Incidence of invasive pneumococcal disease in the Czech Republic and serotype coverage by vaccines, 1997–2006

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SUMMARY

We studied the incidence of invasive pneumococcal disease (IPD) in the Czech Republic by analysing two sources of data. The incidence of pneumococcal meningitis based on routine notification data varied between 0·4 and 0·6/100 000 population between 1997 and 2006. The incidence of IPD based on laboratory surveillance varied between 2·3 and 4·3/100 000 population between 2000 and 2006. The annual IPD incidence remained stable during the study period. Estimates of absolute IPD case-load in the entire country varied from 235 to 437 per year. The age-specific incidence was highest in the <1 year age group, reaching 4·3/100 000 for pneumococcal meningitis in routine notification and 15·7/100 000 for IPD in laboratory-based surveillance data, respectively. A total of 1236 *Streptococcus pneumoniae* isolates from cerebrospinal fluid and sterile body sites were investigated. The most frequent serotypes causing IPD in all ages were 3, 4, 14, 8 and 19F, accounting for 41·5% of all isolates. The most frequent serotypes by age group were: <1 year (6B and 19F); 1–4 years (14, 6B and 23F); 40–64 years (3, 8 and 4), and ⩾65 years (3, 4, 9N and 14). The coverage of serotypes in all age groups by pneumococcal vaccines ranged from 41·5% for 7-valent conjugate vaccine to 67·9% for 13-valent conjugate vaccine. The coverage of serotypes causing IPD is significantly different between infants/children and adults/elderly. PCV-7 coverage by age group was: <1 year (66·0%), 1–4 years (65·1%), 40–64 years (34·4%) and ⩾65 years (39·3%). Similar age differences between infants/children and adults/elderly were found in coverage by PCV-9, PCV-11 and PCV-13. The distribution of serotypes in the total population and individual age groups was stable during the period 2000–2006.

Key words: Pneumococcal invasive disease, serotype coverage, vaccination.

INTRODUCTION

Streptococcus pneumoniae causes serious disease world-wide, especially in infants, young children and the elderly. Pneumococcal conjugate vaccines have become available in recent years and several countries have included these in their routine immunization schedule [1–5]. Data on the incidence of invasive

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pneumococcal disease (IPD) and of pneumococcal serotype coverage by pneumococcal vaccines is crucial for this decision. Some countries have implemented surveillance of IPD prior to the introduction of routine conjugate pneumococcal vaccination. These countries will be able to assess the impact and costs *vs.* benefits of pneumococcal vaccination.

In the Czech Republic pneumococcal 23-valent polysaccharide vaccine is recommended for patients with underlying diseases and the elderly population. In 2001 a 7-valent pneumococcal conjugate vaccine (Prevenar) was registered and is recommended for children aged $\leqslant 5$ years with an increased risk of pneumococcal infection due to underlying diseases. However, mass vaccination has not yet been introduced.

Within the Czech Republic's list of notifiable diseases, the only IPD syndrome that is included is pneumococcal meningitis. Pneumococcal infection without bacteraemia, constituting a major disease burden both in children and the elderly [6], is not notifiable. To better estimate the serotype-specific incidence of IPD, laboratory surveillance of IPD was established in 2000.

We present results of routine notification of pneumococcal meningitis and of laboratory surveillance. Incidence, mortality and serotype-specific vaccine coverage afforded by current and forthcoming pneumococcal vaccines in the Czech Republic are presented for infants, children, adults and the elderly to inform decision making regarding vaccination.

METHODS

Cases of IPD in the Czech Republic were identified using two data sources: mandatory notifications and a dedicated laboratory surveillance system. Pneumococcal meningitis, including deaths, has been notifiable in the Czech Republic since 1994. Electronic data entry transfer from district to national level and data analysis are carried out using the Epidat program. This is part of the National Health Information System and is governed by legislation on the protection of personal data in health information systems. Epidat was created using programs of the Epi-Info system [7], version 3.3.2. Data are entered continuously and are exported to the National Reference Centre for Analysis of Epidemiological Data once a week. The total and age group-specific annual incidence of pneumococcal meningitis, the mortality due to pneumococcal meningitis and case-fatality

ratio were calculated. The annual census population data were used as denominator data. Results for the period 1997–2006 are presented.

