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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.

Adjusted odds ratio (OR) estimates with 95% confidence intervals (95%CIs) were calculated and significance of overall association was tested using a two-tailed Likelihood Ratio (LR) test. For all logistic regression analyses, the serotypes 1 and 7F were grouped together and served as the reference group. These serotypes have been described to infect mainly young individuals with few comorbidities and have been previously used as reference serotypes [18–21].

Logistic regression analysis was performed using Stata version 11 (Stata Corporation, College Station, TX, USA). Cochran–Armitage test for trend was done with EPI INFO Version 3.4.1 (Centre for Disease Control and Prevention (CDC), Atlanta, GA).

3. Results

This study included 7678 IPD patients aged ≥16 years notified to the FOPH with linked pneumococcal isolate serotype information in Switzerland from 2003 to 2012 (Table 1). In total twenty serotypes/serogroups with an overall proportion of ≥1% were detected. The proportions of 6 of 7 PCV7 serotypes significantly decreased (serotypes 4, 14, 19F, 23F, 6B and 9V) over time while for the remaining (serotype 18C), a decline was also noted albeit not significant. In contrast, the proportion of non-PCV7 serogroup/serotypes increased for non-PCV13 (22, 15, 23, 35 and others) but also PCV13 not included in PCV7 (3, 7F, 19A) serotypes. As for serotypes/serogroups with proportions <1%, only for serotype 6C a significant increase was observed (Table 1).

This study then investigated 3281 IPD patients notified to the FOPH with linked pneumococcal serotype isolate information in Switzerland from 2007 to 2010 in more detail (Table 2). The mean age was 65.4 years (SD 17.4) and there were 1.3 times (95%CI: 1.2–1.4) more female (n = 1841; 56.1%; 95%CI: 54.4–57.8%; Table 2) than male patients. For the majority of these patients, clinical manifestations were known (n = 3054; 93.1%), with pneumonia being the most frequent unique manifestation (n = 2347). Clinical information on manifestation and comorbidities was available for 2854 cases, with 1210 cases aged 16–64 years and 1644 aged ≥65 years for 2007–2010. Number and incidence of serotyped IPD (cases with known serotype and clinical information per 100,000 population) detected from 2007 to 2010 decreased overall (Chi Square for trend; P = 0.01). The decrease was pronounced in those aged ≥65 years, those with pneumonia and those with comorbidities. The overall case-fatality rate was 11.4% with significant decrease within 2007–2010 (P = 0.03; Table 2). Table 3 compares IPD cases in PPV23 vaccinated (n = 82) and non-vaccinated (n = 1682) individuals from 2007 to 2010. Results showed a significantly lower proportion of PPV23 serotypes in vaccinated adults (P < 0.001) (Table 3). In contrast, an increase of serotype 6A (P < 0.001), which is not included in PPV23, was noted.

In order to investigate any correlation between the different serotypes/serogroups and age, two-tailed Likelihood Ratio (LR) and a multivariable logistic regression was performed. Serotype/serogroup was significantly associated with age (≥65 years; P < 0.001). Subsequent single serotype analysis showed that cases with serotypes/serogroups 6A, 23F, 6B, 11, 14 and 15 infection were most significantly (OR > 2) associated with the age ≥65 years compared to those infected with the serotypes of the reference group (1 and 7F) (Fig. 1A).

Serotype was also associated with case fatality (P = 0.001) and scrutinizing the individual serotypes revealed that serotypes 3, 19A and 19F were saliently associated with increased case-fatality, compared to the reference group (Fig. 1B).

As for the manifestations, suffering from pneumonia (P < 0.001), meningitis (P < 0.01) and bacteremia without focus (P < 0.01) was associated by serotype, too. IPD due to serotypes/serogroups 35,

Table 1
Serotypes of *S. pneumoniae* causing invasive pneumococcal disease (IPD) in patients aged ≥16 years, Switzerland (2003–2012).

