiveness of one or more doses of PCV7 against VT-IPD was 92% [16] – a finding remarkably similar to ours. Because four of the seven case-patients available for this analysis were eligible for catch-up doses only, we unfortunately cannot differentiate between the effectiveness of a 2 + 1 schedule from that of the catch-up doses.

The findings of this study are consistent with other data from Uruguay that demonstrate PCV7 impact. Prior to PCV7 introduction, in 2007, it was estimated that 58% of IPD among children < 2 years was due to vaccine serotypes and 30% among children < 5 years [30]. Within one year post–introduction (2009), the proportion had fallen to 9% and 23% respectively [31]. A study of the impact of PCV7 introduction on trends for pneumonia and meningitis hospitalizations at the national reference pediatric hospital reported a decline of 56% for rates of all-cause community acquired pneumonia and 48% for pneumococcal community acquired pneumonia among children < 14 years as well as a 59% reduction in pneumococcal meningitis among <2 years olds per 10,000 admissions [32]. Those data combined with the findings of this case control study provide strong evidence of PCV7 impact and effectiveness in Uruguay.

This study has a number of limitations. The number of cases was very small and did not permit separate estimations of the effectiveness of primary series and the catch-up dose; nonetheless because of the high effectiveness of the vaccine we were able to detect statistically significant vaccine effectiveness. Because of the limited data available on both cases and controls, we were not able to adjust for potentially important confounders in the analysis, such as underlying medical problems. Cases were detected through a passive laboratory-based surveillance system, and it is possible that cases captured by this system may be different from cases that go undetected, which may limit the generalizability of the findings. Cases of IPD might also have been missed if children were treated empirically without obtaining a culture, although we are unaware of any changes in blood culture practice during the study period. It is also possible that IPD cases not detected through surveillance might have been included as controls; however such misclassification bias would be expected to bias toward lower vaccine effectiveness.

Controls were identified through an immunization registry; in most settings this would be considered a biased source for controls, since children included in the registry would have a higher likelihood of vaccination that those children not included. However, in Uruguay, where the immunization registry is considered the most complete list of children in the country and contains both vaccinated and non-vaccinated children, the source of controls was unlikely to be biased. In addition, because the registry data were readily available, we enrolled all controls who met matching criteria for a case rather than enrolling a subset of eligible controls as is typically done in case–control vaccine effectiveness studies; inclusion of all eligible controls likely minimized selection bias. The primary strength of this study is that it utilized existing data to provide local evidence of the effectiveness of a newly introduced vaccine.

We have demonstrated how routine laboratory-based IPD surveillance and serotype data and a high quality immunization registry that includes all children can be used to estimate PCV7 effectiveness. We were able to show, using only preexisting data sources, that PCV7 is highly effective against VT-IPD using a 2 + 1 schedule and a limited catch-up campaign in a middle-income country. In March 2010, PCV7 was replaced by PCV13, which is expected to provide better serotype coverage in Uruguay. We plan to use the same approach to evaluate the effectiveness of PCV13. Many countries introducing costly new vaccines want to demonstrate local impact and/or effectiveness in order to justify the introduction and sustained use of the vaccine. However, the cost of conducting either cohort or case control studies to measure vaccine impact and effectiveness can be prohibitive. Investments in strengthening epidemiologic surveillance and immunization registries may allow other countries to provide data needed to support PCV use in routine immunization programs.

Conflict of Interest

None declared

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Review

Cost analysis of an integrated vaccine-preventable disease surveillance system in Costa Rica☆

C.M. Toscano[a,*], M. Vijayaraghavan[b], H.M. Salazar-Bolaños[c], H.M. Bolaños-Acuña[d], A.I. Ruiz-González[d], T. Barrantes-Solis[e], I. Fernández-Vargas[f], M.S. Panero[g], L.H. de Oliveira[h], T.B. Hyde[b], iVPD Working Team[1]

[a] Department of Community Health, Institute of Tropical Pathology and Public Health, Federal University of Goiás, Goiânia, Goiás, Brazil
[b] Global Immunization Division, U.S. Centers for Disease Control and Prevention, Atlanta, GA, United States
[c] Costa Rica Ministry of Health, San José, Costa Rica
[d] Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud, San José, Costa Rica
[e] Hospital San Vincente de Paúl, Heredia, Costa Rica
[f] Caja Costarricense de Seguro Social, San José, Costa Rica
[g] Pan American Health Organization Costa Rica Country Office, San José, Costa Rica
[h] Comprehensive Family Immunization Project, Pan American Health Organization, Washington, DC, United States

