Invasive pneumococcal disease in patients with an underlying pulmonary disorder

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Abstract

Chronic pulmonary disease is a recognized risk factor for invasive pneumococcal disease (IPD). However, previous studies have often not been large enough to allow detailed analyses of less prevalent pulmonary diseases, and findings regarding case fatality have been inconsistent. We examined the associations between an underlying pulmonary disease and IPD, and the impact of these diseases on the case fatality rate. Patients with IPD $\geq$18 years of age, between 1990 and 2008, were identified in microbiological databases. The associations between IPD and the pulmonary diseases were assessed using conditional logistic regression, comparing IPD cases to ten control subjects per case, randomly selected from the general population (matched for gender, year of birth and county of residence). Adjustments were made for other co-morbidities, level of education and socio-economic status, 4085 cases of IPD and 40 353 controls were identified. A more than four-fold increased risk of IPD was seen in chronic obstructive pulmonary disease, a doubled risk in asthma and a five-fold increased risk in subjects with pulmonary fibrosis. In univariate analysis, sarcoidosis and bronchiectasis were associated with a two-fold to seven-fold increase in the risk of IPD, but there was no statistical support for the associations when adjustments for confounders were made. No increased risk was seen in subjects with a history of pneumoconiosis or allergic alveolitis. The mortality following IPD was not increased in patients with chronic obstructive pulmonary disease, asthma, pulmonary fibrosis or bronchiectasis. Several chronic pulmonary diseases increase the risk of IPD but mortality following IPD seems not to be affected.

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Introduction

Streptococcus pneumoniae is an encapsulated Gram-positive pathogen with the potential to cause invasive disease. It is a major cause of community-acquired pneumonia and bacterial meningitis. In Sweden, invasive pneumococcal disease (IPD) has been a notifiable disease since 2004, and around 1500 cases are reported annually to the Swedish Institute for Communicable Disease Control, corresponding to an annual incidence of 15–19 cases/100 000 inhabitants [1].

Chronic obstructive pulmonary disease (COPD) and, recently, asthma [2] are recognized risk factors for acquiring IPD, but risk estimates published in previous studies are often based on case series or studies with aggregated denominator data on co-morbidities, and have in many cases, not been large enough to allow multivariate analysis or detailed analysis of less prevalent pulmonary diseases [3,4]. In addition, it is not clear whether an underlying pulmonary disease increases the risk of death following IPD [3,5,6].

In this large population-based case–control study, nested in the population of southern Sweden, an area with around 1.6 million inhabitants, we examined the association between a

history of chronic pulmonary disease and IPD, and the effect of underlying pulmonary diseases on mortality following IPD, comparing IPD cases with randomly selected control subjects from the general population.

Methods

Ethics

The study was approved by the Lund University Research Ethics Committee (203/2008, 223/2009, 398/2011).

Setting

Swedish health care is publicly financed, with few private care-givers in secondary care. A unique, lifelong ten-digit personal identity number assigned to each person living in Sweden provides the possibility of cross-referencing information in national databases.

Case retrieval and control selection

All individuals $\geq$18 years of age, living in southern Sweden, showing growth of *S. pneumoniae* in a culture from a normally sterile site (e.g. blood, cerebrospinal fluid, pleural effusion) were identified in the databases at the seven microbiological laboratories covering the area (Kristianstad 1991–2008, Lund 1991–2008, Malmö 1990–2008, Halmstad 1995–2008, Kalmar 1990–2008, Karlskrona 1994–2008 and Växjö 1987–2008). For each case, ten control subjects were randomly selected from the general population, matched for gender, year of birth and county of residence on 31 December the year before the diagnosis of IPD. All cases and controls were cross-referenced to national databases to obtain personal information on vital status, and information on level of education and socio-economic status.

