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Incidence of pneumococcal disease in children in Germany, 2014–2019: a retrospective cohort study

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Abstract

Background Novel, expanded valency pneumococcal conjugate vaccines (PCVs) are in development to reduce the burden of pneumococcal disease (PD) in children. To understand the potential value of new vaccines in Germany, this study estimated the residual burden of PD in children < 16 years old from 2014 to 2019, using administrative health data from a large German claims database.

Methods Outpatient and inpatient cases of all-cause pneumonia (ACP), pneumococcal pneumonia (PP) and invasive pneumococcal disease (IPD) were identified in the InGef database. Incidence rates (IRs) with 95% confidence intervals (CI) were calculated as number of episodes/person-years (PY) at risk. The Mann-Kendall test assessed time trends in incidence.

Results There were no significant trends in IRs of IPD or PP from 2014 to 2019. For ACP, IRs declined from 2014 to 2019; 2,213 (CI 2,176-2,250) to 1,503 (CI 1,472-1,534) per 100,000 PY ($p = 0.017$). IRs of ACP and PP were highest among children aged 12–23 months; 4,672 (CI 4,584-4,762) and 20.8 (CI 15.3–27.5) per 100,000 PY, respectively. For IPD, children 5–11 months-old had the highest IRs, at 14.7 (CI 9.0-22.7) per 100,000 PY.

Conclusions From 2014 to 2019 there were no discernible trends in the IRs of PP or IPD, but the IRs of ACP declined in children aged < 16 years. The highest IRs of ACP, PP and IPD were observed in children < 2 years of age, highlighting the importance of infant pneumococcal vaccination in the prevention of pediatric PD. The clinical burden of pediatric PD in Germany persists. Continued surveillance of changing pneumococcal burden, serotype distribution, antimicrobial resistance and vaccination status is critical to better understand the factors driving incidence of PD and to inform future vaccination strategies.

Keywords Pneumonia, Pneumococcal disease, Pneumococcal conjugate vaccine, Healthcare claims, Incidence.

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Background

Pneumococcal disease (PD) is an infection caused by the bacterium *Streptococcus pneumoniae* (*S. pneumoniae)* [1]. A large proportion of PD is vaccine preventable. Invasive pneumococcal disease (IPD), a severe form of PD, occurs when *S. pneumoniae* enters a normally sterile site such as the blood or cerebrospinal fluid, including infections such as bacteremia, meningitis, osteomyelitis and sepsis. *S. pneumoniae* is the most common bacterial cause of pneumonia in children [2]. The World Health Organization (WHO) has estimated that annually, PD is responsible for over 300,000 deaths worldwide in children aged < 5 years [3]. Childhood pneumonia remains the leading cause of mortality worldwide in children of this age group [4].

The first pneumococcal conjugate vaccine (PCV), targeting seven pneumococcal serotypes (PCV7), was licensed for children < 2 years-old in 2000. Since 2006, universal vaccination of children aged < 2 years has been recommended in Germany [5, 6]. The 10-valent (PCV10) and 13-valent (PCV13) PCVs were introduced in April and December 2009, respectively, to expand coverage to additional serotypes. PCV13 is currently used for most infants in Germany [7]. The PCV schedule includes four doses for premature infants – single doses at 2, 3, and 4 months of age, with a booster dose at 11 months (3+1 immunization schedule). Whereas for infants born at term, since August 2015, the recommendation has been three doses (2+1 schedule) at 2, 4 and 11 months. It was anticipated that a reduction in doses for full-term infants may result in greater vaccine acceptance and adherence, outweighing the potential risk of additional cases of PD in an epidemiologic risk-benefit assessment, as well as predicted cost savings [8]. The national immunization schedule is developed and updated once a year by the German Standing Committee on Vaccination (STIKO) [9]. Monitoring the burden of childhood IPD and pneumonia is critical to assess the effectiveness of pneumococcal vaccination strategies.

Following the introduction of PCV7 and PCV13, a decrease in the overall incidence of PD has been reported worldwide [10–16], with a large proportion of remaining IPD attributed to non-PCV13 serotypes and persistence of certain serotypes included in PCV13 (predominantly serotype 3, 19 A, 19 F) [17]. In 2017, non-PCV13 serotypes accounted for >70% of IPD in children aged < 5 years in Europe [18]. In Germany, several studies have demonstrated a reduction in PCV7 and PCV13 serotypes and incidence rates (IRs) of IPD in children, following the introduction of PCVs [17, 19–22]. These data are derived from voluntary hospital surveillance systems, and IRs reported have wide confidence intervals (CIs) due to the small absolute case numbers identified.

Until 2020, reporting of IPD via surveillance systems was not mandatory and cases were reported at the hospitals' discretion, therefore all IPD cases were unlikely to be captured. Prior studies have demonstrated the importance of comparing surveillance data to data from other sources, to better interpret observed trends [23]. Therefore, further studies utilizing data from large, national administrative health databases capturing all IPD cases are beneficial. Data on non-invasive disease (i.e., pneumonia) since the introduction of PCV13 in Germany are also lacking. Only one study, in 2013, described a reduction in non-invasive disease for children aged < 10 years in Germany for 2007–2011 versus 2003–2006 [24].

