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Effectiveness of three pneumococcal conjugate vaccines to prevent invasive pneumococcal disease in Quebec, Canada

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ABSTRACT

Background: In Quebec, a pneumococcal conjugate vaccine (PCV) program was implemented in December 2004. The recommended schedule is 2 + 1 doses for low-risk infants. PCV-7 was first used (including catch-up for children <5 years of age), replaced by PCV10 in June 2009, and by PCV13 in January 2011 (no catch-up in both instances). From the beginning, >90% of children received the recommended number of doses.
Objective: To assess the effectiveness of the three PCVs sequentially used to prevent invasive infectious disease (IPD).
Methods: IPD cases in children 2–59 months during the years 2005–2013 were eligible. Controls were randomly identified in the provincial health insurance registry. Parents were interviewed and immunization records reviewed. Vaccine effectiveness (VE) was computed using multivariate logistic regression models.
Results: Out of 889 IPD cases reported, full participation was obtained for 516 cases (58%) and for 1767 controls. Against vaccine-type IPD, VE (≥1 dose) was 90% (82–95%) for PCV7, 97% (84–99%) for PCV10 and 86% (62–95%) for PCV13. Against 19A IPD, VE was, respectively, 42% (−9% to 69%), 71% (24–89%), and 74% (11–92%). VE (≥2 doses) against PCV13-type IPD was 85% for PCV10 (66–94%), 85% for PCV13 (55–94%), and 89% (58–97%) for a mixed PCV10 + PCV13 schedule.
Conclusions: All three PCV vaccines showed high level of protection against IPD caused by serotypes included in their formulation and there was a high level of cross-protection against 19A for PCV10. No substantial difference was seen between PCV10, PCV13, or a mixed PCV10 + PCV13 schedule.

1. Introduction

Invasive pneumococcal disease (IPD) constitutes a public health problem worldwide [1]. In Canada, the 7-valent CRM_{197} pneumococcal conjugate vaccine (PCV7) was licensed in May 2001. In the province of Quebec, high-risk children and those living in Nordic regions were offered a four (3 + 1) dose schedule of PCV7 starting in October 2002 [2]. Quebec was the first jurisdiction in the world to recommend a 3-dose (2 + 1) schedule for the routine immunization of infants, vaccines being offered respectively, at age 2, 4 and 12 months [3]. This publicly funded program was launched in December 2004, along with a catch-up program consisting of 2 doses for 12–23 month-old children and 1 dose for 2–5 year-old children. Vaccine uptake was low (<20%) up to the end of the year 2004 and increased very rapidly thereafter [4]. Since 2005, 97% of infants are receiving at least one PCV dose and 93% are receiving the recommended number of doses by age 24 months [5]. Starting in June 2009, the 10-valent protein-D pneumococcal conjugate vaccine (PCV10) replaced PCV7, and in January 2011, the 13-valent CRM_{197} vaccine (PCV13) replaced PCV10, with no catch-up in both instances [6,7].

In Canada, marked changes in the epidemiology of IPD have been observed since the introduction of universal immunization of children with PCVs [8]. In Quebec, the incidence rate in children less than 5 years of age decreased from 63/100,000 in 2004, to 19/100,000 in 2012, with a progressive decline in the proportion

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of cases caused by the serotypes included in the three PCVs [9].

Since January 1st, 2005, IPD cases in children less than 5 years of age are prospectively enrolled in a province-wide case–control study. Results pertaining to the PCV program implementation period 2005–2007 have been published previously [10]. The objective of the present analysis was to assess the effectiveness of the three PCVs sequentially used in the context of a 2 + 1 doses recommendation during the period 2005–2013.

2. Methods

Details on the methodology have been described in a previous publication [10]. Laboratory-confirmed IPD cases in children aged 2–59 months notified to regional public health authorities during the years 2005–2013 were eligible for study. Serotyping was performed at the Quebec Public Health laboratory. A breakthrough case was defined as IPD occurrence 10 days or more after a PCV dose.

Parents were contacted by the regional public health services and invited to participate. Those who agreed were contacted by the research team for a telephone interview and invited to provide a written authorization to review the child's immunization records. Controls were identified randomly in the registry of persons covered by the universal provincial health insurance. Each month, an age-stratified sample of children was provided. The number of controls in each stratum was calculated to obtain 15 controls for each expected IPD case and to allow 5 controls to be interviewed. The expected number of IPD cases was determined *a priori* on the basis of the predicted PCV7 coverage in the target population (95%) and global PCV7 effectiveness against *Streptococcus pneumoniae* (89%) [11].