Serotype/ serogroup	Coverage by the vaccine[b]	IPD cases with serotype and clinical information known, no. (%)										
		Year										P[c]
		2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
4	7, 13	62 (9.4)	49 (6.7)	66 (8.4)	71 (9.6)	56 (7.0)	68 (7.8)	66 (7.4)	45 (6.3)	38 (4.9)	25 (3.6)	**<.001**
6B	7, 13	27 (4.1)	22 (3.0)	31 (4.0)	31 (4.2)	28 (3.5)	20 (2.3)	17 (1.9)	13 (1.8)	18 (2.3)	9 (1.3)	**<.001**
9V	7, 13	31 (4.7)	44 (6.0)	55 (7.0)	44 (5.9)	62 (7.8)	54 (6.2)	44 (4.9)	19 (2.6)	13 (1.7)	11 (1.6)	**<.001**
14	7, 13	107 (16.2)	115 (15.7)	105 (13.4)	104 (14.0)	109 (13.7)	87 (10.0)	76 (8.5)	47 (6.5)	45 (5.8)	25 (3.6)	**<.001**
18C	7, 13	14 (2.1)	17 (2.3)	22 (2.8)	24 (3.2)	30 (3.8)	16 (1.8)	14 (1.6)	20 (2.8)	14 (1.8)	9 (1.3)	.06
19F	7, 13	21 (3.2)	22 (3.0)	28 (3.6)	37 (5.0)	35 (4.4)	32 (3.7)	24 (2.7)	17 (2.4)	19 (2.4)	8 (1.1)	**.002**
23F	7, 13	33 (5.0)	40 (5.5)	51 (6.5)	48 (6.5)	50 (6.3)	54 (6.2)	50 (5.6)	22 (3.1)	20 (2.6)	26 (3.7)	**<.001**
1	13	26 (3.9)	43 (5.9)	35 (4.5)	29 (3.9)	27 (3.4)	31 (3.6)	37 (4.1)	35 (4.9)	23 (3.0)	26 (3.7)	.1
3	13	83 (12.6)	85 (11.6)	104 (13.3)	79 (10.6)	96 (12.0)	121 (13.9)	129 (14.4)	99 (13.8)	131 (16.9)	109 (15.5)	**<.001**
7F	13	48 (7.3)	67 (9.1)	61 (7.8)	59 (7.9)	78 (9.8)	72 (8.3)	90 (10.1)	77 (10.7)	83 (10.7)	78 (11.1)	**.001**
19A	13	18 (2.7)	25 (3.4)	20 (2.6)	16 (2.2)	30 (3.8)	35 (4.0)	53 (5.9)	65 (9.0)	92 (11.9)	80 (11.4)	**<.001**
6A[d]	13	14 (2.1)	24 (3.3)	22 (2.8)	31 (4.2)	32 (4.0)	29 (3.3)	31 (3.5)	23 (3.2)	15 (1.9)	17 (2.4)	.5
8		31 (4.7)	36 (4.9)	52 (6.6)	53 (7.1)	28 (3.5)	47 (5.4)	45 (5.0)	37 (5.1)	46 (5.9)	41 (5.8)	0.8
10		10 (1.5)	8 (1.1)	6 (0.8)	9 (1.2)	6 (0.8)	13 (1.5)	11 (1.2)	6 (0.8)	15 (1.9)	13 (1.8)	.2
11		16 (2.4)	14 (1.9)	18 (2.3)	11 (1.5)	11 (1.4)	24 (2.8)	21 (2.4)	11 (1.5)	19 (2.4)	13 (1.8)	1.0
22[e]		19 (2.9)	29 (4.0)	22 (2.8)	24 (3.2)	24 (3.0)	28 (3.2)	46 (5.2)	51 (7.1)	54 (7.0)	48 (6.8)	**<.001**
6C[d]		ND	ND	ND	ND	2 (0.3)	4 (0.5)	9 (1.0)	15 (2.1)	16 (2.1)	15 (2.1)	**<.001**
9		30 (4.6)	25 (3.4)	23 (2.9)	15 (2.0)	20 (2.5)	37 (4.2)	24 (2.7)	28 (3.9)	27 (3.5)	29 (4.1)	.6
15		10 (1.5)	8 (1.1)	6 (0.8)	12 (1.6)	8 (1.0)	17 (2.0)	14 (1.6)	17 (2.4)	18 (2.3)	21 (3.0)	**<.001**
23		12 (1.8)	4 (0.5)	4 (0.5)	10 (1.3)	5 (0.6)	11 (1.3)	14 (1.6)	10 (1.4)	13 (1.7)	17 (1.4)	**.01**
35		ND	7 (1.0)	7 (0.9)	7 (0.9)	6 (0.8)	8 (0.9)	12 (1.3)	13 (1.8)	5 (0.6)	16 (2.3)	**.03**
Others[a]		47 (7.1)	49 (6.7)	45 (5.7)	29 (3.9)	55 (6.9)	63 (7.2)	66 (7.4)	49 (6.8)	52 (6.7)	67 (9.5)	**.02**
Total		659 (100)	733 (100)	783 (100)	743 (100)	798 (100)	871 (100)	893 (100)	719 (100)	776 (100)	703 (100)	