The National Reference Laboratory (NRL) for Streptococci and Enterococci, which is also a WHO Collaborating Centre for Reference and Research on Streptococci receives pneumococcal isolates from the entire country for confirmation and serotyping. From 2000 onwards, the NRL requested local laboratories to send all pneumococcal isolates from blood and normally sterile sites and to provide information about the size of their catchment population. The total and age-specific incidence of IPD was calculated. Results for the period 2000–2006 are presented.

Case definitions

IPD is defined by the isolation of *S. pneumoniae* from blood, cerebrospinal fluid, or other normally sterile sites. Only one isolate per disease episode has been included in the analysis. Pneumococcal meningitis cases, being a part of total IPD, are defined by the isolation of *S. pneumoniae* from cerebrospinal fluid.

Strain identification and serotyping

Each isolate was identified by standard methods and confirmed as *S. pneumoniae* by optochin sensitivity and bile solubility. *S. pneumoniae* isolates were serotyped at the NRL by the Quellung reaction using antisera (Statens Serum Institut, Copenhagen, Denmark).

Vaccine coverage

Total and age group-specific coverage afforded by different vaccines was calculated as the percentage of serotypes included in current and forthcoming pneumococcal vaccines in isolates obtained from IPD cases in the Czech Republic during the study period (2000–2006). The vaccine serotypes are presented in Table 1.

Statistical analysis

The χ^2 test was used to compare the coverage by pneumococcal vaccines in the age groups <5 years and $\geqslant 40$ years. Yates' correction was used for χ^2 and *P* values [7]. The trend of incidence and of case fatality was assessed by quadratic regression analysis.

Table 1. *Serotypes included in current and forthcoming pneumococcal vaccines*

Vaccine	Serotypes
PCV-7	4, 6B, 9V, 14, 18C, 19F and 23F
PCV-9	4, 6B, 9V, 14, 18C, 19F, 23F, 1 and 5
PCV-11	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 3 and 7F
PCV-13	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 3, 7F, 6A and 19A
PPV-23	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 3, 7F, 19A, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F

PCV-7, 7-valent pneumococcal conjugate vaccine; PCV-9, 9-valent pneumococcal conjugate vaccine; PCV-11, 11-valent pneumococcal conjugate vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; PPV-23, 23-valent pneumococcal polysaccharide vaccine.

RESULTS

Routine notification of pneumococcal meningitis, 1997–2006

The annual incidence of notified pneumococcal meningitis varied between 0·4 and 0·6/100 000 in the period 1997–2006 (Table 2). The annual incidence of pneumococcal meningitis remained stable during the study period ($P = 0.317$). The age group-specific incidence was highest in the <1-year-olds (4·3/100 000), followed by age groups 1–4 years, 40–64 years and ⩾65 years (Fig. 1). The case-fatality ratio of pneumococcal meningitis in this period was 13·7%. The age-specific case-fatality ratio was highest in the ⩾65 years age group (24%), and lowest in the 5–14 years group (0%). Among children aged <5 years, the case-fatality ratio was <5% [<1 year (2·3%), 1–4 years (4·6%)]. In age groups aged >14 years, case fatality increased with age. This increase was statistically significant ($P < 0.041$).

Laboratory surveillance of IPD, 2000–2006

Fifty-one local laboratories participated in this prospective study. The population of their catchment area was 5 694 000, representing 55·6% of the Czech Republic's population. In total 1236 *S. pneumoniae* isolates from IPD cases were received during the study period. Of these, 375 were isolated from cerebrospinal fluid, 829 from blood and 32 from other normally sterile body sites. The annual incidence of IPD ranged from 2·3 to 4·3/100 000. There was no trend in IPD incidence over time during the study

period (Table 2). Estimates of the number of IPD cases for the entire country varied from 235 to 437 per year. The age-specific incidence of IPD was highest among children aged <1 year (15·7/100 000), followed by age groups 1–4 years (8·2), 40–64 years (4·0) and those aged ⩾65 years (7·3). The incidence of IPD in children aged <5 years was 9·7/100 000. The annual laboratory-based incidence of pneumococcal meningitis varied between 0·6 and 1·6/100 000 population during the study period. The age group-specific incidence was highest in the <1-year-olds (ranging from 2·1 to 18·4/100 000 population).