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ABSTRACT

Introduction: Following World Health Organization recommendations set forth in the Global Framework for Immunization Monitoring and Surveillance, Costa Rica in 2009 became the first country to implement integrated vaccine-preventable disease (iVPD) surveillance, with support from the U.S. Centers for Disease Control and Prevention (CDC) and the Pan American Health Organization (PAHO). As surveillance for diseases prevented by new vaccines is integrated into existing surveillance systems, these systems could cost more than routine surveillance for VPDs targeted by the Expanded Program on Immunization.
Objectives: We estimate the costs associated with establishing and subsequently operating the iVPD surveillance system at a pilot site in Costa Rica.
Methods: We retrospectively collected data on costs incurred by the institutions supporting iVPD surveillance during the preparatory (January 2007 through August 2009) and implementation (September 2009 through August 2010) phases of the iVPD surveillance project in Costa Rica. These data were used to estimate costs for personnel, meetings, infrastructure, office equipment and supplies, transportation, and laboratory facilities. Costs incurred by each of the collaborating institutions were also estimated.
Results: During the preparatory phase, the estimated total cost was 128,000 U.S. dollars (US$), including 64% for personnel costs. The preparatory phase was supported by CDC and PAHO. The estimated cost for 1 year of implementation was US$ 420,000, including 58% for personnel costs, 28% for laboratory costs, and 14% for meeting, infrastructure, office, and transportation costs combined. The national reference laboratory and the PAHO Costa Rica office incurred 64% of total costs, and other local institutions supporting iVPD surveillance incurred the remaining 36%.
Conclusions: Countries planning to implement iVPD surveillance will require adequate investments in human resources, laboratories, data management, reporting, and investigation. Our findings will be valuable for decision makers and donors planning and implementing similar strategies in other countries.

Contents

☆ *Disclaimer*: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author. Tel.: +55 62 8199 2229.
E-mail address: ctoscano@terra.com.br (C.M. Toscano).

[1] See Appendix A for the list of iVPD Working Team.

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1. Introduction

Given the increasing availability and introduction of new vaccines in the developing world, accurate assessments of disease burden and vaccination impact will be necessary. Systems that integrate surveillance for diseases prevented by new vaccines such as rotavirus, influenza, *Haemophilus influenzae* type b (Hib), and *Streptococcus pneumoniae* (pneumococcus) with existing surveillance systems for polio, measles, rubella, diphtheria, and tetanus are needed to maintain support and long-term sustainability of vaccination programs.

In 2007, the World Health Organization published the Global Framework for Immunization Monitoring and Surveillance (GFIMS), which outlines recommendations for ministries of health to enhance national surveillance of vaccine-preventable diseases (VPDs) [1]. Rather than implementing new disease-specific and vertical VPD surveillance systems, the GFIMS recommends that VPD surveillance be placed in a "unified framework" that builds upon the strengths of existing surveillance systems. The goals of an integrated VPD (iVPD) surveillance system are to identify and capitalize on the efficiencies of combining surveillance systems and disease surveillance objectives and to reduce costs by eliminating duplication of efforts while providing quality surveillance.

2. Implementation of iVPD surveillance in Costa Rica

In 2009, Costa Rica was the first country to implement iVPD surveillance following the GFIMS. The Costa Rica Ministry of Health (MoH) coordinated the initiative, with technical assistance from the U.S. Centers for Disease Control and Prevention (CDC), Pan American Health Organization (PAHO) headquarters, and the PAHO Costa Rica office. The planning and preparation for iVPD surveillance implementation (the preparatory phase of the project) took place from January 2007 to August 2009; activities during this project phase included a series of meetings to prepare the standardized surveillance protocol as well as training materials and sessions for personnel. In September 2009, the iVPD surveillance system began operating in a single pilot sentinel hospital, the *Hospital San Vicente de Paúl* (HSVP), so that experience could be gained before expanding to other sites. At this site, iVPD surveillance was incorporated into existing VPD surveillance.

