Epidemiology and outcome of invasive pneumococcal disease among adults in Belgium, 2009–2011

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This epidemiological study examined morbidity and case fatality of invasive pneumococcal disease (IPD) in adults in Belgium as well as distribution and antibiotic susceptibility of *Streptococcus pneumoniae* serotypes. Adults hospitalised with microbiologically proven IPD were prospectively enrolled. The study started in 2009 with patients aged ≥50 years, whereas in 2010 and 2011, patients aged ≥18 years were included. The clinical presentation, patient profile, treatment, outcome, and mortality were recorded during hospitalisation. Outcome was also assessed one month after discharge. Of the 1,875 patients with IPD identified, 1,332 were included in the analysis. Bacteraemic pneumonia, affecting 1,049 of the patients, was the most frequent IPD type (79%), and chronic obstructive pulmonary disease and cancer were the main comorbidities. One-third of patients required admission to intensive care unit. A total of 208 (16%) patients died during hospitalisation and an additional 21 (2%) within one month after discharge. Case fatality rates of ≥20% were observed in patients with chronic heart failure, hepatic disease, and renal insufficiency. Serotypes 7F, 1, 19A, and 3 were the most prevalent and together accounted for 47% (569/1,214) of all IPD cases and 42% (80/189) of mortality. Of the patient isolates, 21% (255/1,204) were resistant to erythromycin and 22% (264/1,204) to tetracycline. Penicillin non-susceptibility was mostly found in serotype 19A isolates. These baseline data are essential when assessing the impact of pneumococcal conjugate vaccination in adults in the future.

Introduction

In industrialised countries, the risk of invasive pneumococcal disease (IPD) remains high among older adults despite the availability of the 23-valent pneumococcal polysaccharide vaccine (PPV23) since 1983 [1]. In a large number of these countries, including Belgium, PPV23 is recommended since 1985 for all adults ≥65 years of age and for persons between two and 64 years-old at high risk for pneumococcal infections due to living conditions or underlying medical conditions including asplenia, human immunodeficiency virus (HIV) infection, immunodeficiency or chronic cardiac, pulmonary, renal or hepatic diseases as from 50 years of age [2,3]. In 2004, the 7-valent pneumococcal conjugate vaccine (PCV7) for infant vaccination became available in Belgium in a 3+1 schedule at full charge of the parents and, in 2007, PCV7 was added free of charge to the universal infant vaccination programme in a 2+1 schedule at two, four and 12 months of age. Since September 2011, PCV7 has been replaced by the 13-valent pneumococcal conjugate vaccine (PCV13) in the Belgian childhood vaccination schedule. In 2011, PCV13 was also approved by the European Medicines Agency for the prevention of IPD in adults ≥50 years of age [4]. The Belgian recommendations regarding pneumococcal vaccination in adults were updated in July 2013 to also include PCV13 [2], however, there is no publicly funded pneumococcal vaccination programme for adults in Belgium.

A national IPD surveillance programme has existed in Belgium since 1986. It monitors the number of cases for all ages, type of IPD, serotypes or serogroups, and antibiotic susceptibility, but only few clinical data [5]. An active IPD surveillance network for young children started in Belgium in 2002 [6,7]. It showed that, two years after implementation of PCV7 in children <2 years of age, the incidence of vaccine-serotype IPD declined by 96% in this population but that the incidence of non-vaccine-serotype IPD increased two to three-fold [6]. Because the clinical data to assess the burden of disease in adults were lacking, a prospective, active, hospital-based study was started in 2009 to analyse the morbidity and case fatality rate of IPD in adults

aged ≥18 and ≥50 years, the distribution of pneumococcal serotypes and their antibiotic susceptibility, and the factors affecting disease outcome. We report the results for three years (2009–2011) of this study to document the epidemiology and the burden of IPD before the introduction of PCV13.

Methods

Study design

This is a prospective, active, hospital-based epidemiological study of IPD in adults in Belgium. Fifty hospitals participated, corresponding to 44% of the acute care hospitals in Belgium. Three of these hospitals provided data for only the first year of the study, five during two years, and 42 during the three-year study period.

Adults hospitalised with microbiologically confirmed IPD (defined as isolation of *Streptococcus pneumoniae* from a normally sterile body site such as blood or cerebrospinal fluid) were eligible for inclusion. During the first year of study (2009), only adults aged ≥50 years were included, but as of 2010, the study was extended to all adults aged ≥18 years. The patient or a legal representative gave an informed consent for inclusion. If no informed consent was obtained, the patient was considered as a screen failure and clinical data were excluded from the analysis. The study was approved by the institutional review boards and local ethics committees of the participating hospitals.