Novel, expanded valency vaccines are in development to further reduce the burden of PD in children. A 15-valent PCV was recently approved across the US and Europe for infants, children and adolescents [25–27]. To understand the potential value of new vaccines in Germany, quantifying the incidence and trends of IPD and pneumonia and the residual burden that remains prior to the introduction of higher valency PCVs is important. This study used claims data from the InGef research database; capturing all inpatient and outpatient pneumonia and IPD to estimate IRs, time trends and fatality rates of pneumococcal pneumonia (PP), all-cause pneumonia (ACP) and IPD in children aged < 16 years old in Germany from 2014 to 2019.

Methods

The methods, as reported in the "data source" and "study design" sections, have been partly described previously elsewhere [28–31].

Data source

The InGef (Institute for Applied Health Research Berlin) research database is comprised of individual-level, de-identified longitudinal claims data for around 8 million individuals across all geographic regions in Germany. A sample dataset of approximately 4 million individuals was used for this study. This dataset covers 5% of the German population and is nationally representative in terms of age and sex [32]. All diagnoses are recorded using the German modification of the 10th revision of the International Classification of Diseases (ICD-10-GM). Claims data for ambulatory services and procedures are reported by the German uniform evaluation standard (EBM;'Einheitlicher Bewertungsmaßstab') and procedures conducted in hospital by the German Procedure Classification (OPS;'Operationen und Prozedurenschlüssel').

Study design

The study population included children aged < 16 years. The study period was between January 1, 2014 and

December 31, 2019. Children born during the study period were included in the study from their estimated date of birth (the 1st of the respective quarter or the first day of insurance) or the date they started contributing data to the InGef database. For children born before 2014, their study entry date was assigned as January 1, 2014 or the date they started contributing data to InGef within the study period.

Six yearly cohorts were established to assess the incidence of pneumonia and IPD within each calendar year of the study period. Individuals started contributing data to each yearly cohort from the latest of the following dates: start of the study year, estimated date of birth, or the date they started contributing data to the InGef database. During each study year, each individual was followed up until the first of the following censoring criteria: end of observation in the InGef database (earliest date of either the end of insurance provider contributing data to InGef, death from any cause, or end of study year) or end of the study period (December 31, 2019).

The study population was described by age (0–4 months, 5–11 months, 12–23 months, 2–4 years, 5–15 years, in alignment with STIKO pneumococcal vaccination recommendations [6]), sex, region (East, West, and Berlin), and underlying medical conditions. Although becoming unified in 1990, East and West Germany were formerly defined as different federal states, with different attitudes towards vaccination; historically, Eastern states having higher vaccination rates [33, 34]. Regional results are therefore displayed by East Germany, West Germany, and Berlin (East Berlin formerly part of East Germany, West Berlin formerly part of West Germany).

Underlying medical conditions linked to higher risk of PD were described according to the 2017/2018 STIKO recommendations for at-risk/high-risk individuals [6] and data availability within the InGef database. Underlying medical conditions were assessed in a 12-month look-back period for each individual, except for individuals < 12 months old, and for the 2014 cohort (no medical history available prior to 2014).

Study population

The source population for this study included children aged 0–15 years in Germany with statutory health insurance, insured with a provider contributing data to the InGef research database.

Inclusion criteria

Children aged < 16 years at the start of each study year (each calendar year of the study period i.e. January 1 of 2014 to 2019).

Exclusion criteria

No exclusion criteria were applied.

Outcomes

Two definitions of pneumonia were used in the present study: PP and ACP, both of which excluded any IPD (Additional file 1, Supplementary Table 1). PP was defined as pneumonia cases where *S. pneumoniae* was known to have a causative role. ACP was defined as pneumonia of any etiology, including of bacterial, viral, and unknown cause (ICD-10-GM J12-J18; and codes for viral pneumonia, J10.0 and J11.0), but excluding any IPD. Although the outcome of ACP includes diagnoses such as viral pneumonia and may therefore overestimate the burden of pneumonia caused by *S. pneumoniae*, inclusion of PP alone would likely underestimate true disease burden as diagnostic tests to identify causative pathogen are often not performed in real-world practice [35]. Furthermore, evidence suggests that PCVs may have an impact on ACP and viral lower respiratory tract diseases, in addition to vaccine-type PD [36–38]. Interactions between *S. pneumoniae* and viruses are implicated in the pathogenesis of both bacterial and viral pneumonia, in addition to other respiratory diseases [37, 39–41]. Evaluation of broader health outcomes such as ACP is therefore important when considering the potential public health benefits of pneumococcal vaccination strategies.

IPD was defined as invasive cases where pneumococcus was known to have a causative role (Additional file 1, Supplementary Table 2); capturing meningitis, bacteremic pneumonia, bacteremia without focus and other IPD (e.g. pneumococcal pericarditis, endocarditis, osteomyelitis, arthritis/polyarthritis).

Pneumonia (PP and ACP) and IPD cases were identified from outpatient and inpatient data. For outpatients, only diagnosis by calendar quarter was available, therefore at least one prescription of an antibiotic or a diagnostic test in the same quarter was required to validate an outpatient diagnosis. The date of the first antibiotic prescription (identified via Anatomical Therapeutic Chemical, ATC, codes) or diagnostic test (identified via EBM and OPS codes - Additional file 1, Supplementary Table 3) within each quarter with a pneumonia or IPD diagnosis was then assigned as the diagnosis date.

