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The burden of invasive pneumococcal disease in children with underlying risk factors in North America and Europe

M. A. Rose,[1] D. Christopoulou,[2] T. T. H. Myint,[3] I. de Schutter[4]

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[1]Children's Hospital, Goethe University, Frankfurt, Germany
[2]Pfizer Ltd, Tadworth, Surrey
[3]Pfizer Pharmaceuticals, Paris, France
[4]Department of Pediatric Pulmonology, CF-Clinic and Pediatric Infectious Diseases, Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

Correspondence to:
Markus A. Rose,
Pneumologie / Allergologie / Infektiologie
Zentrum der Kinder- und Jugendmedizin, J.W. Goethe Universität,
Theodor Stern Kai 7, 60590 Frankfurt
Tel.: + 069 6301 5754
Fax: + 069 6301 6061
Email: Markus.Rose@kgu.de

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Markus A. Rose has received research funding and speaker's fees from Wyeth/Pfizer, Germany. Dina Christopoulou is an employee of Pfizer Ltd, UK. Tin Tin Htar Myint is an employee of Pfizer Pharmaceuticals, France. Iris de Schutter has been an invited speaker for Pfizer and has participated in advisory boards for GlaxoSmithKline Biologicals and Pfizer in the past 3 years.

SUMMARY

Background: Characterisation of risk groups who may benefit from pneumococcal vaccination is essential for the generation of recommendations and policy. **Methods:** We reviewed the literature to provide information on the incidence and risk of invasive pneumococcal disease (IPD) in at-risk children in Europe and North America. The PubMed database was searched using predefined search terms and inclusion/exclusion criteria for papers reporting European or North American data on the incidence or risk of IPD in children with underlying medical conditions. **Results:** Eighteen references were identified, 11 from North America and 7 from Europe, with heterogeneous study methods, periods and populations. The highest incidence was seen in US children positive for human immunodeficiency virus infection, peaking at 4167 per 100,000 patient-years in 2000. Studies investigating changes in incidence over time reported decreases in the incidence of IPD between the late 1990s and early 2000s. The highest risk of IPD was observed in children with haematological cancers or immunosuppression. Overall, data on IPD in at-risk children were limited, lacking incidence data for a wide range of predisposing conditions. There was, however, a clear decrease in the incidence of IPD in at-risk children after the introduction of 7-valent pneumococcal conjugate vaccine into immunisation programmes, as previously demonstrated in the general population. **Conclusion:** Despite the heterogeneity of the studies identified, the available data show a substantial incidence of IPD in at-risk children, particularly those who are immunocompromised. Further research is needed to determine the true risk of IPD in at-risk children, particularly in the post-PCV period, and to understand the benefits of vaccination and optimal vaccination schedules.

Review criteria
The PubMed database was searched using predefined search terms, with predefined inclusion and exclusion criteria applied to the search results. Information from papers identified relevant to the research questions was tabulated in full, and summarised in the body of the manuscript.

Message for the clinic
Data on the incidence of IPD in children with underlying medical conditions are limited, and more research is needed to determine the true risk of disease. The available data show a substantial incidence of IPD in at-risk children, particularly those who are immunocompromised, with a corresponding increase in risk compared with healthy children.

Introduction

Invasive pneumococcal disease (IPD), which includes potentially fatal conditions such as meningitis, septicaemia and pneumonia, is responsible for an estimated 11% of all deaths worldwide in children aged < 5 years (1). Before 2000, the only pneumococcal vaccine available was a 23-valent purified capsular polysaccharide vaccine (PPV-23), which is associated with poor or absent immunogenicity in children < 2 years of age and immunodeficient patients, and failure at any age to induce immunological memory following revaccination (2).

A seven-valent pneumococcal conjugate vaccine (PCV-7) against key *Streptococcus pneumoniae* serotypes was licenced in the USA in February 2000 and subsequently in the European Union and Canada (3,4). Since then, many countries have introduced universal PCV immunisation programmes (between 2006 and 2008 in Europe, for example). In the USA and Canada, pneumococcal vaccination is recommended for universal childhood vaccination in children under 59 months of age, and in older children (60–71 months and >60 months of age, respectively) in individuals at high risk of IPD (5,6). In some European countries, such as the UK, France and Germany, PCV-7 was first recommended only for children at high risk of pneumococcal infection before being introduced into national immunisation programmes (3). These universal vaccination programmes with PCV-7 have led to major improvements in public health, with significant decreases in the incidence of vaccine-type IPD and, to a lesser extent, a decrease in overall IPD in most countries (4,7–10). As the introduction of PCV-7, however, the epidemiology of *S. pneumoniae* has evolved, with changes in serotype distribution (11). Higher valent PCVs – PCV-10 and PCV-13 – have subsequently

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Table 1 Risk categories for invasive pneumococcal disease included in the review*

