Methods and challenges for the health impact assessment of vaccination programs in Latin America

ABSTRACT

OBJECTIVE: To describe methods and challenges faced in the health impact assessment of vaccination programs, focusing on the pneumococcal conjugate and rotavirus vaccines in Latin America and the Caribbean.

METHODS: For this narrative review, we searched for the terms “rotavirus”, “pneumococcal”, “conjugate vaccine”, “vaccination”, “program”, and “impact” in the databases Medline and LILACS. The search was extended to the grey literature in Google Scholar. No limits were defined for publication year. Original articles on the health impact assessment of pneumococcal and rotavirus vaccination programs in Latin America and the Caribbean in English, Spanish or Portuguese were included.

RESULTS: We identified 207 articles. After removing duplicates and assessing eligibility, we reviewed 33 studies, 25 focusing on rotavirus and eight on pneumococcal vaccination programs. The most frequent studies were ecological, with time series analysis or comparing pre- and post-vaccination periods. The main data sources were: health information systems; population-, sentinel- or laboratory-based surveillance systems; statistics reports; and medical records from one or few health care services. Few studies used primary data. Hospitalization and death were the main outcomes assessed.

CONCLUSIONS: Over the last years, a significant number of health impact assessments of pneumococcal and rotavirus vaccination programs have been conducted in Latin America and the Caribbean. These studies were carried out few years after the programs were implemented, meet the basic methodological requirements and suggest positive health impact. Future assessments should consider methodological issues and challenges arisen in these first studies conducted in the region.

DESCRIPTORS: Health Impact Assessment. Immunization Programs. Mass Vaccination, organization & administration. Rotavirus Vaccines. Pneumococcal Vaccines.
INTRODUCTION

In the last thirty years, scientific and technological advances have resulted in the development and marketing of several new vaccines, increasing the opportunities to prevent morbidity and mortality related to infectious diseases of public health importance.55 In the 2000s, global and regional initiatives and commitment to immunization reduced prices of these new vaccines, which became accessible for low- and middle-income countries. Consequently, national immunization programs have been offering new vaccines.55 For instance, Brazil has provided eight new vaccines in the last eight years: rotavirus, in 2006; 10-valent pneumococcal conjugate and meningococcal C conjugate, in 2010; inactivated polio vaccine (IPV), in 2012; varicella, in 2013; and hepatitis A, in 2014, all of those in childhood schedule; in 2014, the human papillomavirus (HPV) vaccine, for teenage girls, and the tetanus-diphtheria-acellular pertussis (Tdap) vaccine, for pregnant women, were also introduced in 2014.

Once a new vaccine is introduced into routine immunization, it is necessary to monitor vaccine coverage, vaccine effectiveness and safety as well as the health impact of the vaccination program. Country differences in burden of disease, serotype and genotype distribution, health services organization and access, clinical practices, and surveillance systems prevent the use of international evidence as a guarantee of good results after implementing a program. Furthermore, vaccination programs may result in complex effects, changing the average age of infection, seasonal patterns of disease and genotype or serotype distribution.

Published studies use conflicting terms to describe different types of effects.24 Vaccine effectiveness is defined as the ability of a vaccine to protect against disease when used under field conditions (routine practice).24 Vaccine effectiveness refers to the protection conferred by individual immunization on vaccinated persons.24 Vaccination programs affect all people, even if only part of the population is vaccinated. When many people are immunized, the pathogen transmission decreases, which reduces the disease incidence and, consequently, protects the unvaccinated ones (indirect effect or herd protection). The health impact of a vaccination program refers to the total effects of the program, meaning the total (direct and indirect) effect on the vaccinees and the indirect effect on unvaccinated persons.24

Real-life effects of a vaccine administered in a health program are mainly evaluated in observational studies as experimental designs are no longer ethical once the vaccine is part of a health policy. Vaccine effectiveness may be estimated by comparing vaccinated and unvaccinated persons from the same population in cohort or case-control studies. The health impact of a vaccination program is estimated by comparing all individuals of the population affected by the vaccination program with a reference population unaffected by any program, usually the same population before and after program implementation. Different methodological approaches of differing complexity may be used.24

Countries with national health information systems, academic expertise in health services research, disease burden measurement and technology assessment in health care, policy makers, epidemiological surveillance, and immunization program professionals with experience in vaccine evaluations might have a more favorable context to conduct a health impact assessment (HIA) of vaccination programs.51 Nevertheless, introducing a new vaccine may be the opportunity for countries to create conditions for this evaluation, and others to follow, particularly if international organizations stimulate and support these initiatives.

The World Health Organization recommended that all national immunization programs offer rotavirus vaccine and pneumococcal conjugate vaccine (PCV),56,57 which have been introduced in Latin America and the Caribbean (LAC) from 2006 and 2008, respectively (Table 1). Hence, LAC countries have already had time to conduct HIA of rotavirus and pneumococcal vaccination.

