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Invasive pneumococcal disease in Northern Alberta, not a Red Queen but a dark horse

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ABSTRACT

Background: The consequences of the introduction of various pneumococcal protein conjugate vaccines (PCV) for children and adults is poorly understood.
Objective: We undertook a population-based cohort study of invasive pneumococcal disease (IPD) in Northern Alberta (Canada) from 2000 to 2014, years spanning pre-and early PCV (2000–2004) vs PCV-7 (2005–2009) vs PCV-13 (2010–2014) time periods.
Design: We collected clinical, laboratory, and *Streptococcus pneumoniae* serotype information on all patients from 2000 to 2014. We determined changes in presentation, outcomes, serotypes, and incidence in children and adults across time periods.
Setting: There were 509 cases of IPD in children, an 80% decrease over time. Rates of empyema (4.0–15.7%, $p < 0.001$), ICU admission (13.1–20%), and mortality (1.8–8.4%, $p < 0.001$) increased over time. There were 2417 cases of IPD in adults. Unlike children, incidence of IPD did not change nor did rates of empyema. ICU admissions increased ($p = 0.004$) and mortality decreased (18.7–16.5%, $p = 0.002$). The total number of serotypes causing IPD remained stable in children (22 vs 26 vs 20) while they decreased in adults (49 vs 47 vs 42).
Conclusions and relevance: For children, PCV vaccination strategies resulted in decreased overall rates of IPD and we observed increased rates of empyema and mortality; for adults, there was no change in IPD rates although disease severity increased while mortality decreased. On a population-wide basis, our results suggest that current PCV vaccination strategies are associated with an overall decrease in IPD but disease severity seems to be increasing in both children and adults.

1. Introduction

Streptococcus pneumoniae with 97 serotypes is a major cause of disease in children and adults worldwide [1]. Prior to introduction of PCV in North America the seven most prevalent serotypes causing IPD were 4, 6B, 9V, 14, 18C, 19F and 23F [2]. The introduction of pneumococcal protein conjugate vaccine (PCV) with 7 serotypes – 4, 6B, 9V, 14, 18C, 19F, 23F occurred in US in 2000 [3] and Alberta, Canada in 2002 [4]. A 13-valent pneumococcal protein conjugate vaccine with the above 7 serotypes plus an additional 6 serotypes (1, 3, 5, 6A, 7F, 19A) was introduced in the US and Alberta as a provincially funded program in 2010 [4,5]. Starting in 2002 with PCV-7, the schedule for childhood immunization with this vaccine was an injection at 2, 4, and 12 months. The same schedule was followed for PCV-13 starting in 2010. Children who received a full PCV-7 series are to receive a dose of PCV-13 prior to their fifth birthday. Twenty-three valent pneumococcal polysaccharide vaccine (PPV-23) has been available to adults since 1997 (for those over 65 years of age and those at increased risk for pneumococcal infection) and since 2010 PCV-13 has been available to adults but is not funded by Government. PCV-13 has been available to all children since 2013 as part of the Government funded immunization program. We do not know what percentage of the adult population has received pneumococcal vaccine.

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These pneumococcal protein conjugate vaccines have resulted in a marked reduction in IPD due to vaccine serotypes, especially in children <2 years [3,5,6]. At the same time, there has been a considerable increase in the rate of empyema complicating pneumonia in children [7,8] and the impact of the vaccines in adults is highly debated [9]. It has been postulated that the introduction of these vaccines has caused selective pressure on pneumococcal populations resulting in serotype diversity with serotypes rarely present before vaccine introduction and not in the vaccine are now causing invasive pneumococcal disease – so called serotype replacement (9,10). Indeed, this is also often referred to as the "Red Queen" hypothesis, drawn from ***Through the Looking Glass***, wherein the Queen of Hearts states: "Now, *here*, you see, it takes all the running you can do, to keep in the same place" [10,11].

To better understand the potential impact of PCV vaccines over time at the population level, we analyzed data from a 15-year prospective study of all IPD cases in Northern Alberta, Canada. We hypothesized that we would see a reduction in IPD in young children and there would be a change in some IPD related outcomes in both children and adults.

2. Material and methods

2.1. Definitions

Cases of IPD were defined as per the Canadian national case definition of isolation of *S. pneumoniae* from a normally sterile site such as blood, cerebrospinal fluid, pleural fluid, biopsy tissue, joint aspiration, pericardial fluid, or peritoneal fluid [12]. IPD is a notifiable disease in Alberta therefore all invasive pneumococcal isolates are submitted to the Provincial Laboratory for Public Health (PLPH) for further characterization. While the case definition of IPD changed in 2009 to allow inclusion of cases with Streptococcus pneumoniae DNA detected by polymerase chain reaction in specimens from sterile sites [http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09pdf/35 s2-eng.pdf] we continued to use the previous definition [12] in order to maintain stability of case ascertainment.