Before implementation of iVPD surveillance, VPD surveillance in Costa Rica included syndromic surveillance for acute flaccid paralysis (AFP), febrile rash, and influenza-like illnesses along with surveillance for tetanus, diphtheria, and pertussis in all health care facilities in the country. Nationwide passive surveillance for AFP and febrile rash was conducted in all health care facilities with the objective of tracking progress toward meeting disease eradication and elimination goals. Sentinel surveillance for influenza-like illnesses was based in outpatient clinics and emergency rooms to monitor circulating strains and detect outbreaks.

During the implementation of iVPD, sentinel syndromic surveillance for bacterial meningitis (Hib, pneumococcus, meningococcus), severe diarrhea (rotavirus), and severe acute respiratory illnesses (SARI) (pertussis, influenza, Hib, pneumococcus) was incorporated into the existing VPD surveillance networks. Hyde and colleagues provide more detailed information on the development and implementation of the iVPD surveillance system [2].

HSVP, a 250-bed public hospital managed by *Caja Costarricense de Seguro Social* (Social Security Fund of Costa Rica [CCSS]), is the only hospital in the province of Heredia (estimated population: 450,000), a metropolitan area of the country. The hospital laboratory performs bacterial isolation and identification and rotavirus rapid diagnostic testing. The national reference laboratory, *Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud* (Costa Rican Institute for Research and Training on Nutrition and Health [INCIENSA]), located in the country's capital, performs diagnostic testing for viral diseases and serotyping of selected bacterial agents. INCIENSA receives specimens and isolates from HSVP daily.

The Costa Rica MoH is responsible for the general coordination of iVPD surveillance; CCSS, which is responsible for health care for the population covered by the social security health system (approximately 90% of the population), provides oversight of iVPD surveillance. INCIENSA is under the jurisdiction of the MoH. CDC and PAHO provided technical and financial support for establishing iVPD surveillance.

3. Processing of specimens

When HSVP identifies a suspected VPD case, the health care provider completes a standardized case report form, enters clinical and epidemiological information about the patient into a standardized electronic spreadsheet, and obtains the appropriate specimens according to the presenting clinical syndrome (Table 1). All patients <5 years of age who present with a severe acute respiratory illness undergo an on-site chest radiograph.

Depending on the type of testing and etiologic agents considered in the differential diagnosis (Table 1), the HSVP laboratory or INCIENSA tests the specimens. A single specimen from a person with a suspected VPD may be tested for one or more etiologic agents according to the surveillance protocol. Some of the differential diagnoses considered are not VPDs, including dengue, respiratory syncitial virus, adenovirus, and parainfluenza virus.

To better understand the resources required for iVPD surveillance, we analyzed the costs of establishing and implementing iVPD surveillance at a pilot site in Costa Rica. We believe these cost data will help to evaluate the pilot program itself, stimulate the development of new and efficient ways to carry out program activities, and plan future program needs, budget allocation, and fundraising. Finally, program cost data will aid in analyses of the cost-effectiveness of iVPD surveillance in Costa Rica and will provide valuable cost information for other countries and regions planning such surveillance.

4. Methods

We included retrospectively collected cost data from each of the participating institutions that supported iVPD surveillance in Costa Rica, recorded all cost data in local currency units (Costa Rican colones), and converted the figures to U.S. dollars (US$) using the

Table 1
Syndromes and age groups targeted for surveillance, samples collected for each syndrome, and processing of specimens: integrated vaccine-preventable disease surveillance system, Costa Rica, September 2009–August 2010.

Syndrome	Age group targeted for surveillance	Specimen type(s)	Laboratory diagnostic procedures	Etiologic agents evaluated	Processing lab location
Meningitis	<5 years	Cerebrospinal fluid, blood	Gram stain, latex agglutination test, culture, typing, antimicrobial susceptibility testing	*S. pneumoniae*, *N. meningitidis*, *H. influenzae*, other *Streptococcus*	Sentinel hospital laboratory, INCIENSA
Acute flaccid paralysis	<15 years	Stool	PCR Viral isolation	Poliovirus Poliovirus	INCIENSA INCIENSA, international/regional reference laboratory
Severe acute diarrhea	<5 years	Stool	Latex agglutination test ELISA	Rotavirus Rotavirus	Sentinel hospital INCIENSA
Rash and fever illness	All ages	Blood	ELISA Genotyping	Measles/rubella/dengue Measles/rubella	INCIENSA INCIENSA
Severe acute respiratory illness	≥5 years <5 years	Nasopharingeal/oropharingeal aspirate Nasopharingeal/oropharingeal aspirate, blood, chest X-ray	Chest radiograph, blood culture Immunofluorescence, PCR, viral isolation	*S. pneumoniae*, *H. influenzae* *B. pertussis*, influenza virus, respiratory syncitial virus, adenovirus, parainfluenza virus types 1–3	Sentinel hospital laboratory INCIENSA