The objective of this study was to describe the methodological approaches (study design, data sources and outcomes of interest) used and the challenges to conduct HIA of PCV and rotavirus vaccination programs, with focus on LAC countries.

METHODS

This is a narrative literature review of HIA of PCV and rotavirus vaccination programs, with focus on LAC countries. A search in Medline and LILACS, using the terms “rotavirus”, “pneumococcal”, “conjugate vaccine”, “vaccination”, “program”, and “impact”, was conducted on June 10, 2013 (PCV) and September 20, 2013 (rotavirus) and repeated on April 30, 2014. The review was supplemented with a search in Google Scholar to assess grey literature such as articles published in non-indexed journals, guidelines, and technical reports. There were no limits for publication year. Studies published in English, Spanish and Portuguese were eligible.

Three reviewers screened the identified abstracts and full texts and selected original articles that assessed the health impact of vaccination programs in LAC countries. Economic evaluations, mathematic models,
vaccine efficacy or effectiveness studies and impact reviews were excluded. The references of all included articles were cross-checked and a hand search was carried out to identify further articles.

Data were extracted by one reviewer using a template developed specifically for this study and checked for accuracy by a second one. Data extracted from each study included: author, year, country, study design, data sources, clinical syndrome of interest, outcomes, and main results. Differences between reviewers were solved by discussion.

ANALYSIS OF RESULTS

We initially identified 207 articles in the search: 92 on pneumococcal and 115 on rotavirus vaccination programs. After applying the exclusion criteria based on title and abstract reading, and checking for duplicates,
we read 37 articles on PCV and 60 articles on rotavirus vaccine in full. The search update added seven articles to the set. Finally, we reviewed 33 studies on HIA of vaccination programs conducted in LAC, 25 of which assessed rotavirus and eight, PCV vaccination programs.

Of the 20 Latin American countries, 14 have introduced rotavirus vaccine in their immunization programs since 2006, and we identified at least one published HIA for eight of them (Table 1).12,27 In the Caribbean, only three of 25 countries have introduced rotavirus vaccine in their immunization programs since 2009 and no published HIA was identified. Since 2008, 17 Latin American countries have introduced PCV in their immunization programs and we identified at least one published HIA for five of them. Since 2009, five countries in the Caribbean have introduced PCV in their immunization programs and no published vaccination HIA was identified (Table 1).2 The 33 included LAC studies are described in Tables 2, 3 and 4 according to vaccine, data sources, country, and study design. In most LAC countries, rotavirus vaccines have been introduced earlier than PCV. Consequently, more HIA of rotavirus vaccination programs have been performed and published (25/33, 75.8%). Most studies were conducted in Brazil (15/33, 45.5%), mainly on rotavirus (13/25, 52.0%). Three of the eight studies on pneumococcal vaccine were conducted in Uruguay, one of the first LAC countries to implement a PCV childhood vaccination program.2,25

Ecological studies (interrupted time series analyses and other studies comparing pre- and postvaccination periods) were the most frequent (25/33, 75.7%). Cohorts (3), case series (3) and cross-sectional (2) studies were also conducted. Data sources were mainly secondary epidemiological or administrative databases (16/33, 48.5%). Surveillance data (8/33, 24.2%) and primary data collection (7/33, 21.2%) were also used. Two studies mixed data from both surveillance and health information systems.6,11 The study design was tied to data characteristics.

**Study design**

Ecological studies are frequently used to evaluate epidemiological impact, especially when using large non-disease-specific databases, as they allow tracking population disease trends over time in relation to the timing of interventions. They allow both short- and long-term assessment of the vaccination program in a general population, but the establishment and measurement of causal relationship are limited because changes in disease incidence after vaccine introduction cannot be attributed exclusively to the intervention. Natural variations and secular trends affect disease incidences in the absence of vaccination.11 Changes in social and health conditions and improvement in access to health care system during the study may also influence the results of before-after studies.11 Strategies to control the effects of possible confounding factors include study design (comparison with other diseases or similar countries) and analyses (statistical methods to estimate the expected occurrence of the outcome using patterns before vaccine introduction, for example).

The rates of diarrhea-related hospitalizations and deaths of under-five children have been declining in LAC countries in the last three decades due to safe water supply, improvements in sanitation and hygiene, breastfeeding promotion, better nutrition, enhanced access to health care, and proper treatment of diarrhea, including oral rehydration therapy.14 This decline may be misinterpreted, overestimating the impact of vaccination. In some LAC studies, this decrease was already evident before vaccine introduction.14,22,29 Few studies adjusted for these secular trends appropriately in the analyses.5,11,15,41 A Brazilian study used a generalized linear model to compare the postvaccination years with expected rates estimated from prevaccination years adjusted for secular and seasonal trends.9 Two studies, in Mexico, used all-cause hospitalization to control these secular trends.15,43 A neighbor and similar country that had not implemented rotavirus vaccination was used as a control for possible secular trends in a HIA of rotavirus vaccination in four LAC countries.11

