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Brief report

Indirect cohort analysis of 10-valent pneumococcal conjugate vaccine effectiveness against vaccine-type and vaccine-related invasive pneumococcal disease

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ABSTRACT

We applied the indirect cohort method to estimate effectiveness of 10-valent pneumococcal conjugate vaccine (PCV10) among young children in Brazil. Cases of invasive pneumococcal disease (IPD), i.e., *Streptococcus pneumoniae*, detected in normally sterile fluid identified through laboratory-based surveillance and previously enrolled in a matched case-control effectiveness study are included. We estimated PCV10 effectiveness using multivariable logistic regression comparing PCV10 vaccination among children with vaccine-type or vaccine-related IPD vs. children with non-vaccine-type disease. The adjusted effectiveness of ≥1 doses against vaccine-type (72.8%, 95% confidence interval [CI] [44.1, 86.7]) and vaccine-related (61.3%, 95%CI [14.5, 82.5]) IPD were similar to the effectiveness observed in the original case-control study (which required enrollment >1200 controls). We also found significant protection of ≥1 dose against individual vaccine serotypes (14, 6B, 23F, 18C) and against vaccine-related serotype 19A. The indirect cohort methods leverages existing surveillance is a feasible approach for evaluating pneumococcal conjugate vaccines, particularly in resource-limited settings.

1. Introduction

Streptococcus pneumoniae is a leading cause of pneumonia, sepsis and meningitis worldwide [1]. Pneumococcal conjugate vaccines (PCV) are important for reducing pneumococcal morbidity and mortality [2]. A 7-valent PCV (PCV7), available since 2000, was shown to be highly effective against invasive pneumococcal disease (IPD) caused by serotypes included in the vaccine as well as 6A, a vaccine-related serotype [2]. More recently, 10-valent (PCV10) and 13-valent PCVs with substantially better serotype coverage for IPD in the developing world have been increasingly introduced in low- and middle-income counties, where the burden of pneumococcal disease is the greatest [3].

In March 2010, Brazil became the first country to introduce the newly available PCV10 in a national immunization program. PCV10 was licensed based on immunogenicity data [4], and at the time of introduction protection against clinical outcomes was unknown. A case-control study conducted in Brazil using age- and neighborhood-matched controls identified through a national birth registry demonstrated PCV10 effectiveness of an age-appropriate number of doses against vaccine-type IPD (83.8%, 95% confidence interval [CI] 65.9–92.3) and IPD caused by vaccine-related serotypes (77.9%, 95%CI, 41.0–91.7) [5]; the study also reported significant protection against individual vaccine serotypes 14 (87.7%,

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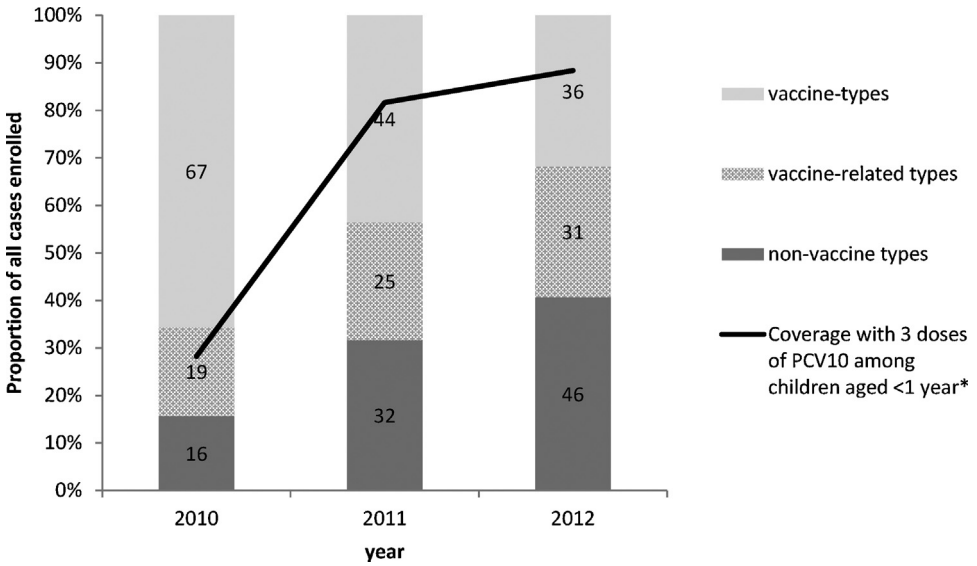

Fig. 1. Proportion of invasive pneumococcal disease cases due to vaccine serotypes, vaccine-related serotypes and non-vaccine serotypes enrolled in study by year and coverage with 3 doses of PCV10 among children aged <1 year. The numbers within each section of the bar represent the number of isolates. *National coverage data for 3 doses of PCV10 among children aged <1 year obtained from http://pni.datasus.gov.br.