Among the 1236 isolates, 52 serotypes were identified (Table 3). Eight isolates could not be typed (two were non-typable and six did not grow). The most frequent serotypes were 3, 4, 14, 8 and 19F. There were differences in the serotype distribution between age groups. The most frequent serotypes by age group were: <1-year-old (6B and 19F), 1–4 years (14, 6B and 23F), 40–64 years (3, 8 and 4), and ⩾65 years (3, 4, 9N and 14). The distribution of serotypes in the total population and individual age groups was stable during the study period.

The coverage of serotypes in all age groups was 41·5% for PCV-7, 47·1% for PCV-9, 62·8% for PCV-11, 67·9% for PCV-13 and 86·1% for PPV-23. The coverage of serotypes causing IPD was different between infants/children and adults/elderly (Fig. 2). Coverage by PCV-7 was 34·4% in the 40–64 years age group and 39·3% in the ⩾65 years group, while it was 66·0% in <1-year-olds and 65·1% in the 1–4 years group. Larger differences were found in coverage by PCV-9, PCV-11 and PCV-13 (Table 3). The differences disappeared with PPV-23 for which the coverage was very similar in all age groups. There was no trend during the study period.

DISCUSSION

We present the first report of IPD incidence in the Czech Republic based on two data sources. As routine notification data cover pneumococcal meningitis only, we also used laboratory-based surveillance data. The differences we found in incidence of pneumococcal meningitis between results from laboratory-based surveillance *vs.* routine notification could be due to underreporting in the latter. As zero reporting is not required in routine notification, it is unclear whether the 50% of non-reporting localities had no cases or simply did not report any cases. For laboratory-based surveillance the denominator was

Table 2. *Number of cases and incidence per 100 000 population of pneumococcal meningitis and invasive pneumococcal disease by year and age group, the Czech Republic, 1997–2006 (routine notification, laboratory-based data)*

