Invasive pneumococcal disease and long-term outcomes in children: A 20-year population cohort study

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Summary

Background Although vaccination against *Streptococcus pneumoniae* infections (such as invasive pneumococcal disease (IPD)) are available, challenges remain in prevention efforts. Moreover, downstream sequelae in children is relatively unknown. Thus, we aimed to evaluate short and long-term health outcomes among children with IPD.

Methods Analysis of *Streptococcus pneumoniae* positive isolates from sterile body sites in children (0−17 years) in Alberta (Canada) from 1999 to 2019 was performed retrospectively (n=888). Cases were age and sex-matched to hospitalized population controls. Linkage to administrative health datasets was done to determine comorbidities and healthcare related outcomes. Cox proportional hazards were used to assess differences in time to mortality and hospitalisation between cases and controls in short (<30-day), intermediate (30−90 day), long-term (>90-day) follow-up.

Findings Proportionally more deaths occurred in cases (4.8 deaths/1000 person-years (PY)) than controls (2.7 deaths/1000 PY), leading to a significant adjusted hazard ratio (aHR) of 1.80 (95% CI 1.22−2.64). This increased risk of death was influenced primarily by short-term mortality (319 vs 36 deaths/1000 PY in cases vs controls respectively, aHR 8.78 [95% CI 3.33−23.18]), as no differences were seen in intermediate (14 vs 7 deaths/1000 PY; aHR 2.03, 95% CI 0.41−10.04) or long-term time intervals (2.4 vs 2.3 deaths/1000 PY, aHR 1.03, 95% CI 0.63 −1.69).

Interpretation IPD continues to negatively impact survival in children despite vaccination. Although long-term impact on mortality and hospitalisations may not be substantial, the immediate effects of IPD are significant.

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Keywords: Invasive pneumococcal disease; Cohort study; Epidemiology; Public Health; Children; Streptococcus pneumoniae

Introduction

Streptococcus pneumoniae is an opportunistic pathogen of the upper respiratory tract that can cause severe illness when it is able to invade sterile body sites − termed invasive pneumococcal disease (IPD). Less than 10% of adults are carriers of the bacteria, while a higher proportion of children (27−64%) carry it in their nasopharynx.[1] Young children (<5 years old) are particularly susceptible to both colonization and infection as they have frequent exposures to other children with *S. pneumoniae*, particularly in settings such as daycares, and do not have fully developed immune systems.[2,3]

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Research in context

Evidence before this study

Existing literature on invasive pneumococcal disease (IPD) in children currently available strongly focuses on demonstrating vaccine effectiveness following pneumococcal conjugate vaccine (PCV) implementation, and particularly in young children (<5 years) that are at highest risk. It has been demonstrated that vaccination not only prevents IPD, but also leads to lower rates of hospitalization, especially in otherwise healthy children. However, there have been few studies investigating childhood hospitalizations and mortality following IPD infections, as there are few deaths and resultant statistical power is low.

Added value of this study

Our study covers a 20-year time span and a large population due to a provincially unified healthcare system. We evaluate the short, intermediate, and longer-term impacts of IPD on hospitalization and mortality rates among children relative to matched controls from the general population.

Implications of all the available evidence

Our study suggests that short-term mortality in children who experience IPD is significant compared to matched controls, however overall long-term survival after the acute infection has been managed is similar to the general population of children. This data may encourage clinicians to have closer short-term follow-up for children that experience IPD.

Prior to the implementation of childhood pneumococcal vaccination, the number of global deaths attributed to pneumococcal disease in children between 1 month and 5 years was estimated to be around 1.8 to 2.0 million - representing 11% of all deaths in this age group.[4,5] To combat pneumococcal deaths in children in the USA and Canada, the Food and Drug Agency and Health Canada approved a 7-valent pneumococcal conjugate vaccine (PCV-7) in 2000 and 2001 respectively, targeting the most virulent and common serotypes at that time.[6,7] PCV-7 was added to routine childhood immunization schedules in many countries around the world and was later replaced by more comprehensive 10 and 13-valent vaccines (PCV-10 was approved in 2009 in Canada,[8] PCV-13 was approved in Canada and the United States in 2010[6,9]). In a Danish study, PCV-7 was introduced into the childhood immunization schedule in 2007, and PCV-13 in 2010.[10] This led to an 80% decrease in IPD caused by PCV-7 covered serotypes by 2008, and a further 94% decrease in PCV-13 covered serotypes by 2011 in children <2 years of age.[10] Along with preventing infections, PCV vaccination has led to reduced rates of hospitalisation related to IPD infections,[11] particularly in otherwise healthy children.[12]

In addition to decreased hospitalisation rates, widespread vaccination has resulted in decreased mortality by vaccine-covered serotypes, as evidenced in studies performed in South Africa, England and Wales that compared mortality in children <5 years before and after routine immunisation.[13,14] However, despite the observed benefits of vaccination on childhood mortality, prevention remains difficult due to serotype replacement, vaccine hesitancy, and inequitable vaccine distribution particularly in lower income countries.[15] Furthermore, understanding the changing trends of IPD and its impacts in children is difficult. For example, research investigating short and long-term mortality in children with IPD has been limited to date, due to low events and statistical power in this population.[10,16] This has influenced IPD studies in children to focus on prevention and vaccine effectiveness, with limited publications investigating long-term adverse health events such as mortality following IPD infection, especially in children over 5 years of age. To fill this knowledge gap and better understand how IPD impacts children of all ages, we assembled a representative population-based cohort of children with IPD, and age- and sex-matched population control subjects without IPD to outline the natural history of an episode of IPD and its relative impact on short, intermediate, and long-term hospitalisation and mortality.