For results presented by inpatient/outpatient setting, outpatient episodes were defined as episodes where all care over the duration of the episode was provided in an outpatient setting. Inpatient episodes were defined as episodes where some of the care over the duration of the episode was provided in an inpatient setting but there may also be outpatient care during the episode.

As analyses were conducted by calendar year, episodes were assigned to each study year. Episodes that crossed calendar years were assigned to the year the episode began. Multiple records were considered independent episodes if separated by ≥ 90 days [42]. Each pneumonia/IPD episode thus ended at the last record within the

episode plus 90 days. Time at-risk was defined as the total follow-up time minus the time with pneumonia/IPD.

Statistical methods

IRs of pneumonia and IPD per 100,000 person-years (PY) were calculated as the number of episodes/the sum of PY at risk. Time trends were assessed using the Mann-Kendall test, to identify any significant changes over the study period (2014–2019) [43, 44]. Case fatality rates were calculated per 100 hospitalized cases of pneumonia/IPD. 95% CIs were calculated using the Wilson score method [45], and the data was assumed to follow a Poisson distribution [46]. Analyses were completed for PP, ACP and IPD, overall, by study year, and then stratified by age group. IRs of pneumonia (PP and ACP) were also stratified by treatment in the inpatient/outpatient setting. All analyses were completed using the statistical software program R, version 3.5.0. If the number of patients with disease episodes or deaths were less than 5 the data were not reported, in accordance with InGef's data protection policies.

Table 1 Baseline characteristics of the study population, *N* = 916,805 (2014–2019)

Age (years) at study entry (mean, SD)	6	5.22
Age group at study entry, (*n*, %)		
0–4 months	245,272	26.75
5–11 months	21,110	2.30
12–23 months	40,385	4.40
2–4 years	126,764	13.83
5–15 years	483,274	52.71
Sex		
Male	471,991	51.48
Female	444,814	48.52
Underlying medical conditions for 2015 cohort*, **(n, %)**		
No at-risk medical condition	609,198	89.24
Any at-risk medical condition	67,001	9.82
Chronic diseases		
Diabetes mellitus	2,089	0.31
Chronic pulmonary disease (incl. asthma)	48,728	7.14
Chronic heart disease	11,535	1.69
Neurological disorders	8,195	1.20
Any high-risk medical condition	9,359	1.37
Cancer	931	0.14
Cerebrospinal fluid leak	8	0.00
Chronic renal disease	848	0.12
Cochlear implant	1,078	0.16
Functional or anatomic asplenia, sickle cell disease/ other hemoglobinopathy, congenital or acquired asplenia, splenic dysfunction, splenectomy	737	0.11
HIV infection	27	0.00
Immuno-compromising diseases	5,287	0.77
Organ transplant	431	0.06
Chronic liver disease	408	0.06
Autoimmune disease	368	0.05

*Underlying medical conditions were assessed in a 12-month look-back period for each individual from the date of study entry. Risk groups (at-risk vs. high-risk) are not mutually exclusive. Length of look-back was dependent on available data, as per the age of the individual (i.e. children aged < 12 months). As no medical history was available prior to 2014, results are displayed for the 2015 cohort.

SD = standard deviation, n = number of children.

Results

The final study population included 916,805 children aged < 16 years, contributing 3,608,716 PY at-risk. Individuals were followed up for a median of 4.3 (interquartile range 2.2-6.0) years. The mean age of individuals was 6 years (standard deviation 5.2) at study entry (Table 1). From the five age groups most children were 5–15 years old (52.7%) at study entry, and from the West region of Germany (82.4%). The most common comorbidity was chronic pulmonary disease (range: 5.2% in 2019 to 7.1% in 2015).

PP

Overall, PP IRs remained steady between 2014 and 2019, from 7.1 (CI 5.2–9.5) to 8.2 (CI 6.0-10.8) per 100,000 PY (p=0.272, no statistically significant trend), although there was a drop in 2015 (3.7 (CI 2.3–5.5) per 100,000 PY) (Table 2). Similarly, no time trends were observed for PP IRs when stratified by inpatient (p=0.469) or outpatient setting (p=0.719) (Table 3). For children aged 0–4 months, 5–11 months, and 12–23 months, IRs were too low to report for some years (< 5 children with episodes of PP), therefore assessment of time trends by age was not possible (Additional file 1, Supplementary Table 4).

Overall, the IR of PP during the study period was highest for children aged 12–23 months, at 20.8 (CI 15.3–27.5) per 100,000 PY; over fivefold higher than in children aged 5–15 years (Table 2). Similar results were reported for both outpatient and inpatient settings (Table 3).

The number of deaths was too low to report.