Co-morbidity

Through linkage with the National Inpatient Registry and the Cancer Registry information was obtained on all available hospital discharge and cancer diagnoses. The Inpatient Registry has been operating in southern Sweden since the early 1970s, apart from the counties of Kronoberg (1987) and Blekinge (1984). It came into operation nationwide in 1987. Visits to hospital outpatient clinics and emergency departments have been recorded nationwide since 2001.

The following chronic pulmonary diseases were taken into consideration: COPD, asthma, pulmonary fibrosis, sarcoidosis, bronchiectasis, allergic alveolitis and pneumoconiosis registered >30 days to 5 years before the first IPD diagnosis or the corresponding date in control subjects. In addition, we noted discharge diagnoses of other non-pulmonary diseases conferring increased risk of IPD, liver disease, renal failure, heart failure, cerebrospinal fluid leakage, rheumatoid arthritis and other connective tissue diseases, alcohol-related diseases, diabetes mellitus, haematological and non-haematological cancer, human immunodeficiency virus infection and immunodeficiency [4]. Codes for transplantation and splenectomy were noted for the total Inpatient Registry period up to 30 days before index. The specific codes according to the International Classification of Diseases can be found in the Supplementary information, Appendix S1.

Chart review

General validation studies of the Inpatient Registry indicate that coverage is above 98% and that almost 90% of the diagnoses reported are correct [7]. We have previously validated the diagnosis of COPD in the Inpatient Registry in this cohort. The degree of certainty of the diagnosis varied, but < 10% were considered misclassified or having an uncertain COPD diagnosis [8]. A subset of the other pulmonary diagnoses from the four major hospitals in the county of Skåne (Helsingborg, Kristianstad, Lund and Malmö), was validated against the original medical records. The estimated diagnostic accuracy was as follows: asthma (n = 198) 80%, sarcoidosis (n = 17) 95%, pneumoconiosis (n = 7) 100%, pulmonary fibrosis (n = 41) 85% and bronchiectasis (n = 13) 85%.

Statistical analyses

Chi-squared tests, Fisher's exact test and *t*-tests were used to assess the risk factors for IPD and risk factors for in-hospital mortality and death within 28 days of IPD diagnosis. The associations between IPD and underlying pulmonary diseases were assessed using conditional logistic regression. Separate models were fitted for each pulmonary disease. Adjustments were made for other chronic non-pulmonary diseases, total duration of hospital stay, level of education and socio-economic status. Interactions between disease status, age at inclusion, gender and time since the previous hospital visit for pulmonary disease, on outcome were assessed by examining odds ratios in different strata of the covariates and by including interaction terms in the fully adjusted models.

The associations between death within 28 and 90 days of IPD diagnosis and underlying lung disease were assessed using logistic regression, adjusted for age, gender, clinical presentation and other co-morbidities. Likelihood ratio tests were performed to test for differences and interactions. All analyses were performed using STATA/SE (version 10.1 for Windows; StataCorp LP, College Station, USA).

Results

A first episode of IPD was identified in 4135 individuals ≥18 years of age, corresponding to an average rate of 16/100 000 annually. In the control group, 185 individuals were excluded because of suspected reused personal identification numbers, and another 708 individuals because of death before the date of diagnosis of the corresponding cases. Fifty of the IPD cases and 96 control subjects had records of both COPD and asthma and were excluded from the main analyses. A total of 4085 cases and 40 353 matched controls were subjected to the final analyses.

The median age at inclusion was 67 years (range 18–103 years), and 49.4% were men. Among the cases, 96.4% had bacteraemia, 3.2% had pneumococcal growth in the cerebrospinal fluid (with or without bacteraemia) and 2.4% positive culture from other normally sterile sites (with or without bacteraemia). According to the hospital discharge codes in the Inpatient Registry, 70.7% of the IPD cases had pneumonia, 5.9% had meningitis, 2% had miscellaneous foci (e.g. arthritis, peritonitis etc.), and 21.5% had no specific focus (i.e. primary bacteraemia or no recorded focus).