Note. PCR: polymerase chain reaction; ELISA: enzyme-linked immunosorbent assay.

mean 2009 annual exchange rate of 573 Costa Rican colones per U.S. dollar [3]. We adjusted all costs to 2010 U.S. dollar equivalents.

We collected data on all resources used in the process of establishing and implementing iVPD surveillance activities, including capital costs (one-time purchases) and recurrent (ongoing) costs, for the preparatory phase (January 2007 through August 2009) and the first year of the implementation phase (September 2009 through August 2010). Preparatory phase costs are one-time costs incurred during the project, while those associated with the implementation phase are annual costs required each year for ongoing iVPD surveillance. For the implementation phase, we present costs per 100,000 population.

Costs incurred at the country level included national-level (MoH, CCSS, and INCIENSA) costs and sentinel hospital (HSVP) costs. Costs incurred by international institutions supporting surveillance (PAHO headquarters, the PAHO Costa Rica office, and CDC) were also included. The investigators collected primary cost data at the country level during October 2010 through January 2011, when each institution compiled resource utilization and costing data, followed by a 1-week additional data collection period during February 2011, when the rest of the data were collected and verified.

For each institution, we categorized resources as personnel, infrastructure, office equipment and supplies, transportation, laboratory facilities, or meetings. We did not consider information system support and maintenance costs, as no specific system was established for iVPD surveillance. We reviewed documents related to iVPD surveillance activities and conducted interviews with key staff to ascertain CDC and PAHO cost data. In the final costing results, we report CDC and PAHO donations to laboratory institutions involved in iVPD surveillance in Costa Rica as costs from the laboratory institution performing the activity.

We determined *personnel costs* by collecting data on the number of staff persons, including their annual remuneration, and by interviewing staff at each institution to estimate the time dedicated to iVPD surveillance. We apportioned total personnel costs attributable to iVPD surveillance according to the ratio of staff time allocated to iVPD relative to all other activities. Remuneration packages include base salary and any benefit packages, such as those for dangerous/risky activities, exclusive work at the institution, certain career paths, and length of service; a 1-month salary bonus at the end of every year; a retirement contribution (9.17% of the employee's salary); and support for children at school.

With respect to *meeting costs*, we considered all meetings, including routine and one-time training sessions, during both the preparatory and implementation phases and recorded the number of participants, by institution, at each of the meetings. For international travel, we included costs of airfare and per diems; for local travel, we calculated approximate costs by multiplying average per diem estimates by the number of meeting days.

We classified infrastructure, office, transportation, and laboratory costs as either capital or operational costs. Capital costs are typically one-time expenditures on buildings, vehicles, laboratory, and office equipment that will be used over a period of time. We applied an annual 5% depreciation rate to buildings, vehicles, and office and laboratory equipment over 50-year, 10-year, and 5-year useful-life time horizons, respectively. We assumed the scrap value of the capital items at the end of their useful life to be zero. Operational costs included costs for supplies, utilities, security, maintenance, and repairs. We multiplied total capital and operational costs by estimated fractions of costs attributable to iVPD surveillance.

Capital infrastructure costs are building or office/laboratory space costs. *Operational infrastructure costs* include costs for utilities (communication, electricity, water, and cleaning), security, maintenance, and repairs.

We estimated current market values for building and spaces and computed the estimated attributable iVPD surveillance fraction for capital costs by dividing the number of full-time-equivalent (FTE) surveillance staff by the total staff in the building or as a percentage of the building area occupied by surveillance FTE staff.

We also estimated annual operational costs and computed the estimated attributable fraction for operational costs by dividing the number of FTE surveillance staff by the total staff in the building (or total staff in the country, if building-specific costs were not available). We then multiplied total capital and operational costs by estimated cost fractions attributable to iVPD surveillance to estimate annual operational costs.