Data source	Clinical syndrome	Age group	No. of cases (incidence/100 000 population)										Average incidence
			1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	
RN	PM	0–11 mo.	3 (3·3)	5 (5·5)	0 (—)	5 (5·6)	3 (3·3)	4 (4·4)	5 (5·4)	6 (6·3)	1 (1·0)	4 (3·8)	4·3
		1–4 yr	4 (0·9)	2 (0·5)	3 (0·8)	3 (0·8)	7 (1·9)	8 (2·2)	4 (1·1)	4 (1·1)	4 (1·1)	4 (1·1)	1·3
		5–9 yr	1 (0·2)	4 (0·6)	1 (0·1)	6 (1·0)	5 (0·9)	3 (0·6)	4 (0·8)	1 (0·2)	1 (0·2)	2 (0·4)	0·6
		10–14 yr	0 (—)	1 (0·1)	2 (0·3)	3 (0·5)	2 (0·3)	2 (0·3)	1 (0·2)	0 (—)	4 (0·7)	2 (0·4)	0·3
		15–19 yr	0 (—)	1 (0·1)	2 (0·3)	2 (0·3)	0 (—)	1 (0·1)	4 (0·6)	2 (0·3)	0 (—)	1 (0·1)	0·2
		20–39 yr	13 (0·4)	3 (0·1)	8 (0·3)	12 (0·4)	10 (0·3)	9 (0·3)	3 (0·1)	4 (0·1)	6 (0·2)	4 (0·1)	0·2
		40–64 yr	26 (0·8)	15 (0·4)	14 (0·4)	21 (0·6)	24 (0·7)	26 (0·8)	29 (0·8)	23 (0·7)	31 (0·9)	30 (0·8)	0·8
		≥65 yr	11 (0·8)	10 (0·7)	8 (0·6)	11 (0·8)	10 (0·7)	7 (0·5)	9 (0·6)	10 (0·7)	9 (0·6)	15 (1·0)	0·7
		Unknown	0 (—)	0 (—)	0 (—)	0 (—)	0 (—)	0 (—)	0 (—)	0 (—)	0 (—)	0 (—)	
		All	58 (0·5)	41 (0·5)	38 (0·4)	63 (0·6)	61 (0·6)	60 (0·6)	59 (0·6)	50 (0·5)	56 (0·5)	62 (0·6)	0·5
LB	PM	0–11 mo.	n.a.	n.a.	n.a.	7 (18·4)	5 (12·1)	5 (9·4)	2 (2·1)	3 (6·4)	3 (5·4)	6 (10·7)	9·4
		1–4 yr	n.a.	n.a.	n.a.	5 (3·2)	7 (4·2)	9 (4·2)	6 (3·3)	4 (2·2)	4 (1·9)	6 (2·9)	3·2
		5–9 yr	n.a.	n.a.	n.a.	5 (2·0)	3 (1·1)	2 (0·6)	4 (1·7)	0 (—)	1 (0·4)	3 (1·2)	1·0
		10–14 yr	n.a.	n.a.	n.a.	3 (1·1)	3 (1·0)	2 (0·5)	1 (0·3)	2 (0·7)	2 (0·6)	1 (0·3)	0·6
		15–19 yr	n.a.	n.a.	n.a.	3 (1·0)	0 (—)	0 (—)	4 (1·2)	1 (0·3)	0 (—)	2 (0·5)	0·4
		20–39 yr	n.a.	n.a.	n.a.	14 (1·1)	9 (0·6)	7 (0·4)	8 (0·5)	4 (0·3)	4 (0·2)	3 (0·2)	0·4
		40–64 yr	n.a.	n.a.	n.a.	27 (1·9)	21 (1·3)	17 (0·8)	24 (1·4)	12 (0·7)	25 (1·3)	21 (1·1)	1·2
		≥65 yr	n.a.	n.a.	n.a.	7 (1·1)	6 (0·9)	8 (0·9)	12 (1·7)	4 (0·6)	9 (1·1)	17 (2·1)	1·2
		Unknown	n.a.	n.a.	n.a.	0 (—)	0 (—)	0 (—)	0 (—)	0 (—)	1 (—)	0 (—)	
		All	n.a.	n.a.	n.a.	71 (1·6)	55 (1·2)	50 (0·8)	61 (1·2)	30 (0·6)	49 (0·9)	59 (1·0)	1·0
LB	IPD	0–11 mo.	n.a.	n.a.	n.a.	10 (26·3)	6 (14·5)	7 (13·1)	4 (8·4)	6 (12·8)	7 (12·5)	12 (21·5)	15·7
		1–4 yr	n.a.	n.a.	n.a.	9 (5·8)	20 (11·9)	18 (8·3)	18 (9·9)	12 (6·7)	12 (5·6)	17 (8·2)	8·2
		5–9 yr	n.a.	n.a.	n.a.	10 (4·0)	8 (2·9)	5 (1·4)	8 (3·5)	3 (1·3)	4 (1·6)	4 (1·6)	2·3
		10–14 yr	n.a.	n.a.	n.a.	3 (1·1)	5 (1·7)	2 (0·5)	2 (0·6)	2 (0·7)	4 (1·2)	4 (1·2)	1·0
		15–19 yr	n.a.	n.a.	n.a.	3 (1·0)	0 (—)	2 (0·5)	7 (2·1)	5 (1·5)	1 (0·3)	3 (0·8)	0·9
		20–39 yr	n.a.	n.a.	n.a.	15 (1·1)	21 (1·5)	16 (0·9)	25 (1·6)	24 (1·6)	20 (1·1)	19 (1·1)	1·3
		40–64 yr	n.a.	n.a.	n.a.	53 (3·7)	72 (4·6)	51 (2·5)	79 (4·5)	54 (3·2)	94 (4·8)	71 (3·6)	4·0
		≥65 yr	n.a.	n.a.	n.a.	34 (5·6)	49 (7·5)	38 (4·5)	75 (10·5)	48 (6·9)	62 (7·7)	62 (7·7)	7·3
		Unknown	n.a.	n.a.	n.a.	1 (—)	4 (—)	2 (—)	0 (—)	3 (—)	1 (—)	0 (—)	
		All	n.a.	n.a.	n.a.	138 (3·1)	185 (3·9)	141 (2·3)	218 (4·3)	157 (3·1)	205 (3·6)	192 (3·4)	3·4