Overall 39.5% of the IPD cases had a hospital contact for any of the recorded diseases, >30 days to 5 years before first IPD diagnosis, as compared with 19.5% among control subjects ($p < 0.001$). The demographic characteristics are given in Table 1. The specific odds ratios for IPD in patients with underlying diseases are outlined in Table 2.

TABLE 1. Demographic characteristics of the study population

	IPD cases *n* = 4085 (100%)	Control subjects[a] *n* = 40 353 (100%)	p-value
Age category			
18–59 years	1418 (34.7%)	14 142 (35.1%)	
60–79 years	1717 (42.0%)	17 167 (42.5%)	
≥80 years	950 (23.3%)	9044 (22.4%)	
Gender			
Male	2018 (49.4%)	19 900 (49.3%)	
Level of education			< 0.01
Primary education	1471 (36.0%)	14 323 (35.5%)	
Secondary education	1254 (30.7%)	11 488 (28.5%)	
Upper secondary education	814 (19.9%)	8152 (20.2%)	
College/University	341 (8.4%)	4489 (11.1%)	
No information	205 (5.0%)	1900 (4.7%)	
Socio-economic status			< 0.01
Non-manual	748 (18.3%)	8622 (21.4%)	
Manual	939 (23.0%)	9236 (22.9%)	
Other	332 (8.1%)	3353 (8.3%)	
Outside workforce[b]	2066 (50.6%)	19 142 (47.4%)	
Co-morbidity[c]			
Previous hospitalization	2442 (59.8%)	16 372 (40.6%)	<0.01
Total duration of hospital stay			
Mean/median (days)[d]	23.7/5	11.1/0	<0.01
Heart failure	333 (8.1%)	1387 (3.4%)	<0.01
Liver disease	56 (1.4%)	88 (0.2%)	<0.01
Renal failure	62 (1.5%)	128 (0.3%)	<0.01
CSF leakage	0	0	NA
Connective tissue disease	181 (4.5%)	579 (1.5%)	<0.01
Alcohol-related disease	124 (3.0%)	292 (0.7%)	<0.01
Diabetes mellitus	298 (7.3%)	1369 (3.4%)	<0.01
HIV	10 (0.2%)	3 (0.01%)	<0.01
Immunodeficiency	17 (0.4%)	22 (0.05%)	<0.01
Haematological cancer	200 (4.9%)	101 (0.3%)	<0.01
Solid cancer	243 (6.0%)	1538 (3.8%)	<0.01
Splenectomy[e]	4 (0.1%)	1 (0.00)	<0.01
Transplant recipient	21 (0.5%)	22 (0.05%)	<0.01

CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IPD, invasive pneumococcal disease.
[a]Control subjects were matched for year of birth, gender and county of residence on 31 December the year before IPD diagnosis.
[b]Subjects with no information on socio-economic status were mainly retired, unemployed, living on disability benefit, homemakers or students.
[c]Co-morbidity recorded >30 days to 5 years before first positive culture and the corresponding date in the control subjects, see Appendix S1 for specific International Classification of Diseases codes.
[d]>30 days up to 5 years before first positive culture.
[e]Codes of splenectomy and transplantation were recorded for the total registry period up to >30 days before index.

COPD

In total, 726 individuals, of whom 57.9% were men, had a history of COPD. Among the cases, 248 (6.1%) had a history of COPD, whereas the corresponding number among the control subjects was 478 (1.2%). This corresponds to a five-fold increase in the risk of acquiring IPD, after adjustment for other co-morbidity, level of education and socio-economic status. The results are outlined in detail in Table 3.

The risk of IPD increased with the total number of previous hospital visits for COPD ($p < 0.001$ for trend), and decreased with time since the preceding hospital visit for COPD ($p < 0.01$ for trend), as illustrated in Figure 1. Evidence was found of an interaction between COPD status and age at index (p 0.01), but not with gender or socio-economic status.