[a] All serotypes/serogroups with an overall proportion of <1% were combined to one group ("others"), with the exception of serotype 6C which is listed separately.
[b] Coverage by the vaccine PCV7 (7) and PCV13 (13). PPV23 serotypes are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.
[c] Exact P values for Cochran–Armitage χ^2 test of trend. P < 0.05 is indicated in bold.
[d] Isolates of serogroup 6 were not differentiated into 6A or 6C for 2003–2006.
[e] Isolates of serogroup 22 were differentiated into 22F and non-22F serotypes in 2007–2012. In total, 22 (2007), 26 (2008), 45 (2009), 47 (2010), 53 (2011) and 48 (2012) isolates of 22F were received.
ND, not done.

Table 2
Characteristics of the study population: patients aged ≥16 years with invasive pneumococcal disease of known serotype after the introduction of PCV7, Switzerland (2007–2010).

	No. of cases with known serotype and clinical information per calendar year (no. of cases per 100,000 population)				
	2007	2008	2009	2010	P[a]
Total cases ≥16 years notified	912	971	1012	784	
Total cases ≥16 years with known serotype	798 (12.6)	871 (13.5)	893 (13.7)	719 (10.9)	0.01
Age group					
16–49 years	156 (4.3)	187 (5.1)	179 (4.8)	136 (3.6)	0.1
50–64 years	170 (11.8)	187 (12.8)	215 (14.4)	163 (10.8)	0.7
≥65 years	472 (38.0)	497 (38.9)	499 (38.1)	420 (31.6)	0.007
Deaths within 90 days	100 (1.6)	100 (1.6)	99 (1.5)	74 (1.1)	0.03
Clinical manifestation known[b]	755	806	818	675	
Pneumonia[c]	589 (9.3)	606 (9.4)	637 (9.8)	515 (7.8)	0.01
Meningitis[c]	42 (0.7)	49 (0.8)	41 (0.6)	31 (0.5)	0.1
Bacteremia w/o focus	89 (1.4)	97 (1.5)	86 (1.3)	84 (1.3)	0.4
Others[d]	35 (0.6)	54 (0.8)	54 (0.8)	45 (0.7)	0.5
Comorbidities known[e]	715	766	767	621	
0	220 (3.5)	250 (3.9)	264 (4.1)	215 (3.3)	0.6
≥1	496 (7.8)	516 (8.1)	503 (7.7)	406 (6.1)	<0.001

[a] *P*-values for Cochran–Armitage χ^2 test of trend.
[b] Clinical manifestations were not known for 5.4%, 6.7%, 8.4% and 6.1% of patients for 2007, 2008, 2009 and 2010, respectively.
[c] Patients who presented with both pneumonia and meningitis are listed with meningitis.
[d] Other manifestations included arthritis and the ones which are inserted by text from the physicians (amongst others otitis, mastoiditis, sinusitis, epiglottitis, endocarditis, peritonitis, empyema).
[e] Comorbidities were not known for 10.4%, 12.1%, 14.1% and 12.6% of patients for 2007, 2008, 2009 and 2010, respectively.