ACP

Overall, ACP IRs declined between 2014 and 2019 from 2,213 (CI 2,176-2,250) to 1,503 (CI 1,472-1,534) per 100,000 PY (p=0.017) (Table 2). Similar declines were reported for IRs of ACP when stratified by inpatient/outpatient setting (Table 3) and for each age group (Table 4). Trends over time were statistically significant for ACP IRs in the outpatient setting (p=0.017), but not for the inpatient setting (p=0.056). Trends over time for each age group were statistically significant, except for the 12–23 month-old and 5–15 year-old age groups (p=0.060 and 0.056, respectively).

Overall, the IR of ACP was over fourfold higher in children aged 12–23 months in comparison to children aged 5–15 years. In the outpatient setting, the IR of ACP was highest in the 12–23 month-old and 2–4 year-old age

Table 2 Incidence rates of PP, ACP and IPD overall, by age group and by study year

	PP			ACP			IPD		
	***N* episodes**	**Rate per 100,000 PY**	**[95% CI]**	***N* episodes**	**Rate per 100,000 PY**	**[95% CI]**	***N* episodes**	**Rate per 100,000 PY**	**[95% CI]**
All individuals	237	6.57	[5.76–7.46]	67,699	1,883.90	[1,869.73-1,898.14]	117	3.24	[2.68–3.89]
By age group									
0–4 months	5	7.42	[2.41–17.31]	1,113	1,654.02	[1,558.26-1,754.12]	NR^	-	
5–11 months	15	11.01	[6.16–18.16]	3,735	2,757.64	[2,669.90-2,847.53]	20	14.68	[8.97–22.68]
12–23 months	48	20.76	[15.30-27.52]	10,694	4,672.18	[4,584.05-4,761.59]	22	9.51	[5.96–14.40]
2–4 years	78	11.52	[9.11–14.38]	26,234	3,910.73	[3,863.55-3,958.35]	25	3.69	[2.39–5.45]
5–15 years	91	3.64	[2.93–4.47]	25,923	1,040.62	[1,027.99-1,053.36]	44	1.76	[1.28–2.37]
By study year#									
2014	45	7.09	[5.17–9.49]	13,969	2,212.67	[2,176.12-2,249.67]	17	2.68	[1.56–4.29]
2015	23	3.65	[2.31–5.47]	12,475	1,987.38	[1,952.66-2,022.57]	15	2.38	[1.33–3.92]
2016	36	5.82	[4.08–8.06]	12,731	2,067.13	[2,031.38-2,103.36]	15	2.42	[1.36-4.00]
2017	49	8.01	[5.93–10.59]	10,906	1,790.73	[1,757.28-1,824.66]	32	5.23	[3.58–7.39]
2018	39	6.43	[4.57–8.79]	9,965	1,648.33	[1,616.13-1,681.02]	15	2.47	[1.38–4.08]
2019	49	8.16	[6.04–10.79]	8,991	1,502.81	[1471.91-1534.20]	25	4.16	[2.70–6.15]
Trend test (*p*-value) *		0.272			0.017			0.47	

PP was defined as pneumonia cases where *S. pneumoniae* was known to have a causative role. Diagnostic tests for causative pathogen are often not performed in real-world practice, and codes for PP thus likely underestimate true disease burden. ACP was therefore additionally reported, as a proxy. ACP was defined as pneumonia cases caused by any pathogen (ICD-10-GM J10.0, J11.0, J12-J18). IPD was defined as invasive cases where pneumococcus was known to have a causative role (meningitis, bacteremic pneumonia, bacteremia without focus and other IPD [pneumococcal pericarditis, endocarditis, osteomyelitis, arthritis/polyarthritis]). * Mann-Kendall test for trend. ^ Number not reported, since number of patients with disease episodes is < 5, in accordance with InGef's data protection policies. #N episodes by study year do not always sum to N episodes overall, due to insurance censoring. *PP = pneumococcal pneumonia, ACP = all-cause pneumonia, IPD = invasive pneumococcal disease, CI = confidence interval, N = number of, PY = person-years.*

Table 3 Incidence rates of PP and ACP by setting (inpatient/outpatient)