General baseline information was collected at inclusion, including detailed demographics, type of IPD, laboratory data, relevant medical history, and previous vaccination against *S. pneumoniae* and seasonal influenza. The clinical presentation, complications, diagnostic procedures, and treatment were documented by the treating physician during hospital stay. The disease outcome and persisting symptoms and signs were documented at discharge and one month after discharge. All patients were managed according to the hospital's standard protocol for IPD.

Microbiology

Pneumococcal culture was carried out by the clinical microbiology laboratory of each hospital using routine techniques. Pneumococcal isolates inoculated on blood agar plates or tubes were sent to the Belgian National Reference Laboratory for Pneumococci (University of Leuven, Belgium) for capsular typing and antibiotic susceptibility testing.

Serotyping of pneumococcal isolates was done by phase-contrast microscopy using the Quellung reaction with serotype/serogroup-specific sera obtained from the Statens Serum Institute (Copenhagen, Denmark). Antibiotic susceptibility was assessed using the disk diffusion method on Mueller Hinton blood agar plates: penicillin (oxacillin, 1 µg), erythromycin (15 µg), tetracycline (30 µg), and ofloxacin (5 µg). Isolates were categorised as fully susceptible, intermediately resistant, or resistant according to the interpretive standards (document M100-S22) of the Clinical and Laboratory Standards Institute (Wayne, PA) [8].

For isolates with oxacillin zone diameters ≤19 mm, penicillin minimum inhibitory concentrations (MICs) were determined with Epsilometer (E)-test on Mueller Hinton blood agar plates. For the interpretation of penicillin MIC results, criteria for parenteral penicillin (non-meningitis) were used.

Statistical analysis

Calculations and statistical analyses were performed with SAS (version 9.3 for Windows) statistical package (SAS Institute, Cary, NC). Quantitative variables were expressed as means and standard deviations (SD) or as medians and interquartile ranges (IQR). Categorical findings were summarised in frequency tables. Mean values were compared by one way analysis of variance, whereas proportions were compared using the chi-squared or Fisher's exact test. The association between outcome at discharge and covariates (age, IPD type, comorbidities, and vaccination status) was assessed by univariate and multivariate ordinal logistic regression and was expressed as an odds ratio with a 95% confidence interval (95% CI). In general, 'age' was preferred to age categories. A two-tailed p-value <0.05 was considered statistically significant.

Results

Participants

A total of 1,875 patients hospitalised with IPD were eligible. Informed consent was not obtained for 467 patients and, therefore, clinical data from these patients were excluded from analysis. In most cases, the informed consent was not obtained because of the patient's poor physical condition or because the patient was discharged before microbiological confirmation of IPD. Average age and sex ratio of these patients were similar to the analysed population (data not shown).

To avoid inclusion of nosocomial IPD cases, 76 IPD cases were also excluded because the interval between hospitalisation and blood draw was ≥5 days. Thus, 1,332 patients were included in the analysis, with only 220 of them being between 18 and 49 years of age partly because patients in this age group were only included during the last two years of the study. A total of 208 patients died during hospitalisation. Of the 1,124 patients who were discharged from hospital, 141 (13%) were lost to follow-up so that one-month follow-up results were analysed in 983 patients.

Of the total 1,332 patients included in the analysis 52% were male and the mean age was 66 years (range: 18–98). Three age groups comprising 18 to 49 year-olds, 50 to 64 year-olds and those aged ≥65 years were considered for the study, however in some analyses patients aged ≥50 years were compared to those aged 18 to 49 years. Baseline characteristics for the three age

Table 1

Baseline characteristics of patients with invasive pneumococcal disease by age group, Belgium, 2009–2011 (n=1,332)

Characteristics	Age group, n (%)			P value
	18–49 years (n=220)	50–64 years (n=370)	≥65 years (n=742)	
Sex				
Female	110 (50)	176 (48)	348 (47)	0.72
Male	110 (50)	194 (52)	394 (53)	
Living condition				
At home	218 (99)	361 (98)	621 (84)	<0.0001
In nursing home or other care centre	1 (<1)	7 (2)	116 (16)	
Unknown	1 (<1)	2 (<1)	5 (<1)	
Comorbidities[a]				
Any	118 (54)	274 (74)	627 (85)	<0.0001
Chronic obstructive pulmonary disease	15 (7)	89 (24)	231 (31)	<0.0001
Cancer	13 (6)	81 (22)	203 (27)	<0.0001
Heart failure	3 (1)	40 (11)	206 (28)	<0.0001
Diabetes	11 (5)	47 (13)	146 (20)	<0.0001
Renal insufficiency	3 (1)	32 (9)	144 (19)	<0.0001
Immunosuppression	21 (10)	51 (14)	100 (14)	0.32
≥ 2 comorbidities per patient	50 (23)	154 (42)	399 (54)	<0.0001
Previous vaccination against *Streptococcus pneumoniae*				
Yes	10 (5)	20 (5)	62 (8)	0.0023
No	179 (81)	242 (65)	401 (54)	
Unknown	31 (14)	108 (29)	279 (38)	
Previous vaccination against influenza				
Yes	18 (8)	79 (21)	326 (44)	<0.0001
No	181 (82)	230 (62)	278 (38)	
Unknown	21 (10)	61 (17)	138 (19)	
Oral antibiotics within 24 hours before admission				
Yes	14 (6)	15 (4)	37 (5)	0.46
No	206 (94)	354 (96)	705 (95)	
Unknown	0 (0)	1 (<1)	0 (0)	