Rotavirus disease classically shows natural year-to-year variation, making it difficult to determine to which extent changes in disease trends are related to vaccination or to natural changes. Biennial increase in rotavirus activity has been reported in the postvaccine era.55 Unimmunized susceptible children accumulate during seasons with low rotavirus activity and the higher number of susceptible individuals facilitates transmission during a subsequent season.53 Temporal variability in rotavirus genotype distribution also occurs naturally, independent of vaccination.3,10 Proper assessment of vaccination impact requires monitoring for longer periods and careful interpretation.10

There is evidence of decreasing trends in pneumonia incidence and mortality in low- and middle-income countries from 2000 to 2010, attributed to economic and social developments, reduction in the prevalence of risk factors, expansion and improvement in case management and also the implementation of PCV and *Haemophilus influenzae* type b (Hib) childhood vaccination programs.56 Pneumonia also has a seasonal pattern and the observation period must last at least a year to consider these variations. Two LAC studies adjusted for possible secular trends in pneumonia rates using nonrespiratory and diarrhea events as controls (Table 4).1,7
### Table 2. Methodological characteristics of health impact assessments of rotavirus vaccination programs conducted in Latin American and Caribbean countries, based on secondary data (vital statistics, health services utilization or surveillance data).

| Author/Year | Country | Study design/Methodological comments | Data source | Clinical syndrome | Outcome | Main results |
|-------------|---------|--------------------------------------|-------------|------------------|---------|--------------|
| De Oliveira11 (2013) | Bolivia, El Salvador, Honduras, and Venezuela | Ecological (interrupted time-series analysis) Control: Argentina, which still had not introduced the vaccine into its national immunization program during the study period | Databases of the sentinel surveillance network of rotavirus diarrhea and records on hospitalizations and deaths from the ministries of health | All-cause diarrhea | Number and rates of hospitalizations | Reductions in diarrhea-related deaths and hospitalization in all four countries as opposed to the control country |
| Rissardo45 (2010) | Brazil (Parana state) | Ecological (comparison of years before and after vaccine introduction) Limitations: short observation period after vaccine introduction; lack of adjustment for secular trends | National health information system on hospitalizations | All-cause diarrhea | Number and rates of hospitalizations | Significant decrease of diarrhea-related hospitalizations observed in children under one year of age after vaccine introduction. No impact evidenced among children aged one to four years |
| Do Carmo9 (2011) | Brazil | Ecological (interrupted time-series analysis, comparing event rates after vaccine introduction with expected rates estimated from prevaccine years) | National health information system on hospitalizations | All-cause diarrhea | Mortality and hospitalization rates | Decreased rates of under-five diarrhea-related mortality and hospital admissions in the first three years after vaccine introduction, with largest reduction among children under two years of age |
| Lanzieri29 (2011) | Brazil | Ecological (comparison of years before and after vaccine introduction) Limitations: lack of adjustment for secular trends | National mortality information system; national hospital information system, which covers the public health system | All-cause diarrhea | Mortality rates | Decreasing rates of diarrhea-related deaths previous to vaccine introduction |
| Gurgel22 (2011) | Brazil | Ecological (comparison of trends before and after vaccine introduction) Limitations: lack of adjustment for secular trends | National hospital information system | All-cause diarrhea | Hospitalizations and deaths | Reduction in hospitalizations preceded the vaccine introduction |
| Fernandes17 (2014) | Brazil (Sao Paulo state) | Ecological (comparison of years before and after vaccine introduction) Limitations: lack of adjustment for secular trends | National health information system (public health system) | All-cause diarrhea | Hospitalization rates by the human development index of each municipality and diarrhea-related hospitalization costs | Decreased rates of hospitalizations among under-five children in all categories of municipal development, with greater decrease in the least developed areas. Seasonal blunting in diarrhea hospitalizations. Savings in hospitalization costs in all municipal categories |
| Esparza-Aguilar14 (2009) | Mexico | Ecological (comparison of years before and after vaccine introduction) | National health information systems on mortality and population | All-cause diarrhea | Number of deaths and cumulative death rates | Decrease in diarrhea-related deaths previous to vaccine introduction. Greater mean annual reduction after vaccine introduction |
| Richardson44 (2010) | Mexico | Ecological (comparison of years before and after vaccine introduction) | National health information system on mortality and population | All-cause diarrhea | Deaths | Decline in diarrhea-related deaths after vaccination |
| Quintanar-Solares43 (2011) | Mexico | Ecological (comparison of years before and after vaccine introduction) Control: all-cause hospitalization | National health information system | All-cause diarrhea | Number of hospital admissions | Reduction in diarrhea-related hospitalizations only among children under 12 months of age in the first year after vaccine introduction, and among children under 24 months of age in the second year |
