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ABSTRACT

Background: Immunocompromising conditions and advanced age (≥65 years) are associated with a high risk for invasive pneumococcal disease (IPD). We investigated the risk and outcomes of IPD in adults with underlying conditions in the post-PCV7 era in The Netherlands.
Methods: IPD data from 2008 to 2012 was obtained from the national pneumococcal surveillance system, covering 25% of the Dutch population. Population estimates of underlying conditions were derived from the primary care data (2012). IPD incidence in adults with immunocompromising conditions (high risk group) and non-immunocompromising comorbidities (medium risk group) were compared to the "normal risk group" without diagnosed comorbidities. Case-fatality and ICU admission in the different risk groups was analyzed by logistic regression. Serotype specific propensities to affect high risk group IPD patients were calculated.
Results: Adults with a high risk condition have a 18-fold (95% CI 15.6–21.2) and 3-fold (95% CI 2.6–3.9) higher risk compared to the normal risk group for IPD at age 18–64 years and 65 years and older, respectively. In case of a medium risk condition, the risk is 5-fold (95% CI 4.3–5.7) and 2-fold (95% CI 1.9–2.6) higher in age groups 18–64 and ≥65 years old. Likewise, IPD patients with a high or medium risk condition have a higher case-fatality (after adjustment for age, odds ratio: 2-fold (95% CI 1.5–3.5) and 1.4-fold (95% CI 1.0–2.1), respectively). Several serotypes (e.g. 6A, 6B, 23A and 23B) are associated with a significantly higher propensity to cause disease in high risk patients.
Conclusions: The risk for IPD and death in the post-PCV7 era has remained considerably high in adults and elderly with underlying conditions. The identification of serotypes with a high propensity to affect risk groups can be important for selecting (future) vaccine serotypes.

1. Introduction

Streptococcus pneumoniae in adults is a major cause of pneumonia and may cause severe and often life threatening invasive pneumococcal infections (IPD). The highest pneumococcal disease incidence occurs at the extremes of life in children under 5 years of age, due to immature immunity and in the elderly of 65 years and older, due to progressing immunosenescence and comorbidities [1–3]. Furthermore, irrespective of age, the presence of certain underlying conditions is associated with a substantially increased risk for IPD and death, in particular in case of severely immunocompromising conditions such as HIV or haematological malignancies [4].

For children, effective vaccination-based preventive strategies for pneumococcal disease have become available after 2000, with the licensure and implementation of the first 7-valent pneumococcal conjugate vaccine (PCV7) with impact against IPD and pneumonia [5,6]. In adults, prevention through vaccination has been implemented in many countries since 1983 when a 23-valent pneumococcal polysaccharide vaccine (PPV23) became available. In adults, the polysaccharide vaccine is shown to be protective against IPD. There is however no conclusive evidence that PPV23 protects against non-invasive pneumococcal community-acquired

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pneumonia and that the vaccine has impact in adults with comorbidities, in particular in case of immunodeficiency [7]. In The Netherlands, guidelines recommend PPV23 for restricted groups of high risk persons with functional or anatomical asplenia and cerebrospinal fluid leakage [8]. Consequently, less than 1% of the population has been vaccinated with PPV23 [9,10].

The extended 10- and 13-valent pneumococcal conjugate vaccines that have become available since 2009 are shown to be better immunogenic in elderly and adults also in case of underlying comorbidity as compared to PPV23 [11,12]. Recently, a randomized controlled trial (CAPITA) vaccinating healthy immunocompetent adults aged 65 years and older with the 13-valent pneumococcal conjugate vaccine (PCV13, [Pfizer]) showed 75% protection against vaccine serotype IPD [13]. This renews the interest to extensively assess risk groups for IPD and the influence of underlying conditions on IPD outcomes.

We investigated the incidence and relative risk for IPD in the presence of defined underlying conditions in adults aged 18–64 years and in elderly aged 65 years and older in the post-PCV7 era (from 2008 to 2012, 2–6 year after implementation of routine PCV7 vaccination in infants). Although, population-based risk for IPD in persons with underlying conditions was assessed before in other countries, including the UK and US [4,14,15], data from The Netherlands provide the unique opportunity to asses IPD risks in the post-PCV7 era in a population naïve to PPV23.