[a] Only comorbidities found in more than 10% of the patients are shown.

groups are described in Table 1. The number of cases increased with age and the majority were ≥65 years-old. Comparing the number of cases per year per age group (110 in the 18–49 years, 121 in the 50–64 years and 237 in the ≥65 years) with the size of the population in Belgium per age group at the time of the study (4.6 million 18–49 year-olds, 2 million 50–64 year-olds and 1.8 million ≥65 year-olds), there appeared to be almost three times more cases in the 50 to 64 years age group compared to the 18 to 49 years, and almost six times more cases in the ≥65 year-olds.

Most patients had at least one chronic comorbidity, and the proportion increased from 54% (118/220) in patients aged between 18 and 49 years to 85% (627/742) in patients aged ≥65 years. Furthermore, 45% (603/1,326) of patients had ≥2 predisposing comorbidities. Chronic obstructive pulmonary disease and cancer were the most frequent comorbidities in the two older age groups. Even though the vast majority of patients had a comorbidity or were at an age where pneumococcal vaccination is recommended, less than 10% (92/1,332) were vaccinated with PPV23. Vaccination against seasonal influenza increased with increasing age, from 8% (18/220) in patients aged between 18 and 49 years to 44% (326/742) in patients aged ≥65 years. Nearly 5% (66/1,332) of patients took oral antibiotics within 24 hours before hospitalisation.

Type and outcome of invasive pneumococcal disease

Of the 1,332 patients, 1,049 (79%) had bacteraemic pneumonia (Table 2). Patients aged between 18 and 49 years were hospitalised for a median duration of 7.5 days (IQR: 5–13) compared to 12 days (IQR: 7–22) for patients aged ≥50 years. Admission to an intensive care unit (ICU) was more frequent in older patients (42% (154/370) in 50–64 year-olds vs. 25% (54/219) in 18–49

Table 2

Distribution of invasive pneumococcal disease types by patient age, Belgium, 2009–2011 (n=1,332)

Type of IPD	Total (n=1,332)	Age group, n (%)		
		18–49 years (n=220)	50–64 years (n=370)	≥65 years (n=742)
Bacteraemic pneumonia	1,049 (79)	170 (77)	276 (75)	603 (81)
Empyema	94 (7)	21 (10)	32 (9)	41 (6)
Meningitis	73 (6)	8 (4)	32 (9)	33 (4)
Bacteraemia without focus[a]	73 (6)	8 (4)	17 (5)	48 (7)
Other (e.g. septic arthritis, endocarditis, or peritonitis)	43 (3)	13 (6)	13 (4)	17 (2)

IPD: invasive pneumococcal disease.

[a] *Streptococcus pneumoniae* isolated from blood culture without localised infection identified.

Table 3

Admission to intensive care unit and disease outcome at discharge by age and type of invasive pneumococcal disease, Belgium, 2009–2011 (n=1,329)[a]

Category	n	Admission to ICU n (%)	Outcome at discharge			Univariate OLR	
			Cured n (%)	Discharged with persisting symptoms n (%)	Death n (%)	Odds ratio (95% CI)	Overall p value
Total[a]	1,329	434 (33)	884 (67)	237 (18)	208 (16)	–	–
Age in years							
18–49	219	54 (25)	157 (72)	49 (22)	13 (6)	1	0.044
50–64	370	154 (42)	240 (65)	83 (22)	47 (13)	1.42 (0.98–2.04)	
≥65	740	226 (31)	487 (66)	105 (14)	148 (20)	1.52 (1.10–2.12)	
Type of invasive pneumococcal disease							
Bacteraemic pneumonia	1,049	303 (29)	722 (69)	169 (16)	155 (15)	1	0.0049
Empyema	94	49 (52)	49 (52)	35 (37)	10 (11)	1.61 (1.07–2.45)	
Meningitis	73	59 (81)	38 (52)	16 (22)	19 (26)	2.06 (1.31–3.25)	
Bacteraemia without focus	73	12 (16)	51 (70)	4 (6)	18 (25)	1.12 (0.69–1.84)	
Other (e.g. septic arthritis, endocarditis, or peritonitis)	43	11 (26)	24 (56)	13 (30)	6 (14)	1.53 (0.84–2.79)	

CI: confidence interval; ICU: intensive care unit; OLR: ordinal logistic regression; SD: standard deviation.