23, 19F and 15 infection were clearly (OR > 2) associated with a bacteremia without focus compared to infection with a reference group serotype 1 and 7F (Fig. 2A). In addition, meningitis was associated with serotypes 35, 15, 11, 18C and 23F (OR > 6) compared to the reference group. These findings were independent of age, sex and number of comorbidities. As for pneumonia, none of the serotypes was more likely than the chosen reference group. In more detail, serotypes 15, 35, 18C, 19F, 23, 23F, 6B and 11 were the rarest and resulted in OR < 0.5.

As for morbidity, serotype was associated with different numbers of comorbidities (i.e. having at least one versus no comorbidity; $P < 0.001$). Results displayed that cases infected with serotypes other than serogroup 8 suffered from one or more comorbidities significantly more often than those infected with the serotypes of the reference group (1 and 7F) (Fig. 2B). Among these serotypes/serogroups OR were highest for 23, 35, 6B, 19F and 20. Of those, serogroups 20 and 35 are neither covered by PCV7 nor PCV13.

Regarding type of comorbidity, immunosuppression ($P < 0.001$) but not chronic diseases ($P = 0.2$) and pre-existing underlying respiratory disease ($P = 0.4$) were significantly associated with serotype using the two-tailed Likelihood Ratio (LR) test. As for the first, cases infected with serotypes/serogroups other than 4 and 8 were more often immunocompromised than those infected with the serotypes of the reference group (1 and 7F) (Fig. 2C).

4. Discussion

This population-based study evaluates the serotype epidemiology of invasive *S. pneumoniae* isolates, from 2003 to 2012 including association of causing serotype with IPD characteristics and case-fatality in adult Swiss residents aged ≥16 years reported from 2007 to 2010. The study period for the latter covered the years after recommendation of the complementary vaccination with PCV7, but before recommendation of PCV13 for infants [13,22]. During that period, 920 of about 6.5 million Swiss residents aged ≥16 years were diagnosed with an IPD per year in mean (i.e. 14.2/100,000). It was possible to link approximately 90% of reported IPD cases with a corresponding pneumococcal isolate. Therefore, the completeness of this linkage was very high indicating a very high participation of involved laboratories.

Table 3
Proportions of pneumococcal serotypes in adult patients with and without 23-valent pneumococcal polysaccharide vaccine (PPV23).

Serotype/serogroup[a]	Vaccine coverage[b]	PPV23 vaccinated (*n* = 82)	Not vaccinated (*n* = 1698)	NA (*n* = 1490)	*P* (3 × 2)[c]	*P* (2 × 2) (excluding NA)[d]
14	7, 13	5 (6.1)	169 (10.0)	143 (9.6)	0.49	0.25
18C	7, 13	3 (3.7)	36 (2.1)	38 (2.6)	0.53	0.35
19F	7, 13	1 (1.2)	55 (3.2)	55 (3.7)	0.43	0.31
23F	7, 13	3 (3.7)	100 (5.9)	68 (4.6)	0.20	0.40
4	7, 13	3 (3.7)	132 (7.8)	101 (6.8)	0.25	0.25
6B	7, 13	1 (1.2)	41 (2.4)	35 (2.4)	0.78	0.49
9V	7, 13	6 (7.3)	97 (5.7)	81 (5.4)	0.80	0.54
1	13	0 (0.0)	80 (4.7)	46 (3.1)	**0.01**	**0.04**
19A	13	7 (8.5)	94 (5.5)	85 (5.7)	0.50	0.25
3	13	8 (9.8)	224 (13.2)	201 (13.5)	0.62	0.40
7F	13	6 (7.3)	169 (10.0)	143 (9.6)	0.70	0.40
6A	13	9 (11.0)	50 (2.9)	58 (3.9)	**<0.001**	**<0.001**
All PPV23 serotypes		52 (63.4)	1399 (82.4)	1187 (79.7)	**<0.001**	**<0.001**