Asthma

In total, 380 individuals, of whom 36.3% were men, had a previous diagnosis of asthma: 71 (1.7%) among the IPD cases and 309 (0.8%) among the controls. This corresponds to a two-fold increase in the risk of IPD when adjusted for other co-morbidity, level of education and socio-economic status.

There was an overlap between asthma and COPD, as mentioned above. However, repeating the analyses including individuals with records of both COPD and asthma, adjusting for both, only lowered the estimates slightly: COPD aOR 4.3, 95% CI 3.6–5.1, asthma aOR 1.6, 95% CI 1.3–2.0.

Other chronic pulmonary diseases

A history of pulmonary fibrosis was associated with a five-fold increase in risk of IPD (Table 3). Previous sarcoidosis and bronchiectasis was associated with a two-fold to seven-fold increase in the risk of IPD in univariate analysis, but there was no statistical support for the associations when adjustments were made for co-morbidity, level of education and socio-economic status. There was no evidence of an association with a history of pneumoconiosis or allergic alveolitis (Table 3).

TABLE 2. The relationship between risk factors and invasive pneumococcal disease

	Univariate OR (95% CI)[a]	Multivariate OR (95% CI)[b]
Level of education		
Primary education	1	1
Secondary education	1.9 (1.2–2.9)	1.9 (1.2–3.0)
Upper secondary education	1.7 (1.1–2.6)	1.8 (1.1–2.38
College/University	1.3 (0.8–2.0)	1.4 (0.9–2.3)
No information	1.7 (1.1–2.5)	1.5 (1.0–1–0)
Socio-economic status		
Non-manual	1	1
Manual	1. (1.1–1.3)	1.0 (0.9–1.2)
Other	1.2 (1.0–1.3)	1.1 (0.9–1.2)
Outside workforce[c]	1.4 (1.2–1.5)	1.1 (1.1–1.3)
Co-morbidity[d]		
Any chronic pulmonary disease	4.4 (3.9–5.1)	3.6 (3.1–4.1)
Heart failure	2.5 (2.2–2.9)	1.7 (1.4–1.9)
Liver disease	6.3 (4.5–8.9)	3.8 (2.6–5.5)
Renal failure	5.0 (3.7–6.8)	3.0 (2.1–4.3)
Connective tissue disease	3.2 (2.7–3.9)	2.7 (2.3–3.3)
Alcohol-related disease	4.4 (3.6–5.5)	3.8 (3.0–4.7)
Diabetes mellitus	2.3 (2.0–2.6)	1.7 (1.5–1.9)
Human immunodeficiency virus	50.0 (11.0–228.1)	53.0 (11.5–244.4)
Immunodeficiency	7.6 (4.0–14.4)	1.4 (0.7–3.1)
Haematological cancer	20.5 (16.1–26.3)	19.7 (15.3–25.5)
Solid cancer	1.6 (1.4–1.8)	1.5 (1.3–1.7)
Splenectomy	8.2 (5.7–12.0)	6.2 (4.0–9.4)
Transplant recipient	9.4 (5.2–17.2)	2.1 (1.0–4.4)
Total days of hospitalization	1.0 (1.0–1.0)	1.0 (1.0–1.0)

[a]Odds ratio for invasive pneumococcal disease for the specific diseases compared with not having the disease, estimated using a conditional logistic regression model.
[b]Odds ratio for invasive pneumococcal disease for the specific diseases compared to not having the disease, estimated using a conditional logistic regression model adjusting for all other variables in the table: from likehood ratio test.
[c]Subjects with no information on socio-economic status were mainly retired, unemployed, living on disability benefit, homemakers or students.
[d]Co-morbidity recorded >30 days to 5 years before first positive blood culture with IPD and the corresponding date in the control subjects, see Appendix S1 for specific International Classification of Diseases codes, codes of splenectomy and transplantation were recorded for the total registry period up to >30 days before index.