[a] Data missing for three patients.

year-olds; p=0.001) and for patients with meningitis (81% (59/73); p=0.0001) (Table 3). Only 16% (12/73) of patients with bacteraemia without focus were admitted to ICU. Depending on the age group, the median durations of stay in an ICU varied from four to six days (IQR: 2–15), with four days for the 18 to 49 year-olds, six days for the 50 to 64 year-olds and five days for those aged ≥65 years, The median durations of hospitalisation after discharge from ICU were seven to 10.5 days (IQR: 0–21), with seven days for the 18 to 49 year-olds, nine days for the 50 to 64 year-olds and 10.5 for those 65 years-old and over. The median duration of ICU stay was significantly higher for deceased patients (9 vs. 5 days, p=0.0009).

For empirical treatment before the microbiological results became available, the three most used antibiotics on patients with available data (n=1,327) were amoxicillin-clavulanic acid intravenous (in 615 (46%) patients), third-generation cephalosporin (in 116 (9%) patients), and fluoroquinolones (in 71 (5%) patients). Also, 65 (5%) patients received a combination of amoxicillin-clavulanic acid and macrolides. After microbiological diagnosis, antibiotic treatment was changed to amoxicillin in 142 patients and penicillin in 151 patients. Overall, the antibiotic treatment was adapted in 55% (723/1,327) of patients after the microbiological results became available. The majority of the 73 patients with meningitis were treated with third-generation cephalosporin (51 patients) or penicillin (16 patients).

During hospitalisation 16% (208/1,329) of patients died. Duration of hospitalisation was significantly lower in deceased patients (median, 9 vs. 11 days; p=0.0013).

Of the 1,329 patients with outcome data at discharge, 884 (67%) were cured and 237 (18%) had persisting

symptoms and signs, including 18 with persistent fatigue (8%), 16 with pleural pain (7%), 49 with dyspnoea (21%), and 86 with pleural infiltrate (36%). Persisting symptoms and signs were less common in patients with bacteraemia without focus than in patients with other types of IPD, and patients with empyema had the highest rate of persisting symptoms and signs. Of the 983 patients with available one-month follow-up data, an additional 21 (2%) patients died within one month of discharge, 749 (76%) patients were cured, and 213 (22%) still had persisting symptoms and signs. The case fatality rate at discharge was highest for meningitis, lowest for empyema, and increased with increasing age (from 6% (13/219) in patients aged 18–49 years to 20% (148/740) in those aged ≥65 years; p<0.0001). The case fatality rate for meningitis decreased with increasing age (from 37% (3/8) in patients aged 18–49 years to 18% (6/33) in patients aged ≥65 years), whereas the case fatality rate of bacteraemia without focus increased (from 0% (0/8) in patients aged 18–49 years to 31% (15/48) in patients aged ≥65 years). A case fatality rate higher than 20% was seen for patients with comorbidities such as asplenia, alcoholism, renal insufficiency, hepatic disease, or heart failure (Table 4). Multivariate logistic regression showed that the risk of death was higher for patients with heart failure, renal insufficiency, and alcoholism but not for patients with chronic obstructive pulmonary disease, immunosuppression, or cancer. For patients admitted to ICU, case fatality rate was 22% (12/54) in patients aged <50 years and 32% (122/380) in patients aged ≥50 years.

Pneumococcal serotype distribution and antibiotic susceptibility

Of the 1,214 serotypes identified in isolates, serotypes 7F (159 isolates (13%)) serotypes 1 (154 isolates (13%)), serotypes 19A (145 isolates (12%)), and serotypes 3 (111 isolates (9%)) accounted for nearly half of IPD cases in adults (Figure 1). Serotype 1 was more prevalent in patients aged between 18 and 49 years (27% (54/200), p<0.0001), whereas serotype 3 was more prevalent in those aged ≥65 years (13% (84/669), p<0.0001). Serotype 7F was the most prevalent in patients with

Table 4

Disease outcome at discharge for patients with invasive pneumococcal disease, by comorbidity, Belgium, 2009–2011 (n=1,329)[a]