Methods

IPD Cases

From 1999 to 2019, all cases of IPD occurring in children <18 years of age were identified and collected in Alberta, Canada (population of children <18 years in Alberta ~ 1 million in 2016[17]). As a nationally notifiable disease since 2000,[1] all positive isolates of *Streptococcus pneumoniae* collected from a sterile body site have complete capture and documentation. These represent all cases of bacteraemia (septicaemia), bacteraemic pneumonia, and meningitis in children <18 years of age, and less common sterile site infections (i.e., synovial, pericardial, and peritoneal fluids). Standardized patient reporting forms were used by trained nurses, hired to collect supplementary data on IPD cases as part of an ongoing surveillance program of cases identified between 1999 and 2014, including vitals, laboratory results, antimicrobials, comorbidities, serotype, specimen source, and demographic information. Data collected on cases from 2015 to 2019 were more limited in scope (only included IPD date, sex and age). Only the primary IPD case was used for analysis in individuals who experienced >1 episode; n=21, representing 2.4% of children with IPD. PCV-7 was introduced in Alberta in 2002, with immunisation rates for children having

been ~90% depending on the study setting during the initial time of the study from 2002 to 2004.[18,19] Canadian estimates of pneumococcal vaccine uptake in children in 2017 was ~81.4%.[20] No consent was required as this is secondary use of deidentified data.

Matched controls

Each case was matched to two controls, when available, who did not have a history of IPD; however, it is possible that they could have had another type of invasive bacterial disease. As cases were often hospitalized, where possible, hospital controls were preferred as both groups likely have poorer underlying health compared to non-hospitalized controls. Controls were matched on sex, age (+/− 1 year), hospitalisation +/− 3 months from the case, and with no history of IPD (n=1348, 76.8%). If more than 2 controls were identified, 2 controls were randomly selected from the pool of eligible controls for that case. If no matched hospitalized control was available in this time frame, matched controls were obtained from the provincial general population registry (n=408, 23.2%) using the same matching criteria.

Linkage to administrative data

All individuals living in Alberta are assigned a unique lifetime healthcare identification number (PHN) allowing complete linkage to administrative health datasets. Mortality outcomes were identified through linkage to Alberta Vital Statistics, which compiles all deaths and migration data. Additionally, all healthcare services are collected within the province as part of Alberta's integrated healthcare system which allowed for all hospitalisation outcomes to be identified by linkage to the Discharge Abstract Database (DAD). This also allowed for comorbidities to be identified through linkage to physician visits, hospital (DAD), and ambulatory care visits that occurred before each respective index date, using International Classification of Diseases Ninth and Tenth Edition (ICD-9 and 10) standardized diagnostic coding.

Outcome measures

The primary outcome of this study was time to mortality following IPD index date or pseudo matched index date for controls. As mortality is uncommon in children, the secondary outcome of interest was time to hospitalisation. This was defined as the time to first hospitalisation for children who were not initially hospitalized at the time of their IPD diagnosis or time to re-hospitalisation in those patients initially hospitalized at the time of IPD diagnosis and subsequently discharged. Both primary and secondary outcomes were segmented into three-time intervals: short-term (<30 days following index date), intermediate-term (30−90 days following index date), and long-term (>90 days following index date). Mortality within 30 days is expected to be directly associated with acute IPD infection as others have noted[21,22] while intermediate and long-term mortality may not explicitly be from acute infection but rather a result of downstream, yet currently unknown, IPD sequelae.

Statistical analysis

Survival analyses were performed to establish time to mortality and time to hospitalisation following index date in the <30-day, 30−90 day, and >90 daytime intervals. IPD index date (or pseudo index date for controls) was defined as time zero, after which patients were followed until they had an event (died or hospitalized), left the province, or reached the end of follow-up on March 31, 2019. Subjects that left the province or died were excluded from subsequent time interval analyses. Cox proportional hazard models were used to assess differences between cases and controls after adjusting for any residual confounding effects of age due to the 1-year age bands.

Cox models were further stratified by the patient characteristics of sex, age, and Paediatric Comorbidity Index (PCI) score,[23] to investigate relationships potentially concealed when using the full model. Age was stratified into clinically relevant categories of 0−1, 1−2, 2−5, 5−10 and 10−18 years.[3] PCI scores were generated from ICD diagnostic coding of all events prior to the index date and categorized by a score of 0−1 (no multimorbidity) or ≥2 (multimorbidity). In addition, as race is known to be a strong predictor of outcomes in IPD, we further compared indigenous to non-indigenous cases to determine if event rates were different. To examine possible effects related to advances in medical care over time, a segmented analysis was performed separating cases and their matched controls identified in 1999−2004, 2004−2009, 2009−2014 and 2014 −2019. Finally, to observe differences in illness severity in IPD cases not hospitalized at IPD diagnosis, analyses were done comparing hospitalized IPD cases to non-hospitalized IPD cases.