RN, Routine notification; LB, laboratory based; PM, pneumococcal meningitis; IPD, invasive pneumococcal disease; n.a., data not available.
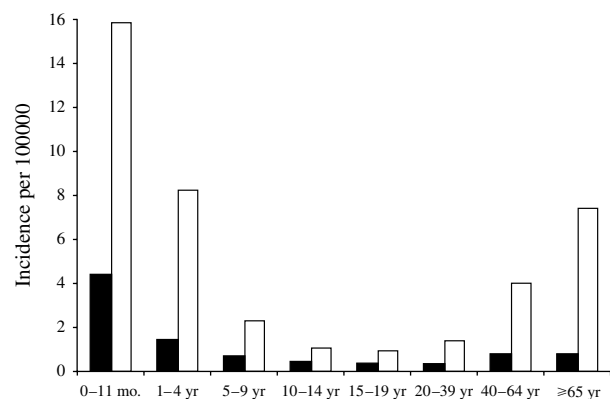
Fig. 1. Pneumococcal meningitis (■) and invasive pneumococcal disease (□), Czech Republic, 2000–2006, age-specific incidence. Pneumococcal meningitis = routine notification data ($n = 411$); invasive pneumococcal meningitis = laboratory-based data ($n = 1236$).

Fig. 2. Age-specific vaccine coverage of serotypes causing invasive pneumococcal disease, Czech Republic, 2000–2006 (laboratory-based data) ($n = 1000$). PCV-7, heptavalent pneumococcal conjugate vaccine; PCV-9, 9-valent pneumococcal conjugate vaccine; PCV-11, 11-valent pneumococcal conjugate vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; PPV-23, 23-valent pneumococcal polysaccharide vaccine.

only the population of the catchment area of laboratories actively participating in the study. However, participating laboratories were spread over the entire country and generated data expected to be representative of the Czech Republic. Implementation of active surveillance of IPD covering the whole country is essential in order to assess the epidemiological situation and recommend an appropriate vaccination strategy [4–6, 8].

The incidence of IPD in children aged < 5 years in Europe before the introduction of vaccination varied widely from 2·8 to 42/100 000 [9–19]. The annual incidence of IPD found by laboratory-based surveillance in the Czech Republic in the period 2000–2006 ranged from 2·3 to 4·3/100 000. Age-specific incidence of IPD was highest in children aged <1 year, reaching 15·7, followed by the 1–4 years group (8·2). IPD incidence in children aged < 5 years was 9·7, which is consistent with the pre-vaccination incidence in Switzerland (7·6) [16] and Germany (8·9) [11]. In some countries the pre-vaccination incidence was higher: 14·5 in England and Wales [12], 24·2 in Finland [15], 42 in Israel [9], while in others it was lower: 2·8–6·3 in Italy [20] and 5·8 in The Netherlands [10]. Our results might be biased by the following: (1) in the laboratory-based surveillance presented in this paper only 55·6% of the total population of the Czech Republic was covered by the participating laboratories; (2) blood-culturing rate is low in the Czech Republic. The geographical and temporal variations of incidence could be explained by real differences in the epidemiological situation in individual countries,
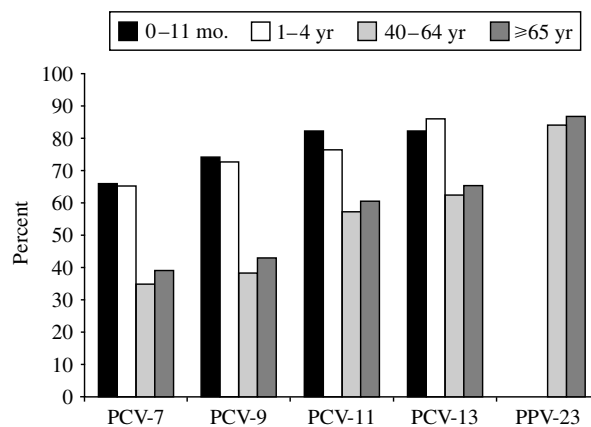
however, under-reporting and variability in blood-culturing rates play a significant role [19, 20].

