



Challenges to estimating vaccine impact using hospitalization data



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ABSTRACT

Because the real-world impact of new vaccines cannot be known before they are implemented in national programs, post-implementation studies at the population level are critical. Studies based on analysis of hospitalization rates of vaccine-preventable outcomes are typically used for this purpose. However, estimates of vaccine impact based on hospitalization data are particularly prone to confounding, as hospitalization rates are tightly linked to changes in the quality, access and use of the healthcare system, which often occur simultaneously with introduction of new vaccines. Here we illustrate how changes in healthcare delivery coincident with vaccine introduction can influence estimates of vaccine impact, using as an example reductions in infant pneumonia hospitalizations after introduction of the 10-valent pneumococcal conjugate vaccine (PCV10) in Brazil. To this end, we explore the effect of changes in several metrics of quality and access to public healthcare on trends in hospitalization rates before (2008–09) and after (2011–12) PCV10 introduction in 2010. Changes in infant pneumonia hospitalization rates following vaccine introduction were significantly associated with concomitant changes in hospital capacity and the fraction of the population using public hospitals. Importantly, reduction of pneumonia hospitalization rates after PCV10 were also associated with the expansion of outpatient services in several Brazilian states, falling more sharply where primary care coverage and the number of health units offering basic and emergency care increased more. We show that adjustments for unrelated (non-vaccine) trends commonly employed by impact studies, such as use of single control outcomes, are not always sufficient for accurate impact assessment. We discuss several ways to identify and overcome such biases, including sensitivity analyses using different denominators to calculate hospitalization rates and methods that track changes in the outpatient setting. Employing these practices can improve the accuracy of vaccine impact estimates, particularly in evolving healthcare settings typical of low- and middle-income countries.

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1. Introduction

In recent decades, the use of vaccines against infectious diseases of global importance has grown substantially. Efficacy is always assessed in pre-licensure trials before regulators approve a new vaccine. However, the real-world impact of vaccines can be greater or smaller than efficacy due to indirect factors such as herd immunity and serotype replacement. Moreover, pre-licensure trials are performed under idealized conditions and often exclude certain high-risk individuals. Therefore, studies that assess the impact of

newly introduced vaccines on disease rates at the population level are critical.

In real-world populations, however, nothing is static. Estimating vaccine effects with accuracy is always complicated by other changes that occur in the population around the time the vaccine is introduced. Unrelated trends can be particularly pronounced in rapidly developing countries, where the introduction of a new vaccine often occurs concomitant with unrelated improvements in public health.

Because population-based surveillance data are rarely available on a large scale, and laboratory confirmation of the causative pathogen is often not possible, vaccine impact evaluations often rely on proxy measures of disease rates at the community level. Hospital admission data have been widely used for that purpose,

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often by comparing hospitalization rates for a disease within the same population before and after vaccine introduction [1–3].

Electronic hospitalization databases are effective tools for public health research, surveillance and planning, providing systematic and low-cost information about large populations. However, hospitalization data are also prone to specific biases and confounding that can affect estimates of vaccine impact, as admission rates are closely linked to changes in broad societal trends that affect not only biological susceptibility to disease, but also healthcare delivery itself.

Here we investigate how changes in healthcare delivery influence estimates of vaccine impact by exploring the association between hospitalization rates and healthcare access and quality. As a case study, we focus on changes in infant hospitalization rates for pneumonia after introduction of the 10-valent pneumococcal conjugate vaccines (PCV10) in Brazil in 2010.

Our results indicate that commonly employed adjustments are not always sufficient to control for changes in hospitalization rates unrelated to vaccine introduction, particularly in evolving healthcare settings. We discuss several ways to identify and address these biases.

2. Methods

To examine how changes in healthcare use and delivery affect hospitalization rates, we calculated several metrics of healthcare utilization, quality, and access before and after PCV10 introduction. We then explored how changes in these metrics were associated with simultaneous changes in crude hospitalization rates for pneumonia and comparison outcomes. We focused the analysis on infants <12 months, the primary group targeted for vaccination.