Cox proportional hazard assumptions for mortality and hospitalisation models were tested using Log-Minus-Log (LML) Plots and no violations were found. A p-value of <0.05 was used for statistical significance. All analyses were performed using STATA Statistical Software Version 15 (StataCorp, College Station TX).

Patient and Public Involvement: Patients with IPD were recruited for this study and were not involved with the design, conduct, reporting, or dissemination plans of our research.

Ethics approval: Ethics approval was granted by the University of Alberta Health Research Ethics Board (Pro00071271).

Role of the funding source: This work was supported by a grant-in-aid from Pfizer Canada, and Wyeth Canada Inc. The funders had no role in the design of the

study or data analysis, and they have not seen the manuscript prior to publication.

Results

Patient demographics

From 1999 to 2019, there were 888 unique primary IPD events in children < 18 years in the province of Alberta (Figure 1) that were age and sex-matched to 1756 controls (868 [97.7%] cases had two matched controls). 56.6% of cases were males, with a mean age of 3.8 years (standard deviation (SD) 4.1), median age of 2.0 years (interquartile range [IQR] 1.1–4.8), and 62 (12.5%) out of 496 cases with known status were indigenous. Most cases (76.6%) occurred in those less than 5 years of age. Of the patients who had data available on the site of pneumococcal infection (82%), bacteraemia was the most common (59.2%), followed by baecteremic pneumonia (25.9%), meningitis (8.8%), and unspecified or other source (29.4%). These sites were not mutually exclusive as cases could have multiple infected sites. Overall, 409 (46.0%) of cases had at least one underlying condition. Relative comorbidities between cases and controls were generally comparable – the most prevalent comorbidities in cases were gastrointestinal conditions (21.1%), congenital malformations (16.4%), and asthma (13.7%). Most cases had serotyping available (98.4%) - the three most common serotypes identified were 14, 19F, and 6B (Table 1). Overall, 408 cases were hospitalized (45.9%), and 49 died (5.5%). Of the 49 deaths, 8 (16.3%) had meningitis, 27 (55.1%) had bacteraemia/septicaemia, 17 (34.7%) had pneumonia, and 15 (30.6%) had another/unknown positive source (not mutually exclusive).

Time to mortality (primary outcome)

Overall, 49 deaths (5.5%) in cases and 55 (3.1%) in controls occurred over the entire follow-up period. Of 385 female cases, 25 (6.5%) died and of the 503 male cases, 24 died (4.8%). By age, there were 11 deaths in children cases aged 0–1 year (*N*=192, 5.7%), 7 deaths between 1-2 years (*N*=241, 2.9%), 17 deaths between 2–5 years (*N*=247, 6.9%), 5 deaths between 5–10 years (*N*=113, 4.4%), and 9 deaths between 10 and 18 years (*N*=95, 9.5%). Comparatively, controls had 9 (*N*=381, 2.4%), 14 (*N*=479, 2.9%), 11 (*N*=484, 2.3%), 13 (*N*=226, 5.8%), and 8 (*N*=186, 4.3%) deaths in the same respective age groups (Figure 2).

Events by time interval for cases and controls are presented in Table 2. Adjusted hazard ratios (aHRs) comparing cases to controls for <30-day, 30-90 day, and >90 daytime periods were 8.78 (95% CI 3.33–23.18),