		Pneumococcal pneumonia			All-cause pneumonia		
		Number of episodes	Rate per 100,000 PY	95% CI	Number of episodes	Rate per 100,000 PY	95% CI
Outpatients	**All individuals**	128	3.55	2.96–4.22	54,278	1,509.12	1,496.45-1,521.87
	By study year						
	2014	25	3.94	2.55–5.82	11,296	1,787.55	1,754.73-1,820.82
	2015	14	2.22	1.21–3.73	10,120	1,610.78	1,579.55-1,642.47
	2016	23	3.72	2.36–5.58	10,384	1,684.60	1,652.35-1,717.32
	2017	23	3.76	2.38–5.64	8,752	1,435.88	1,405.95-1,466.28
	2018	20	3.30	2.01–5.09	7,818	1,292.11	1,263.62-1,321.07
	2019	26	4.33	2.83–6.35	6,998	1,168.77	1,141.54-1,196.48
	Trend test*	*p*-value = 0.719			*p*-value = 0.017		
	By age group						
	0–4 months	0	0.00	0.00-5.47	183	271.48	233.57-313.79
	5–11 months	7	5.14	2.07–10.59	2,226	1,639.13	1571.73-1708.66
	12–23 months	23	9.95	6.30-14.92	7,987	3,479.81	3403.91-3556.98
	2–4 years	40	5.91	4.22–8.05	21,631	3,219.18	3,176.42-3,262.37
	5–15 years	58	2.32	1.76-3.00	22,251	892.90	881.21-904.71
Inpatients	**All individuals**	109	3.02	2.48–3.64	13,421	372.23	365.96-378.58
	By study year						
	2014	20	3.15	1.93–4.87	2,673	421.76	405.92-438.06
	2015	9	1.43	0.65–2.71	2,355	373.81	358.87-389.22
	2016	13	2.10	1.12–3.59	2,347	379.70	364.49-395.38
	2017	26	4.25	2.78–6.23	2,154	352.55	337.82-367.76
	2018	19	3.13	1.88–4.89	2,147	354.08	339.26-369.38
	2019	23	3.83	2.43–5.75	1,993	332.25	317.83-347.17
	Trend test *	*p*-value = 0.469			*p*-value = 0.056		
	By age group						
	0–4 months	5	7.42	2.41–17.31	1,227	3,124.88	2952.46-3304.75
	5–11 months	8	5.87	2.54–11.57	8,168	2,278.25	2229.11-2328.20
	12–23 months	25	10.81	7.00-15.96	974	2,872.93	2695.31-3059.17
	2–4 years	38	5.61	3.97–7.71	4,603	681.19	661.66-701.16
	5–15 years	33	1.32	0.91–1.86	3,672	147.11	142.39-151.95

* Mann-Kendall test for trend

groups; 3,480 (CI 3404–3557) and 3,219 (CI 3,176-3,262) per 100,000 PY, respectively. In the inpatient setting, the IR of ACP was highest in the 0–4 month-old age group, at 3,125 (CI 2952–3305) per 100,000 PY.

Hospital case fatality rates across the total study period were 0.23 (CI 0.16–0.33) deaths per 100 hospitalized cases (31 deaths).

IPD

A low number of IPD episodes were identified over the study period, ranging from 20 episodes in children aged 5–11 months, to 44 episodes in children aged 5–15 years (Table 2). Number of episodes (and therefore rate) were too low to report for children aged 0–4 months (<5 children with episodes of IPD).

Overall, IRs of IPD increased between 2014 and 2019, from 2.7 (CI 1.6–4.3) to 4.2 (CI 2.7–6.2) per 100,000 PY; however, this increase was not statistically significant ($p=0.47$). By age group, the IRs of IPD during the study period were highest in children aged 5–11 months and 12–23 months, at 14.7 (CI 9.0-22.7) and 9.5 (CI 6.0-14.4) per 100,000 PY, respectively. For each age group, incidence was too low to report for some years, therefore assessment of time trends was not possible (Additional file 1, Supplementary Table 5).

The IRs of meningitis, bacteremic pneumonia, bacteremia without focus and other IPD were 1.3 (CI 1.0-1.8), 0.6 (CI 0.4–0.9), 1.1 (CI 0.8–1.6) and 0.2 (0.1–0.4) per 100,000 PY, respectively (Additional file 1, Supplementary Table 6). Meningitis comprised 41.0% of IPD versus 17.9%, 35.0% and 6.0% for bacteremic pneumonia, bacteremia without focus, and other IPD, respectively. Frequencies in some age groups were too small to report (<5 children with episodes) for meningitis, bacteremic pneumonia, bacteremia without focus and other IPD.

Throughout the entire study period, there were zero deaths among the 105 hospitalized IPD cases.

Table 4 Incidence rates of ACP overall, by age group and study year

	Overall (2014–2019)[#]	2014	2015	2016	2017	2018	2019	Trend test (*p*-value) *
Overall (all age groups)								
N episodes	67,699	13,969	12,475	12,731	10,906	9,965	8,991	0.017
Rate per 100,000 PY [95% CI]	1,883.90 [1,869.73-1,898.14]	2,212.67 [2,176.12-2,249.67]	1,987.38 [1,952.66-2,022.57]	2,067.13 [2,031.38-2,103.36]	1,790.73 [1,757.28-1,824.66]	1,648.33 [1,616.13-1,681.02]	1,502.81 [1471.91-1534.20]	
0–4 months								
N episodes	1,113	197	190	194	188	164	174	0.024
Rate per 100,000 PY [95% CI]	1,654.02 [1,558.26-1,754.12]	1,808.80 [1,565.02-2,079.79]	1,712.54 [1,477.68-1,974.12]	1,699.73 [1,468.96-1,956.48]	1,658.50 [1,429.89-1,913.27]	1,447.15 [1,234.14-1,686.37]	1,560.64 [1,337.36-1,810.53]	
5–11 months								
N episodes	3,735	733	654	663	604	557	500	0.009
Rate per 100,000 PY [95% CI]	2,757.64 [2,669.90-2,847.53]	3,386.11 [3,145.38-3,640.37]	2,942.36 [2,721.15-3,176.77]	2,900.94 [2,684.30-3,130.41]	2,653.53 [2,446.10-2,873.85]	2,424.77 [2,227.56-2,634.77]	2,219.63 [2,029.32-2,422.99]	
12–23 months								
N episodes	10,694	2,144	1,849	1,915	1,618	1,711	1,533	0.060
Rate per 100,000 PY [95% CI]	4,672.18 [4,584.05-4,761.59]	5,875.95 [5,629.84-6,130.06]	4,877.47 [4,657.66-5,104.97]	4,985.33 [4,764.52-5,213.73]	4,094.43 [3,897.34-4,298.92]	4,355.34 [4,151.39-4,566.71]	3,906.24 [3,713.12-4,106.79]	
2–4 years								
N episodes	26,234	5,507	4,816	4,790	4,076	3,904	3,789	0.003
Rate per 100,000 PY [95% CI]	3,910.73 [3,863.55-3,958.35]	4,849.82 [4,722.56-4,979.63]	4,217.37 [4,099.09-4,338.19]	4,194.10 [4,076.15-4,314.58]	3,529.65 [3,422.11-3,639.70]	3,323.97 [3,220.51-3,429.91]	3,221.05 [3119.30-3325.28]	
5–15 years								
N episodes	25,923	5,388	4,966	5,169	4,420	3,629	2,995	0.056
Rate per 100,000 PY [95% CI]	1,040.62 [1,027.99-1,053.36]	1,200.69 [1,168.84-1,233.18]	1,122.81 [1,091.79-1,154.48]	1,204.93 [1,172.30-1,238.23]	1,052.55 [1,021.75-1,084.05]	877.61 [849.28-906.63]	734.56 [708.49-761.35]	