2.1. Data on hospitalizations

In Brazil, access to the public health service is, in principle, universal, and comprehensive data are available on people who receive public care (82% of the population in 2012). We obtained de-identified, age-stratified monthly data on hospitalizations (Jan2003–Dec2013) from the Unified Health System (SIH-SUS, Ministry of Health; [4]), which maintains a nationwide database that records all hospitalizations paid by the government. This database has been shown to record pneumonia hospitalization incidence in infants as reliably as prospectively collected primary hospitalization data [5].

To minimize the number of nosocomial pneumonia cases included in the time series, we excluded hospitalizations associated with “treatment packages”—sets of services, supplies and procedures—unrelated to community-acquired pneumonia (Table S1). We also excluded records in which the “length of stay” field was inconsistent with the discharge and admission dates (representing instances where a patient was immediately readmitted following discharge). We also excluded records from union, university, and self-financed hospitals, as those did not contribute consistently to the database.

2.2. Inpatient healthcare delivery: use of public hospitals and hospital capacity

Although access to public health is universal, some citizens opt for a privately financed tier of care perceived to offer better quality and faster access. To determine the size of the infant population actually using the public system (SUS) and thus represented in the hospitalization database, we subtracted the number of infants enrolled in private insurance plans offering hospitalization

coverage [6] from the total infant population (Brazilian Institute of Geography and Statistics).

We considered hospital bed supply (hospital beds available in SUS; [7]) as a measure of hospital capacity.

2.3. Healthcare delivery: outpatient care access and quality

Because many pneumonia hospitalizations are preventable by appropriate care and management, improvements in outpatient services at the time of PCV10 introduction might reduce pneumonia hospitalizations. We focused on three metrics: (i) the number of health units offering basic healthcare services [8]; (ii) the percentage of the population appropriately covered by health teams [9], defined by the government as the number of teams working in an area multiplied by 3000 (based on the recommendation that each team can provide proper care for 3000 people) and divided by the population living in the area, and (iii) the total number of UPAs (Unidades de Pronto Atendimento; [10]), i.e. emergency care units placed in many municipalities starting in 2008; UPAs are designed to reduce the demand for hospital services, and are equipped to treat cases of higher complexity than basic healthcare units.

We also examined potential changes in the quality of outpatient care by analyzing trends in rates of “potentially avoidable hospitalizations” (PAHs), a group of disease outcomes often used as an indicator of primary care quality; we used the list of PAHs adopted by the Brazilian government (Table S2). In theory, improvements in prevention and early disease management at the outpatient setting should lower PAH rates.

2.4. PCV10 uptake

Brazil introduced PCV10 in its National Immunization Program (PNI) in March 2010. To estimate PCV10 coverage, we calculated the percentage of eligible infants (6–23 months) who had at least the 3 recommended routine doses (at 2, 4 and 6 months) using the age-cohort method described in [11]. Data on doses administered by state, month and age was provided by PNI [12]; live birth statistics (SINASC, [13]) were used to estimate rates. Nationally, PCV10 coverage reached 33%, 76% and 89% by December 2010, 2011 and 2012, respectively.

2.5. Data analysis

We first examined the consistency of ICD10 pneumonia coding from 2003 to 2012. We found that the pattern of codes assigned for many disorders changed dramatically in January 2008, coincident with substantial changes in the system used to reimburse hospitals, which relaxed the specificity of ICD10 reporting requirements. For example, the frequency of pathogen-specific codes such as J13 (pneumococcal pneumonia) and J14 (*H. influenzae* pneumonia) fell sharply, while the number of J18 codes (pneumonia, organism unspecified) rose (Fig. S1). We therefore limited our pre-post analysis to the period starting in January 2008.

We next tested the association between changes in hospitalization rates before and after PCV10 introduction and concomitant changes in the healthcare metrics previously described. Changes in hospitalization rates were estimated as in [14], by calculating the ratio (incidence rate ratio, or IRR) between the average annual incidence rate two years post-PCV (2011–12) and two years pre-PCV10 (2008–09), with their corresponding 95% confidence intervals [15]. The association between IRR and relative changes in healthcare metrics were tested with Pearson and Spearman correlations.

Because our aim was to illustrate the effect of broader changes in healthcare delivery on simultaneous changes in crude rates of hospitalization rather than to estimate vaccine impact itself, we

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