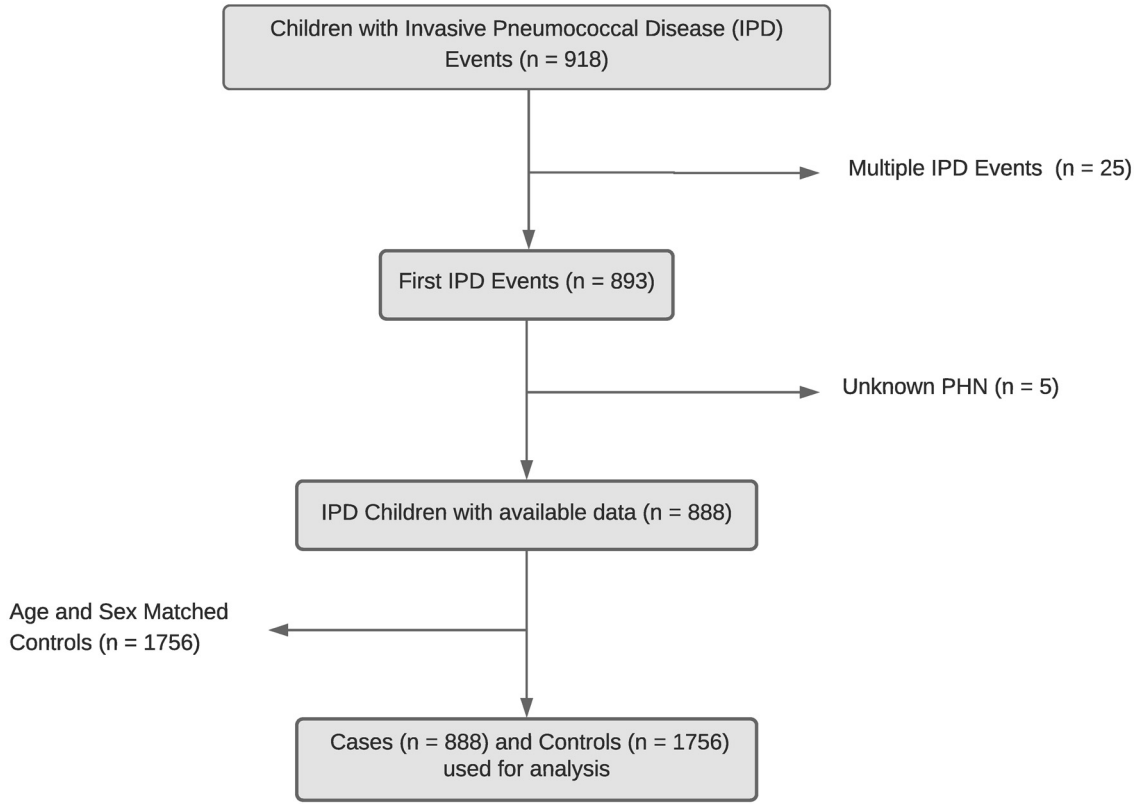

Figure 1. Flow Diagram of case and control inclusion.

	Cases, *n* (%)	Controls, *n* (%)
Overall	888 (100%)	1756 (100%)
Male	503 (56.6%)	911 (56.4%)
Female	385 (43.4%)	765 (43.6%)
Mean Age (SD)	3.8 (4.1) years	3.8 (4.1) years
0–1 year	192 (21.6%)	381 (21.7%)
1–2 years	241 (27.2%)	479 (27.3%)
2–5 years	247 (27.8%)	484 (27.6%)
5–10 years	113 (12.7%)	226 (12.8%)
10–18 years	95 (10.7%)	186 (10.6%)
Indigenous	62 (12.5%)	
Type of IPD		
Pneumonia	230 (25.9%)	
Positive Blood Culture	191 (83.0%)	
Positive Pleural Fluid	6 (2.6%)	
Positive Peritoneal Fluid	1 (0.5%)	
Unknown	32 (13.9%)	
Meningitis	78 (8.8%)	
Bacteremia/Septicemia	526 (59.2%)	
Unspecified/Other	261 (29.4%)	
Hospitalized at Index Date	458 (51.6%)	1348 (76.8%)
Serotype	**Cases, *n***	
1	18	
3	38	
4	36	
5	23	
6A	28	
6B	76	
7F	19	
8	12	
9V	33	
12F	11	
14	116	
15A	17	
15B	14	
15C	13	
18C	53	
19A	61	
19F	74	
22F	42	
23B	14	
23F	24	
33F	30	
35B	11	
35F	12	
38	13	
Other Serotype	86	
Unknown	14	

Table 1 *(Continued)*

	Cases, *n* (%)	Controls, *n* (%)
Pediatric Comorbidities		
Alcohol Abuse	3 (0.3%)	2 (0.1%)
Anemia	34 (3.8%)	70 (4.0%)
Anxiety	3 (0.3%)	17 (1.0%)
Any Malignancy	43 (4.8%)	77 (4.4%)
Asthma	122 (13.7%)	318 (18.1%)
Cardiovascular Conditions	101 (11.4%)	194 (11.0%)
Chromosomal Anomalies	15 (1.7%)	43 (2.4%)
Conduct Disorder	0 (0%)	13 (0.7%)
Congenital Malformations	146 (16.4%)	347 (19.8%)
Depression	7 (0.8%)	38 (2.2%)
Developmental Delays	74 (8.3%)	208 (11.8%)
Diabetes	6 (0.7%)	23 (1.3%)
Drug Abuse	6 (0.7%)	18 (1.0%)
Eating Disorders	0 (0%)	1 (0.1%)
Epilepsy	56 (6.3%)	118 (6.7%)
Gastrointestinal Conditions	187 (21.1%)	388 (22.1%)
Rheumatologic Disorders	9 (1.0%)	41 (2.3%)
Menstrual Disorders	6 (0.7%)	12 (0.7%)
Nausea and Vomiting	4 (4.8%)	127 (7.2%)
Pain Conditions	71 (8.0%)	163 (9.3%)
Psychotic Disorders	1 (0.1%)	11 (0.6%)
Sleep Disorders	21 (2.4%)	49 (2.8%)
Smoking	0 (0%)	1 (0.1%)
Weight Loss	12 (1.4%)	24 (1.4%)

***Table 1*: Demographic Information for Cases and Controls.**

2·03 (95% CI 0.41–10.04), and 1.03 (95% CI 0.63 –1.69), respectively (Table 2). Due to the low number of deaths, the resulting confidence intervals are wide - nevertheless the first 30 days demonstrate statistical significance (p<0.001) (Figure 3). Stratified models by age, sex, and PCI score for mortality are shown in Table 3 with few statistical differences noted among the strata, although low or no events were noted in many strata.