We calculated the costs of *office equipment and supplies* used for iVPD surveillance. We derived separate estimates of bacteriology and virology laboratory costs for INCIENSA and of epidemiology and laboratory costs for HSVP.

We derived *transportation costs* from the capital costs of vehicles (the percentage of days per year the vehicle was used for iVPD surveillance activities) and operational costs, which we calculated by estimating an average fuel consumption of 4.5 l of gasoline per round trip (assuming an average distance of 45 km and a fuel economy figure of 10 km/l of gasoline) at an average cost of 588 Costa Rican colones/l of gasoline. We also included estimated costs of insurance, taxes, and maintenance. We estimated costs for transportation by taxi using information on the number of trips and the average taxi fare for each destination. We computed operational (fuel) costs as the product of fuel consumption, average distance, and number of trips. We included the costs for transporting clinical specimens from HSVP to INCIENSA in hospital transportation costs, assuming one daily round trip, and included the costs for shipment of specimens from Costa Rica to the regional reference laboratory in the calculation of PAHO transportation.

Laboratory costs included costs related to laboratory equipment, laboratory and medical supplies, and chest X-rays. For high-value laboratory equipment (valued at more than US$5000), the exact year of purchase was used if this information was available. We assumed that all other equipment items were purchased in 2008. We multiplied total laboratory equipment costs by the estimated fraction of cost attributable to iVPD surveillance, which was estimated as the number of FTE laboratory staff dedicated to iVPD surveillance divided by the total laboratory staff. We used current market prices to estimate the cost of donated equipment and supplies. Laboratory costs included the cost of testing for all etiologic diagnostic agents considered in relation to the syndromes under surveillance (Table 1).

To determine the cost of *medical supplies*, we initially estimated the number of respiratory, blood, and stool samples collected and then used this estimate to itemize the number of medical supplies required for collection of these specimens. Next, we multiplied this figure by the individual cost of the supply item. We assumed that all patients with a suspected severe acute respiratory illness underwent a chest radiograph, at an estimated cost of US$26 (30% of the private-sector cost).

We then stratified all estimated costs by activity or cost components, the institution bearing the cost, whether the cost was capital or operational, and whether it was associated with the preparation phase or the implementation phase. For INCIENSA, we further stratified the costs by bacteriology and virology; for HSVP, we stratified costs according to epidemiology, laboratory, and medical supplies (for sample collection).

We used Microsoft Excel to compile and analyze the data. For the preparatory phase, we estimated the costs for personnel and meetings. For the implementation phase, we estimated costs for all of the major categories described above, disaggregated by capital and operational costs.

5. Results

The total cost for the preparatory phase of Costa Rica's iVPD surveillance system was US$128,101, US$82,000 (64%) for personnel and US$46,101 (36%) for meeting airfares and per diems.

The total cost for a single year of iVPD surveillance implementation was US$422,149: US$245,736 (58%) for personnel costs, US$ 117,674 (28%) for laboratory costs, and US$ 58,379 (14%) for the remaining cost categories (meetings, infrastructure, office, transportation). Institutional costs included US$153,689 (36%) for INCIENSA, US$117,675 (28%) for the PAHO Costa Rica office, US$70,100 (17%) for CCSS, and US$69,781 (17%) for HSVP (Table 2). Considering the population covered by the iVPD surveillance system, the estimated cost was US$91,846 per 100,000 population.

Costs by major categories and by cost-bearing institution, disaggregated by capital and operational costs, are presented in Table 2. Personnel costs represented the greatest proportion (58%) of iVPD surveillance implementation costs, which were borne entirely by national Costa Rican institutions. PAHO Costa Rica office personnel costs accounted for 41% of total personnel costs.

Laboratory-related costs represented 28% of total costs. INCIENSA was responsible for 81% (US$94,815) of total laboratory costs, among which 94% were costs associated with laboratory supplies. Supplies donated by PAHO headquarters and CDC (influenza, rotavirus, measles, and rubella diagnostic kits and polymerase chain reaction testing for influenza) accounted for 23% (US$16,650) of INCIENSA virology laboratory supply costs. CDC also contributed US$2700 to HSVP for a refrigerator and consumables (e.g., sheep blood agar), accounting for 10% of laboratory costs.

