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Serotype epidemiology of invasive pneumococcal disease in Swiss adults: A nationwide population-based study

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ABSTRACT

Background: In Switzerland, the heptavalent (PCV7) and 13-valent pneumococcal conjugate vaccine (PCV13) were recommended for all infants aged <2 years in 2007 and 2011, respectively. Due to herd effects, a protective impact on the invasive pneumococcal disease (IPD) rates in adults had been expected.
Methods: Within this study, data from the nationwide mandatory surveillance was analyzed for all adult patients ≥16 years with IPD of known serotype/serogroup during 2003–2012. Trend (for IPD cases from 2003 to 2012) and logistic regression analyses (2007–2010) were performed to identify changes in serotype distribution and to identify the association of serotypes with age, clinical manifestations, comorbidities and case fatality, respectively.
Findings: The proportion of PCV7 serotypes among all IPD cases ($n = 7678$) significantly declined in adults from 44.7% (2003) before to 16.7% (2012) after the recommendation of PCV7 ($P < 0.001$). In contrast, the proportion of non-PCV7 serogroup/serotypes increased for non-PCV13 but also PCV13 serotypes (not included in PCV7) at the same time. Serotype distribution varied significantly across ages, clinical manifestations and comorbidities. Serotype was furthermore associated with case fatality ($P = 0.001$). In a multivariable logistic regression model, analyzing single serotypes showed that case-fatality was increased for the serotypes 3 ($P = 0.008$), 19A ($P = 0.03$) and 19F ($P = 0.005$), compared to serotype 1 and 7F.
Conclusion: There was a significant decline in PCV7 serotypes among adults with IPD in Switzerland after introduction of childhood vaccination with PCV7. Pneumococcal serotypes were associated with case fatality, age, clinical manifestation and comorbidities of IPD in adults. These results may prove useful for future vaccine recommendations for adults in Switzerland.

1. Introduction

Invasive pneumococcal infections (IPD) are among the most important vaccine-preventable infections in humans causing significant morbidity and mortality world-wide [1]. The risk of IPD is highest at the extremes of age and in patients suffering from comorbidities [2].

At the beginning of the 21st century, the heptavalent conjugated pneumococcal polysaccharide vaccine (PCV7) became available – covering the serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Addition of PCV7 to the infant vaccination schedules has greatly reduced IPD and non-invasive pneumonia in vaccinated infants at different geographical sites [3,4]. Serotype redistribution caused by vaccine selection pressure and probably other, yet unknown factors, have necessitated an enlargement of the vaccine's serotype spectrum. PCV13, covering in addition the serotypes 1, 3, 5, 6A, 7F, and 19A, has recently become available and is now replacing PCV7 in many countries worldwide. In some countries like the USA, Canada and, to a lesser extent, in England and Wales, adults were found to profit from indirect protection (i.e. 'herd immunity') due to high PCV7 vaccination coverage in infants [2,5–7]. In other European

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countries such as Spain, the Netherlands and France, this benefit could not be observed that clearly [4,8]. As for Switzerland, no such effect was described 3 years after introduction of PCV7 in a recent, pooled analysis of multiple surveillance sites [9]. The reason for a lack of measurable herd effects in some countries may be due to a low vaccination coverage or a rapid and important serotype redistribution resulting in the emergence of non-PCV7 serotypes such as 1, 3, 7F, 19A and others [4]. However, the mechanism by which this redistribution takes place is largely unknown and introduction of new strains and/or capsule switch due to recombination among existing strains is possible [10,11].

In 2001 PCV7 vaccination was recommended for children <5 years at increased risk for IPD. In November 2005, PCV7 vaccination became recommended for all children younger than 2 years in Switzerland which included a 2 + 1 dosing schedule at 2, 4 and 12 months without catch-up campaign. According to the Swiss National Vaccination Coverage Survey, the vaccine coverage was about 53% for one dose, 50% for 2 doses and 37% for 3 doses at the age of 2 years in 2008–2010 [12]. In 2005–2007, the PCV7 coverage was only about 2% for the first dose. Since 2011, PCV13 replaces PCV7. In addition, the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been recommended for individuals aged ≥65 years or those ≥2 years with known risk factors for IPD since 2000 [13]. However, the protection efficacy of the currently used PPV23 seems to be limited [14]. This raises the question whether PCV13 could replace or supplement PPV23 vaccination in these two age groups in Switzerland. Apart from prospective efficacy studies, this decision should in part be based on the age-dependent IPD serotype epidemiology, too. The main objective of this study is thus the description of the current serotype epidemiology of IPD in adult Swiss residents. The specific objectives are: (i) analysis of temporal trends of single serotypes, (ii) association of serotypes with age and clinical manifestations, (iii) association of serotypes with type and number of different comorbidities and (iv) correlation between serotype and case-fatality.