In addition, we assessed the association between underlying conditions and IPD outcome (30-day mortality and ICU admission) and the propensity of individual serotypes to affect high risk adults. These data are helpful for policy makers deciding about preventive strategies with the now available 10- or 13-valent pneumococcal conjugate vaccines in specific age and risk groups. Furthermore, serotype specific propensities can be used by vaccine manufacturers for selecting serotypes to be included in future pneumococcal vaccines for these risk groups.

2. Methods

2.1. IPD data

The Dutch pneumococcal surveillance system is based on voluntary reporting of all invasive pneumococcal disease cases by nine geographically distributed sentinel laboratories, which cover approximately 25% of the Dutch population (≈4.2 million inhabitants, including 2.6 million adults aged 18–64 years and 0.65 million adults ≥65 years). The laboratories were selected based on their high % of isolates that are sent in (>90%). Pneumococcal isolates obtained from blood or cerebrospinal fluid (CSF) of hospitalized patients or patients at the emergency department were received for serotyping by Quellung reaction by The Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM, Amsterdam, The Netherlands). Clinical information of all IPD patients, from June 1, 2004–May 31, 2012 was retrospectively extracted from hospital medical records using a standardized form, as previously reported [1,16,17]. The post-PCV7 period was defined as the period June 1, 2008 to May 31, 2012, when PCV7 herd effects were clearly apparent and before PCV10 herd effects in adults had started to be present (PCV7 was implemented in the national immunization programme (NIP) for infants in 2006 and was replaced by the vaccine Synflorix (PCV10, [GSK]) from 2011 onwards) [18].

2.2. Population data

Population estimates of underlying conditions were derived from the national information network of primary care data (LINH) using 2012 as the representative year. These data were based on International Classification of Primary Care (ICPC) & Anatomical Therapeutic Chemical classification system (ATC) codes and originally collected for monitoring compliance in persons eligible for yearly influenza vaccination in general practices [19]. ICPC & ATC codes used to match underlying conditions in the population with the IPD data are described in the supplementary material (Supplementary Table 1). LINH data form a representative sample of the Dutch population with regard to age, gender, geographical distribution and degree of urbanization [20]. Population estimates of underlying conditions in the pre-PCV7 period were not available since the coding system had changed.

2.3. Definitions of risk groups

We defined the same groups eligible for influenza vaccination (in The Netherlands) as risk groups for IPD [19], since the increased susceptibility is based on the same risk factors. Patients with the following conditions are defined at risk for IPD: immunocompromised conditions including HIV/AIDS, chronic renal disease (defined as renal insufficiency/need for dialysis or nephrotic syndrome) and other immunocompromising conditions (defined as liver disease, lymphoma, leukaemia, myeloma, asplenia/splenectomy or primary immunodeficiency), and non-immunocompromised conditions including chronic lung disease, chronic cardiovascular disease and diabetes.

These underlying conditions are further classified in three risk groups for IPD: high risk (immunocompromised conditions as defined above), medium risk (non-immunocompromised conditions as defined above without any of the high risk immunocompromised conditions) and normal risk (no presence of any of the underlying conditions as defined above). The three risk groups are mutually exclusive. In addition, presence of more than one underlying condition did not change the risk group classification of the person as such information was not available for the population estimates. Furthermore, presence of one or more of the evaluated conditions was classified as '≥1 condition'.

2.4. Data analysis

We used IPD surveillance data of IPD patients aged 18 years and older from the post-PCV7 era (June 1, 2008 to May 31, 2012) and assessed the risk and outcomes of disease in those persons with underlying conditions. Since IPD data coverage was 25% of the whole population, we also extrapolated primary care (LINH) data of 2012 to 25% of Dutch population (StatLine Statistics, Netherlands) over the period 2008–2012. We assumed a stable presence of proportions with underlying conditions in the population over time.

The LINH data and IPD surveillance data were combined to calculate incidence of IPD within the risk groups, as number of cases per 100,000 persons per year, with the population estimates as denominator and the IPD surveillance data as numerator. We compared the incidence rate of IPD in a risk group with the incidence rate in normal risk persons. Differences in incidence rates were tested with χ^2, and relative risks (RR) with 95% confidence intervals (CI) were calculated using 2×2 tables [21] after stratification for age group (18–64 and ≥65 years old).