2.2. Clinical data collection

From 2000 to 2014, data were collected on all patients in Northern Alberta with IPD. For each case, a research nurse collected sociodemographic, clinical, functional, and laboratory data using a standardized case report form (CRF). Underlying illnesses were recorded according to the attending physician's documentation in the medical record. This study received approval from the institutional research review committees of the Northern Alberta Health Regions (former regions 4 through 9) as well as the University of Alberta ethics review board.

2.3. Identification and serotyping of S. Pneumoniae isolates

S. pneumoniae isolates were confirmed as *S. pneumoniae* based on characteristic morphology and optochin susceptibility prior to serotyping [13]. All pneumococcal isolates that exhibited a positive Quellung reaction using type specific antisera obtained from Statens Serum Institute, Copenhagen, Denmark were assigned a serotype designation [14]. The sera from the Statens Serum Institute will type 91 of the 97 pneumococcal serotypes. Strains that were susceptible to optochin but which failed to serotype using the Quellung assay, were assayed further using AccuProbe™ *Streptococcus pneumoniae* culture identification test, Gen-Probe, San Diego, CA, to confirm the species identification.

2.4. Data analysis

As we were most interested in the potential impact of various formulations of the PCV vaccine between 2000 and 2014, the study population was divided into three mutually exclusive groups – those with IPD from 2000 to 2004, representing the pre-widespread use of PCV 7 era [recognizing that it takes time to achieve widespread coverage with a vaccine in a province such as Alberta with large sparsely populated areas]; from 2005 to 2009, representing the PCV 7 era; and 2010–2014, representing the PCV-13 era. We further subdivided the study population into children (defined as those $\leq$17 years of age) and adults. Sociodemographic variables, clinical characteristics, major in-hospital complications (e.g., presence of cellulitis, meningitis, admission to the intensive care unit [ICU], need for chest tube and all-cause in-hospital mortality) are presented using standard descriptive statistics. In addition, IPD serotypes over time and percent of serotypes potentially covered by PCV vaccine formulations were explored according to age groups. All characteristics and outcomes were compared between our three time periods stratified on age using ANOVA, chi-squared tests, or Fisher's exact tests as appropriate. IPD related incidence rates were also calculated per 100,000 population according to various age groups. Complete data capture were available for sociodemographics. If there was no recording of an underlying illness or in-hospital complication, it was assumed that the illness or complication was not present. All analyses were performed with Stata SE, version 12.1 (Stata, College Station, TX).

3. Results

3.1. IPD in children

3.1.1. Clinical characteristics and outcomes

Overall, 509 cases of IPD occurred in children between 2000 and 2014 with 274 cases in 2000–2004 (54%), 152 (30%) in 2005–2009, and 83 (16%) from 2010 to 2014. Significant differences were noted in the characteristics and outcomes over the three time periods (Table 1). Changes in characteristics of the population included an increase in the percentage of Indigenous children and a decrease in the percentage treated as outpatients and a decrease in the percentage with no comorbid illnesses. Changes in outcomes included an increase in empyema (4.0% vs 7.2% vs 15.7%), need for a chest tube (5.1% vs 8.6% vs 18.1%), admission to the ICU (13.1% vs 17.1% vs 24.1%) and in-hospital mortality (1.8% vs 3.3% vs 8.4%) were observed from 2000 to 2004, 2005 to 2009 and 2010 to 2014, respectively. Table 2 gives a comparison of those who died vs those who lived in the 2010–2014 period.

Alberta Health Services reported in 2013, 81% of the children in Northern Alberta had had received three doses of PCV-13 by age 2 [15].

3.2. Serotype data

There were changes in position of the most common serotypes causing IPD (Supplemental Table 1). In the pre and early PCV period, 4 of the 6 most common serotypes (4, 6B, 19F, 9V) were in the PCV 7 vaccine, but by the 2005–2009 period only 1 of these (19F) remained in the top 6. During 2010–2014, following PCV 13 introduction, 4 of the 6 top serotypes were included in the PCV 13 vaccine. Serotype 19F remained in the top 6 throughout the 15 years of the study. The top 6 serotypes accounted for an increasing percentage of the total cases – 46%; 52% and 68% respectively. The number of serotypes accounting for the total cases in each of the three time periods were 22, 26 and 20 respectively.