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Impact of pneumococcal conjugate vaccine in children morbidity and mortality in Peru: Time series analyses

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ABSTRACT

Streptococcus pneumoniae is the leading cause of bacterial pneumonia, meningitis and sepsis in children worldwide. Despite available evidence on pneumococcal conjugate vaccine (PCV) impact on pneumonia hospitalizations in children, studies demonstrating PCV impact in morbidity and mortality in middle-income countries are still scarce. Given the disease burden, PCV7 was introduced in Peru in 2009, and then switched to PCV10 in late 2011. National public healthcare system provides care for 60% of the population, and national hospitalization, outpatient and mortality data are available.

We thus aimed to assess the effects of routine PCV vaccination on pneumonia hospitalization and mortality, and acute otitis media (AOM) and all cause pneumonia outpatient visits in children under one year of age in Peru.

We conducted a segmented time-series analysis using outcome-specific regression models. Study period was from January 2006 to December 2012. Data sources included the National information systems for hospitalization, mortality, outpatient visits, and RENACE, the national database of aggregated weekly notifications of pneumonia and other acute respiratory diseases (both hospitalized and non-hospitalized). Study outcomes included community acquired pneumonia outpatient visits, hospitalizations and deaths (ICD10 codes J12-J18); and AOM outpatient visits (H65-H67). Monthly age- and sex-specific admission, outpatient visit, and mortality rates per 100,000 children aged <1 year, as well as weekly rates for pneumonia and AOM recorded in RENACE were estimated.

After PCV introduction, we observed significant vaccine impact in morbidity and mortality in children aged <1 year. Vaccine effectiveness was 26.2% (95% CI 16.9–34.4) for AOM visits, 35% (95% CI 8.6–53.8) for mortality due to pneumonia, and 20.6% (95% CI 10.6–29.5) for weekly cases of pneumonia hospitalization and outpatient visits notified to RENACE. We used secondary data sources which are usually developed for other non-epidemiologic purposes. Despite some data limitations, our results clearly demonstrate the overall benefit of PCV vaccination in Peru.

1. Introduction

Streptococcus pneumoniae is the leading cause of bacterial pneumonia, meningitis and sepsis in children worldwide [1]. It is also responsible for milder but more common diseases such as sinusitis and acute otitis media (AOM). In Latin America and the Caribbean (LAC), pneumonia burden in children is significant, with pneumonia incidence rates estimated at 836 per 100,000 children under 5 years of age [2]. *S. pneumoniae* related pneumonia is responsible for an estimated 16,980 annual deaths in children aged less than 5 years of age [1]. Cohort and surveillance data review showed a median incidence of X-ray confirmed pneumonia of approximately 2100 per 100,000 in children aged <2 years the Region [2].

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In February 2000, the first 7-valent pneumococcal conjugate vaccine (PCV7) was licensed and made available commercially [3]. More recently, two additional PCVs have been made market available: the 10-valent (PCV10); and the 13-Valent (PCV13) [4].

The World Health Organization (WHO) recommends universal introduction of PCV in all National Immunization Programs; especially in countries with high child mortality [5]. The LAC countries were the first to introduce PCV in 2008 in its routine public vaccination programs [6].

Studies on PCV impact have demonstrated significant reductions in pneumonia hospitalizations in children after PCV vaccine introduction, mostly in developed countries [7–12]. However, such studies are still scarce in middle-income countries with high disease burden. Recently, PCV impact on pneumonia was demonstrated in Brazil among children aged 2 months to 2 years [13,14].

A study commissioned by the Peruvian Ministry of Health in 2008 indicated pneumonia ranking as the second cause of loss of healthy life years [15]. Another study has demonstrated the importance of IPD in children in the country [16]. Given the disease burden, PCV7 was introduced in Peru in 2009 as a 3 dose schedule at 3, 5, and 12 months of age. In 2010, Peru changed its schedule to 2, 4 and 12 months of age, following WHO and manufacturers recommendations [17]. In late 2011 PCV7 was replaced by PCV10.