Information obtained during telephone interviews included the history of PCV and influenza vaccination, the existence of asthma or any other high-risk medical condition listed as an indication for a 4-dose regimen (diabetes, chronic lung, heart, kidney or liver disease, hemoglobinopathy, metabolic disease, congenital or acquired immunodeficiency, CFR leak, and cochlear implant, prematurity), as well as ethnicity, birth weight, gestation length, current breastfeeding or age at weaning, daycare, number of adults and siblings in the household, passive smoking, family income, and mother's educational level. Parents were asked to provide the name and address of their family physician, the private clinic, the public health unit, or the hospital where the child might have received vaccines and they were invited to provide a written authorization to review the child's immunization records. Vaccine providers were contacted to obtain additional information for children with incomplete information on dates of vaccine administration, or when the number of PCV doses reported was less than recommended. To be counted, a vaccine dose had to be administered at least 10 days before disease onset or the date of interview for controls. The study protocol was approved by the research ethics committee of the Quebec University Hospital.

SAS 9.3 software (SAS Institute, Cary, NC) was used for all statistical analyses. Statistical significance was determined for $p < 0.05$ (two-sided test). To account for the actual distribution of IPD risk factors in the Quebec population, controls were weighted using the inverse of the sampling fraction in the age strata to which they belonged. Sampling fractions were computed independently for each year, using annual population estimates. For each control, the weight was calculated as: (inverse of the sampling fraction of age strata in the year)/(mean of inverse sampling fractions of all controls in the year). Doing so, the average weight of all controls = 1. This weight was retained in all multivariate analyses. PCV effectiveness was calculated as one minus the odds ratio (OR) and expressed as a percentage. In a first step, ORs were computed using a weighted unconditional multivariate logistic model, adjusting for sampling variables: age (in 8 categories), calendar year (in 8 categories) and PCV history (no vaccination or ≥1 dose). Thereafter, other variables were sequentially tested and retained when their p value was <0.05 or when the OR value associated with PCV immunization was modified by more than 10%. A model containing sampling variables (year and age) and all significant predictors of IPD risk was built (maximally adjusted model). In a second step, the model was reduced to its most parsimonious format (minimally adjusted model) by keeping sampling variables in the model but excluding other variables that did not introduce confounding (>10% modification of OR) in VE estimates, even if significantly associated with disease risk. The minimally adjusted model was used for all VE estimations according to type of vaccine or schedule and was adjusted for age, year, season and underlying medical condition (any indication for a 4th dose, including severe prematurity, or asthma). For this purpose, dummy variables for each vaccine schedule (PCV7, PCV10, PCV13 or mixed schedules, with or without distinction for the number of doses received) were introduced in the model, using the 'no vaccination' category as the reference. In addition, stratified analyses were performed to assess VE according to age, time period, and exact number of PCV doses.

3. Results

During the 8-year study period, 889 laboratory-confirmed eligible IPD cases were reported in children less than 5 years old. Initial consent to participate in the case–control study was obtained from 689 parents (78% of total). The others could not be contacted or declined the invitation. No telephone contact could be made for 9 cases initially recruited, 9 parents declined further participation and 3 cases were found to be not eligible. Telephone interviews were performed with 668 parents and written authorization to verify children's immunization records was provided by 516 of them (58% of total cases and 77% of those who have been interviewed). The characteristics of IPD cases included in the final analysis ($n = 516$) and of those excluded because the immunization status could not be verified ($n = 152$) were compared and there was no statistically significant difference in the distribution of serotypes, year of disease occurrence, medical condition and age categories. However, full participants had higher family income and maternal education level.

A list of 7962 potential controls was obtained. A telephone contact was attempted for 3610 of them before the necessary number of controls was reached. No phone number was found for 221 selected controls, phone numbers were not in use or no contact could be established for 452 other controls, 6 parents were not able to answer the questionnaire in French or English and 318 parents refused to participate. A total of 2613 parents agreed to be interviewed, and written authorization to verify the child's immunization records was provided by 1767 of them (50% of those selected for interview and 68% of those interviewed), for a final ratio of 3.4 controls per case.

The characteristics of cases and control are shown in Table 1 and additional information on the distribution of cases is included in Supplement Tables 1 and 2. PCV7-serotypes represented 13% of total IPD cases and were mostly identified in the 2005–2009 period. The most frequent serotype was 19A ($n = 167$; 32% of total cases), with 7F in second position ($n = 38$; 7% of total cases). Only 7% of IPD cases were not serotyped. The highest proportion of IPD cases were observed in children 12–23 months of age (36% of total). Unvaccinated children represented 16% of IPD cases and 19% of controls. The annual number of IPD cases had a bimodal distribution with a first peak in 2005, followed by a sharp decrease in 2006, a second peak in