[a] PCV13 serotypes/serogroups are illustrated (with the exception of serotype 5).
[b] Vaccine coverage is indicated for PCV7 (7), and PCV13 (13). PPV23 serotypes are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.
[c] 3 × 2 χ^2-test. $P < 0.05$ is indicated in bold.
[d] 2 × 2 χ^2-test (excluding patients for whom vaccination status were not available (NA)). $P < 0.05$ is indicated in bold.

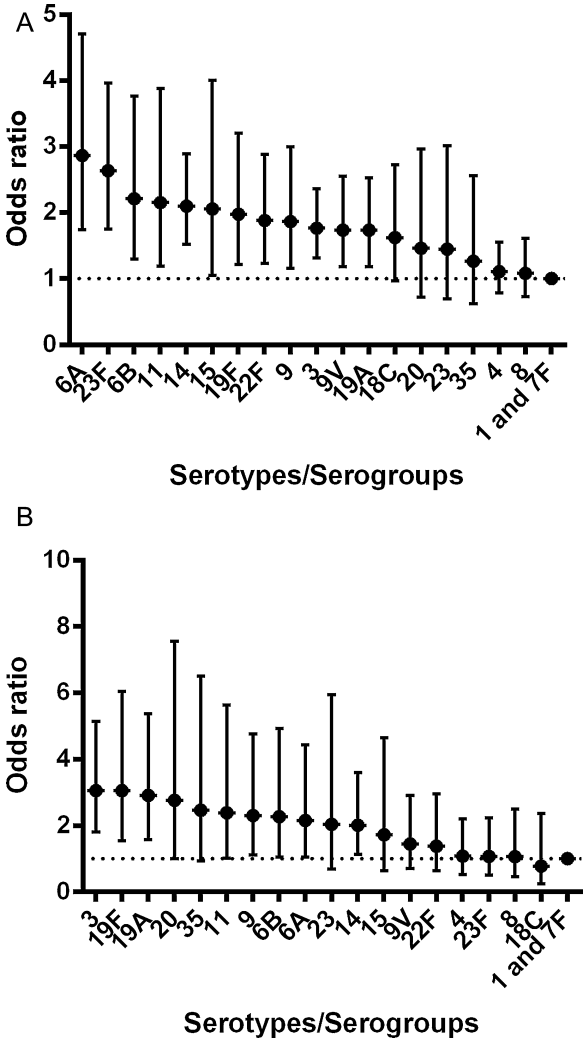

Fig. 1. Multivariable logistic regression analysis. Association analysis of serotype/serogroup with (A) patient's age (≥65 years) and (B) death. Odds ratios (OR) were adjusted for age categories, number of comorbidities and clinical manifestation (bacteremia without focus, pneumonia and meningitis). Serotypes/serogroups with proportion of <1% were combined to one group (other) for the analysis but omitted in the graphs. For the analysis, the serotypes 1 and 7F were grouped and served as reference. Serotypes are sorted according to OR and 95% confidence intervals are shown.