| Gastañaduy20 (2013) | Mexico | Ecological (comparison of years before and after vaccine introduction) | National health information systems Data were classified into three regions, according to indicators of economic development | All-cause diarrhea | Deaths according to regional human development index | Reduction in diarrhea-related mortality sustained for four years after vaccine introduction. Comparable declines across the three regions of different levels of development |
| Esparza-Aguilar15 (2014) | Mexico | Ecological (comparison of years before and after vaccine introduction) Control: all-cause hospitalization | National health information systems | All-cause diarrhea | Hospitalization rates according to the human development index of the state | Reduction in diarrhea-related hospitalizations of children under 24 months of age in all regions after vaccine introduction. Clear blunting of seasonal peaks |
| Study | Country | Study Design | Study Population | Data Collection Method | Endpoints | Findings |
|-------|---------|--------------|-----------------|------------------------|-----------|----------|
| Nieto Guevara (2008) | Panama | Cross-sectional study (comparison of years before and after vaccine introduction) | National mortality information system; hospital discharge database of five sentinel hospitals | National surveillance for diarrhea (six hospitals) | All-cause diarrhea | Hospitalizations; length of stay | No decrease in hospitalizations observed after vaccine introduction |
| Bayard (2012) | Panama | Ecological (comparison of years before and after vaccine introduction) | All-cause diarrhea of presumed infectious origin | Health impact assessment of vaccination programs Sartori AMC et al. | Hospitalization rates and healthcare visits | Decrease in diarrhea-related mortality and hospitalization rates after vaccine introduction |
| Yen (2011) | El Salvador | Ecological (comparison of years before and after vaccine introduction) | Sentinel surveillance system (seven hospitals); national surveillance for diarrhea-related healthcare visits (inpatient and outpatient) in public healthcare facilities | Sentinel surveillance system | All-cause diarrhea and rotavirus-positive diarrhea | | Decreases in both hospitalizations and healthcare visits due to diarrhea |
| Orozco (2009) | Nicaragua | Ecological (comparison of years before and after vaccine introduction) | National population-based surveillance for acute gastroenteritis events in healthcare facilities (Ministry of Health) | All-cause diarrhea | Number of outpatient visits and hospitalizations | Decreases in diarrhea-related hospitalizations and medical visits |
| Molto (2011) | Panama | Ecological (monthly trend analysis – comparison of years before and after vaccine introduction) | National surveillance for diarrhea (six hospitals) | National surveillance for diarrhea (six hospitals) | All-cause diarrhea | Hospitalizations | Reduction in diarrhea-related hospitalizations. Greater reduction during rotavirus seasonal months. All regions showed reduction in the ratio of diarrhea-related to non-diarrhea hospitalizations in the second year after vaccine introduction |
| Morillo (2010) | Brazil (Sao Paulo state) | Descriptive. Retrospective analyses of data collected in a five-year period, including two years before and two years after vaccine introduction | Laboratory-based data from diarrhea surveillance | Laboratory-based data from diarrhea surveillance | Rotavirus-positive diarrhea | Proportion of rotavirus and rotavirus genotype distribution | Decrease in the proportion of rotavirus-positive samples before vaccine introduction. Emergence of the G2P[4] genotype after vaccine introduction |
| Carvalho-Costa (2011) | Brazil | Ecological | Laboratory-based surveillance: data from regional rotavirus reference laboratories in 18 of the 27 Brazilian federated units | Laboratory-based surveillance: data from regional rotavirus reference laboratories in 18 of the 27 Brazilian federated units | Rotavirus-positive diarrhea | Frequency of rotavirus and genotype distribution | Reduction in the proportion of rotavirus-related diarrhea in the years after vaccine introduction. Emergence of the G2P[4] genotype in the year before vaccination, with decrease in its detection in the last year of observation, probably reflecting natural genotype oscillations |
| Pereira (2011) | Brazil (Parana state) | Descriptive | Laboratory-based data from one tertiary hospital | Laboratory-based data from one tertiary hospital | Rotavirus-positive diarrhea | Proportion of rotavirus-positive samples | Decline in the proportion of rotavirus-positive cases two years before vaccine implementation |
| Dulgheroff (2012) | Brazil (Minas Gerais state) | Descriptive. Data from a four-year period after vaccine introduction were compared with prevaccination data from other studies conducted in the same region | Data from two laboratories that collect and analyze specimens from private and public hospitals and pediatric clinics from the region | Data from two laboratories that collect and analyze specimens from private and public hospitals and pediatric clinics from the region | Rotavirus-positive diarrhea and rotavirus genotype characterization | Proportion of rotavirus among hospitalized and outpatient acute gastroenteritis cases | Reduction in rotavirus-related diarrhea in comparison with prevaccination studies. Great reduction in genotype diversity with predominance of G2P[4] |
Table 3. Methodological characteristics of health impact assessments of rotavirus vaccination programs conducted in Latin American and Caribbean countries, based on primary data collection.