Within the cases, compared to non-indigenous children, indigenous children had a similar risk of death over all time periods examined (aHR <30 days 2.20 [95% CI 0.68–7.12]; aHR 30-90 days uninterpretable due to low events; and aHR >90 days 0.80 [95% CI 0.18–3.62]). No significance was found in any strata in the intermediate or long-term follow-up periods. According to underlying IPD diagnosis, children with meningitis within the first 30 days was associated with the highest aHR relative to controls (aHR 39.30) followed by pneumonia (aHR 8.32), bacteraemia (aHR 7.56), and other/unknown (aHR 6.56) (supplementary Table 1). Few differences by IPD diagnosis were observed over the other time periods, although events rates were relatively low by IPD diagnosis for some time periods. Overall, irrespective of age, meningitis consistently was associated with the highest relative mortality

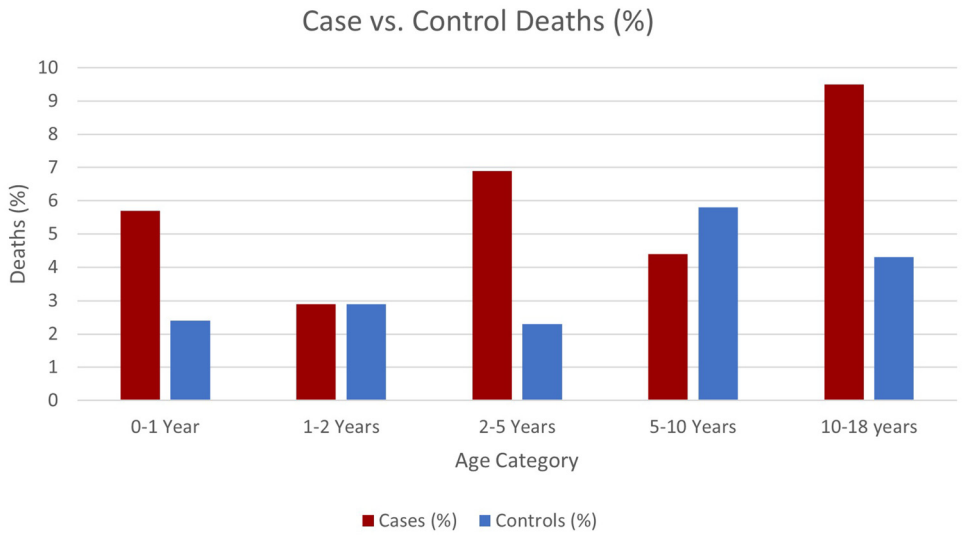

Figure 2. Percentage of deaths in IPD cases versus controls, by age category.

compared to controls (supplementary Table 2). The most common serotypes (6B, 14, 18C, 19A, 19F, and 22F) had the highest number of deaths (2, 3, 2, 2, 4, respectively). All other serotypes had either one or no deaths.

In cases between 1999 and 2004 there were 21 (4.9%) deaths, 10 deaths (5.7%) between 2004 and 2009, 11 deaths (9.7%) between 2009 and 2014, and 7 deaths (4.0%) between 2014 and 2019. Mortality rates in cases were generally higher in all years evaluated, although only the 2004-2009 period showed statistically higher rates compared to controls (aHR 2.91, 95% CI 1.11–7.64). There were no statistical differences in the 1999–2004, 2009–2014, or 2014–2019 time periods (aHR 1.68 [95% CI 0.94–3.01], aHR 1.67 [95% CI 0.76–3.68], and aHR 1.54 [0.57–4.12], respectively), *p*-value for linear trend = 0.57.

Sub-analysis of mortality data among hospitalized and non-hospitalized IPD cases

Investigation of deaths in cases hospitalised (*n*=34) vs. not hospitalised (*n*=15) at IPD diagnosis showed no difference in mortality in the first 30 days: 400 deaths/1000 PY in hospitalised cases vs. 236 deaths/1000 PY in non-hospitalised cases (aHR 1.69 [95% CI 0.71–4.02]). Comparison of deaths in the 30–90-day period is not interpretable, as there were no deaths in the non-hospitalised cases (3 deaths in hospitalised cases). After 90 days following IPD, cases hospitalised at index date experienced higher mortality compared to cases that were not hospitalised (aHR 2.96 [95% CI 1.21–7.26]). Analysis stratified by sex, comorbidity score, and age categories revealed that the only significant difference in strata was in female mortality >90 days after IPD.

Moreover, as not all cases and controls could be perfectly matched according to hospitalisation status as time of IPD, we conducted a post-hoc analysis by including hospitalisation status a time of IPD as a covariate in our models. No material change in aHR was observed for any of the estimates was observed (<30 days aHR 10.09 [95% CI 3.77–27.05]; 30–90 days: aHR 3.07 [95% CI 0.62–15.21]; >90 days: aHR 1.36 [95% CI 0.82 –2.25]).