Immunocompetent at-risk groups	Immunocompromised at-risk groups
• Chronic/cyanotic heart disease	• Congenital or primary immunodeficiency (e.g. agammaglobulinemia, SCID, CVID, complement deficiency [particularly early component deficiencies: C1, C2, C3, C4])
• Chronic liver disease	• Secondary immunodeficiency (e.g. HIV)
• Chronic renal disease	• Bone marrow, haematopoietic stem cell and solid organ transplant recipients
• Chronic respiratory disease (e.g. cystic fibrosis)	• Neoplastic diseases (HL, NHL, lymphomas, leukaemias, other diseases of the blood-forming organs)
• Chronic lung disease/bronchopulmonary dysplasia	• Asplenia or dysfunction of the spleen, including sickle-cell disease
• Chronic/severe asthma	• Iatrogenic immunosuppression
• Recurrent pulmonary infections	• Chromosomal aberration (e.g. Down's syndrome)
• Preorgan-transplant patients	• Nephrotic disease
• CNS malformations, cerebrospinal leaks, liquor shunts	
• Cochlear implant recipients	
• Metabolic disease (e.g. diabetes)	
• Coeliac disease	
• Care home residents/permanent institutionalisation because of illness	
• Smoking/exposure	
• Prematurity	

*Definition of some individual risk categories (e.g. chronic/severe asthma) may vary between publications and between guidelines.
CNS, central nervous system; CVID, common variable immunodeficiency; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; IPD, invasive pneumococcal disease; NHL, non-Hodgkin lymphoma; SCID, severe combined immunodeficiency.

been introduced to adapt to these changes and have gradually superseded PCV-7 (2).

In children, PCV-10 is licenced for those aged 6 weeks to 5 years, and PCV-13 is licenced for those aged 6 weeks to 17 years (12–14) – these vaccines are currently used in general childhood immunisation programmes – whereas PPV-23 is recommended for children ≥2 years of age in whom there is an increased risk of morbidity and mortality from pneumococcal disease (15). Some health authorities and scientific societies, however, also recommend the use of PCV-13 in a broader range of individuals at increased risk of IPD, particularly, those with underlying medical conditions such as innate or acquired immunodeficiency, deficient splenic function, cochlear implants or cerebrospinal fluid leak (16–19). Characterisation of those risk groups who may benefit from PCV-13 is essential for the generation of recommendations and for helping policy makers to produce policy for vaccination programmes based on the best available evidence (20,21). We conducted, therefore, a literature review to provide up-to-date information on the incidence and risk of invasive IPD in Europe and North America in children with underlying conditions that place them at increased risk of IPD.

Methods

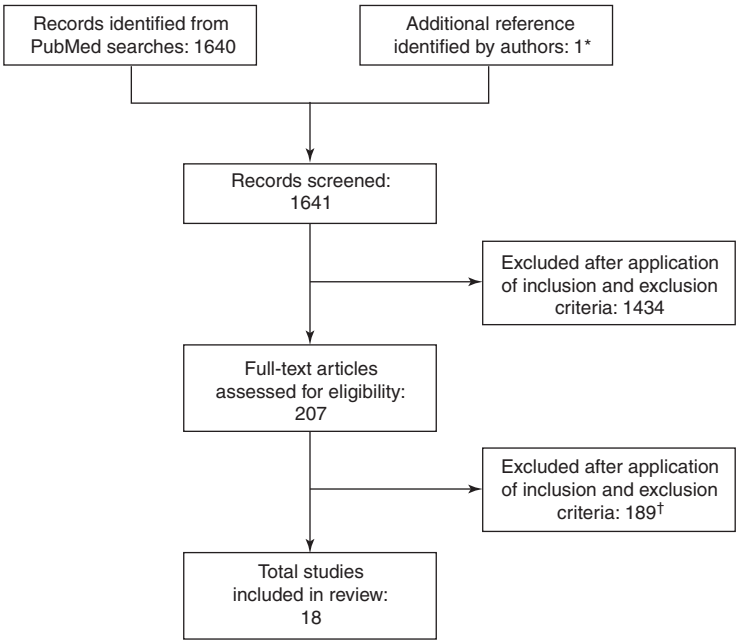
A search of the PubMed database was conducted using the following search string: 'pneumococc* AND (pneumonia OR sinusitis OR meningitis OR bacteremia OR bacteraemia OR sepsis OR osteomyelitis OR septic arthritis OR endocarditis OR peritonitis OR pericarditis OR cellulitis OR soft tissue infection OR brain abscess OR mastoiditis OR empyema OR septicaemia OR "invasive pneumococcal disease" OR "invasive pneumococcal infection")'. A built-in PubMed filter was used to limit the search to studies in children (0–18 years of age), and search results were limited to papers published in English between 1 January 2005 and 31 July 2012.

Papers were included in the review if they reported data from Europe or North America on the incidence or risk of IPD in 'at-risk' children, defined as those with underlying medical conditions placing them at increased risk of IPD (Table 1).