Logistic regression was used to analyze the association between the specific risk groups (high, medium and normal risk groups), the individual underlying conditions (chronic lung disease, chronic cardiovascular disease, diabetes, HIV/AIDS, chronic renal disease and immunocompromised (other) conditions), the '≥1 condition' group and outcomes of IPD (30-day mortality and ICU admission) using the IPD data (using SPSS version 22). Multivariable logistic regression models, including age group (18–64 and ≥65 years old), were performed to analyze the adjusted association between the specific risk groups, the '≥1 condition' group and outcomes of IPD.

Table 1
Number (No.) and percentage (%) of persons with underlying conditions in the national information network general practitioner care (LINH) data 2012.

	18–64 years old		≥65 years old	
	No.	%	No.	%
Total	140,627	100.0	33,647	100.0
Normal risk	118,924	84.6	10,369	30.8
Medium risk	19,456	13.8	20,480	60.9
Chronic lung disease	9762	6.9	6438	19.1
Chronic cardiovascular disease	12,168	8.7	20,113	59.8
Diabetes	5156	3.7	6574	19.5
High risk	2247	1.6	2798	8.3
HIV/AIDS	104	0.1	10	0.0
Chronic renal disease	419	0.3	1300	3.9
Immunocompromised (other)	1773	1.3	1577	4.7
≥1 condition	21,703	15.4	23,278	69.2

Likewise, the adjusted associations between individual underlying conditions and outcomes of IPD were assessed by including age group (18–64 and ≥65 years old) and all other individual underlying conditions in the logistic regression model. These conditions were selected based on their previous associations with IPD and or case-fatality [4,14,15]. A p-value of <0.05 was considered statistically significant.

The proportion of high risk group patients within a specific serotype (i.e. serotype specific propensity to affect high risk group patients) was compared to the overall proportion of high risk group patients in all other serotypes combined. To assess serotype specific propensity to cause disease in high risk group IPD patients we now used all available surveillance data from June 1, 2004 to May 31, 2012 in patients ≥18 years old (n = 4535). We assumed stable propensities of serotypes to affect high risk groups over time. Likewise, we assessed serotype specific propensity to cause disease in normal risk group IPD patients. Differences were tested with Fisher's exact test (using SPSS version 22), a p-value of <0.05 was considered statistically significant.

3. Results

3.1. Prevalence of underlying conditions in general population

The prevalence of underlying conditions was assessed in 174,274 adults of 18 years and older (Table 1) as based on the primary care (LINH) data. In the 18–64 years old adults, 85% had none of the selected conditions (normal risk group) while 14% were defined to be at medium risk for IPD and 2% at high risk (Table 1). In persons 65 years and older, 31% were defined to be normal risk, and 61% and 8% were considered at medium and high risk, respectively.

3.2. Risk of IPD in medium and high risk persons

Of 960 IPD cases in patients aged 18 to 64 years that were covered by the national pneumococcal surveillance database, 47% (448/960) were without predisposing underlying conditions (normal risk group), while 38% (363/960) was diagnosed with a medium risk condition and 16% (149/960) with a high risk condition. In persons with a high risk condition, the IPD incidence rate was 18-fold higher than in the normal risk group (95% CI 14.6–21.2, 89/100,000 vs 5/100,000 persons per year, Table 2). The highest risk was observed for persons with HIV/AIDS, who showed a 61-fold increased IPD incidence rate (95% CI 40.7–92.3, 308/100,000 persons per year) compared with the normal risk group, though the number of HIV cases were small (n = 24). For persons in the medium risk group, the IPD incidence rate was 5-fold higher compared to normal risk persons (95% CI 4.3–5.7, 25/100,000 vs 5/100,000 persons per year). Overall, adults with one or more underlying conditions (incidence 32/100,000 persons per year) had a 6-fold increased IPD incidence rate (95% CI 5.5–7.1).