	Cases		Controls		Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*p*-value
	n/N (%)	Events/1000 PY (95% CI)	n/N (%)	Events/1000 PY (95% CI)			
<30 Days	22/888 (2.5%)	318.8 (210.0–484.2)	5/1756 (0.3%)	36.0 (15.0–86.5)	8.78 (3.33–23.19)	8.78 (3.33–23.18)	<0.001
30–90 Days	3/864 (0.3%)	14.1 (4.6–43.7)	3/1745 (0.2%)	7.0 (2.3–21.6)	2.02 (0.41–10.01)	2.03 (0.41–10.04)	0.39
>90 Days	24/860 (2.8%)	2.4 (1.6–3.5)	47/1739 (2.7%)	2.3 (1.7–3.1)	1.03 (0.63–1.69)	1.03 (0.63–1.69)	0.90

***Table 2*: Mortality outcomes of patients with IPD relative to matched controls.**

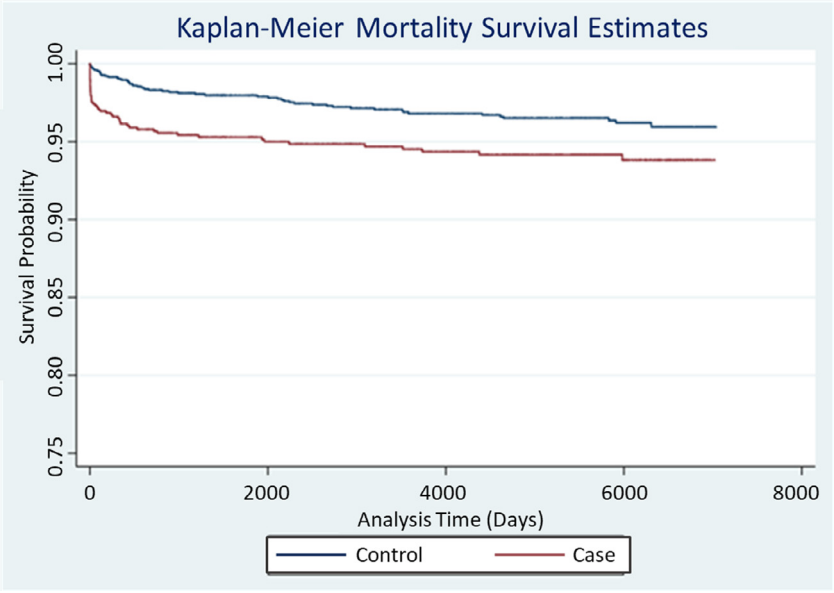

Figure 3. Overall mortality Kaplan-Meier survival estimates curve comparing cases to controls.

	Short Term (<30 days)		Intermediate (30–90 days)		Long Term (>90 days)	
	aHR (95% CI)	***p*-value**	**aHR (95% CI)**	***p*-value**	**aHR (95% CI)**	***p*-value**
Overall Model	8.78 (3.33–23.18)	<0.001	2.03 (0.41–10.04)	0.39	1.03 (0.63–1.69)	0.90
Pediatric Comorbidity Index Scores						
Score < 2	24.05 (3.14–184.0)	0.002	1.92 (0.12–30.78)	0.65	1.66 (0.64–4.29)	0.30
Score ≥ 2	5.31 (1.63–17.25)	0.005	2.26 (0.32–16.06)	0.42	0.96 (0.54–1.73)	0.54
Age Groups						
< 1 y/o	N/A	N/A	2.06 (0.13–32.88)	0.61	1.01 (0.30–3.36)	0.98
1–2 y/o	N/A	N/A	2.01 (0.13–32.08)	0.62	0.47 (0.13–1.66)	0.24
2–5 y/o	7.93 (1.68–37.33)	0.01	2.01 (0.13–32.14)	0.62	2.03 (0.76–5.41)	0.16
5–10y/o	2.00 (0.13–31.98)	0.62	N/A	N/A	0.66 (0.21–2.04)	0.47
10–18 y/o	4.04 (0.74–22.04)	0.11	N/A	N/A	1.74 (0.53–5.70)	0.36
Sex						
Female	22.12 (2.86–171.32)	0.003	0.68 (0.07–6.50)	0.73	1.18 (0.59–2.34)	0.64
Male	5.47 (1.74–17.18)	0.004	N/A	N/A	0.89 (0.44–1.81)	0.75

***Table 3*: Case vs. control adjusted hazard ratios for age categories by time interval - time to mortality.**
*N/A = not enough deaths to interpret.
[a] - *P*<0.001 for interaction by age groups.
[b] - *P*<0.03 for interaction by comorbidity groups.

	Cases		Controls		Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*p*-value
	n/N (%)	Events /1000 PY	n/N (%)	Events /1000 PY			
<30 Days	205/888 (23.1%)	3728	135/1756 (7.7%)	1020	3.38 (2.72−4.20)	3.38 (2.72−4.20)	<0.001
30-90 Days	30/662 (4.5%)	186	92/1611 (5.7%)	236	0.79 (0.52−1.19)	0.78 (0.52−1.17)	0.23
>90 Days	173/629 (27.5%)	27	475/1514 (31.4%)	33	0.82 (0.69−0.98)	0.82 (0.69−0.98)	0.03

***Table 4*: Time to first hospitalization in children with IPD relative to matched controls.**

Time to hospitalisation (secondary outcome)

Events by time interval for cases and controls are presented in Table 4. Comparing hospitalisations in cases vs. controls, aHRs for <30 days, 30−90 days, and >90-day follow-up periods were 3.38 (95% CI 2.72−4.20), 0.78 (95% CI 0.52−1.17) and 0.82 (95% CI 0.69−0.98) respectively (Table 4). Statistically significant differences were found in all time intervals except for 30−90 daytime. IPD cases had higher rates of hospitalisation within the <30-day model, while controls had slightly higher rate of hospitalisations >90 days following index date.