TABLE 3. Relative risks of invasive pneumococcal disease (IPD) for individuals with an underlying pulmonary disease in separate age groups, and the effect of an underlying pulmonary disease on the risk of death within 28 days of IPD

	Age group															
	18–59 years			60–79 years			≥80 years			All						
Pulmonary disease	IPD cases $n = 1\,418$[a]	Controls $n = 14\,142$[b]	OR (95% CI)[c]	IPD cases $n = 1\,717$[a]	Controls $n = 17\,176$[b]	OR (95% CI)[3]	IPD cases $n = 950$[a]	Controls $n = 9\,045$[b]	OR (95% CI)[c]	IPD-cases $n = 4\,085$[a]	Controls $n = 40\,353$[b]	OR (95% CI)[c]	aOR (95% CI)[d]	Mortality $n = 495$[e]	aOR (95% CI)[f]
COPD	25	25	10.3 (5.8–18.0)	147	253	6.3(5.1–7.8)	76	200	4.0(3.0–4.8)	248	478	5.6 (4.8–6.6)	4.7 (4.0–5.6)	34/248	0.9 (0.6–1.3)
Asthma	26	54	4.9(3.0–7.8)	31	167	1.9(1.3–2.9)	14	88	1.5(0.9–2.7)	71	309	2.3 (1.8–3.0)	2.0 (1.5–2.6)	4/71	0.4 (0.2–1.3)
Sarcoidosis	2	5	4.0(0.8–20.6)	2	12	2.5(0.7–8.8)	0	2	–	4	19	2.6(1.0–7.0)	2.0(0.7–6.2)	1/4	–
Pneumoconiosis	0	0	–	1	5	2.0(0.2–17.1)	0	3	–	1	8	1.3(0.2–10.0)	1.9(0.2–16.1)	1/1	–
Pulmonary fibrosis	2	3	6.5(1.1–39.1)	7	6	11.6(3.9–34.4)	5	11	4.4(1.5–12.6)	14	20	6.8(3.5–13.6)	5.1(2.5–10.4)	4/14	2.1(0.6–6.5)
Bronchiectasis	7	7	9.9(3.4–28.3)	2	8	2.5(0.5–11.8)	2	0	–	11	15	7.2(3.3–15.7)	1.9(0.7–5.2)[g]	0/11	–
Allergic alveolitis	1	1	9.5(0.6–151.8)	0	2	–	0	2	–	1	5	2.0(0.2–16.8)	1.9(0.2–16.5)	0/1	–

COPD, chronic obstructive pulmonary disease.
[a]Number of IPD cases admitted to hospital for the specific disease >30 days to 5 years before index date.
[b]Number of control patients, matched for age, gender and county of residence, on 31 December the year preceding IPD in the corresponding case.
[c]Odds ratio for IPD for the specific diseases compared with not having the disease, estimated using a conditional logistic regression model.
[d]Odds ratio for IPD for the specific diseases compared with not having the disease, estimated using a conditional logistic regression model adjusting for other co-morbidities previously shown to be associated with increased risk of IPD, level of education and socio-economic status.
[e]Number of IPD patients who died within 28 days of first positive culture.
[f]Odds ratio for death within 28 days for the specific diseases compared with not having the disease, estimated using logistic regression, adjusted for clinical presentation, gender, age and other co-morbidity (yes/no).
[g]The effect of bronchiectasis was mainly confounded by a history of organ transplant.

Mortality following IPD

Among the 4085 IPD cases, 495 (12.1%) died within 28 days of the first positive culture, 618 (15.1%) died within 90 days. The median age at death was 77 years (range 30–103 years). The all-cause mortality risk within 28 days varied with clinical presentation (meningitis 20.8%, pneumonia 8.2%, miscellaneous foci 3.8% and primary bacteraemia (or no recorded focus) 24.4%).

A previous diagnosis of COPD, asthma, pulmonary fibrosis or bronchiectasis was not associated with death within 28 or 90 days, according to logistic regression models adjusting for age, gender, clinical presentation and other co-morbidity. The modest number of subjects with sarcoidosis, pneumoconiosis or allergic alveolitis among IPD patients, prevented any reliable inferences concerning mortality risk.