Of 1264 IPD cases in patients aged 65 years and older (referred to as elderly), only 16% (201/1264) were without predisposing underlying conditions (normal risk group), while 70% (888/1264)

Table 2
Number (No.) and percentage (%) of IPD patients with underlying conditions in IPD surveillance data from 2008–2012 and incidence calculated with the projected number of persons at risk in the general population extrapolated from Table 1 stratified for age group. Incidences of IPD in patients with underlying conditions are compared to incidences in normal risk groups. RR = relative risk, CI = confidence interval.

	18–64 years old				≥65 years old			
	No. (%)	IPD cases/ 100,000 persons	RR	95% CI	No. (%).	IPD cases/ 100,000 persons	RR	95% CI
Total	960(100)	9.12			1264(100)	48.99		
Normal risk	448(46.7)	5.03	1.0		201(15.9)	25.28	1.0	
Medium risk	363(37.8)	24.93	5.0	4.31–5.69	888(70.3)	56.54	2.2	1.92–2.61
Chronic lung disease	207(21.6)	28.34	5.6	4.77–6.64	413(32.7)	83.65	3.3	2.8–3.92
Chronic cardiovascular disease	266(27.7)	29.21	5.8	4.99–6.75	872(69.0)	56.53	2.2	1.92–2.61
Diabetes	123(12.8)	31.88	6.3	5.19–7.73	273(21.6)	54.15	2.1	1.79–2.57
High risk	149(15.5)	88.61	17.6	14.63–21.19	175(13.8)	81.56	3.2	2.63–3.95
HIV/AIDS	24(2.5)	308.38	61.3	40.65–92.31	0(0)	0.00	0.0	NA
Chronic renal disease	13(1.4)	41.46	8.2	4.75–14.29	36(2.8)	36.11	1.4	1–2.04
Immunocompromised (other)	121(12.6)	91.20	18.1	14.82–22.14	141(11.2)	116.59	4.6	3.72–5.72
≥1 condition	512(53.3)	31.53	6.3	5.52–7.11	1063(84.1)	59.55	2.4	2.03–2.74

Table 3
Risk factors associated with 30-day mortality in IPD patients ≥18 years old.

	30-day mortality (number of deaths/total number of cases, %)	Unadjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Normal risk group	47/649 (7)	1.0	1.0[c]
Medium risk vs normal risk group	174/1251 (14)	2.1 (1.5–2.9)	1.4 (1.0–2.1)[c]
Chronic lung disease		1.0 (0.8–1.4)	0.9 (0.7–1.2)[d]
Yes	79/620 (13)		
No	200/1604 (13)		
Chronic cardiovascular disease		2.2 (1.7–2.9)	1.6 (1.2–2.2)[d]
Yes	189/1138 (17)		
No	90/1086 (8)		
Diabetes		1.0 (0.7–1.4)	0.8 (0.6–1.1)[d]
Yes	51/396 (13)		
No	228/1828 (13)		
High risk vs normal risk group	58/324 (18)	2.8 (1.9–4.2)	2.3 (1.5–3.5)[c]
HIV/AIDS		1.4 (0.5–4.1)	2.9 (0.9–8.7)[d]
Yes	4/24 (17)		
No	275/2200 (13)		
Chronic renal disease		3.2 (1.7–5.9)	2.6 (1.4–4.9)[d]
Yes	15/49 (31)		
No	264/2175 (12)		
Immunocompromised (other)		1.3 (0.9–1.9)	1.4 (0.9–2.0)[d]
Yes	40/262 (15)		
No	239/1962 (12)		
≥1 condition vs normal risk group	232/1575 (15)	2.2 (1.6–3.1)	1.6 (1.1–2.3)[e]
≥65 years old		2.9 (2.1–3.8)	2.6 (1.9–3.6)[c]
Yes	215/1264 (17)		
No	64/960 (7)		

OR = odds ratio; CI = confidence interval.
[a] Odds ratio and 95% confidence interval of association with mortality in univariable logistic regression model.
[b] Odds ratio and 95% confidence interval of association with mortality in multivariable logistic regression model.
[c] ORs are adjusted for risk groups and age group (18–64 and ≥65 years old). High, medium and normal risk groups were entered as categorical variables with normal risk group as reference.
[d] ORs are adjusted for chronic lung disease, chronic cardiovascular disease, diabetes, HIV/AIDS, chronic renal disease, immunocompromised (other) and age group (18–64 and ≥65 years old).
[e] ORs are adjusted for age group (18–64 and ≥65 years old).