ACP was defined as pneumonia cases caused by any pathogen (ICD-10-GM J10.0, J11.0, J12-J18; including codes for viral pneumonia, J10.0 and J11.0). * Mann-Kendall test for trend. [#]N episodes by study year do not always sum to N episodes overall, due to insurance censoring. *ACP = all-cause pneumonia, CI = confidence interval, N = number of, PY = person-years*

Discussion

In this large retrospective cohort study, no significant trends in IRs were observed overall for PP or IPD, but IRs for ACP declined from 2014 to 2019 in children aged < 16 years. For ACP and PP, children 12-23-months-old had the highest IRs, whereas children aged 5-11-months-old had the highest IRs of IPD, highlighting the importance of infant pneumococcal vaccination in the prevention of pediatric PD. For ACP, the case fatality rate was low (0.2 deaths per 100 hospitalized cases). For PP, number of deaths were too low to report. There were no deaths among the 105 hospitalized IPD cases.

Young infants aged < 2 years are particularly susceptible to infections, in part due to an immature immune response and more frequent exposures to *S. pneumoniae* [47]. However, maternal antibodies against PD provide some protection to full-term infants within the first months of life [48]. This aligns with results of the present study, whereby the highest IRs of pneumonia and IPD were in children aged 12-23-months and 5-11-months, respectively.

IRs of ACP were around fourfold higher in the outpatient setting compared to the inpatient setting. IRs of PP were similar in the outpatient and inpatient setting, although case numbers of PP were low, making it challenging to interpret potential trends. For ACP, children aged 0–4 months, 5–11 months and 12–23 months were more frequently treated in the inpatient setting, whereas children aged 2–4 years and 5–15 years were more frequently treated as outpatients. In children aged < 5 years, almost 50% of inpatient ACP episodes were reported in infants aged 0–4 or 5–11 months. This is consistent with the literature from other high-income countries (Canada and Italy), where infants < 6 months old comprise approximately 50% of hospitalized pneumonia cases in children < 6 years old [49, 50]. This may reflect the clinical management patterns for children aged < 2, whereby there is difficulty monitoring their clinical progress as outpatients. Clinical guidelines in Germany suggest that inpatient admission should be considered in infants aged < 6 months with pneumonia, in alignment with results in the present study where the vast majority of PP and ACP episodes in infants aged 0–4 months were treated in the inpatient setting [51].

Differences in study design, study period, case definitions and age groupings make it difficult to compare incidence between studies. However, our findings are in alignment with other studies of ACP [42] and IPD in Germany [17, 21, 52]. Pelton et al. reported that ACP rates in children aged < 5 years were almost fivefold greater compared to children aged 5–17 years in the healthy group (without any risk conditions) between 2009 and 2012 in Germany: 3,779 per 100,000 PY and 730 per 100,000 PY, respectively [42]. In this study, IRs of ACP and PP were almost fourfold greater in children aged 12–23 months and 2–4 years, versus those aged 5–15 years. Weinberger et al. compared incidence of IPD from 2007 to 2016 in children < 16 years old [21]. As in the present study, they found the highest IRs of IPD in children aged < 2 years. The maximum impact of PCV vaccination on overall IPD incidence was reported in 2012/13 (-48% [95% CI: -55%; -39%]) with a rebound to -26% [95% CI: -36%; -16%] in 2015/16. Perniciaro et al. reported IPD IRs in younger children (< 6 years-old) in Germany from 2007 to 2015 [52], where IPD incidence remained steady from 2014 to 2015, fluctuating between approximately 3.0-3.5 per 100,000. Similar results were observed by van der Linden and colleagues in another study in Germany from 2003 to 2018 [17]. IRs reported in the present study are slightly higher than reported by Perniciaro and van der Linden. This is likely because both authors used voluntary hospital surveillance data (cases reported at the hospitals' discretion) which would not have captured all IPD cases as in this study, utilizing data from a large healthcare claims database.