95%CI, 60.8–96.1); 6B (82.8%, 95%CI, 23.8–96.1) and vaccine-related serotype 19A (82.2%, 95%CI, 10.7–96.4). Those results were useful for the Brazilian Ministry of Health to justify the investment in PCV10 introduction. However case-control studies can be costly and complex to implement; such evaluations are not feasible for many resource-poor settings.

The Indirect cohort, or 'Broome' method, was developed to examine effectiveness of polysaccharide pneumococcal vaccine [6]. It is a case-only analysis in which the vaccination status of vaccine-type IPD case-patients is compared with that of non-vaccine-type. This method was used to evaluate PCV7 effectiveness in the United States [7], England and Wales [8] and Germany [9]. In the United States, the results of the indirect cohort were consistent with those of a case-control vaccine-effectiveness study that enrolled age- and geographically-matched controls identified through birth registries [10]. We conducted an indirect cohort analysis with data from Brazil to compare with results from the case-control study and to provide further insight into PCV10 protection against vaccine-type and vaccine-related IPD.

2. Methods

Methods for identifying and gathering data on cases have been described elsewhere [5]. Briefly, cases were identified through laboratory-based surveillance in 10 states in Brazil from March 2010 to December 2012. Cases were defined as *S. pneumoniae* detected from a normally sterile site (e.g., blood or cerebrospinal fluid) in a child age-eligible to receive ≥1 PCV10 dose. Initially cases were identified by culture only; however starting in December 2010, some study sites detected cases using polymerase chain reaction (PCR). Pneumococcal isolates submitted to Brazil's national reference laboratory were serotyped using the Quellung reaction; cases detected by non-culture methods were serotyped by PCR [5]. After obtaining written informed consent from the parent or guardian of the child, epidemiologic data were gathered through in-person interviews conducted by study personnel using a standardized questionnaire. Vaccination histories were abstracted from case-patients' immunization cards. The recommended PCV10 schedule included three primary doses (at 2, 4 and 6 months) and a booster dose (12 months). Catch-up schedules for children aged 3–11 months at the time of introduction included one to three primary doses (based on age) plus a booster dose; a single dose was recommended for children aged 12–23 months.

Cases were considered vaccine-type if due to serotypes included in PCV10 (1, 4, 5, 6B, 7F, 9 V, 14, 18 C, 19F or 23F), and vaccine-related if in the same serogroup as a vaccine-type (i.e., 6A, 6C, 6D, 7C, 9N, 18A, 18B, 19A and 23A). All others were classified as non-vaccine-type. Vaccine doses received ≥14 days before the child sought medical care were included in the analysis. Children with the recommended number of PCV10 doses for their age were considered up-to-date. Those who had received a pneumococcal vaccine other than PCV10 were excluded. We used *chi* square to compare proportions and Wilcoxon–Mann–Whitney test to compare medians. We calculated odds of receipt of ≥1 PCV10 doses and up-to-date PCV10 vaccination (compared with 0 doses) among vaccine-type or vaccine-related cases versus non-vaccine-type cases and used logistic regression to estimate vaccine effectiveness as 1-odds ratio for PCV10 vaccination ×100%. To adjust for confounders, we started with basic models that included vaccination status, date of medical attention, and age at illness as independent variables (latter two included as continuous variables). Additional covariates were included one by one in basic models for effectiveness against vaccine-type and vaccine-related disease; any that altered the odds ratio by 10% or more were included in multivariable analysis.

3. Results

A total of 398 IPD cases were identified; 15 (3.7%) declined participation, 26 (6.5%) were not located, 32 (8.0%) had undetermined serotype, and 9 (2.3%) had received other pneumococcal vaccines. Among 316 cases included in analysis, 147 (46.5%) were vaccine-type, 75 (23.7%) were vaccine-related, and 94 (29.7%) were non-vaccine-type. The proportion of vaccine-type cases declined from 2010 to 2012, as vaccine coverage increased (Fig. 1). Median ages of case-patients with vaccine-type, vaccine-related and non-vaccine-type IPD were similar (Table 1). Case-patients with vaccine-type disease were less likely than those with non-vaccine-type to attend daycare, have received routine vaccination against diphtheria-tetanus-pertussis-*Haemophilus influenzae* type B (Hib) and have a mother with <12 years of education. Receipt of ≥1 PCV10 dose was significantly higher among non-vaccine-type cases

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