| Author/Year | Country                   | Study design                                                                 | Data source                                                                 | Clinical syndrome                                                                 | Outcome                                                                 | Main results                                                                                                                                 |
|-------------|---------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Gouvea21 (2009) | Brazil (Rio de Janeiro, RJ) | Hospital-based survey including three years and a half before and one year after vaccine introduction | Primary data collection at the emergency room of one hospital. Data gathered from medical bulletins and patient records. Vital statistics obtained from the Brazilian Ministry of Health | All-cause diarrhea and laboratory-confirmed rotavirus diarrhea                   | Number of emergency room visits, hospitalizations and deaths, and genotype distribution | The study was unable to clearly show the impact of vaccination. Gastroenteritis visits and hospitalizations showed significant year-to-year variation. A gradual decrease in rotavirus strain diversity was observed in the prevaccination years |
| Safadi48 (2010) | Brazil (Sao Paulo, SP)    | Prospective cohort including years before and after vaccine introduction       | Prospective primary data collection in a private hospital, with routine rotavirus testing for all under-five children hospitalized for acute gastroenteritis | All-cause diarrhea and rotavirus-positive diarrhea                              | Number of hospitalizations and genotype characterization                 | Reduction in the number of all-cause and rotavirus-related diarrhea hospitalizations; delay in the rotavirus seasonal peak; and predominance of G2P[4] genotype in the postvaccination period |
| Borges8 (2011) | Brazil (Goiania, GO)      | Cross-sectional. Data collection restricted to the postvaccination period was compared with prevaccination studies conducted in the same region Limitations: small sample size, data collection in a period shorter than 1 year | Primary data collection in seven day care centers. Children were enrolled independent of gastrointestinal symptoms | Rotavirus-positive diarrhea, genotype characterization                          | Proportion of rotavirus-positive samples                                                                                           | Presence of rotavirus in 3.6% of all samples and 10.4% of samples from children with diarrhea were rotavirus-positive, which is less than what was previously observed by other studies in the region (14.4%-37.2%). G2P[4] was the predominant circulating genotype |
| Assis2 (2013) | Brazil (Juiz de Fora, MG) | Cross-sectional, including pre- and postvaccination years. Limitations: small sample size, compromising genotype distribution analyses. Data cannot be generalized to the entire Country | A university virology laboratory | Rotavirus-positive diarrhea                                                      | Frequency of rotavirus-diarrhea and genotype characterization              | Decrease in the proportion of rotavirus-positive diarrhea after vaccine introduction. The G1P[6] genotype was most frequent before vaccine introduction and replaced by the G2P[4] genotype in the year of vaccine introduction and after |
| Leboreiro90 (2013) | Mexico                   | Case series. Retrospective (pre-vaccination) and prospective (post-vaccine introduction) analysis of a case series | Hospital medical records of children treated in one hospital, including the emergency room and hospital wards | All-cause diarrhea and rotavirus-positive diarrhea                              | Frequency and severity of diarrhea                                          | Reduction in rotavirus-related diarrhea; reduction in rotavirus diarrhea severity among vaccinated children |

Primary data
Table 4. Methodological characteristics of health impact assessments of pneumococcal conjugate vaccination programs conducted in Latin American and Caribbean countries.

| Author/Year | Country | Study design | Data source | Clinical syndrome | Outcome | Main results |
|-------------|---------|--------------|-------------|-------------------|---------|--------------|
| **Secondary data** | | | | | | |
| Afonso (2013) | Brazil (five capitals) | Ecological (interrupted time-series analysis) Control: non-respiratory causes Limitations: short observation period after vaccine introduction (one year) | National hospitalization information system (public health system). Data from five capitals that had good data quality and high PCV-10 vaccination coverage | All-cause pneumonia | Hospitalization rates among children aged two months to two years | Significant declines in the hospitalization rates for pneumonia in three capitals (Belo Horizonte, Curitiba and Recife), but not in the other two (Sao Paulo and Porto Alegre). Prevaccination hospitalization rates for pneumonia varied substantially by city. Hospitalization rates for non-respiratory causes also decreased in all cities, but at a lower rate |
| Nieto Guevara (2013) | Panama | Descriptive (retrospective), comparing a three-year period including pre- and postvaccination years. Involved indigenous population. Limitations: results cannot be generalized | Medical records of a secondary-level referral hospital, based on discharge diagnosis of pneumonia given by the treating physician and coded according to ICD | All-cause pneumonia | Hospitalization rates and transfers to the regional hospital among under-five children | Reduction in hospitalization rates and referrals for pneumonia were observed after vaccine introduction. Results cannot be generalized |
| Pírez (2011) | Uruguay | Descriptive (retrospective), comparing a three-year period before vaccine introduction with a one-year period after | A national tertiary referral pediatric hospital database, complemented by medical records, laboratory databases and reports from the national information system on notifiable diseases | All-cause pneumonia, pneumococcal pneumonia, pneumococcal meningitis | Hospitalization rates among children aged one month to 14 years | Reduction in hospitalization rates for pneumococcal pneumonia and pneumococcal meningitis after PCV-7 introduction. Non-vaccine serotypes 1, 5, 7F, 19A, and 24F became the most frequent causes of pneumococcal pneumonia after vaccine introduction. There were changes in the national hospital admissions aimed to decrease hospitalizations during the study. These changes did not affect the rates of hospital discharges for acute gastroenteritis, the control disease analyzed |
| Pírez (2014) | Uruguay | Descriptive (retrospective), comparing years before (2003-2007) and after (2009-2012) vaccine introduction | Microbiology laboratory database and patient records of a single site | All-cause pneumonia, pneumococcal pneumonia, pneumococcal serotypes | Hospitalization rates among children aged zero to 14 years | Significant reduction in hospitalization rates. A clear two-step reduction in hospitalization rates for pneumonia after each introduction of PCV (PCV-7 and PCV-13). Significant reduction in PCV-13 vaccine serotypes and increase in non-vaccine serotypes after the vaccination program implementation |
| Becker-Dreps (2014) | Nicaragua (León) | Descriptive, comparing a period before (2008-2010) and after (2011-2012) vaccine introduction. Control: healthcare visits due to diarrhea | Epidemiological database of 107 public health facilities (93 healthcare centers, 13 primary care centers, 1 public referral hospital) | Pneumonia | Hospitalization rates, outpatient visits among children aged 0 to 14 years and infant mortality | Reduction in hospitalization and outpatient visits for pneumonia and decrease in infant mortality after vaccine introduction. No changes in overall healthcare visits for diarrhea during the study period |