had a medium risk condition and 14% (175/1264) a high risk condition. In elderly with a high risk condition, the IPD incidence rate was 3-fold larger than in the normal risk elderly (95% CI 2.6–3.9, 82/100,000 vs 25/100,000 persons per year, Table 2). The highest risk, with a 5-fold increased IPD incidence rate (95% CI 3.7–5.7), was observed for elderly with an immunocompromised (other) condition, which consisted of lymphoma, leukaemia, myeloma, asplenia/splenectomy, primary immunodeficiency and liver disease (incidence of 117/100,000 persons per year). The medium risk group in elderly had a 2-fold higher IPD incidence rate compared to normal risk elderly (95% CI 1.9–2.6, 57/100,000 vs 25/100,000 persons per year). Overall, elderly with one or more underlying conditions had a 2-fold increased IPD incidence rate (95% CI 2.0–2.7, 60/100,000 persons per year).

Incidence rate in normal risk group persons was higher in elderly aged 65 years and older (25/100,000 persons per year) compared to adults aged 18 to 64 years (5/100,000 persons per year). Subsequently, the magnitude of relative risk in adults with underlying conditions compared to the normal risk group was less pronounced in elderly of 65 years and older because the incidence rate in the reference group (normal risk age ≥65 years) was already high. Nevertheless, IPD incidence rates in elderly with underlying conditions were higher than in adults aged 18 to 64 years, with exception of chronic renal disease and HIV/AIDS.

3.3. Logistic regression of mortality and ICU admission in medium and high risk IPD patients

Table 3 shows that high risk group IPD patients also had a significantly higher odds ratio (OR) of mortality compared to normal risk group adults after adjustment for age, with OR 2.3 (95% CI 1.5–3.5). Also medium risk group patients had a significant higher adjusted odds ratio of death (OR: 1.4; 95% CI 1.0–2.1). Chronic renal disease (adjusted OR: 2.6 95% CI 1.4–4.9) and chronic cardiovascular disease (adjusted OR: 1.6 95% CI 1.2–2.2) were also independently associated with death. HIV/AIDS and immunocompromised (other) conditions were not significantly associated with an increased OR of death. In contrast, chronic lung disease and diabetes were independently associated with a non-significant lower OR of death after adjustment for other underlying conditions and age. No association was observed between ICU admission and the presence of high and medium risk conditions (Supplementary Table 2, adjusted OR 1.0; 95% CI 0.8–1.4 and 1.1; 95% CI 0.8–1.4, respectively). Likewise, none of the separately analyzed underlying conditions were associated with an increased OR for ICU admission.

3.4. Propensity of serotypes to cause disease in high and normal risk IPD patients

To assess serotype specific propensity to cause disease in high and normal risk group IPD patients we used all available surveillance data from June 1, 2004 to May 31, 2012 in patients ≥18 years old ($n = 4535$). Fig. 1 shows that serotypes 15B, 10A, 33F and 18C were significantly more common in high risk group patients (52, 39, 30 and 28%, respectively) than average (16%). Furthermore, all serotypes within group 6 (6A, 6B and 6C) were more common in high risk patients and this was significant for 6A and 6B (29 and 26%, respectively). Also both serotypes from group 23 (23A and 23B) had a significantly higher propensity to cause disease in high risk patients (38 and 37%, respectively). Fig. 2 shows that serotypes

