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Serotype distribution of invasive *Streptococcus pneumoniae* in adults 65 years of age and over after the introduction of childhood 13-valent pneumococcal conjugate vaccination programs in Canada, 2010–2016

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ABSTRACT

The 13-valent conjugate vaccine (PCV13) was recommended for childhood immunization programs in 2010 in Canada and has decreased the incidence of invasive pneumococcal disease (IPD) in children and changed the epidemiology of IPD in adults. This study investigated the epidemiology of IPD in adults 65 years of age and older in Canada. A total of 7282 invasive *S. pneumoniae* isolated from adults ≥65 years old were serotyped from 2010 to 2016 and antimicrobial susceptibility was performed on 2527 isolates. Serotyping was performed by Quellung reaction using commercial antisera and antimicrobial susceptibilities were determined by broth microdilution. PCV7 serotypes decreased non-significantly from 2010 to 2016 from 9.1% (n = 96) to 6.7% (n = 72) while the additional six PCV13 serotypes declined significantly from 39.5% (n = 418) to 18.6% (n = 201) ($p < 0.05$). The 23-valent pneumococcal polysaccharide vaccine (PPV23) and non-vaccine (NVT) serotypes increased from 26.3% (n = 278) to 36.2% (n = 393) ($p < 0.05$), and from 25.1% (n = 266) to 38.4% (n = 416) ($p < 0.05$), respectively. There were no significant changes in antimicrobial resistance rates from 2011 to 2016: 24.1% of the IPD from adults ≥65 years were resistant to clarithromycin (n = 609), 10.0% to doxycycline (n = 254), 11.8% to penicillin (n = 299), 5.2% to cefuroxime (n = 131), 6.6% to clindamycin (n = 168), 6.0% to trimethoprim-sulfamethoxazole (n = 152), and 0.5% (n = 12) to ceftriaxone. Although overall incidence of IPD in adults ≥65 years has remained relatively constant from 2010 to 2016, childhood PCV13 vaccination programs have been successful in indirectly reducing IPD caused by PCV13 serotypes in adults through herd immunity effects.

1. Introduction

Streptococcus pneumoniae is a common microorganism of the human nasopharynx which can cause severe invasive pneumococcal

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disease (IPD) such as bacteraemia and meningitis. Globally it has caused an estimated 1.6 million deaths annually primarily among young children and seniors [1].

A small number of the 97 currently recognized pneumococcal serotypes [2] cause the majority of disease and vaccines targeting the capsule polysaccharide (CPS) of these strains have been very successful in directly reducing the burden of IPD in children, and indirectly in adults through herd immunity effects [3–8]. Beginning in 2002 a 7-valent conjugate vaccine became available in the Canadian market, followed in 2009 by a 10-valent product [9]. A 13-valent pneumococcal conjugate vaccine (PCV13) targeting serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 7F and 19A, was recommended for use in Canada in 2010 [10] and all provinces and territories incorporated the vaccine into their routine pediatric immunization schedule program between June 2010 and January 2011. Although there may be some regional variability, overall Canadian survey data for children suggest high coverage of this vaccine with over 80% of children having received full series of PCV13 by 2 years of age [11]. Despite wide spread reports of the emergence of non-vaccine serotypes (NVT) through serotype replacement or capsule switch events [12–16], there has not been an overall increase in disease to pre-PCV13 levels in children [12–14,17–19].

Adult vaccines for pneumococcal disease include the 23-valent pneumococcal polysaccharide vaccine (PPV23), which has been available since 1996 with efficacy in preventing invasive disease but has limited effectiveness with respiratory disease [7,20,21]. PPV23 is not licenced for routine use in young children and has little efficacy on carriage, an important reservoir for the transmission and spread of invasive disease [5,22–24]. PPV23 has also had little effect on IPD prevalence rates of constituent serotypes in adults, possibly due to low coverage, or due to the lower effectiveness of a non-conjugated polysaccharide vaccine [22,25–27]. In a 2014 Canadian immunization coverage survey only 36.5% of adults over the age of 65 years have been immunized with PPV23 [28].

PCV13 was approved for use in adults ≥50 years of age in early 2012 based on its non-inferiority with PPV23 [24,29,30]. An adult PCV13 vaccine trial, Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), showed a reduced number of invasive infections caused by PCV13 serotypes as well as 49% efficacy to other serotypes [24,31], and sustained immunity for at least 5 years has been reported [32]. The efficacy data presented in the CAPiTA study led the Advisory Committee on Immunization Practices (ACIP) in the USA and a variety of European countries to introduce a single dose of PCV13 prior to PPV23 [33,34]. The cost effectiveness of PCV13 vaccinations may however be tempered by assumptions made about herd immunity effects and effectiveness metrics related to non-invasive disease [35] and some modelling work has suggested that over time, the indirect effects in older adults may result in near elimination of PCV13 serotypes when PCV13 is part of the routine childhood immunization programs [8].