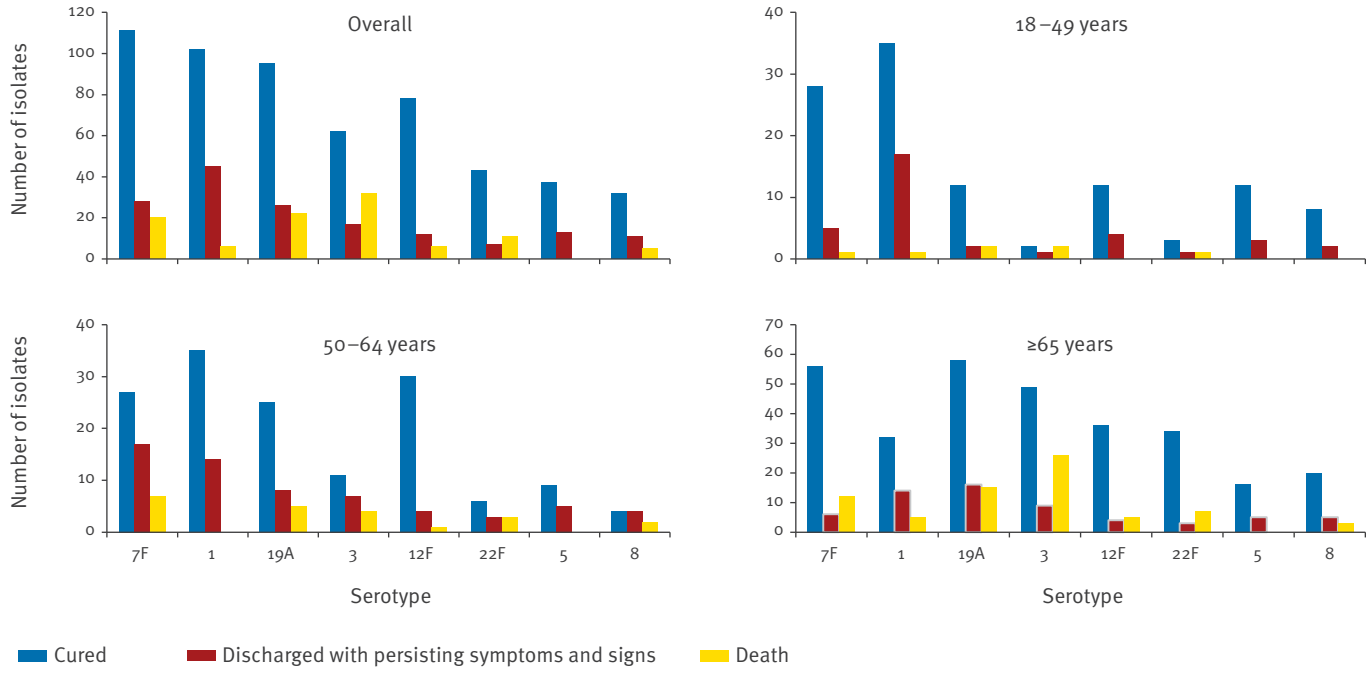
Category	n	Outcome at discharge			Univariate OLR		Multivariate OLR	
		Cured n (%)	Discharged with persisting symptoms n (%)	Death n (%)	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Total[a]	1,329	884 (67)	237 (18)	208 (16)	–	–	–	–
Comorbidity								
No	313	217 (69)	67 (21)	29 (9)	1	–	–	–
Any	1,016	667 (66)	170 (17)	179 (18)	1.29 (0.98–1.69)	0.067	1.20 (0.91–1.60)	0.20
Number of comorbidities, mean ± SD	1,323	1.43 ± 1.19	1.4 ± 1.22	1.88 ± 1.28	1.18 (1.08–1.29)	0.0004	–	–
COPD	335	226 (68)	56 (17)	53 (16)	0.97 (0.75–1.26)	0.83	0.90 (0.69–1.19)	0.47
Asthma	68	47 (69)	12 (18)	9 (13)	0.88 (0.52–1.48)	0.63	0.88 (0.51–1.51)	0.65
Heart failure	249	141 (57)	44 (18)	64 (26)	1.85 (1.41–2.43)	<0.0001	1.70 (1.26–2.30)	0.0006
Renal insufficiency	179	103 (58)	25 (14)	51 (29)	1.82 (1.34–2.48)	0.0001	1.63 (1.16–2.29)	0.0047
Hepatic disease	104	62 (60)	15 (14)	27 (26)	1.56 (1.05–2.31)	0.027	1.38 (0.91–2.10)	0.13
Immunosuppression	172	116 (67)	28 (16)	28 (16)	0.99 (0.71–1.38)	0.93	0.96 (0.67–1.39)	0.84
HIV infection	24	18 (75)	3 (13)	3 (13)	0.68 (0.27–1.70)	0.41	0.96 (0.37–2.50)	0.93
Cancer	296	192 (65)	48 (16)	56 (19)	1.17 (0.90–1.52)	0.26	1.16 (0.87–1.54)	0.31
Diabetes	203	136 (67)	37 (18)	30 (15)	0.98 (0.72–1.34)	0.91	0.83 (0.59–1.15)	0.26
Asplenia	11	6 (55)	1 (9)	4 (36)	2.15 (0.70–6.55)	0.18	2.18 (0.69–6.87)	0.18
Alcoholism	59	28 (48)	13 (22)	18 (31)	2.37 (1.45–3.86)	0.0006	2.79 (1.65–4.73)	0.0001
Hypertension	78	54 (69)	12 (15)	12 (15)	0.89 (0.55–1.45)	0.65	0.92 (0.56–1.52)	0.74
Smoking	26	21 (81)	4 (15)	1 (4)	0.44 (0.16–1.20)	0.11	0.59 (0.13–1.62)	0.30
Previous IPD	14	7 (50)	4 (29)	3 (21)	1.82 (0.67–4.97)	0.24	1.84 (0.65–5.19)	0.25
Tuberculosis	8	5 (63)	0 (0)	3 (38)	1.68 (0.44–6.37)	0.45	2.04 (0.52–7.91)	0.31
Other	154	101 (66)	29 (19)	24 (16)	1.05 (0.74–1.48)	0.79	1.05 (0.73–1.51)	0.78