Results

In total, 1640 references were identified by the literature search, of which 1435 were excluded on the basis of the title or abstract; the remaining 18 references met the inclusion and exclusion criteria (Figure 1) (22–39). A further 10 papers were identified that reported incidence of IPD in indigenous populations and specific ethnic populations considered to be at increased risk of IPD (40–49). While these socioeconomic risk groups are outside the scope of this review, the details of these papers are presented in supplementary tables for the reader's interest (Tables S1 and S2).

Of the 18 included studies, six looked at several different time points within a specific period (1989–



*One recent reference was included in PubMed, but had not been tagged at the time of the search. It was therefore incorrectly excluded by the applied filters.
†Includes 10 papers covering socioeconomic risk factors, which were excluded from the review, but are presented in Supplementary Tables 1 and 2 for information.

Figure 1 Results of literature search and evaluation of identified studies according to Preferred Reporting Terms for Systematic Reviews and Meta-Analyses

2006 (24), 1995–2002 (25,31), 1995–2004 (26), 1996–2005 (27) and 2001–2007 (39)). The other studies reported overall data in a single period of time: 1963–2003 (23), 1964–2003 (36), 1977–2005 (32), 1980–2005 (37), 1990–2001 (28), 1995–2000 (29), 1995–2002 (35), 1996–2002 (38), 1997–2003 (34), 1997–2004 (30), 2001–2004 (33) and 2008–2009 (22). Half of the studies were conducted in the USA (24–27,30,33,35,38,39), three studies in the UK (22,23,29), two each in Canada (28,31) and Denmark (32,37), and one each in Germany (34) and Sweden (36). All 18 studies were conducted in children, although only two included children of any age from 0 to 18 years (24,31). The remaining studies limited the age range of the children included (Tables 2 and 3).

Sixteen of the 18 studies reported on IPD as a whole (22–29,32–39), although two of those 16 also looked at specific conditions (meningitis (29) and bacteraemia (24)). The remaining two studies focused specifically on meningitis (30,31). With regard to outcomes, six of the 18 studies included data only on the incidence of IPD (24–26,29–31), eight included data only on risk (32–39), and the remaining four included both incidence and risk data (22,23,27,28).

Incidence of IPD

Data on the incidence of any IPD in at-risk children are shown in Table 2. The overall incidence ranged from 1 to 4167 per 100,000 patient-years**,** with the exception of one study of human immunodeficiency virus [HIV] in US children**.** This study had no reported cases of IPD in children aged < 5 years after the introduction of highly active antiretroviral therapy in 1996, leading to a stated incidence of 0 in 2000 and 1997–1999 (24). The highest incidence was seen in children aged > 5 years with HIV in the USA, peaking at 4167 per 100,000 patient-years in 2000 (24). The incidence in children with sickle-cell disease in the USA was also high, with a peak of 3630 per 100,000 patient-years in 1995–1999 (26), although two other studies reported lower incidences for a similar time period (170–301 per 100,000 patient-years) (25,27).

Across age groups, higher incidences of IPD were generally seen in younger vs. older children. In a study in children with sickle-cell disease, for example, the incidence in those aged < 2 years was 335–3630 per 100,000 patient-years, compared with 134–2044 for those aged < 5 years (26). Similarly, a study in the UK in a predefined high-risk group (diabetes mellitus, chronic renal, hepatic or pulmonary disease, neoplastic disease, chronic immunosuppression) found an incidence of 38.6–75.3 per 100,000 patient-years in children aged < 1 year, compared with 1–11.6 per 100,000 patient-years in children aged 1–14 years (29).

Table 2 Incidence of general invasive pneumococcal disease in children

Citation (country)	Methodology	Age range (years [median])	N*	Time period	Incidence (per 100,000 patient-years)
Asplenia/splenic dysfunction					
van Hoek 2012 (UK) (22)	National GP database study	2–15 [–]	11	08–09	19
Chronic heart disease					
van Hoek 2012 (UK) (22)	National GP database study	2–15 [–]	48	08–09	16
Chronic renal disease					
van Hoek 2012 (UK) (22)	National GP database study	2–15 [–]	33	08–09	46
Chronic liver disease					
van Hoek 2012 (UK) (22)	National GP database study	2–15 [–]	9	08–09	117
Chronic respiratory disease					
van Hoek 2012 (UK) (22)	National GP database study	2–15 [–]	19	08–09	50
Coeliac disease					
Thomas 2008 (UK) (23)	Regional hospitalisation database	< 15 [–]	~2200	63–03	113[†]
Diabetes					
van Hoek 2012 (UK) (22)	National GP database study	2–15 [–]	9	08–09	15
HIV infection					
Steenhoff 2008 (PA, USA) (24)	Retrospective cohort study	0.2–16.8 [6.3]	20	89–06	1200
				89–95	1862
				1996	2128
				97–99	292
				2000	3101
				01–06	860
		0.2–< 5 [–]	–	89–95	2174
				1996	2273
				97–99	0
				2000	0
				01–06	1724
		5–16.8 [–]	–	89–95	1000
				1996	2000
				97–99	444
				2000	4167
				01–06	716
van Hoek 2012 (UK) (22)	National GP database study	2–15 [–]	6	08–09	398
Immunosuppression					
van Hoek 2012 (UK) (22)	National GP database study[‡]	2–15 [–]	174	08–09	162
Sickle-cell disease					
Adamkiewicz 2008 (GA, USA) (25)	Surveillance database study	≤10 [–]	1247	95–99	170
				2000	140
				2001	70
				2002	40
Halasa 2007 (TN, USA) (26)	Database (Medicaid) study	< 5 [–]	21	95–99	2044
				2000	1077
				01–04	134
		< 2 [–]	16	95–99	3630
				2000	3012
				01–04	335
Poehling 2010 (TN, USA) (27)	State-managed healthcare database study (Hb S or C trait)	< 5 [–]	38	96–05	139.8
			21	96–00	260.8
			7	01–05	46.0
	State-managed healthcare database study (Hb S trait)	< 5 [–]	30	96–05	142.6
			19	96–00	300.9
			3	01–05	25.6
	State-managed healthcare database study (Hb C trait)	< 5 [–]	8	96–05	130.1
			2	96–00	115.0
			4	01–05	113.7