Continue
### Surveillance data

| Study | Country | Design | Methodology | Findings |
|-------|---------|--------|-------------|----------|
| Hortal 2007 | Uruguay | Two prospective cohorts – a three-year study before and a three-year study after vaccine introduction | Population-based surveillance system carried out in two municipalities. The study was conducted in four hospitals (two public and two private) | All-cause pneumonia and changes in serotypes after vaccine introduction |
| Hortal 2012 | Uruguay | | | |
| Santos 2013 | Brazil (Sao Paulo, SP) | Case series including years before and after vaccine introduction | Prospective data collection at one university hospital that attends a population of approximately 408,000 inhabitants | Decrease in invasive pneumococcal disease cases among children under 2 years of age and decrease in vaccine serotypes after vaccine introduction |
| Parra 2013 | Colombia | Case series on invasive pneumococcal disease and two transversal studies (before and after vaccine introduction) on nasopharyngeal carriage | Laboratory surveillance (SIREVA II) data on invasive pneumococcal disease and primary data collection on nasopharyngeal carriage | Decrease in invasive pneumococcal disease isolates after vaccine introduction |

**ICD:** International Classification of Diseases; **PCV:** pneumococcal conjugate vaccine; **PCV-7:** 7-valent pneumococcal conjugate vaccine; **PCV-10:** 10-valent pneumococcal conjugate vaccine; **PCV-13:** 13-valent pneumococcal conjugate vaccine
Access to hospitalization information systems is increasing and they have been considered very useful as data sources in vaccination program impact analysis (Table 2). A study in Goiania, Midwestern Brazil, used database linkage of secondary administrative hospitalization data and primary population-based surveillance data and found similar hospitalization rates for community-acquired pneumonia in children.

In many countries, burden of pneumococcal and rotavirus disease estimates are based on national sentinel-based surveillance data and the HIA of vaccination program relies on these data. Seven LAC studies evaluated the impact of rotavirus vaccination based on surveillance data (Table 2). Information on the catchment population of the sentinel hospitals is unavailable for most sites, precluding incidence rates estimation, which constitutes a limitation. Depending on the number of sentinel sites and their location, these data cannot be generalized for the entire population. The World Health Organization has proposed a sentinel surveillance system for rotavirus and invasive bacterial diseases, but some LAC countries established population-based surveillance for diarrhea with data collection for hospitalizations and outpatient visits at public health facilities. These population-based systems were used in HIA of rotavirus vaccination in Nicaragua and El Salvador, the latter in combination with sentinel hospital data. Population-based surveillance data were also used in HIA of a PCV program in Uruguay.

The sensitivity of surveillance systems may change over time: variations in methods, case definitions, population under surveillance and reporting patterns may affect the results of before-after studies. In the era of PCV and rotavirus vaccines, most countries strengthened their surveillance systems to inform for decisions on vaccination policies. Furthermore, vaccine introduction increases disease awareness, testing and reporting.

In LAC, invasive bacterial diseases surveillance was first organized as a laboratory-based surveillance system, the Sistema de Redes de Vigilancia de los Agentes Bacterianos Responsables de Neumonia y Meningitis (SIREVA II – Surveillance Network System for the Bacterial Agents Responsible for Pneumonia and Meningitis), created in 1993, initially in six countries (Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay). The SIREVA II Regional 2012 Report contains data on pneumococcal serotypes and antibiotic resistance from 19 Latin American countries and the Caribbean Epidemiology Center. SIREVA II is a voluntary reporting system and its coverage varies a lot among countries, and caution is advised when using it to estimate invasive pneumococcal disease incidence and impact of PCV. In general, laboratory-based data lacks demographic and clinical information, which limits the analyses. Furthermore, laboratory procedures to identify the pathogen may change over time. Despite these limitations, SIREVA II is the best source of data on pneumococcal serotype distribution in the region and may allow assessing serotype replacement after vaccine introduction. Understanding serotype replacement is critical in low- and middle-income countries, where most deaths from pneumococcus occur, with greater diversity of serotypes causing disease and nasopharyngeal colonization early in infancy.