A recent meta-analysis of data from 27 high-income countries (including Germany) from 2010 to 2016 found persisting burden of IPD for children < 5 or 5–18 years following the introduction of PCV13 [53]. Other studies across the EU [54], Germany [17, 21, 52, 55], the UK [13, 56], France [57], Spain [58], Israel [59, 60] and other countries [18], have reported similar results. Similarly to in Germany (Weinberger et al. [21]), in England and Wales (Ladhani et al. [13]) and in France (Ouldali et al. [57]), national surveillance data has indicated that the maximum benefit of the childhood PCV programme was achieved approximately 4 years after the introduction of PCV13. Childhood vaccination schedules are in general similar across Europe (2 + 1 for full-term infants [61, 62]); with the exception of England, where in January 2020, the 2 + 1 schedule was reduced to a 1 + 1 schedule [63]. In some countries such as Italy, with non-centralized healthcare systems, there are regional variations in vaccination recommendations [64]. In England and Wales, incidence of IPD in children declined until 2013/2014 and then plateaued until 2016/2017 [13]. In 2016/2017, although overall IPD incidence in children aged < 15 years remained at less than a third of pre-PCV7 levels, incidence of non-PCV13 serotypes had doubled for children aged < 5 years since the introduction of PCV7. In France, the incidence of meningitis and non-meningitis IPD rapidly increased in children aged < 15 years from 2015 to 2017; whereas in Germany, the increase reported by Weinberger et al. since 2014/2015 was mainly observed for non-meningitis IPD in children younger than 2 years [21, 57]. Incidence of meningitis versus non-meningitis IPD was too low to report for each year of the present study, therefore it was not possible to explore potential trends in specific

IPD manifestations. While the InGef database does not contain serotype-specific information, persistence of IPD and PP burden is observed from 2014 to 2019. In order to better understand the impact of future PCVs in Germany, it will be critical to identify the serotype distribution of residual IPD and PP in future studies.

Other studies using data from administrative healthcare databases have reported a persistent burden of IPD and pneumonia following the introduction of PCVs. In England, a recent study reported a decline in IRs of IPD, PP and ACP from the pre-PCV7 (2003–2005) to late post-PCV13 period (2015–2019) in children aged ≤ 17 years, using data from primary care and hospital records [65]. However, in 2015–2019, IRs remained substantial; at 1.4, 3.9 and 125 per 100,000 PY, for IPD, PP and ACP, respectively. A study in Liguria, Italy, reported that from 2012 to 2018, IRs of ACP hospitalization in children < 15 years of age remained stable, while PP hospitalizations decreased, and IPD hospitalizations increased; IRs of 4.9, 13, and 4.7 per 100,000 PY, for IPD (2018), PP (2018) and ACP (across the total study period), respectively [66]. One potential reason for the maintained incidence of PD is the increasing burden associated with non-PCV13 serotypes; whereby, the prevalence of pneumococcal serotypes included in PCV13 decreased following PCV13 introduction, to be replaced over time by an increase in non-PCV13 serotypes. This has resulted in a plateau or increase in incidence of IPD in recent years. In Germany, non-PCV7 and non-PCV13 serotypes accounted for 70–84% of IPD cases in the years following PCV introduction [18, 21, 52]. However, current evidence suggests that there is also some persistence of PCV13 serotypes, primarily serotype 3 and 19 A [17, 21], and that PCV13 serotype replacement is highly variable across countries [11]. Country-specific variations of emerging non-PCV13 serotypes could be due to local antibiotic selective pressures [67].

Low vaccine completion rates may also contribute to the persisting burden of PD. Timely adherence to the infant vaccination schedule is low in Germany [52, 68]. Pneumococcal vaccination is often delayed or the booster regimen is not completed on time, potentially due to lack of incentives for pediatricians or parents to adhere to vaccination schedules [68, 69]. In this study, the highest IRs of PP, ACP and IPD were observed in children < 2 years of age; underscoring the importance of improving timely infant vaccine series completion in Germany. Perniciaro and colleagues reported that only 18.4% of children from 2007 to 2017 in Germany with IPD were vaccinated with PCV13 according to the recommended schedule [52]. This could be contributing to the maintained burden of childhood IPD in Germany.

Strengths and limitations

The main strength of this study was the use of the InGef database; a large, healthcare claims database representative of the German population in terms of age, sex, morbidity, mortality, drug prescription and dispensation [32]. This study captured all inpatient and outpatient pneumonia and IPD, as reported in healthcare claims data from the statutory health insurance providers contributing data to InGef.

There were several limitations. Firstly, recent studies have suggested that using administrative databases to assess organism-specific prevalence in pneumonia and other conditions may underestimate true organism-specific burden, due to infrequency of pathogen testing in clinical practice [70–72]. Indeed, prior validation studies suggest that ICD-based claim codes may miss up to one-sixth of IPD diagnoses [73, 74]. This may have led to an underestimation of IPD or PP burden in the present study. In attempt to mitigate this, the burden of ACP was also assessed. As the majority of ACP is thought to be attributed to viral pathogens, estimates for ACP will have overestimated the burden caused by pneumococcus [70].