2. Material and methods

2.1. Data collection

In Switzerland, IPD notification to the Federal Office of Public Health (FOPH) is mandatory for laboratories and physicians within one week after IPD confirmation. Using a standardized IPD reporting form, information on age, gender, vaccination history, clinical manifestation of IPD, comorbidities and death are collected. No patient follow up took place.

Clinical manifestations of IPD to be ticked on the form included invasive pneumonia, meningitis, sepsis and 'others' accompanied by a free-text line. If patients were reported to suffer from sepsis only, we subsequently attributed 'bacteremia without focus' to this group. Patients with pneumonia (including empyema) may simultaneously present with other clinical manifestations. If cases presented with both pneumonia and meningitis, patients were only accounted for the latter. Other manifestations included arthritis and the ones noted by the physician as free text.

Comorbidities reported on the forms included chronic kidney disease, immunosuppression, recurring airway diseases, recurring otitis, splenectomy, nephrotic syndrome, basal skull fracture, chronic lung diseases, diabetes mellitus, functional asplenia, cerebrospinal fistula and 'others' accompanied by a free-text line. The latter were investigated and were assigned to cancer (including hematological malignancy, with and without current chemotherapy), heart disease, liver disease, HIV, transplantation, nicotine and alcohol abuse.

Comorbidities were grouped into three main categories; (i) chronic disease, (ii) immunosuppression and (iii) underlying respiratory disease. In brief, 'chronic disease' included reported chronic kidney disease, nephrotic syndrome, diabetes mellitus, heart and liver disease. 'Immunosuppression' included reported immunosuppression, splenectomy/hemoglobinopathy, cancer, HIV and transplantation. 'Underlying respiratory disease' contained recurrent airway disease, recurrent otitis, chronic lung disease and nicotine abuse. Patients could belong to multiple categories.

All clinical microbiology laboratories are asked to send isolates of *Streptococcus pneumoniae* from a sterile site to the National Reference Laboratory for Invasive Pneumococcal Disease (NZPn).

At the NZPn, isolates were confirmed as *S. pneumoniae* using alpha hemolysis morphology on blood agar plates, bile solubility, optochin sensitivity and molecular typing [15]. Serotypes of confirmed *S. pneumoniae* were determined by the Quellung reaction.

For the serotype trend analysis, all adult Swiss residents ≥16 years with culture-confirmed IPD of known serotype and which were notified during 2003–2012 were included. If a patient suffered from more than one IPD episode per calendar year, only the first was included in the analysis. As for this time period, 8698 cases were registered at the FOPH. Of these, 659 (84%), 733 (86%), 783 (89%), 743 (89%), 798 (88%), 871 (90%), 893 (88%), 719 (92%), 776 (90%) and 703 (86%) cases could be linked with pneumococcal serotype isolate collected at the NZPn, in 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011 and 2012, respectively.

For the investigation of the effect of serotype/serogroup on various outcomes, all adult Swiss residents ≥16 years with culture-confirmed IPD of known serotype and which were notified during 2007–2010 were included.

The IPD surveillance is part of the governmental public health surveillance based on the law for epidemics and is therefore exempted from approval by Institutional Review Boards.

2.2. Statistical analysis

Temporal changes from 2003 to 2012 were analyzed using the Cochran–Armitage test for trend and $P < 0.05$ was considered as being statistically significant. The dynamics of serotypes/serogroups were also evaluated using the Cochran–Armitage test as previously described [16]. Differences in the proportions of pneumococcal serotypes in adult patients with and without PPV23 were tested using 3×2 and 2×2 χ^2-test, respectively (the latter excluding patients for whom vaccination status were not available).

Incidence of IPD cases with known serotype from 2007 to 2010 were calculated and stratified by age, clinical manifestation, comorbidities and death. The Swiss population aged ≥16 years was 6.3, 6.4, 6.5 and 6.6 million for 2007, 2008, 2009 and 2010 respectively [17].

The effect of serotype/serogroup on various outcomes was investigated by multivariable logistic regression analyses. The included outcomes were:

(i) Age group (16–64 versus ≥65 years), adjusted for number of comorbidities (0 versus ≥1), clinical manifestation (meningitis, bacteremia without focus and pneumonia) and sex.
(ii) Death (yes versus no/not reported), adjusted for age, number of comorbidities, clinical manifestation and sex.
(iii) Bacteremia without focus (yes versus no), adjusted for age, number of comorbidities and sex.
(iv) Presence versus absence of different comorbidities (0 versus ≥1), adjusted for age, clinical manifestation and sex.
(v) Presence versus absence of immunosuppression adjusted for age, clinical manifestation and sex.