Discussion

In this population-based study on > 4 000 individuals with IPD, we were able to confirm that the risk of IPD is independently increased for patients suffering from COPD and asthma.

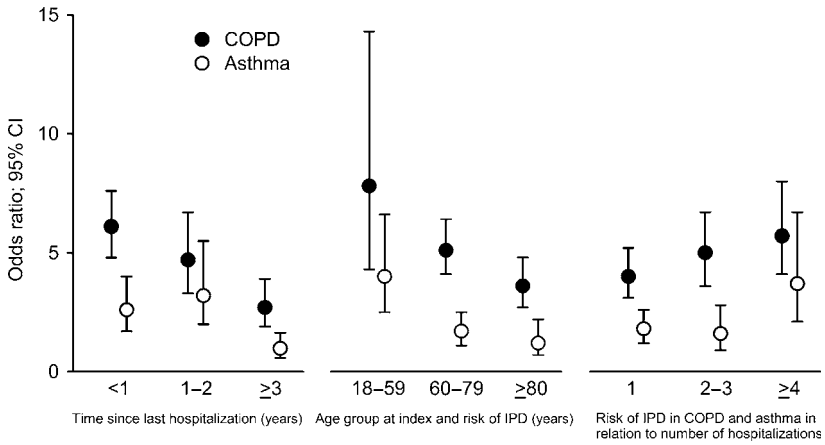

FIG. 1. Odds ratios and 95% confidence intervals for invasive pneumococcal disease (IPD) in patients with chronic obstructive pulmonary disease (COPD) or asthma, according to time since last hospital stay for COPD or asthma (left), age group (centre) and number of hospital visits for COPD or asthma (right), compared with individuals without COPD or asthma, estimated using conditional logistic regression, adjusted for other non-pulmonary co-morbidities conferring increased risk of IPD, total duration of previous hospital stay, level of education and socio-economic status.

Surprisingly, we found an even higher risk in individuals with a diagnosis of pulmonary fibrosis. Despite the increased risk of acquiring IPD, the risk of mortality following IPD was not increased in those with a previous record of COPD, asthma, pulmonary fibrosis or bronchiectasis.

Increasing age-specific IPD incidence rates have previously been reported in patients with chronic lung diseases (a joint effect of age and pulmonary disease) [4]. In our study, the independent effects of COPD and asthma were found to be attenuated with increasing age. This could be attributed to a relatively higher proportion of frail individuals in general in older age groups, diminishing the difference between having a pulmonary disease or not. It could also reflect a higher proportion of patients with less severe pulmonary disease ("survivors") in older age groups.

A combination of host factors and the virulence of the microbe determines the outcome after an encounter with a pathogen. In COPD, innate defence mechanisms in the airways are impaired, mainly by a decrease in mucociliary clearance but several additional mechanisms have been described [9–11]. In addition, the increased risk of IPD in patients with pulmonary disease could partly be mediated by factors such as smoking or immunosuppressive treatment (e.g. corticosteroids).

Smokers have been shown to have an increased risk of IPD in various settings, although it may be difficult to establish the independent effect (not mediated, e.g. through COPD) [12]. The prevalence of smoking in Sweden declined from 25% to 14% between 1990 and 2007 [13]. The current smoking rate in patients diagnosed with COPD in Sweden has been estimated to be around 31%, whereas a survey of COPD patients in specialist care showed that 23% were still smokers [14,15]. Pulmonary fibrosis and pneumoconiosis are associated with increased smoking rates, whereas sarcoidosis and allergic alveolitis are more common in non-smokers [16,17].