In our study, similar age distribution of pneumococcal meningitis was obtained from both data sources, with the highest incidence observed in the lowest age group of <1 year. However, higher numbers of cases resulted from laboratory-based data compared to routine notification.

Differences in serotype distribution in individual age groups were found, with the differences between infants/children vs. adults/elderly especially evident. This finding is consistent with the situation described in other European countries and is a basis for the assessment of coverage by various pneumococcal vaccines and a prediction of their benefit in individual age groups, and consequently for recommendation of vaccination strategy [17, 18, 21–26]. IPD incidence found in age groups 5–9, 10–14, 15–19 and 20–39 years was low and the total number of isolates was only 236. For this reason, the percentage of serotypes for ages 5–39 years was calculated. It was assessed as remaining at a medium level, compared to infants/children vs. adults/elderly.

The coverage of serotypes causing IPD in children aged < 5 years in the Czech Republic in 2000–2006 during the study period which was pre-vaccination, was 64·5% for PCV-7 and increased with increasing valency of pneumococcal vaccines, to 83·5% for PCV-13. The coverage by higher-valent pneumococcal vaccines increases less in infants/children than

Table 3. *Serotypes of* S. pneumoniae *causing IPD in the Czech Republic, 2000–2006 (laboratory-based data) and coverage by pneumococcal vaccines*

Serotype	All ages (%)	<1 yr (%)	1–4 yr (%)	5–39 yr (%)	40–64 yr (%)	≥65 yr (%)
4	9·0*	2·0	3·8	11·5	10·2	8·2
6B	4·4	24·0	12·3	3·0	0·8	4·9
9V	5·7	4·0	8·4	8·0	4·5	5·2
14	7·7	10·0	13·2	6·4	7·4	7·1
18C	3·2	4·0	5·7	4·7	2·1	2·7
19F	6·1	16·0	10·4	3·0	6·4	5·2
23F	5·4	6·0	11·3	6·8	3·0	6·0
Total PCV-7	41·5	66·0	65·1	43·4	34·4	39·3
1	5·3	8·0	7·5	9·8	3·6	3·6
5	0·3	0	0	1·3	0·2	0
Total PCV-9	47·1	74·0	72·6	54·5	38·2	42·9
3	12·3	2·0	3·8	10·2	14·2	15·0
7F	3·4	6·0	0	3·8	4·3	2·5
Total PCV-11	62·8	82·0	76·4	68·5	56·7	60·4
6A	4·5	0	8·5	3·8	5·1	3·6
19A	0·6	0	0·9	0·4	0·4	1·0
Total PCV-13	67·9	82·0	85·8	72·7	62·2	65·0
2	0	0	0	0	0	0
8	6·7	0	2·8	4·3	10·4	5·5
9N	5·1	2·0	1·9	2·6	4·9	8·2
10A	3·2	4·0	0·9	3·8	3·6	3·0
11A	1·7	2·0	0	3·0	1·5	1·6
12F	1·5	0	0·9	1·3	1·9	1·4
15B	1·1	0	0·9	1·7	1·3	0·5
17F	0·7	2·0	0	0	1·1	0·8
20	0·7	0	0	0·4	0·4	1·4
22F	1·6	0	0·9	0·4	1·7	2·7
33F	0·4	0	0·9	0·8	0·2	0·3
Total PPV-23	86·1	92·0	86·5	87·2	84·1	86·8
Non-vaccine†	9·4	8·0	4·7	8·9	10·8	9·6
No. typable	1228	50	106	235	471	366
No. NT	8	2	0	1	3	2
Total	1236	52	106	236	474	368