This study reports current trends of IPD and shifts in the distribution of *S. pneumoniae* serotypes in adults ≥65 years of age following the introduction of the childhood PCV13 vaccine programs in Canada.

2. Materials and methods

A total of 7282 isolates of *S. pneumoniae* from normally sterile clinical sites (blood, central nervous system tissue/fluid, peritoneal fluid, pericardial fluid, synovial fluid, or other deep abscesses and tissues) [36] and pleural fluid from people aged 65 years and older were serotyped from 2010 to 2016. National IPD serotype surveillance in Canada consists primarily of a passive laboratory based system where all invasive isolates from all provincial/territorial public health laboratories are serotyped by the National Microbiology Laboratory (NML), Winnipeg; the Toronto Invasive Bacterial Diseases Network (TIBDN); the Laboratoire de santé publique du Québec (LSPQ); or the Provincial Laboratory for Public Health, Edmonton, Alberta (ProvLab Alberta).

From 2010 to 2016, 3787 invasive isolates representing all isolates collected by the public health laboratories of British Columbia, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Yukon, Northwest Territories and Nunavut were submitted to the National Microbiology Laboratory (NML), Winnipeg for analysis. Serotype data was submitted to the NML for 1108 isolates representing all isolates collected during this time period through an enhanced active surveillance program from every patient presenting symptoms by the Toronto Invasive Bacterial Diseases Network (TIBDN) in the greater Toronto metropolitan region. Submitted serotype data on 1563 isolates from Québec were supplied from an active provincial surveillance system on all isolates from children < 5 years of age, all isolates from northern regions of the province, all isolates collected from individuals ≥5 years of age from 20 sentinel hospital sites from 2010 to 2012, all isolates collected from individuals ≥5 years of age from all hospital sites from 2013 to 2016, and all isolates with a penicillin minimum inhibitory concentration (MIC) ≥0.12 μg/ml. Information on a further 823 isolates typed by the Provincial Laboratory for Public Health, Edmonton, Alberta represented all isolates collected in Alberta over the time period. Patient information collected included patient age, gender, clinical isolation site and date. The national surveillance data presented here consisting of cultures submitted to the NML, and data submitted by the three additional reference laboratories (LSPQ, TIBDN and ProvLab Alberta) accounted for approximately 80% of all IPD cases from adults ≥65 years of age in Canada.

Multiple isolates collected within 14 days from the same patient with identical serotypes were counted once with the most invasive isolation site included, with meningitis related isolates regarded as most invasive followed by blood and other sterile sites. Isolates were screened by optochin disc susceptibility (Oxoid, Basingstoke, Hampshire, UK) and tube bile solubility analyses [37,38]. Serotyping was performed by Quellung reaction using commercial pool, group, type and factor antisera (SSI Diagnostica; Statens Serum Institute, Copenhagen, Denmark) [39,40]. Isolates for which a Quellung reaction was not observed were tested for the presence of the *cpsA* gene using PCR [41] and the species was verified by *rpoB* (beta subunit of RNA polymerase gene) sequence typing [42,43].

Antimicrobial susceptibility testing was performed by the University of Manitoba Health Sciences Centre - Canadian Antimicrobial Resistance Alliance (CARA) on all invasive *S. pneumoniae* isolates submitted to the NML by 8 participating jurisdictions including Saskatchewan, Manitoba, Ontario, Québec, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and 6 of 7 health regions in New Brunswick. Antimicrobial susceptibilities were determined on 2527 isolates representing 34.7% of all Canadian isolates collected from 2011 to 2016 by broth microdilution according to Clinical Laboratory Standards Institute (CLSI) guidelines [44,45] for penicillin (PEN), amoxicillin/clavulanate (AUG), cefuroxime (FUR), ceftriaxone (AXO), clarithromycin (CLA), ertapenem (ERT), meropenem (MER), clindamycin (CLI), vancomycin (VAN), ciprofloxacin (CIP), levofloxacin (LEV), moxifloxacin (MOX), linezolid (LZD), tigecycline (TIG), trimethoprim/sulfamethoxazole (SXT) and doxycycline (DOX). Meningitis resistance breakpoints were used for PEN non-susceptibility (≥0.12 μg/ml), AXO (≥2 μg/ml), and parenteral resistance breakpoints for FUR (≥2 μg/ml). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretative breakpoints for

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