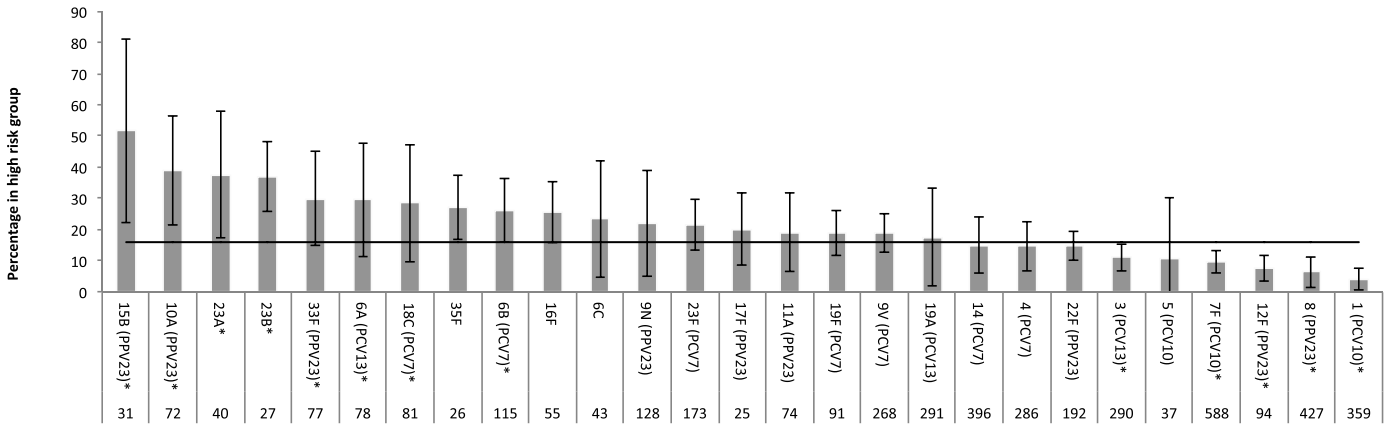

Fig. 1. Serotype specific proportion of high risk group IPD patients with 95% CI (Agresti–Coull method) in patients ≥18 years old. All PCV7, PCV10 and PCV13 serotypes are shown. From other serotypes (including additional PPV23 serotypes) all serotypes with a total of at least 25 cases including 4 high risk group patients are shown (including vaccine types in total 27 serotypes). Proportion of overall IPD patients in a high risk group is plotted as reference line (16%). * Indicates a significant difference between serotype specific proportion of high risk group IPD patients vs the proportion of high risk group IPD patients in all other serotypes tested with Fisher's exact test. The numbers represent the total number of cases per serotype.

1 and 7F were significantly more common in normal risk group patients (53 and 39%, respectively) than average (29%).

4. Discussion

The risk for IPD in the post-PCV7 era has remained considerably higher in adults and elderly with underlying conditions compared to normal risk adults and elderly (without underlying conditions) in a population naïve for PPV23. The risk is highest for adults with an immunocompromising condition (i.e. high risk group). The increased risk is accompanied by a substantially higher case-fatality rate. Also persons with a medium risk group condition (including chronic lung disease, chronic cardiovascular disease and diabetes) have a considerable higher risk for IPD and death. Furthermore, several pneumococcal serotypes are clearly associated with a significantly higher propensity to cause disease in high risk group patients, which could be important for selecting (future) vaccine serotypes.

Our study is in line with other studies that found that adults with immunocompromising conditions (HIV/AIDS, chronic renal disease, and other immunocompromising conditions) are disproportionately vulnerable for IPD [4,14,15]. Likewise these studies observed a markedly higher risk for IPD in adults with medium risk conditions (chronic lung disease, chronic cardiovascular disease and diabetes). Since medium risk conditions are very common in the population, their net contribution to the disease burden of IPD is substantial [20]. Besides a marked increased risk for IPD in persons with underlying conditions, there is also a higher risk of death, especially in patients with high risk group conditions and chronic cardiovascular disease [14]. We did not observe a higher risk for ICU admission in any of the risk groups. This is possibly explained by the fact that patients with certain underlying conditions, or at advanced age, are more often denied ICU admission due to an unfavourable prognosis. In our study 12%, 17% and 15% of the normal, medium and high risk group, respectively, were not admitted to the ICU. Overall, 14% of the 18–64 years old and 16% of the ≥65 years old patients were not admitted to the ICU.