As most countries in the LAC Region, Peru has a national public healthcare system which provides care free of charge to approximately 60% of the population [18]. Hospitalization data for the public healthcare system and mortality data are available nationwide in Peru. In addition, Peru has a national system which monitors outpatient visits occurring in the public healthcare system. Finally, acute respiratory diseases, including hospitalized and outpatient cases, are diseases of mandatory notification. Cases occurring in children younger than 5 years of age are recorded on a weekly basis into a National database (RENACE).

Taking advantage of the availability of these secondary data sources it is possible to assess the impact of PCV vaccination in various disease outcomes. This will help provide important feedback and guidance on national health policies.

2. Objectives

We aimed to assess the effects of routine PCV vaccination on all cause pneumonia hospitalization and mortality in children under one year of age in Peru. Additionally, we assess the impact of PCV on AOM and all cause pneumonia outpatient visits in this population.

3. Methods

3.1. Study design

We conducted interrupted time series analyses using outcome-specific segmented regression models. This was done by using individual-level secondary data from selected databases of the Public Healthcare System. Study period was from January 2006 to December 2012 and target population was children aged <1 year. Segmented regression analysis was chosen as it allows statistically modelling interrupted time series data to draw conclusions about the impact of a given intervention.

3.2. Study site and population

Peru is located in the Andean Region of LAC, with a population of 28,508,000 inhabitants, of whom approximately 584,500 are children less than 1 years of age. Infant and under 5 year old mortality rates in Peru are 37 and 22.4 per 1000 live births, respectively [19].

Three immunization periods were considered: (1) Pre-PCV introduction period: between January 2006 and December 2008, when no PCV vaccination occurred; (2) Transition period: between January 2009 and December 2010, when vaccine was introduced in the country and coverages were mounting; and (3) Post-PCV introduction period: between January 2011 and December 2012, when PCV was routinely offered and coverages achieved high and stable levels.

3.3. Data sources and data cleaning

Data sources included the National Hospitalization Information System, the National Mortality Information system, and the National Information System of Outpatient Visits. In addition, the national database of aggregated weekly notifications of pneumonia and other acute respiratory diseases (both hospitalized and non-hospitalized) - RENACE database - was also analysed. RENACE is meant to be a fast track parallel system allowing for outbreak detection (Table 1).

These data sources include the population covered by the public healthcare services provided by the Ministry of Health. Social security services (ESSALUD) (mandatory for workers) and private sector services were not considered [18].

Study outcomes included community acquired pneumonia outpatient visits, hospitalizations and deaths (coded J12-J18 in ICD-10); and AOM outpatient visits (coded H65-H67 in ICD-10). For descriptive purposes, deaths due to respiratory diseases (Chapter X, other J codes) were also considered.

For morbidity assessment, we considered cases those in which the primary diagnosis was coded as any of the main study outcomes. In mortality databases, the underlying cause of death was considered.

3.4. Data analysis

Mid-year population estimates for year, age and sex obtained from the National Demography/Statistics department [20] were used to calculate monthly age- and sex-specific admission, outpatient visit, and mortality rates per 100,000 children aged <1 year.

PCV coverage for a 2-dose primary series was estimated as the number of second doses of PCV administered to children aged <12 months divided by the number of births, and multiplied by 100, considering data from the National Immunization Registry data [21].

After an initial descriptive analysis, time series for the study outcomes was performed. A generalized linear model with negative binomial distribution was fitted to monthly counts, using a logarithm link function and the population of children under 1 year as an offset. This model allows the interpretation of all results in terms of morbidity and mortality rates. Data from the transition period (2009–2010) were not considered. Except when indicated, all models had a linear trend, a seasonal effect, a variable representing the possible level change, and another variable representing the possible change in trends after the transition period.

Pneumonia hospitalization rates and their respective 95% confidence intervals (CI) were predicted by the model for the post-PCV introduction. Monthly observed and predicted hospitalization rates were compared and are presented. For all models, our main objective was to analyse whether there is vaccine effectiveness, which could be expressed as a level and/or trend change in the expected rates after the vaccination in comparison to pre-PCV rates. Vaccine effectiveness were calculated as percent level change after exponentiation of model coefficients. Considering all

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