Review

Effectiveness of the 7-valent pneumococcal conjugate vaccine against vaccine-type invasive disease among children in Uruguay: An evaluation using existing data

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A B S T R A C T

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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Contents

1. Introduction ................................................................................................................................. 00
2. Methods ..................................................................................................................................... 00
   2.1. Cases .................................................................................................................................... 00
   2.2. Controls ............................................................................................................................... 00
   2.3. Data collection and analysis ............................................................................................... 00
   2.4. Human subjects .................................................................................................................... 00
3. Results ...................................................................................................................................... 00
4. Discussion .................................................................................................................................. 00
   References .................................................................................................................................... 00

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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 v9.2 (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.
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, ≥2 doses 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.

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 PCV7 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
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 [20,21,2,9]. 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.

References