Oral treatment with corticosteroids increases the risk of severe infections, although the underlying disease severity is an important modifier [18]. In a pooled analysis of 14 controlled clinical trials concerning individuals with pulmonary diseases, no increase in infectious complications was seen [18]. However, an increased risk of pneumonia has been reported from meta-analyses of inhaled corticosteroids [19,20], although, no increased risk was reported in pooled analyses of asthma or COPD trials using budesonide [21].

Some patients with pulmonary fibrosis have episodes of rapid deterioration. The majority of these are the result of exacerbations (without any signs of infection) but infectious episodes have been estimated to be the second most important cause [22]. Increased bacterial colonization of the lower airways has been demonstrated [23], and 3 to 14% of deaths in patients with pulmonary fibrosis have been attributed to pulmonary infections [24,25].

Registry-based designs have limitations. The Swedish, publicly financed healthcare system ensures that all patients receiving hospital-based care were captured. But patients only treated in primary care were not included. The sensitivity of detecting chronic pulmonary diseases in the Inpatient Registry was assumed to be non-differential for cases and controls, hence the relative effect measures for IPD will be unaffected.

Previous studies using the Swedish Inpatient Registry, as well as our own patient record reviews in this cohort, indicate that around 80–95% of the diagnoses are correct [7]. Any misclassification of co-morbidity before admission for invasive

pneumococcal disease would presumably be non-differential and, if anything, bias estimates downwards.

Models were adjusted for year of birth, gender and county of residence through the matching procedure, as well as for level of education, socio-economic status, and medical conditions conferring susceptibility to IPD. Residual confounding from factors such as co-morbid conditions only requiring primary care or alcohol intake cannot be ruled out. The clinical presentation was derived from discharge codes from the Inpatient Registry, being less precise than chart reviews. The proportion of IPD patients with no recorded focus is comparable to that reported from some previous studies [6] but greater than others [5,26].

Vaccination with 23-valent pneumococcal polysaccharide vaccine (PPV23) was introduced in Sweden in 1985, and has been recommended by the Board of Health and Welfare since 1994 for individuals aged 65 and over, and those with certain chronic medical conditions, such as chronic pulmonary disease. Vaccination coverage is generally regarded to be low, although it has not been estimated on a national level. According to regional sales statistics, about 600–800 doses of PPV/100 000 inhabitants (all ages) were distributed annually in the county of Skåne in the period 1997–2001 [27]. Conjugated pneumococcal vaccine has been included in the routine childhood immunization programme since 2009. Vaccine coverage in patients with chronic pulmonary disease is presumably higher than in healthy subjects, especially in younger age groups where general vaccination is not recommended. This could have biased estimates of the risk of IPD downwards.

In line with several previous studies, we did not find an increased 28-day or 90-day mortality risk following IPD among those with previous records of COPD, asthma, pulmonary fibrosis or bronchiectasis [3,28,29]. Our exposure definition was based on discharge codes, which does not allow any detailed analyses of the mediators of death from IPD. On the other hand, if an underlying pulmonary disease were associated with increased case-fatality rate, this would be an upstream determinant of pneumococcal disease severity and adjusting for other (downstream) severity markers, e.g. leucocyte count, hypothermia, would obscure the overall effect because these would be on the same biological pathway.

In conclusion, we have conducted a population-based study of IPD cases spanning almost 18 years, covering the residents of southern Sweden, an area with around 1.6 million inhabitants. We believe that the results are generalizable to many settings, although differences in population composition and thresholds for hospitalization are likely to influence the results. Several, but not all, chronic pulmonary diseases increase the risk of acquiring IPD, although the risk of death following IPD seems not to be affected.

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Transparency Declaration

Professor Gunnar Engström was formerly employed as a senior epidemiologist by AstraZeneca R&D. Claes-Göran Löfdahl has been paid for lectures by AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Meda, Novartis, Pfizer and Takeds; taken part in and been paid for ad hoc advisory boards for the same companies; and has had institutional support as unrestricted grants from AstraZeneca, Boehringer-Ingelheim and GlaxoSmithKline.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. The specific codes according to the international classification of Diseases.

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