CI: confidence interval; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; IPD: invasive pneumococcal disease; OLR: ordinal logistic regression; SD: standard deviation.

[a] Data missing for three patients.

Figure 1

Disease outcome at hospital discharge by age and serotype for patients with invasive pneumococcal disease, Belgium, 2009–2011 (n=1,214)



Only the serotypes accounting for at least 4% of isolates overall are shown.

bacteraemic pneumonia (13% (128/968)) and bacteraemia without focus (17% (11/64)), serotype 1 in those with empyema (23% (18/80)), and serotype 19A in cases of meningitis (11% (7/65)).

Serotypes 12F and 22F, not included in PCV13, accounted for 96 (8%) and 61 (5%) of the 1,214 IPD serotyped isolates, respectively. Serotypes 3 (17% (32/188)), 19A (12% (22/188)), and 7F (11% (20/188)) together accounted for nearly 40% of the 188 deaths with available serotype data. The highest case fatality rate was for serotype 6B (6 deaths for 11 cases; 55%) but eight of the 11 patients were ≥65 years of age. Among the six most frequent serotypes, the case fatality rates were 13% (20/159) for serotype 7F, 4% (6/153) for serotype 1, 15% (22/143) for serotype 19A, 29% (32/111) for serotype 3, 6% (6/96) for serotype 12F, and 18% (11/61) for serotype 22F. None of the 50 patients with serotype 5 IPD died.

Most pneumococcal isolates were susceptible to the four antibiotics tested (Table 5). Among the 22 pneumococcal isolates non-susceptible to penicillin, 18 were of serotype 19A. Overall, among the 145 serotype 19A isolates, 14 (10%) were intermediately resistant (MIC= 4 mg/L) and four (3%) resistant (MIC ≥8 mg/L) to penicillin, 95 (66%) were resistant to tetracycline, and 85 (59%) were resistant to erythromycin. Serotype 1, represented by a total of 154 isolates, was also frequently resistant to tetracycline (76 isolates (49%)) and erythromycin (74 isolates (48%)). The 159 serotype 7F isolates were all susceptible to the four antibiotics tested.

Overall, infections caused by the seven serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) represented 7% (83/1,214) of IPD cases (Figure 2). Also, 54% (659/1,214) of cases were caused by the six additional serotypes included in PCV13 (serotypes 1, 3, 5, 7F, 19A, and 6A), while 25% (298/1,214) were caused by the additional serotypes included in PPV23, and 14% (174/1,214) were caused by serotypes not included in any of the pneumococcal vaccines. Among the patients ≥50 years of age, the proportion of PCV7 serotypes decreased from 10% (33/325) in 2009 to 5% (13/252) in 2011 (p=0.028).

Discussion

In 2009, a prospective, active hospital-based study of morbidity and mortality of IPD in adults was started in Belgium. Data collected between 2009 and 2011 showed that mortality due to IPD was high, with up to 20% case fatality in adults ≥65 years of age. Bacteraemic pneumonia was the most frequent clinical type of IPD. Of the 1,214 serotyped isolates, 742 (61%) were included in PCV13, which thus included the most resistant and lethal isolates.