We found a marked increase in IPD incidence rate in normal risk persons (without underlying conditions) with advancing age, which encompasses the increased incidence in persons with underlying conditions. As a result the magnitude of RRs for IPD in persons with underlying conditions compared to normal risk adults was more pronounced between 18 and 64 years of age as in elderly aged 65 years and older. Likewise, after further age stratification of

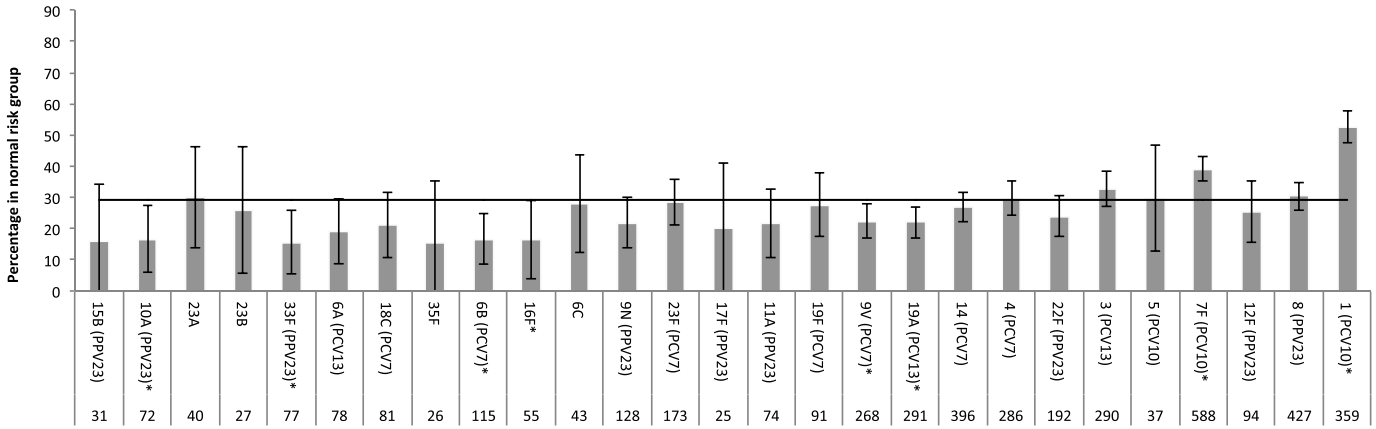

Fig. 2. Serotype specific proportion of normal risk group IPD patients with 95% CI (Agresti–Coull method) in patients ≥18 years old. All PCV7, PCV10 and PCV13 serotypes are shown. From other serotypes (including additional PPV23 serotypes) all serotypes with a total of at least 25 cases including 4 normal risk group patients are shown (including vaccine types in total 27 serotypes). Serotypes are listed in the same order as Fig. 1. Proportion of overall IPD patients in a normal risk group is plotted as reference line (29%). * Indicates a significant difference between serotype specific proportion of normal risk group IPD patients vs the proportion of normal risk group IPD patients in all other serotypes tested with Fisher's exact test. The numbers represent the total number of cases per serotype.

≥65 years old patients (in 65–74 and ≥75 groups), the risk for IPD in persons with underlying conditions remained higher compared to normal risk persons but especially the IPD incidence in normal risk elderly increased with advanced age (data not shown). A similar phenomenon was observed in studies from the UK and US [14,15] and is possibly explained by the decline in reserve capacity of physiologic systems with age, including declining immune function, in elderly referred to as immunosenescence [22], irrespective of comorbidity presence. Immunosenescence is likely to play an important role since older and frail persons have more often attenuated immune responses after pneumococcal vaccination [23].

With exception of chronic renal disease and HIV/AIDS, the IPD incidence in ≥65 year old adults with underlying conditions was higher than in 18–64 year old persons. The lower IPD incidence for chronic renal disease in elderly ≥65 years old is possibly explained by the fact that chronic renal disease in younger adults reflects a different (usually more severe) disease entity than in elderly [24]. Likewise, lower incidences of IPD in elderly patients with underlying renal conditions were reported by Hoek et al. For HIV/AIDS numbers were too small to draw conclusions in elderly, as was the case in the UK [14].

Our findings show multiple serotypes (15B, 10A, 33F and 18C) to be significantly associated with IPD in high risk group patients. Also antigenically related serotypes from group 6 (6A, 6B) and 23 (23A and 23B) had a significantly higher propensity to affect high risk group patients. Other serotypes like serotypes 1 and 7F were significantly more present in normal risk group or "healthy" patients. Serotype 1 and 7F have previously been associated with IPD in healthy patients [25–27] and have a high risk of causing invasive disease [28]. These serotypes, as suggested by Sjostrom et al., act as "primary pathogens". On the other hand other serotypes (e.g. 6A, 23F) with a lower invasive disease potential primarily affect patients with underlying conditions and behave as "opportunistic pathogens" [26,29]. Although other factors such as chance play a role in developing IPD these findings support the hypothesized influence of underlying conditions on the invasiveness of specific serotypes [26,29]. Consequently, this information could be considered if a new vaccine is designed to specifically target high risk groups.