Short-term stratified models for time to hospitalisation revealed statistical significance for every stratum ($p \leq 0.001$), with IPD cases being hospitalised more frequently than controls within the first 30 days (Table 5). Few differences by age, sex, or comorbidity groups were observed; however, interaction effects were observed by age in all stratified time periods and by comorbidity group in the 30−90-day time period ($p<0.05$) (Table 5).

	Short Term (<30 days)[a]		Intermediate (30−90 days)[a]		Long Term (>90 days)[a, b]	
	aHR (95% CI)	*p*-value	aHR (95% CI)	*p*-value	aHR (95% CI)	*p*-value
Overall Model	3.38 (2.72−4.20)	<0.001	0.78 (0.52−1.17)	0.23	0.82 (0.69−0.98)	0.03
Pediatric Comorbidity Index Scores						
Score < 2	4.66 (3.25−6.66)	<0.001	0.81 (0.39−1.68)	0.57	1.05 (0.84−1.32)	0.66
Score ≥ 2	3.09 (2.33−4.09)	<0.001	0.94 (0.57−1.56)	0.82	0.67 (0.50−0.89)	0.006
Age Groups						
< 1 y/o	6.28 (3.66−10.77)	<0.001	1.23 (0.47−3.24)	0.68	1.13 (0.76−1.67)	0.55
1−2 y/o	3.32 (2.17−5.09)	<0.001	0.20 (0.06−0.66)	0.008	0.73 (0.52−1.03)	0.07
2−5 y/o	2.94 (1.93−4.47)	<0.001	1.01 (0.53−1.94)	0.97	0.63 (0.45−0.89)	0.009
5−10 y/o	2.54 (1.49−4.31)	0.001	1.20 (0.30−4.79)	0.80	1.09 (0.68−1.75)	0.72
10−18 y/o	2.75 (1.47−5.14)	0.001	1.34 (0.45−4.01)	0.60	0.85 (0.54−1.35)	0.50
Sex						
Female	3.30 (2.38−4.57)	<0.001	0.73 (0.39−1.37)	0.33	0.97 (0.75−1.25)	0.81
Male	3.45 (2.57−4.62)	<0.001	0.81 (0.47−1.40)	0.45	0.72 (0.56−0.91)	0.006

***Table 5*: Case vs. control adjusted hazard ratios for age categories by time interval - time to first hospitalization.**

[a] $P<0.05$ for interaction by age groups.

[b] $P<0.01$ for interaction by comorbidity groups.

By underlying IPD diagnosis, within the first 30 days children with meningitis had the highest aHR compared to controls (aHR 7.34), followed by pneumonia (aHR 3.93), bacteraemia (aHR 3.90), and other/unknown (aHR 2.08). Again, few statistically significant differences were observed by IPD diagnosis over the other time periods, except for the 30–90-day time-period where meningitis cases were associated with a higher hospitalisation rate (supplementary Table 5).

In IPD cases between 1999 and 2004 there were 169 (39.5%) hospitalisations, 92 hospitalisations (52.9%) between 2004 and 2009, 52 hospitalisations (46.0%) between 2009 and 2014, and 95 hospitalisations (54.9%) between 2014 and 2019. Over time, hospitalisation rates in cases increased slightly compared to controls; 1999–2004 aHR: 1.11 (95% CI 0.92–1.34), 2004–2009 aHR: 1.45 (95% CI 1.12–1.88), 2009–2014 aHR: 1.22 (95% CI 0.87–1.70), and 2014-2019 aHR: 2.15 (95% CI 1.64–2.81), *p*-value for linear trend = 0.28.

Discussion

This 20-year study shows that IPD continues to negatively impact children, with most cases in those <5 years of age, and of male sex. This is consistent with findings in other parts of the world.[3,16] Considering our primary outcome of mortality, although the absolute number of deaths observed was small, the relative number of deaths in IPD cases was nearly double that of controls. In particular, the highest relative risk of death compared to controls were in children with meningitis, although all IPD diagnosis were associated with increased risk. As there are no observable differences between cases and controls in the intermediate and long-term follow-up periods, this effect is influenced primarily by the short-term deaths occurring because of acute infection. Interestingly, despite advances in medical care such as increased use of extracorporeal life support (ECLS),[24,25] the relative rates of death compared to controls remained stable over time with no discernible decrease in trend observed over the time-period of study.

By age strata, the overall hazards for death in children were higher relative to controls in all age categories for both short (<30 days) and intermediate (30–90 days) time periods with few differences observed in the long term (>90 days). Although males are commonly described as being at higher risk of acquiring IPD, both male and female cases had poorer short-term survival compared to controls. Likewise few differences were noted according to the number of comorbidities suggesting that the number of underlying comorbidities may not be a significant factor with respect to IPD related mortality in children in our study. It is important to note that strata specific rates should be interpreted with caution and additional studies are required to further explore potential differences in children by age groups, sex, and paediatric comorbidities.