* The percentage of serotype in individual age category was calculated using number of typeable isolates as the denominator; NT, non-typable and/or not typed; PCV-7, 7-valent pneumococcal conjugate vaccine; PCV-9, 9-valent pneumococcal conjugate vaccine; PCV-11, 11-valent pneumococcal conjugate vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; PPV-23, 23-valent pneumococcal polysaccharide vaccine.
† Non-vaccine serotypes: 7A, 7C, 10F, 13, 15A, 15C, 15F, 16F, 17A, 18A, 18B, 18F, 21, 23A, 24F, 25F, 28A, 28F, 29, 31, 34, 35A, 35B, 35F, 36, 37, 38, 39, 42.

in adults/elderly and it will be necessary to calculate the cost-benefit of higher-valent pneumococcal vaccines carefully, when they are available for age groups showing the highest incidence, i.e. for infants/children. It is desirable to include pneumococcal conjugate vaccines in the routine vaccination scheme of infants in the Czech Republic [27].

An indirect (herd) effect of pneumococcal conjugate vaccine on adults/elderly IPD incidence occurred after its introduction into the routine vaccination scheme of infants [28, 29]. This herd effect is explained by a reduction in the circulation of the pneumococci among vaccinated infants/children and the consequent decrease of IPD incidence in non-vaccinated adults/elderly. It could be expected that this herd effect of pneumococcal conjugate vaccine will also occur in the Czech Republic. Continuing surveillance of IPD will be necessary for the assessment of the

effectiveness of PCV-7 and the evaluation of eventual serotype replacement, i.e. emergence of non-vaccine serotypes after introduction of routine PCV vaccination, as was reported in the United States [30, 31].