During 2007–2010, incidence of IPD cases with known serotype has changed significantly in adults overall and in those ≥65 years in Switzerland. In addition, this study shows a changing serotype distribution of invasive *S. pneumoniae* isolates from 2003 to 2012. This has been described for the PCV7 versus non-PCV7 serotypes recently [9] but our study additionally shows the single serotype epidemiology in Switzerland. The sharp increase of the non-PCV7 serotype 19A is remarkable and has also been observed in other countries [6,23–25]. However, it is not clear if the introduction of PCV7 is exclusively responsible for this observation [26,27]. A significant increase of other non-PCV7 serogroups/serotypes was detected which countered the drop of vaccine serotypes to a certain extent. Increasing numbers of isolates of serotypes 19A, 22F and 6C but not of serogroup 35 have also been described in a study performed at the University Hospitals in Cleveland during 1999–2007 [28].

It is well known that IPD incidence rates increase with advancing age and with various comorbidities like immunosuppression, underlying respiratory diseases and chronic diseases [29]. Hence PPV23 vaccination was recommended for persons with increased

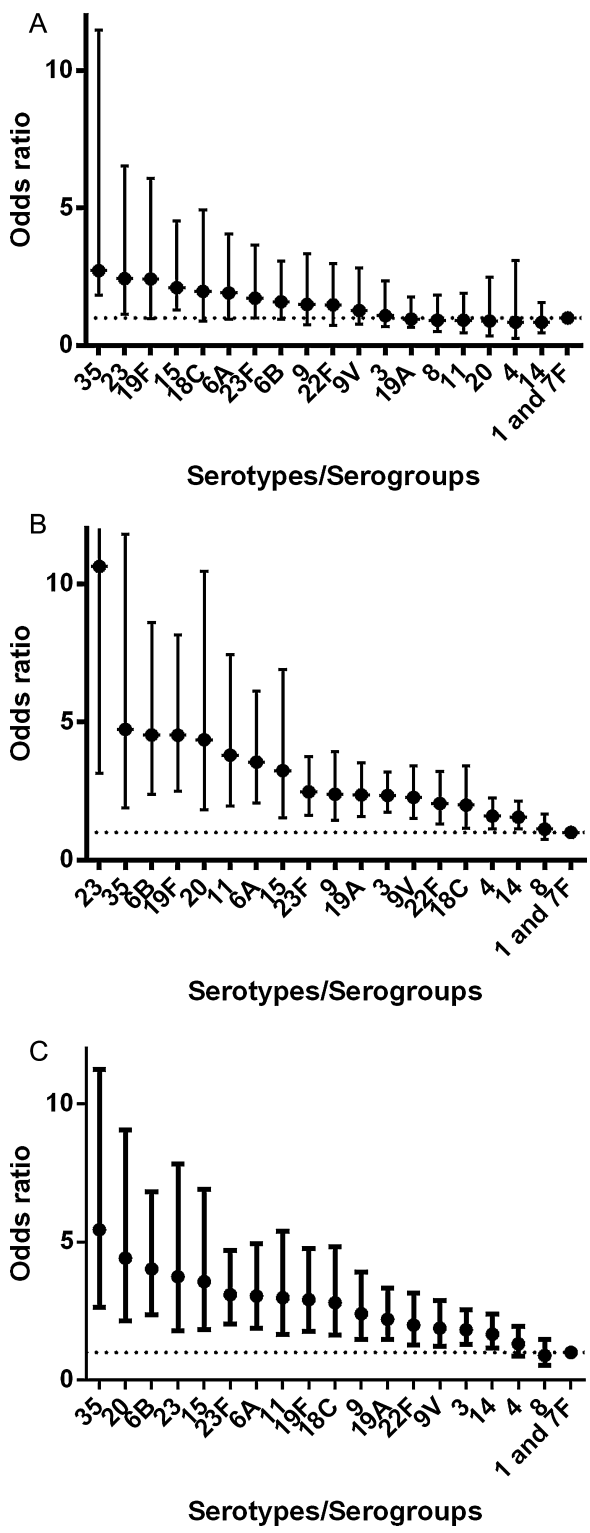

Fig. 2. Multivariable logistic regression analysis. Association analysis of serotype/serogroup with the patients having (A) bacteremia without focus, (B) having one or more comorbidities and (C) being immunocompromised. Odds ratios (OR) were adjusted for age categories, sex and clinical manifestation (bacteremia without focus, pneumonia and meningitis). Serotypes/serogroups with proportion of <1% were combined to one group (other) for the analysis but omitted in the graphs. For the analysis, the serotypes 1 and 7F were grouped and served as reference. Serotypes are sorted according to OR and 95% confidence intervals are shown.