Reports of laboratory-confirmed rotavirus infections from clinical microbiology laboratories that constitute a national- or sentinel-laboratory surveillance system were also used. These data allow assessing the impact of vaccination on rotavirus-confirmed diarrhea and genotype distribution.

Local secondary data including the hospital discharge summary database and medical records of a single hospital have been used as data sources for HIA of vaccination programs. The major limitation of these data is that study results cannot be generalized to the entire population.

Primary data collection was conducted in HIA of PCV and rotavirus vaccination programs in LAC countries (Tables 3 and 4). Primary data collection may be particularly useful in settings where health information system databases are unavailable or unreliable and the surveillance system has not been appropriately implemented. Also, it can provide information unavailable on other data sources, such as rotavirus genotype circulation (Table 3). Limitations of studies based on primary data include the small sample size collected in just one or few sites, precluding generalizing the results to the whole population. Additionally, prospective design may be quite expensive, hampering the sustainability of the study and long-term HIA of the vaccination program.

Study outcome definition

Choosing the clinical syndrome of interest in HIA of vaccination program is an issue. HIA of rotavirus vaccination used mainly all-cause diarrhea as the...
syndrome of interest and hospitalization or mortality rates as outcomes. Only two LAC studies that used population-based surveillance data assessed the impact of rotavirus vaccination on outpatient care (number of healthcare visits). The etiological diagnosis of rotavirus gastroenteritis requires laboratory tests, which are rarely performed in clinical practice since they do not alter the treatment. Rotavirus testing is done at the discretion of the physician, based on institutional practices, which may change over time. Although more specific and precise, using rotavirus-related diarrhea in studies based on secondary data may underestimate the true burden of disease and the impact of the vaccination program. Furthermore, “measuring impact on all-cause diarrhea may be more valuable to decision makers and the public health community because it provides an estimate of the preventable fraction of diarrhea deaths and admissions attributable to rotavirus”.

Most of the eight HIA of PCV in LAC evaluated pneumonia, and non-pyogenic streptococci. Two evaluated invasive pneumococcal disease and one evaluated meningitis. We did not identify any LAC study evaluating the impact of PCV on acute otitis media.

Diagnosing invasive pneumococcal diseases require laboratory tests. In some countries, such as the USA, blood cultures (BC) are performed in routine care for every child with fever without a focus in both hospital and outpatient care, whereas in others, such as most LAC countries, BC are limited to severely ill hospitalized children. BC practices may affect the burden of disease estimates (invasive pneumococcal disease incidence increases parallel to the number of BC samples in a population), the relative frequency of clinical syndromes (higher frequency of bacteremia without focus in countries with higher frequency of BC samples) and the serotype distribution. Previous use of antibiotics before sample collection also affects diagnostic sensitivity. Changes in medical practices may also influence the results of before-after studies. A study of invasive pneumococcal disease before and after the PCV7 program implementation in England and Wales evaluated control pathogens that also depend on blood culture practices and reporting, but for which there had been no public health intervention (Escherichia coli and non-pyogenic streptococci). The etiological diagnosis of non-bacteremic pneumonia by current tests is insufficiently sensitive and specific, and rarely performed in clinical practice. Due to difficulties to isolate the etiological agent, most studies focused their analyses in all-cause pneumonia.

Some of them also evaluated pneumococcal pneumonia (PP). Definitions of pneumonia vary among studies. In general, studies based on secondary data used the diagnosis given by the attending physician, but diagnostic criteria vary among clinicians, health services and health information system databases. Prospective cohorts used more standardized criteria, mainly radiologically-confirmed pneumonia.

Although the clinical diagnosis of acute otitis media does not require additional exams, and the collection of material to isolate pathogens is easier than for pneumonia, LAC countries lack high quality data on acute otitis media incidence and health resource use. Generally, acute otitis media is treated in outpatient services, for which registered information is limited in LAC, hindering the HIA of pneumococcal vaccination on this disease.

**Main results of the health impact assessment of rotavirus and pneumococcal vaccination programs in Latin America**

Most studies showed decreased rates of diarrhea-related deaths, hospital admissions and healthcare visits after rotavirus vaccination implementation (Tables 2, 3 and 4). Blunting or delay of seasonal peaks of diarrheal disease after vaccine introduction has also been reported. Two studies in Mexico and another in Brazil assessed the impact of rotavirus vaccination on diarrhea mortality or hospitalization rates according to the socioeconomic level or human development index of the region. The Mexican studies observed comparable reduction in diarrhea-related deaths and hospitalization in all areas, whereas the Brazilian study showed great reduction in hospitalization rates of under-five children in the least developed areas.