Table 2 Continued

Citation (country)	Methodology	Age range (years [median])	N*	Time period	Incidence (per 100,000 patient-years)
Transplant recipients					
Tran 2005 (ON, Canada) (28)	Retrospective single-centre study	< 5 [–]	522	90–01	176
General high-risk patients					
Melegaro 2006 (UK) (29)	National hospital database study§	< 1 month [–]	–	95–00	75.3
		1–11 months [–]			38.6
		1–4 [–]			11.6
		5–9 [–]			2
		10–14 [–]			1
van Hoek 2012 (UK) (22)	National GP database study¶	2–15 [–]	261	08–09	46

*Total number of patients in analysis. †Based on 3.4 cases per 1000 patients over median follow-up of 3 years.
‡Includes those who are immunocompromised by disease, such as HIV or leukaemia, asplenia or splenic dysfunction. §'High risk' defined as diabetes mellitus, chronic renal, hepatic or pulmonary disease, neoplastic disease, chronic immunosuppression. ¶'High risk' defined as asplenia/splenic dysfunction (including sickle-cell disease and coeliac syndrome), chronic renal, hepatic, heart or respiratory disease (including organ transplantation), diabetes mellitus, immunosuppression (including HIV, leukaemia and bone marrow transplantation), cochlear implants and cerebrospinal fluid leaks. GP, general practitioner; Hb, haemoglobin; HIV, human immunodeficiency virus.

Table 3 Incidence of specific forms of invasive pneumococcal disease in children

Citation (country)	Methodology	Risk category	Age range (years [median])	N*	Time period	Incidence (per 100,000 patient-years)
Meningitis						
Biernath 2006 (USA) (30)	Cohort study	Cochlear implants	< 6 [55 months]	4265	97–04	120
Wilson-Clark 2006 (Canada) (31)b	Postal survey	Cochlear implants	<18 [–]	482	95–02	290
			<6 [–]			
			< 18 [–]	–	95–98	220
					99–02	400
			< 6 [–]	–	95–98	150
					99–02	310
Melegaro 2006 (UK) (29)	National hospital database study †	General high-risk patients	< 1 month [–]	–	95–00	15.6
			1–11 months [–]			15.3
			1–4 [–]			1.7
			5–9 [–]			0.2
			10–14 [–]			0.2
Bacteraemia						
Steenhoff 2008 (PA, USA) (24)	Retrospective cohort study	HIV infection	–	–	08–09	398

*Total number of patients in analysis. †Includes some bacterial meningitis cases related to Neisseria meningitidis or of unknown bacterial type.
HIV, human immunodeficiency virus.

Three US database studies investigated the changing incidence of IPD over time in children with sickle-cell disease (25–27). All three studies showed large decreases in the incidence of IPD between the late 1990s and early 2000s, from 115–3630 per 100,000 patient-years in 1995–2000 to 26–335 in 2001–2005. Similar trends were observed in a retrospective US study in children with HIV in which the incidence decreased from 1862 in 1989–1995 to 860 in 2001–2006 (24).

The incidence of IPD in different clinical presentations (meningitis and bacteraemia) in at-risk children is shown in Table 3. Three studies described the incidence of meningitis (overall range: 0.2–400 per 100,000 patient-years) (29–31). One survey described an increased incidence of meningitis in children with cochlear implants between 1995–98 and 1999–2000, after the introduction of cochlear implant positioners (31). The time between implantation and meningitis infection varied from 7 months to 7.7 years (median: 11 months). In at-risk children, the reported incidence of meningitis in the UK between 1995 and 2000 was higher in children < 11 months of age than

in those aged 1–14 years (29). Regarding other clinical manifestations, the incidence of bacteraemia in HIV-infected children (2008–2009) was 398 per 100,000 patient-years (24).