risk for IPD (i.e. for those aged 65 years and older and those older than 2 years with known risk factors for IPD) in Switzerland. However, despite the broad vaccine usage, the efficacy of PPV23 is generally described as being poor at least in preventing pneumonia [14]. These issues cannot be confirmed or dismissed with our data but in those with a known PPV23 vaccination history, vaccinated patients had a lower proportion of IPD due to PPV23 serotypes, whereas the non-PPV23 serotype 6A was associated with previous PPV23 vaccination.

This study identified individual serotypes which mainly caused IPD in elderly adults and/or in adults with comorbidities. Unfortunately, a few of those serotypes/serogroup are not covered, by PCV13 e.g. serogroups 15, 20 and 35. The latter showed an increasing trend from 2007 to 2010 and may therefore become more important in the future. Our study also illustrates that the serotype was related to the clinical manifestations which was also investigated in a previous study in the Netherlands [30].

A recent population based study from Denmark demonstrated that patients aged 5 years and older infected with serotypes/serogroups 31, 11A, 35F, 17F, 3, 16F, 19F, 15B or 10A more often died than those infected with serotype 1, from 1977 to 2007 [20]. A study performed during the first 4 years after introduction of PCV7 in the United States showed in addition that patients aged >50 years with serotype/serogroup 3, 11A 19F or 23F infection more often died than those with serotype 14 infection [2]. Consistent with our results, both of these studies confirmed the high case fatality of IPD due to serotype 3 and 19F. However, many other studies which analyzed death due to individual serotypes were done before the introduction of PCV7 making a comparison with our study challenging [18,30]. As for our setting, considering that the serotypes 3, 19A and 19F are associated with the highest case fatality, the PCV13 vaccination might be indeed of advantage for adults at increased risk for IPD in Switzerland as those serotypes are included in PCV13. However it can also be expected that the introduction of PCV13 within infants will affect the epidemiology of pneumococcal serotypes within adults which has already been noted within other countries but not yet Switzerland.

Our study has several limitations. By including only serotypes with an overall proportion of ≥1% (with the exception of serotype 6C), some serotypes were neglected which have also significantly risen but have just not yet reached large enough numbers. In addition, data about case fatality may be incomplete as the physicians have to report IPD to the FOPH within one week after IPD confirmation but some IPD patients may die after reporting. No patient follow up took place. In general, no validation of the quality of data was performed for this study. Therefore, variation in the definition criteria to report e.g., a chronic lung disease, diabetes or nicotine abuse could have biased our results. A random misclassification would have produced an underestimation of a true association while selective misclassification could have induced a bias in both directions. Finally, the multivariable logistic regression analyses we performed allow to adjust for possible confounding by age, sex and comorbidities of the association of serotype/serogroup with the analyzed outcomes, but are not capturing the more complex biological interactions between host and bacterial factors in shaping the likelihood of the analyzed outcomes. However, our results are comparable with similar studies from different settings [2,4,6,20]

In conclusion, this is a very detailed population based IPD surveillance study in adults. It documents that IPD case fatality, age (≥65 years), type of manifestation (pneumonia, meningitis and bacteremia without focus), number (≥1) and type of comorbidities (immunosuppression) are significantly and independently associated with serotype. It furthermore identifies the single serotypes driving these observations (e.g., 3, 19A and 19F for case fatality). The results may therefore help as an epidemiological basis for future vaccination recommendations to prevent IPD in distinct adult groups at risk in Switzerland.

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