A strength of this study is that we used IPD data from a complete and consistent surveillance system whereas population data was extracted from a reliable database used to monitor the compliance in risk groups eligible for influenza vaccination. Furthermore, we focussed on the post-PCV7 period, 2–6 years after implementation of PCV7, whereas some other studies used pre- and post-PCV7 data combined to asses risk groups [4,14]. Since major shifts in circulating serotypes were observed after PCV7 introduction, and serotype specific propensities differences in targeting high risk adults exist, the risk of IPD in persons with underlying conditions compared to normal risk persons could have changed. Indeed it has been speculated that patients with certain underlying conditions (e.g. patients with AIDS) or elderly may benefit less from herd protection because they may be more susceptible to emerging serotypes [30–33]. Unfortunately since prevalence data of underlying conditions in the general population were not available for the pre-PCV7 period we could not assess these potential changes. Lastly, our study was performed in a population with negligible PPV23 uptake whereas in other countries, where PPV23 uptake is higher, this could have influenced the observed risks for IPD.

Our study has limitations. Definitions used in the population ICPC and ATC codes did not exactly match the IPD surveillance data. This resulted in slightly broader population definitions of underlying conditions compared to the IPD surveillance. For instance in the population data chronic lung disease included ICPC codes K93 (pulmonary embolus) R70 (generalized tuberculosis) R82 (pleurisy) and neoplasms of the lung (R84, R85, R86) and for the IPD data these were not taken into account. Furthermore, we assumed that the proportion of underlying conditions in the population remain stable over time and we extrapolated 2012 data to 2008–2012, whereas prevalences could have increased over time [20]. Both could have resulted in a modest underestimation of the observed risks in patients with underlying conditions. Nevertheless our findings show a substantial higher risk for these patients.

Furthermore, if a patient had 1, 2 or 3 different non-immunosuppressive conditions it was still classified in the medium risk group. However, it is expected that the risk for IPD increases when more risk factors are present [4]. At last, other factors such as unmeasured underlying conditions (e.g. non-haematological malignancies or mental illnesses), smoking, alcohol abuse, socio-economic status and child contact status could influence the risk for IPD and were not taken into account [4,14,34,35].

5. Conclusions

Quantification of the risk of IPD and outcomes in persons with underlying conditions and elderly can be useful for policy makers to decide about preventive strategies. Since the European population is ageing [36] the burden of pneumococcal disease is likely to increase and vaccination of elderly or risk groups with a pneumococcal conjugate vaccine could be an effective strategy [11,13]. However, herd effects after PCV7 introduction in children already resulted in a substantial decrease in PCV7-type IPD and replacement disease with non-PCV7-type IPD in both elderly ≥65 years and other non-vaccinated adults (with and without underlying conditions) [1]. Therefore, the effect of pneumococcal conjugate vaccines, with same or slightly broader serotype coverage as the vaccine used in the national immunization programme, could be limited. Also for all conjugate vaccines concerns remain about further replacement disease by serotypes not included in the vaccine. For instance emerging serotypes 10A and 33F, which have a significantly increased propensity for causing disease in high risk group patients, are not covered by PCV10 and 13. These data, in addition to serotype specific differences in disease incidence and severity, could be important for selecting (future) vaccine serotypes.

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Conflict of interest statement

G.H.J.W has received a lecturing fee from Pfizer. E.A.M.S has received grant support from Pfizer and GlaxoSmithKline for research on vaccine studies and was involved in Independent Data Monitoring Committees for Pfizer and GlaxoSmithKline vaccine studies (fee paid to the institution). A.v.d.E has received grants from Pfizer for research on pneumococcal infections and participated in Advisory Boards of Pfizer. All other authors report no potential conflicts.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.11.048.

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