Risk of IPD

Thirteen studies described the risk of IPD (Table 4) in 18 different risk populations. The highest risk was observed in children with haematological cancers (adjusted risk ratio: 52.1 [95% confidence interval (CI): 13.7–198.2] (32); standardised incidence ratio [age 5–9 years]: 50.6 [16.1–122.1] (34)) and immunosuppressed children (odds ratio: 41.0 [95% CI: 35.0–48.0]) (22), specifically those with HIV infection (odds ratio: 100.8 [95% CI: 44.7–227.2]) (22). Lower risk ratios ($\leq$ 1.5) were reported for respiratory conditions (32,33), gastrointestinal disease (32) (including coeliac disease (23)), congenital immune deficiency (32), diabetes (32), cerebral palsy (32) and hydrocephalus (32).

Discussion

This review has revealed the limited data available on the incidence of IPD in children with underlying medical conditions. Very few publications were from European countries, although it should be noted that non-English language publications were excluded from the search. Data on incidence in children were also absent for several conditions known to increase the risk of IPD in children and adults, such as cancer, diabetes mellitus, primary immunodeficiencies and other immune-mediated conditions (50–52).

Despite the heterogeneity of study methods, periods and populations, the review clearly shows the increased risk of IPD in at-risk children, particularly those who are immunocompromised, compared with the incidence in the general paediatric population (estimated in the USA at 23.6 per 100,000 children aged $<$ 5 years and at 2.4 per 100,000 in children aged 5–17 years) (53). The incidence of IPD was highest in children with HIV, although one study in children with sickle-cell disease showed a similarly high incidence of IPD. When children of different age groups were compared, the youngest children (i.e. infants) generally had a higher incidence of IPD than older children, although there was still a substantial risk of disease in older children.

In studies in which different time points were described there was a clear decrease in the incidence of IPD after the introduction of PCV-7 vaccination into national immunisation programmes, as has also been observed in the general paediatric and adult populations (54). Importantly, one of the case–controlled studies of IPD risk in children described a lower vaccination rate in children with IPD compared with non-IPD controls (38). While PCVs have a limited number of serotypes, those included are associated with a marked clinical burden (55–59). Vaccination of high-risk children, regardless of age, does therefore provide an opportunity to protect them against IPD. It is noteworthy that PPV-23 vaccination of children older than 2 years and at risk of IPD is recommended in some countries. Unfortunately, pneumococcal vaccination coverage in high-risk children is relatively low compared with routine childhood vaccination with PCVs (60–62). For example, an Italian study in children with HIV infection, cystic fibrosis, liver transplantation or diabetes mellitus found that pneumococcal vaccination rates were below 25% in each group (60). Thus, there is a need for education of healthcare professionals, patients and families regarding the importance of vaccination in at-risk children. The increased risk of IPD with tobacco exposure also highlights the importance of broader educational programmes covering environmental factors that may affect disease risk, particularly in children with other risk factors.

Studies of risk described an increased risk of IPD in children with underlying conditions compared with controls. The highest risk of IPD was seen in immunocompromised children, particularly in patients with HIV infection or haematological cancer. Other chronic conditions (including, among others, congenital forms of immune deficiency, renal disease and heart disease), however, showed non-significant increases in risk compared with controls. This led the authors of one study to suggest that frailty and susceptibility to disease in general, leading to frequent hospital contacts, may be as strong a predictor of IPD as a stabilised specific underlying condition (32).

The main strength of this review is the use of broad inclusion criteria relating to clinical outcomes. Limitations of the review include the predefined risk conditions, which might lead to exclusion of some risk conditions such as hydrocephalus. The studies included were very different in terms of study periods and study methods (survey, surveillance database and cohort studies), providing a very wide range of results. Precaution should be taken when interpreting and comparing these results. Definitions of conditions implying an increased risk for pneumococcal infections and some of the individual risk categories vary between publications. Thus, physicians should refer to their local guidelines and national immunisation recommendations.

In conclusion, data on the incidence of IPD in children with underlying medical conditions are limited, and much research is needed in this area to determine the risk of disease, particularly in the