As in the current study, previous studies in the Netherlands, Spain and the United States (US) have shown that bacteraemic pneumonia predominates in adults [9-11]. Meningitis has been reported to be more frequent in young children [11,12]. In addition, we

Table 5

Antibiotic susceptibility of pneumococcal isolates derived from patients with invasive pneumococcal disease, Belgium, 2009–2011 (n=1,214)

Antibiotic	Pneumococcal isolates, n (%)				Resistant serotypes n (%)[a]
	Susceptible	Intermediate	Resistant	Unknown	
Penicillin	1,189 (98)	14 (1)	8 (1)	3 (<1)	19A: 4 (3); 14: 1 (4); 35: 1 (7); 15A: 1 (8); 20: 1 (20)
Tetracycline	945 (78)	2 (<1)	264 (22)	3 (<1)	1: 76 (49); **19A: 95 (66)**; 12F: 27 (28); 3: 1 (1); 22F: 1 (2); 5: 2 (4); 8: 2 (4); 6A: 8 (20); 14: 9 (39); 33F: 2 (9); 11A: 1 (5); 24F: 5 (26); 35: 1 (7); **15A: 6 (50); 6B: 6 (55)**; 38: 1 (10); 19F: 2 (20); 15F: 2 (29); 9V: 2 (33); 23A: 2 (33); 9A: 1 (20); 20: 1 (20); **15B: 2 (50)**; 15C: 1 (25); **9: 2 (67)**; **15: 1 (50)**; **12B: 2 (50)**; **13: 1 (100)**
Erythromycin	954 (79)	2 (<1)	255 (21)	3 (<1)	1: 74 (48); **19A: 85 (59)**; **14: 13 (57)**; **33F: 14 (64)**; 3: 1 (1); 12F: 5 (5); 22F: 1 (2); 8: 1 (2); 6A: 9 (23); 11A: 4 (19); 9N: 1 (5); 24F: 6 (32); 35: 1 (7); 23B: 1 (8); **15A: 7 (58)**; **6B: 7 (64)**; 38: 1 (10); **19F: 9 (70)**; 15F: 1 (14); 9V: 2 (33); 23A: 2 (33); 9A: 1 (20); 20: 1 (20); 15B: 1 (25); 15C: 1 (25); **33: 1 (100)**
Ofloxacin	1,206 (99)	0 (0)	3 (<1)	5 (<1)	1: 1 (1); 14: 1 (4); 29: 1 (14)

[a] Percentages in this column relate to the proportion of resistant isolates per total isolates of a given serotype. Serotypes with more than 50% of isolates resistant are shown in bold.

confirmed age as a risk factor for IPD and death due to IPD [11]. Chronic illness is another well-known risk factor for IPD [13-15]. In our study, more than three-quarters of patients with IPD had at least one chronic underlying condition. This proportion was even higher for older adults. This confirms that patients with comorbidities have a higher risk of developing IPD. Patients with at least one comorbidity generally also had a higher risk of death in hospital due to IPD.

Universal mass vaccination of children aged <2 years with PCV7 has dramatically decreased the incidence of vaccine-type IPD in this population and, to a lesser extent, in older individuals through herd effect [16-18]. Nevertheless, even with successful mass vaccination, IPD remains a problem. The ongoing national surveillance will help determine how routine use of PCV13 in children further influences the epidemiology of IPD in adults. While PCV7-type IPD has decreased [17,18], non-PCV7-type IPD has risen in many countries [17,19-23]. Accordingly, we found 7% of IPD cases in adults caused by serotypes included in PCV7. Because four of the most frequent serotypes (7F, 1, 19A, and 3) in our study are included in the newly licensed PCV13, they should become less common as the use of PCV13 increases.

Our finding that serotypes 1, 7F, and 19A predominate corresponds with other reports [6,19,23-25]. Serotype 19A was the third most prevalent serotype in adult IPD. Similarly, this serotype was previously reported as the second or third most prevalent serotype in IPD in children <5 years of age [6,7]. This is a concern because serotype 19A is frequently multi-resistant to antibiotics. The incidence of serotype 19A started to increase in children before the introduction of PCV7 and further increased after its introduction [6], suggesting that the rise is partly due to other factors, such as antibiotic consumption and secular trends. Serotypes 12F and 22F were the fifth and sixth most common serotype. Serotype 12 F has also become more common in young children since 2002–2003 [6]. Both serotypes are included in PPV23 but not in PCV13 and should be closely monitored in the future.