Among the 762 clinical specimens collected and tested, 14 cases of influenza A, 51 cases of pertussis, 13 cases of rotavirus diarrhea, and 2 cases of bacteremic pneumonia (1 due to *S. pneumoniae* and 1 due to *H. influenzae* type e) were detected and diagnosed by the iVPD surveillance system (Table 3), in addition to other non-VPD differential etiologies considered in the diagnostic procedures. Costs per confirmed and suspected cases were estimated at US$2069 and US$762, respectively.

The remaining costs included costs associated with transportation (5%), infrastructure (4%), meetings (3%), and office equipment and supplies (2%). CDC was responsible for 45% of total meeting costs and did not directly support other activities during the implementation phase.

In the case of all cost categories for which operational and capital costs were estimated (i.e., infrastructure, office, and transportation costs), operational costs were more significant than capital costs.

Considering all institutions funding the implementation of iVPD surveillance in Costa Rica, the largest cost share was attributed to INCIENSA (36.5%), followed by the PAHO Costa Rica office (28%); CCSS and HSVP were each responsible for 16.5% of the total. PAHO headquarters, CDC, the Costa Rica MoH, and other Costa Rica agencies combined were responsible for a very small portion of iVPD surveillance funding.

6. Discussion

Surveillance system costs are difficult to quantify because they are generally shared with other programs and encompass a broad range of activities. The benefits of surveillance systems are also not easy to quantify, as the impact on the health of a population is indirect [4].

It is unlikely that a universal, fully integrated surveillance system appropriate for all diseases is possible, because of the inherent differences in surveillance objectives and methods for different diseases. Nonetheless, planners can efficiently integrate many elements of a surveillance system; Costa Rica's iVPD surveillance system succeeded in integrating multiple VPDs into an existing surveillance platform. Integrated surveillance systems require adequate infrastructure, and Costa Rica has a number of characteristics that facilitated implementation of iVPD surveillance, including the availability of national sustainable funding for immunization and

Table 2
Total costs (2010 U.S. dollars) during the implementation phase (September 2009–August 2010), by institution: integrated vaccine-preventable disease surveillance system, Costa Rica.

Institution	Personnel	Meetings		Infrastructure		Office		Transportation		Laboratory		
		Flights	Per diems	Capital	Operational	Capital (equipment)	Operational (supplies)	Capital	Operational	Capital (equipment)	Operational (supplies)	Grand total (U.S. dollars and % of total)
CDC		2682	1144									3826 (1)
PAHO headquarters		612	1610									2222 (0.5)
Costa Rica Ministry of Health	2929		134	0	51	66	55	170	74			3480 (1)
Costa Rica Social Security Fund	60,000		134	0	8883	587	134	269	92			70,100 (16.5)
PAHO Costa Rica office	100,961		84	0	945	5168	5955	828	3734			117,675 (28)
INCIENSA			486	418	5673			65	346			
Virology	24,771					266	88			2805	73,122	
Bacteriology	26,621					102	39			2888	16,001	
INCIENSA subtotal	51,392	0	486	418	5673	367	127	65	346	5692	89,122	153,689 (36.5)
HSVP												
Total			268	0	1475			5895	8053			
Epidemiology	27,932					3	731					
Laboratory	2521					3	39					
Virology										53	16,545	
Bacteriology										179	5606	
Biochemistry										120	197	
Hospital: medical supplies											161	
HSVP subtotal	30,454	0	268	0	1475	6	770	5895	8053	351	22,508	69,781 (16.5)
Other Costa Rica agencies			1377									1377 (0.5)
Total by subcategory	245,736	3294	5237	418	17,029	6194	7041	7226	12,300	6044	111,631	422,149
Subtotal by category (U.S. dollars and % of total)	245,736 (58)		8531 (2)		17,446 (4)		13,236 (3)		19,526 (5)		117,674 (28)	422,149 (100)

Table 3
Numbers of samples processed and positive laboratory results, by etiology: integrated vaccine-preventable disease surveillance system, Costa Rica.