Table 4 Risk of IPD in children

Citation (country)	Methodology	Clinical manifestation	Age range (years)	N	Time period	Comparator children	Risk (95% CI)
Chronic organ disease							
Heart disease							
Hjuler 2008 (Denmark) (32)	Surveillance database study (all heart disease)	IPD	0–17	–	1977–2005	Children with no chronic diseases	aRR = 2.4 (1.6–3.4)
	Surveillance database study (chronic heart disease)			14			aRR = 3.6 (1.4–9.6)
	Surveillance database study (congenital heart disease†)			67			aRR = 2.0 (1.4–3.1)
Pilishvili 2010 (USA) (33)	Surveillance study	IPD	3 months–< 5 years	–	2001–2004	Children without IPD	OR = 3.5 (2.1–5.7) ***
van Hoek 2012 (UK) (22)	National GP database study	IPD	2–15	48	2008–2009	No risk factors for IPD	OR = 4.1 (3.1–5.5)
Liver disease							
van Hoek 2012 (UK) (22)	National GP database study	IPD	2–15	9	2008–2009	No risk factors for IPD	OR = 29.6 (15.3–57.2)
Lung disease							
Hjuler 2008 (Denmark) (32)	Surveillance database study (all lung disease)	IPD	0–17	–	1977–2005	Children with no chronic diseases	aRR = 1.4 (1.0–1.9)
	Surveillance database study (chronic airway disease)			25			aRR = 4.1 (2.1–7.9)
	Surveillance database study (asthma)			60			aRR = 1.1 (0.7–1.6)
	Surveillance database study (congenital respiratory malformation)			11			aRR = 0.9 (0.4–1.9)
Pilishvili 2010 (USA) (33)	Surveillance study (chronic lung condition)	IPD	3 months–< 5 years	–	2001–2004	Children without IPD	OR = 3.5 (1.5–8.0) *
	Surveillance study (asthma)						OR = 1.8 (1.5–2.2) ***
Talbot 2005 (USA) (35)	Nested case–control study (asthma)	IPD	2–4	26	1995–2002	Children without IPD	aOR = 2.3 (1.4–4.0)
			5–17	11			aOR = 4.0 (1.5–10.7)
van Hoek 2012 (UK) (22)	National GP database study	IPD	2–15	9	2008–2009	No risk factors for IPD	OR = 12.7 (8.1–20.0)
Renal disease							
Hjuler 2008 (Denmark) (32)	Surveillance database study (all renal disease)	IPD	0–17	–	1977–2005	Children with no chronic diseases	aRR = 4.1 (1.5–11.1)
	Surveillance database study (chronic renal disease)			6			aRR = 18.9 (2.8–127.1)
	Surveillance database study (congenital renal malformation)			7			aRR = 1.6 (0.4–6.3)
Pilishvili 2010 (USA) (33)	Surveillance study (kidney disease [no dialysis])	IPD	3 months–< 5 years	–	2001–2004	Children without IPD	OR = 3.6 (1.1–11.4) *
	Surveillance study (nephrotic syndrome or renal failure)						OR = 14.7 (2.9–76) **
van Hoek 2012 (UK) (22)	National GP database study	IPD	2–15	33	2008–2009	No risk factors for IPD	OR = 11.7 (8.3–16.6)
Gastrointestinal disease							
Hjuler 2008 (Denmark) (32)	Surveillance database study (all gastrointestinal disease)	IPD	0–17	–	1977–2005	Children with no chronic diseases	aRR = 1.5 (0.9–2.4)

Table 4 Continued

Citation (country)	Methodology	Clinical manifestation	Age range (years)	N	Time period	Comparator children	Risk (95% CI)
	Surveillance database study (oesophageal disease)			8			aRR = 1.1 (0.4–3.5)
Genetic disease/congenital malformation							
Hjuler 2008 (Denmark) (32)	Surveillance database study (all genetic disease)	IPD	0–17	–	1977–2005	Children with no chronic diseases	aRR = 2.1 (1.1–4.1)
	Surveillance database study (chromosomal abnormalities)			22			aRR = 2.5 (1.1–5.6)
	Surveillance database study (inborn error of metabolism)			5			aRR = 1.1 (0.3–4.1)
	Surveillance database study (congenital gut malformation‡)			35			aRR = 1.7 (1.0–2.9)
	Surveillance database study (congenital CNS malformation§)			23			aRR = 2.9 (1.4–6.2)
	Surveillance database study (cerebral palsy)			18			aRR = 1.2 (0.5–3.0)
Pilishvili 2010 (USA) (33)	Surveillance study (congenital/developmental disorders)	IPD	3 months–< 5 years	–	2001–2004	Children without IPD	OR = 4.9 (3.0–8.0) ***
Immunosuppression							
Asplenia/splenic dysfunction/splenectomy							
Hjuler 2008 (Denmark) (32)	Surveillance database study	IPD	0–17	6	1977–2005	Children without invasive surgery	aRR = 14.4 (1.3–154.2)
Pilishvili 2010 (USA) (33)	Surveillance study	IPD	3 months–< 5 years	–	2001–2004	Children without IPD	OR = 3.9 (0.6–23.5)
van Hoek 2012 (UK) (22)	National GP database study	IPD	2–15	11	2008–2009	No risk factors for IPD	OR = 4.7 (2.6–8.5)
Coeliac disease							
Ludvigsson 2008 (Sweden) (36)	Cohort study	Sepsis	0–15	–	1964–2003	General population	HR = 3.4 (1.1–10.6)
HIV infection							
van Hoek 2012 (UK) (22)	National GP database study	IPD	2–15	6	2008–2009	No risk factors for IPD	OR = 100.8 (44.7–227.2)
Immunological/metabolic disease							
Hjuler 2008 (Denmark) (32)	Surveillance database study (all immunological/ metabolic disease)	IPD	0–17	–	1977–2005	Children with no chronic diseases	aRR = 2.0 (0.9–4.2)
	Surveillance database study (haemolytic anaemia)			3			aRR = 2.9 (0.6–13.8)
	Surveillance database study (autoimmune disease)			5			aRR = 2.6 (0.6–10.7)
	Surveillance database study (congenital immune deficiency)			12			aRR = 1.4 (0.4–4.8)
	Surveillance database study (diabetes)			1			aRR = 0.4 (0.0–14.8)
Immunosuppression							
Pilishvili 2010 (USA) (33)	Surveillance study (any immunocompromising condition)	IPD	3 months–< 5 years	–	2001–2004	Children without IPD	OR = 4.9 (3.4–6.9) ***