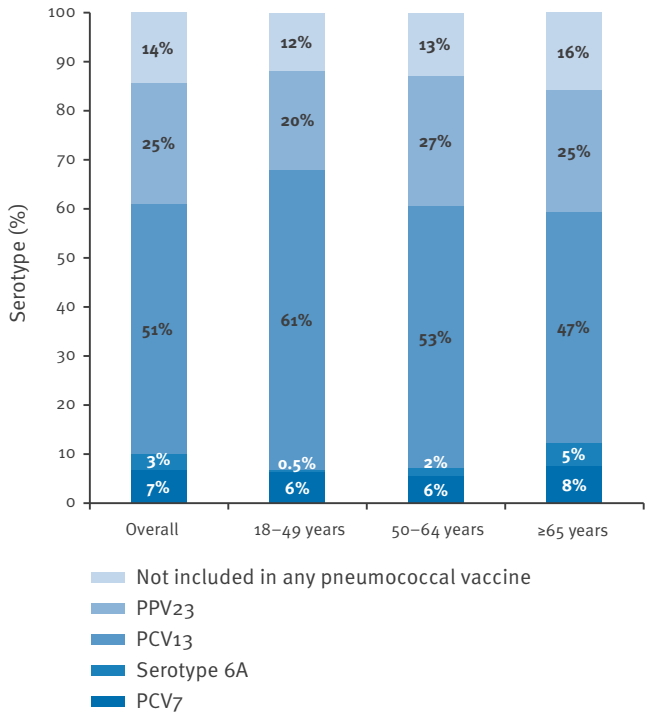
According to a review article, the reported case fatality rate for adult patients hospitalised with IPD has remained relatively stable at approximately 12% since the 1950s [26]. We found a slightly higher rate of 16%. The case fatality rate was low for serotypes 1 and 5 and high for serotypes 3 and 6B, as shown in previous studies in Denmark, the Netherlands and the US, [16,27,28].

One limitation of our study is that older patients may have been over-represented because adults between 18 and 49 years of age were included only from the second year of study (2010), whereas adults≥50 years of age were included from the beginning of the study (2009). However, this should have little impact on the results because per year the majority (51%) of patients were ≥65 years of age, and the data were analysed per age group. Another possible bias of the results is that 543 of the 1,875 (28%) eligible patients were not included in the analysis due to unavailable informed consent or late blood draw. Disease in these patients may have been more severe (patients in ICU) or less severe (patients who left the hospital before microbiological confirmation of IPD) than in the analysed population.

In conclusion, this study showed that, in Belgium, the mortality of IPD in adults is high, with a case fatality rate of 20% in patients ≥65 years of age. The most common and virulent pneumococcal serotypes are included in PCV13, which adds support for the use of

Figure 2

Proportion of invasive pneumococcal disease caused by serotypes included in pneumococcal vaccines, Belgium, 2009–2011 (n=1,214)



The 7-valent pneumococcal conjugate vaccine (PCV7) included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The 13-valent pneumococcal conjugate vaccine (PCV13) included additional serotypes 1, 3, 5, 6A, 7F, and 19A. Compared to PCV13, the 23-valent pneumococcal polysaccharide vaccine (PPV23) did not comprise serotype 6A, but included additional serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F. Serotype 6A was presented separately because it is included in PCV13 but not in PPV23. The total may be different from 100% due to rounding.

this vaccine in combination with the PPV23 in high-risk and older adults. In addition, these data are essential when assessing the impact of PCV13 vaccination in adults in the future.

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Conflict of interest

Jan Verhaegen has received grants from Pfizer. J. F. has received personal fees from Pfizer and is an advisor for the vaccine workgroup of the High Council of Public Health of the Belgian Federal Government and for the vaccine workgroup of the Flemish Government (unpaid activities). B. D. has received personal fees from Pfizer. K. V. H. has received consulting fees from Pfizer, research grants from Pfizer and GlaxoSmithKline Biologicals, and speaker fees from several vaccine manufacturers. Y. V. L. received personal and travel fees from Pfizer. P. V. D. acts as chief and principal investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University has obtained research grants from vaccine manufacturers. W. P. has received funds for advisory board membership from Pfizer, Bayer, AstraZeneca, GlaxoSmithKline Biologicals, Merck-Shering-Plough, and Astellas and research grants from Pfizer, Sanofi-Aventis, Bayer, and AstraZeneca. F. S. was an employee of Pfizer, which has a licensed pneumococcal conjugate vaccine, at the time of the study conduct. W. D. B.: none to declare. Writing assistance in preparation of this manuscript was provided by Dr. Julie Harriague (4 Clinics, Paris, France). This assistance included preparation of the first draft, incorporation of authors' contributions and revisions, and editing, all under the direction of the authors. At all stages, the authors had control over the content of this manuscript, for which they gave final approval and take full responsibility.

Authors' contributions

All authors participated actively since 2009 on the set-up of the study protocol, the follow-up of the study and the preparation of the manuscript.

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