All eight HIA of pneumococcal vaccination programs in LAC showed reduction in the events of interest, mainly hospitalization, after PCV introduction. The Mexican studies observed comparable reduction in diarrhea-related deaths and hospitalization in all areas, whereas the Brazilian study showed great reduction in hospitalization rates of under-five children in the least developed areas.

Table 5 presents a summary of advantages and limitations of study design, data sources, and outcomes used in HIA of vaccination programs.
Despite the strategies to access grey literature, country reports and other local documents may not be included in this review. The classification of epidemiological study designs was heterogeneous and we used the authors’ classification. Furthermore, some studies lack methodological information. These two limitations may affect our analysis and synthesis of knowledge production on HIA of PCV and rotavirus vaccination programs.

The challenges in conducting HIA of vaccination programs are easier to face in countries with reliable and sustainable health information systems and surveillance data as well as expertise in health evaluation. However, LAC countries have managed to do a lot in HIA of pneumococcal and rotavirus vaccination programs in a relatively short time after program implementation. Almost all met basic methodological requirements for HIA and

| Study design                        | Advantages                                                                 | Limitations                                                                 |
|-------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Ecological                          | Relatively simple and less expensive                                       | Cannot establish causal relationships                                       |
|                                     | Allows assessment of the vaccination program in a general population         | It is important to consider adjustment for secular trends and to have a control group (other areas without vaccination programs or other diseases) |
| Cohort                              | Provides the best information about causal relationships                     | Demands more time and resources                                              |
| Descriptive and case series         | Simplest study designs                                                       | Cannot measure prevalence or incidence due to the lack of a well-defined population at risk. |
|                                     | Can detect changes in types of rotavirus and pneumococcus after the introduction of vaccine programs | Give little information about temporal changes in the frequency of diseases |

| Data sources                         | Advantages                                                                 | Limitations                                                                 |
|--------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Health information system databases  | Broad coverage, lower costs, easy access to data and longitudinal follow-up | Lack of standardization in data collection and limitations in completeness and reliability of the available data, database continuity, coverage, representativeness, and sustainability |
| Sentinel-based and laboratory-based surveillance systems | Availability of unpublished data | Information on the catchment population frequently unavailable. |
| Local secondary data (medical records of a single hospital) | Timeliness, low costs, and availability | Data not generalizable for the entire population. |
| Primary data                         | May answer specific research objectives                                     | Small sample size                                                           |
|                                     | More precision and reliability                                               | Not generalizable                                                          |
|                                     |                                                                             | Expensive                                                                  |
|                                     |                                                                             | Sustainability                                                              |

| Clinical syndrome                    | Advantages                                                                 | Limitations                                                                 |
|--------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| All-cause diarrhea                   | Does not require specific laboratory tests.                                  | Less precision for vaccine effect on rotavirus disease.                     |
|                                     | May be more valuable to decision makers                                      |                                                                             |
| Rotavirus-related diarrhea           | More specific and precise                                                   | May underestimate the true burden of disease and the global impact of vaccination programs |
| Pneumonia                            | More frequent                                                               | Challenging and variable definition and diagnosis                           |
| Invasive pneumococcal disease        | More severe and of more precise diagnosis                                   | Diagnosis requires the isolation of $S. pneumonia$, and laboratory tests are not uniformly performed |
| Meningitis                           | More severe, of more precise diagnosis and has more information available since it is a notifiable disease | Less frequent |

| Outcomes of interest                 | Advantages                                                                 | Limitations                                                                 |
|--------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Hospitalization rate                 | Availability of data                                                        | Changes in diagnosis coding may affect estimates. Influenced by availability of beds, hospital admission policies and social factors. Unsuitable for clinical syndromes that are mostly treated in outpatient care such as otitis media |
| Mortality rate                       | More reliable than morbidity data                                           | Measures only results of severe clinical syndromes; thus, changes in less severe conditions will not be identified. Difficulty in discriminating effects of changes in the incidence or treatment of conditions |
suggested a positive health impact. High-quality studies have been conducted in small countries without tradition in research that have prioritized surveillance and registers. Future HIA of vaccination programs should consider the methodological issues and challenges that arose in these first studies conducted in the region as well as in studies from other regions. HIA of vaccination programs should be considered essential in the planning phase of vaccine introduction, with the definition of outcomes, data sources, and responsibilities for data collection and resources. They can also contribute to the validation and methodological development of vaccine cost-effectiveness studies.

AUTHORS’ CONTRIBUTIONS
AMCS, AFN, PCS and HMDN were responsible by the conception and design of the study. AMCS, AFN and TYY conducted data collection, analysis and interpretation. AMCS drafted the article. AFN, PCS, TYY and HMDN critically reviewed the paper contents, and all authors approved the submitted version.

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Research supported by the ProVac Initiative of the Pan-American Health Organization (PAHO – Process SC-01123). The funders had no role in the study design, data analysis and interpretation or final article contents. The authors declare no conflict of interest.