Table 4 Continued

Citation (country)	Methodology	Clinical manifestation	Age range (years)	N	Time period	Comparator children	Risk (95% CI)
	Surveillance study (HIV or immune system disorder)						OR = 14.5 (5.7–36.8) ***
	Surveillance study (systemic steroid use)						OR = 2.2 (1.6–3.0) ***
van Hoek 2012 (UK)(22)	National GP database study	IPD	2–15	174	2008–2009	No risk factors for IPD	OR = 41.0 (35.0–48.0)
Sickle-cell disease							
Pilishvili 2010 (USA)(33)	Surveillance study	IPD	3 months–< 5 years	–	2001–2004	Children without IPD	OR = 5.6 (1.6–19.4) **
Poehling 2010 (TN, USA)(27)	State-managed healthcare database study	IPD (Hb S or C trait)	< 5 [–]	66	1996–2005	White, with normal Hb	RR = 1.77 (1.22–2.55)
		IPD (Hb S trait)		52			RR = 1.80 (1.20–2.69)
		IPD (Hb C trait)		14			RR = 1.66 (0.81–3.39)
Transplant recipients							
Hjuler 2008 (Denmark)(32)	Surveillance database study	IPD	0–17	18	1977–2005	Children without invasive surgery	aRR = 14.3 (3.0–68.2)
Tran 2005 (ON, Canada)(28)	Retrospective single-centre study	IPD	< 5 [–]	522	1990–2001	All < 2 years	p = 0.13 (no RR or OR specified)
						All < 5 years	p < 0.001 (no RR or OR specified)
Neoplastic diseases							
Hjuler 2008 (Denmark)(32)	Surveillance database study (all cancers)	IPD	0–17	–	1977–2005	Children with no chronic diseases	aRR = 19.0 (8.7–41.5)
	Surveillance database study (haematological cancers)			44			aRR = 52.1 (13.7–198.2)
	Surveillance database study (non-haematological cancers)			19			aRR = 8.9 (3.1–26.1)
Meisel 2007 (Germany)(34)	Surveillance database study (acute lymphoblastic leukaemia)	IPD	0–4	5	1997–2003	General population	SIR = 7.6 (2.8–17.0) ***
			5–9	4			SIR = 50.6 (16.1–122.1) ***
			0–14	9			SIR = 11.4 (5.6–20.9) ***
Pilishvili 2010 (USA)(33)	Surveillance study (any cancer)	IPD	3 months–< 5 years	–	2001–2004	Children without IPD	OR = 78.0 (10.2–593) ***
Thomas 2008 (UK)(23)	Regional hospitalisation database	IPD	0–15	–	1963–2003	General population	Rate ratio = 1.39 (0.51–3.03)
Neurological disease							
Hjuler 2008 (Denmark)(32)	Surveillance database study (all neurological disease)	IPD	0–17	–	1977–2005	Children with no chronic diseases	aRR = 2.5 (1.7–3.6)
	Surveillance database study (epilepsy[¶])			37			aRR = 2.5 (1.5–4.2)
	Surveillance database study (hydrocephalus)			17			aRR = 1.0 (0.4–2.4)
Prematurity[††]							
Hjuler 2007 (Denmark)(37)	Multiple database study[‡‡]	IPD	0–< 0.5	22	1980–2005	Gestational age 37–42 weeks	aRR = 2.59 (1.39–4.82)
			0.5–< 2	81			aRR = 1.54 (1.18–2.02)
			2–5	22			aRR = 1.31 (0.79–2.18)
Tobacco exposure							
Haddad 2008 (USA intermountain west)(38)	Telephone survey	IPD	< 1	4	1996–2002	Children without IPD	OR = 0.6 (0.2–2.0)
			1–< 2	6			OR = 1.8 (0.4–7.7)
			2–< 5	5			OR = 2.6 (0.4–15.3)
			5–16	5			OR = 1.2 (0.3–4.6)