Clinical syndrome	Specimen	Suspected etiology	No. samples tested	Confirmed etiology	No. (%) positive
Severe acute respiratory illness	Respiratory	Influenza	240	Influenza type A	14 (5.8)
				Adenovirus	27 (11.3)
				Parainfluenza type 3	4 (1.7)
				Respiratory syncitial virus	91 (37.9)
	Respiratory	Pertussis	231	*B. pertussis*	51 (22.1)
	Blood	Bacteremic pneumonia	186	*H. influenzae* type e	1 (0.5)
				S. pneumoniae type 14	1 (0.5)
Bacterial meningitis	Cerebrospinal fluid	Bacterial meningitis	7	*S. agalactiae*[a]	1 (14.3)
Rash and fever illness	Serum	Dengue	42	Dengue	1 (2.4)
Severe acute diarrhea	Stool	Rotavirus	47	Rotavirus	13 (27.7)
Acute flaccid paralysis	Stool	Poliovirus	9	None	0 (0.0)

[a] Group B *Streptococcus*.

VPD surveillance, the existence of laboratory capacity, and a functional VPD surveillance platform.

To our knowledge, very few studies have included cost analyses of surveillance systems [5–7], and ours is the first study reporting the costing of an iVPD surveillance system. Although available surveillance system costing studies are not directly comparable to ours, personnel and laboratory costs also represent the major cost components in these studies [5–7].

7. Conclusion

Our evaluation demonstrated that the costs incurred during the preparatory phase of the project, costs that are usually not captured or reported, were considerable. As expected, personnel costs accounted for the largest share of costs during the implementation phase. It is important to account for the high labor benefit packages offered by employers in Latin American countries, which result in higher personnel costs than in countries with lower benefit packages. Laboratory costs accounted for the second largest share, and these costs are particularly important in syndromic surveillance systems in which laboratory diagnostic testing for various etiologic agents in a variety of clinical specimens is performed, as is the case with surveillance for many of the diseases prevented by newer vaccines and their differential diagnoses. Thus, such surveillance systems require more laboratory resources and a larger budget share than non-integrated systems for the laboratory component of surveillance. Among the various institutions supporting iVPD surveillance, costs borne by INCIENSA were highest, including personnel, equipment, supplies, and other cost components. This finding is similar to results reported by other authors [7].

One limitation of this study is that we did not estimate baseline costs of existing VPD surveillance before implementation of iVPD surveillance. Also, iVPD surveillance was implemented not at the national level but as a pilot in a sentinel hospital. Finally, we did not consider the cost-effectiveness of the system. As modeled and discussed in an earlier study [8], we believe that integrated surveillance systems can improve the cost-effectiveness of public health surveillance.

Our findings provide information and guidance to other countries and regions considering implementation of integrated VPD surveillance, as well as donors, immunization partners, policymakers, and decision-makers. A commitment of national and international resources to public health surveillance systems will be required as other countries and regions plan to implement integrated VPD surveillance. These systems will require investments to strengthen national capacities in terms of human resources, laboratories, data management, reporting, and epidemic response. It is expected that such investments will yield higher surveillance quality. Results from this evaluation could provide data inputs for a cost-effectiveness analysis of iVPD surveillance in Costa Rica; we suggest using these data to implement such studies as a means of providing evidence to support decision-making on investing in integrated VPD surveillance systems.

Conflict of interest

None of the authors report a conflict of interest.

Appendix A. iVPD Working Team

Pan American Health Organization (PAHO): Maria Susana Panero, Jennifer Sanwogou, Rodrigo Rodriguez, Lucia H. Oliveira, Jon Andrus; *U.S. Centers for Disease Control and Prevention (CDC):* Maya Vijayaraghavan, Terri Hyde, Carla Lee, Marc-Alain Widdowson, Jennifer Verani, Cindy Friedman, Eduardo Azziz-Baumgartner, Adriana Lopez, Aisha Jumaan, Vance Dietz; *Caja Costarricense de Seguro Social (CCSS), Costa Rica:* Isabel Fernández Vargas, Vicenta Machado Cruz; *Vice Minister of Health, Costa Rica:* Ana Morice; *Ministerio de Salud, Costa Rica:* Hilda Ma. Salazar Bolaños, Maria Ethel Trejos Solórzano, Jorge Arturo Solano López; *Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud (INCIENSA):* Elena Campos Chacón, Grettel Chanto Chacón, Hilda Ma. Bolaños Acuña, Elizabeth Sáenz Bolaños, Jenny Lara Araya, Ana Isela Ruiz González, Germán Picado García; *Hospital Saint Vincent de Paúl (HSVP), Costa Rica:* Tatiana Barrantes Solís, Gonzalo Salvador Zúñiga, Steven Campos Sáenz, Jorge Chacón De La O.

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