In the InGef database, for outpatient data, only diagnosis by calendar quarter was available. Therefore, at least one prescription of an antibiotic or a diagnostic test in the same quarter was required to validate an outpatient diagnosis. In Germany, clinical guidelines highlight that not all children with pneumonia may need treatment with antibiotics [51]. Specifically, if there is evidence of viral etiology (or no evidence of bacterial etiology), or there are no signs of fever or signs of bronchial obstruction (thus viral infection is likely), it is recommended that children are not treated with antibiotics. Similarly, German clinical guidelines also highlight that in most cases, a diagnosis of pneumonia can be made based on history and clinical findings without a need for further diagnostic tests. Thus, our study may not have captured cases of outpatient ACP likely of viral etiology, that did not need antibiotic treatment nor diagnostic tests.

The number of IPD and PP cases in this study were small resulting in IRs with wide CIs, so the assessment of trends may not be precise and should be interpreted with caution. Only quarter of birth as opposed to exact date of birth is available in the InGef database and therefore age groupings (particularly for those aged < 2 years) as reported in the present study are also not precise and should be interpreted with caution. This is an inherent limitation to the InGef database.

Information on causal pneumococcal serotype was not available in the InGef database, so this study could not explore if the maintained burden of IPD and PP was due to exposure to non-PCV13 serotypes. In future studies of pneumococcal burden, it will be critical to complement administrative data with pathogen and serotype

laboratory information obtained from other sources. Information on vaccination status and PCV schedule adherence was not captured, therefore this study could not determine whether maintained PD burden was due to low vaccine completion rate. However, three recent studies in the InGef database (the same data source used for the present study) reported that for those born in 2013, 2016 and 2018, the rate of unvaccinated infants remained at a considerable level, and vaccinations were often delayed [8, 75, 76]. Of those born in 2018 (and 2016/2013, respectively), 47% (41/65%) of premature infants and 74% (72/68%) of full-term infants had received the recommended 3+1 and 2+1 PCV doses after 24-months of follow-up; approximately 50% receiving the booster dose according to recommended timelines. Low vaccine completion rates and schedule adherence could thus be contributing to the maintained burden of PD in this study. Increased efforts are required to increase adherence to PCV recommendations in Germany, and protect vulnerable children<2 years of age [8]. Ongoing surveillance studies are needed to better understand what factors are driving PD incidence, including detection of the causative serotype, antimicrobial resistance, and vaccination adherence.

Conclusion

The highest IRs of PP, ACP and IPD were observed in children<2 years of age, highlighting the importance of infant pneumococcal vaccination in the prevention of pediatric PD. Incidence of PP or IPD did not vary significantly between 2014 and 2019 in children aged<16 years in Germany, however the IRs of ACP declined. The clinical burden of PP, ACP and IPD persists in children in Germany. Continued surveillance of changing pneumococcal burden, serotype distribution, antimicrobial resistance and vaccination status is critical to better understand the factors driving incidence of PD and to inform future vaccination strategies.

Abbreviations

ACP	All–cause pneumonia
CI	Confidence interval
EBM	Einheitlicher Bewertungsmaßstab–German uniform evaluation standard
ICD-10–GM	10th revision of the International Classification of Diseases, German Modification
InGef	Institute for Applied Health Research Berlin GmbH
IPD	Invasive pneumococcal disease
IR	Incidence rates
OPS	Operationen und Prozedurenschlüssel–German procedure classification
PCV	Pneumococcal conjugated vaccine
PD	Pneumococcal disease
PP	Pneumococcal pneumonia
PY	Person–years
S. pneumoniae	Streptococcus pneumoniae
STIKO	German standing committee on vaccination
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

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None.

Author contributions

All authors have approved the submitted manuscript. TH, DO, WG, DH contributed to the study conception and design. All programming and analyses were conducted by DO and WG. BP, RB, NQ contributed to the acquisition and interpretation of the study results. BP and RB drafted the manuscript, with revisions made by TH, DO, DH, NQ, WG, JW, TB, TW, MW, and SM.

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Data availability

The data that support the findings of this study are stored within the Institute for Applied Health Research Berlin GmbH (InGef, www.InGef.de). Restrictions apply to the availability of these data, and they are not publicly available, due to German data protection laws (Bundesdatenschutzgesetz). Analysis datasets can be assessed upon request, at InGef in Berlin (info@ingef.de), if required. Access to patient-level data is not possible and all analyses must be conducted by InGef. Requests for bespoke analyses/ aggregate results are reviewed and approved by InGef.

Declarations

Ethics approval and consent to participate

All patient-level data in the InGef research database are de-identified to comply with German data protection regulations. Use of the study database for healthcare services research is therefore fully compliant with German federal law and, accordingly, Institutional Review Board/ethical approval and informed consent of the patient was not required.

Participant consent for publication

Not applicable.

Competing interests

All authors declare financial and non-financial conflicts of interest. TW, JW, MW and SM are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. TB is an employee of MSD Sharp & Dohme GmbH, Germany, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. TH was employed by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA at the time of this study. BP, RB and NQ are employed by OXON Epidemiology. DH is employed by WIG2. DO is employed by InGef and WG was employed by InGef at the time of this study.

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