Table 4 Continued

Citation (country)	Methodology	Clinical manifestation	Age range (years)	N	Time period	Comparator children	Risk (95% CI)
Pilishvili 2010 (USA)(33)	Surveillance study (household exposure to smoking)	IPD	3 months–< 5 years	–	2001–2004	No tobacco exposure	OR = 1.4 (1.2–1.7) ***
	Surveillance study (> 20 cigarettes/day)						OR = 1.7 (1.2–2.4) ***
	Surveillance study (11–20 cigarettes/day)						OR = 0.9 (0.6–1.3)
	Surveillance study (1–10 cigarettes/day)						OR = 1.7 (1.3–2.2) ***
General high-risk patients							
Haddad 2008 (USA intermountain west)(38)	Telephone survey§§	IPD	0–16	32	1996–2002	Children without IPD	32 of 120 cases vs. 1 of 156 controls (no RR or OR specified)
Hjuler 2008 (Denmark)(32)	Surveillance database study (all chronic diseases¶¶)	IPD	0–17	744	1977–2005	Children with no chronic diseases	aRR = 2.4 (2.0–2.9)
	Surveillance database study (all chronic diseases excluding high-risk groups†††)			–			aRR = 2.1 (1.7–2.6)
Hsu 2011 (MA, USA)(39)	Surveillance database study‡‡‡	IPD	0–17	14	2001–2002	Children with no known risk conditions	–
			0–17	23	2002–2003		aOR = 1.5 (0.7–3.3)
			0–17	11	2003–2004		aOR = 0.9 (0.4–2.1)
			0–17	20	2004–2005		aOR = 1.6 (0.7–3.5)
			0–17	14	2005–2006		aOR = 0.8 (0.4–1.9)
			0–17	13	2006–2007		aOR = 0.6 (0.3–1.5)
			5–17	39	2001–2007		aOR = 2.8 (1.8–4.5)
Pilishvili 2010 (USA)(33)	Surveillance study§§§	IPD	3 months–< 5 years	–	2001–2004	Children without IPD	OR = 3.3 (2.4–4.5) ***
van Hoek 2012 (UK)(22)	National GP database study¶¶¶	IPD	2–15	261	08–09	No risk factors for IPD	OR = 11.7 (10.2–13.3)

*p < 0.05; **p < 0.01; ***p < 0.001. †Septal heart defects contributed to 40%. ‡Major contributors were biliary atresia (26%) and oesophageal atresia (20%). §Major contributors were cerebral cysts (20%), microcephalus (20%) and congenital hydrocephalus (20%). ¶Concomitant chronic neurological disease in 43%. ††'Prematurity' defined as gestational age 19–36 weeks. ‡‡Databases include national Streptococcus, civil registration, childcare, birth, patient and labour market databases. §§'High risk' defined as any underlying chronic illness (including cancer, asplenia, lupus, renal failure, liver disease, congenital heart disease, immunosuppressive therapy to prevent transplant rejection, and CNS disorders characterised by severe developmental delay, failure to thrive, or craniofacial structural abnormalities). ¶¶The total number is lower than the number of specific chronic diseases because patients may have > 1 of the specific chronic diseases. †††Excluding children with cancer, chronic renal disease, splenectomy or transplantation; not adjusted for specific chronic diseases. ‡‡‡'High-risk' defined as sickle-cell disease, congenital or acquired asplenia or splenic dysfunction, HIV infection, cochlear implants, congenital immune deficiency, diseases associated with immunosuppressive therapy or radiation therapy, chronic cardiac disease, chronic pulmonary disease, chronic renal insufficiency, cerebrospinal leaks from congenital malformation, skull fracture or neurological procedure, diabetes mellitus, premature birth (< 38 weeks) or low birth weight (< 2500 g). §§§'High risk' defined as any chronic disease. ¶¶¶'High risk' defined as asplenia/splenic dysfunction (including sickle-cell disease and coeliac syndrome), chronic renal, hepatic, heart or respiratory disease (including organ transplantation), diabetes mellitus, immunosuppression (including HIV, leukaemia and bone marrow transplantation), cochlear implants and cerebrospinal fluid leaks.
aOR, adjusted odds ratio; aRR, adjusted rate ratio; CI, confidence interval; CNS, central nervous system; GP, general practitioner; Hb, haemoglobin; HIV, human immunodeficiency virus; HR, hazard ratio; IPD, invasive pneumococcal disease; OR, odds ratio; RR, relative risk; SIR, standardised incidence ratio.

post-PCV period. The data available, however, clearly show a substantial incidence of IPD in at-risk children, particularly those who are immunocompromised; there is also a corresponding significant increase in risk compared with healthy children.

Recently, PCV-13 became available for the prevention of IPD, pneumonia and acute otitis media in children 6 weeks to 17 years of age, and for the prevention of IPD in adults > 50 years of age (13). Furthermore, a number of European countries are

recommending the use of PCVs in individuals with underlying diseases or conditions. Current vaccination recommendations aim to protect against the maximum number of serotypes by combining PCV-13 with PPV-23 (5,19). Further research is needed, however, to understand the benefits of PCVs and the optimal vaccination schedule in this population. After implementation of vaccination programmes, surveillance remains of the utmost importance to our understanding of how the risk of disease and the causative serotypes evolve.

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Author contributions

All authors were involved in the concept/design of the review, analysis of the data, and drafting, critical review and approval of the manuscript.

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Supporting Information

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

Table S1. Incidence of IPD in children from a) indigenous populations; and b) non-white ethnic groups

Table S2. Risk of IPD in indigenous populations and non-white ethnic groups

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