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Whitney CG, et al.** Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. *Lancet* 2006; **368**: 1495–1502.
2. **Kellner JD, et al.** Progress in the prevention of pneumococcal infection. *Canadian Medical Association Journal* 2005; **173**: 1149–1151.
3. **Butler JRG, et al.** The cost-effectiveness of pneumococcal conjugate vaccination in Australia. *Vaccine* 2004; **22**: 1138–1149.
4. **Pebody RG, et al.** Pneumococcal vaccination policy in Europe. *Eurosurveillance* 2005; **10**: 174–178.
5. **Lopalco P (Editorial team).** Use of 7-valent pneumococcal conjugate vaccine in EU. *Eurosurveillance* 2006; **11**(12): E061207.3.
6. **Grijalva CG, et al.** Decline in pneumonia admission after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet* 2007; **369**: 1179–1186.
7. **Dean AG, et al.** Epi-Info™: a general purpose microcomputer program for health information systems. *American Journal of Preventive Medicine* 1991; **7**: 178–182.
8. **Vergison A, et al.** Epidemiologic features of invasive pneumococcal disease in Belgian children: passive surveillance is not enough. *Pediatrics* 2006; **118**: 801–809.
9. **Dagan R, et al.** Epidemiology of invasive childhood pneumococcal infections in Israel. *Journal of the American Medical Association* 1992; **268**: 3328–3332.
10. **Spanjaard L, et al.** Epidemiology of meningitis and bacteremia due to *Streptococcus pneumoniae* in The Netherlands. *Acta Paediatrica* (Suppl.) 2000; **89**: 22–26.
11. **Von Kries R, et al.** Proportion of invasive pneumococcal infections in German children preventable by pneumococcal conjugate vaccines. *Clinical Infectious Diseases* 2000; **31**: 482–487.
12. **Miller E, et al.** Epidemiology of invasive and other pneumococcal disease in children in England and Wales 1996–1998. *Acta Paediatrica* (Suppl.) 2000; **89**: 11–16.
13. **McIntosh EDG, Fritzell B, Fletcher MA.** Burden of paediatric invasive pneumococcal disease in Europe, 2005. *Epidemiology and Infection* 2006; **7**: 1–13.
14. **Pebody RG, et al.** Pneumococcal disease surveillance in Europe. *Eurosurveillance* 2006; **11**: 171–178.
15. **Escola J, et al.** Epidemiology of invasive pneumococcal infections in children in Finland. *Journal of the American Medical Association* 1992; **268**: 3323–3327.
16. **Venetz I, Schopfer K, Muhlemann K.** Paediatric invasive pneumococcal disease in Switzerland, 1985–1994. *International Journal of Epidemiology* 1998; **27**: 1101–1104.
17. **Ispahani P, et al.** Twenty year surveillance of invasive pneumococcal disease in Nottingham: serogroups responsible and implications for immunisation. *Archives of Disease in Childhood* 2004; **89**: 757–762.
18. **Kaltoft MS, Zeuthen N, Konradsen HB.** Epidemiology of invasive pneumococcal infections in children aged 0–6 years in Denmark: a 19-year nationwide surveillance study. *Acta Paediatrica* (Suppl.) 2000; **89**: 3–10.
19. **Hausdorff WP.** Invasive pneumococcal disease in children: geographic and temporal variations in incidence and serotype distribution. *European Journal of Pediatrics* 2002; **161**: 135–139.
20. **D'Ancona F, et al.** Incidence of vaccine preventable pneumococcal invasive infections and blood culture practices in Italy. *Vaccine* 2005; **23**: 2494–2500.
21. **Hausdorff WP, et al.** Which pneumococcal serogroups cause the most invasive disease: Implications for conjugate vaccine formulation and use. Part 1. *Clinical Infectious Diseases* 2000; **30**: 100–121.
22. **Bossen Konradsen H, Staum Kaltoft M.** Invasive pneumococcal infections in Denmark from 1995 to 1999: epidemiology, serotypes, and resistance. *Clinical and Diagnostic Laboratory Immunology* 2002; **9**: 358–365.
23. **O'Brien KL, Dagan R.** The potential indirect effect of conjugate pneumococcal vaccines. *Vaccine* 2003; **21**: 1815–1825.
24. **Pedersen MK, et al.** Systemic pneumococcal disease in Norway 1995–2001: capsular types and antimicrobial resistance. *Epidemiology and Infection* 2004; **132**: 167–175.
25. **Serrano I, et al.** Invasive *Streptococcus pneumoniae* from Portugal: implications for vaccination and antimicrobial therapy. *Clinical Microbiology and Infection* 2004; **10**: 652–656.
26. **Von Kries R, et al.** Prediction of the potential benefit of different pneumococcal conjugate vaccines on invasive pneumococcal disease in German children. *Pediatric Infectious Disease Journal* 2002; **21**: 1017–1023.
27. **WHO position paper.** Pneumococcal conjugate vaccine for childhood immunization. *Weekly Epidemiological Record* 2007; **82**: 93–104.
28. **Hammitt LL, et al.** Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an

explanation of trends in invasive pneumococcal disease. *Journal of Infectious Diseases* 2006; **193**: 1487–1494.

29. **Isaacman DJ, *et al.*** Indirect effects associated with widespread vaccination of infants with heptavalent pneumococcal conjugate vaccine (PCV7; Prevnar). *Vaccine* 2007; **25**: 2420–2427.

30. **Byington CL, *et al.*** Temporal trends of invasive disease due to *Streptococcus pneumoniae* among children in the Intermountain West: emergence of nonvaccine serogroups. *Clinical Infectious Diseases* 2005; **41**: 21–29.

31. **Gonzalez BE, *et al.*** *Streptococcus pneumoniae* serogroups 15 and 33: an increasing cause of pneumococcal infections in children in the United States after the introduction of the pneumococcal 7-valent conjugate vaccine. *Pediatric Infectious Disease Journal* 2006; **25**: 301–305.