The secondary outcome of time to hospitalisation was used as a supplementary marker of poor health outcomes. In every time interval and stratum, the risk of children being admitted to hospital within 30-days was significantly higher in cases compared to controls, suggesting that despite the majority being initially managed in the hospital, short-term downstream sequelae are common. Some of these sequelae includes pneumonia complications and neurological damage, with immunocompromised children at highest risk.[26] Some intermediate and long-term strata show that risk of hospitalisation in these time periods were lower in cases compared to matched controls. Further investigation is needed to explore this trend, but it may reflect increased monitoring of children by clinicians over time, an increased risk of death in the most vulnerable cases and therefore surviving children are simply at lower risk, or underlying comorbidities and health conditions that could not be readily captured in our data. We also observed increasing rates of hospitalisation over time between 1999 and 2019. The reasoning for this is unknown, but possible explanations may relate to serotype replacement, a proportional increase in the number of more severe meningitis cases, shift in clinical practice where children with IPD are more aggressively monitored/managed within the hospital system, or other unknown factors which could not be accounted for in our analyses.

Others have described reduced rates of hospitalisation of children with IPD after implementation of the PCV-13 vaccine,[11,12] however our study spanned the implementation periods of both the PCV-7 and PCV-13 vaccines, and we did not find significant reductions in hospitalisation or mortality rates when comparing cases and controls. Indeed, the proportion of hospitalisations in children with IPD increased from 2009 to 2014 (although this may reflect a decreased incidence rate of IPD at the population level after vaccine implementation).

To our knowledge, a long-term IPD study of this duration, spanning the introduction of two PCV vaccines, over this wide a geographical area, and in children of all ages has not been previously performed. This allowed us to determine trends in childhood IPD mortality and hospitalisation outcomes over time. However, there were limitations to consider and address in future studies. Identification of hospitalisation status at IPD diagnosis was difficult to determine, therefore deaths that occurred in the Emergency Department prior to being officially admitted were not included in hospitalised cases. Despite this, most case deaths still occurred in those hospitalised at diagnosis, indicating that there were differences in case severity requiring further evaluation. For instance, otherwise healthy children

presenting with occult bacteraemia and not requiring hospitalisation may not be appropriate to group with cases with severe illness needing intensive medical interventions. In addition, our results only describe sequelae of IPD leading to death or hospitalisation and do not represent the full spectrum of sequelae that although not as severe, may still greatly affect quality of life.

Another important limitation of our study is that vaccination status of the cases was unknown. As the most frequent serotypes were those covered by vaccines, it would be useful to know if these were breakthrough infections or infections occurring in unvaccinated children. Another limitation is that data capture was performed using a passive surveillance system, so complete case capture is difficult to achieve. However, as Alberta's healthcare system is integrated provincially, linkage to administrative datasets is robust and the quality and validity of these databases are routinely checked both provincially and federally.[27,28] Moreover IPD is a notifiable disease in the province and therefore few, if any diagnosed cases, would have been missed. As mentioned previously, in much of the mortality data, statistical power was limited; however, it is unlikely to change as our study encompassed a large geographical population and captured all IPD cases in children over a 20-year time span. We also had limited information on either race or socio-economic status in our data which are important factors in infectious disease disparities such as IPD. Lastly, mortality according to underlying source infection should be interpreted cautiously as event rates were small and some of this data between 2015 and 2019 was determined according to ICD-10 coding. Moreover, it is also highly possible that the most seriously ill children died before microbiology cultures from more invasive sites (i.e., spinal tap for CSF) could be completed.

In conclusion, when compared to matched controls, short-term mortality in children with IPD continues to be significant. However, over the intermediate and long-term time periods, children with IPD had similar survival rates compared to matched controls. Therefore, our data indicate that if a child survives the acute effects of IPD, their long-term mortality does not differ substantially from matched population controls however additional sequelae which were not collected following infection may affect overall quality of life. These findings are relevant for clinicians, because promoting prevention of infection through vaccination will reduce mortality. However, if a child becomes infected with invasive pneumococcal disease, they require close follow-up and treatment to reduce the risks of acute sequelae that may persist.

Contributors

GJT and TJM designed the original study of which this is a continuation. DTE conceived the study idea and design. KAV conducted all analyses. DTE and KAV authored the first draft of the manuscript. All authors contributed to editing and approval of the final version of the manuscript.

Data sharing statement

A Data Disclosure Agreement with Alberta Health Services was obtained (RA88876). Being administrative health data, the data cannot be shared publicly. However, requests for the data can be sent to Alberta Health and Alberta Health Services. No special access privileges were granted to the authors.

Declaration of interests

All authors have completed the Unified Competing Interest form and declare: no support from any organization for the submitted work; GJT received grand-in-aid funding from Pfizer for pneumococcal research from 2012 to 2015 and funding from Wyeth Canada Inc. for pneumococcal research from 2005 to 2011; GJT participated on the Pfizer Advisors and Vaccine Experts (PAVE) committee on PCV20 and new vaccines pipeline and Prevnar Infant Consults Meeting in Toronto, Ontario February 22 & 23 2019. Sarah Forgie is the President of the Association for Medical Microbiology and Infectious Diseases Canada (AMMI Canada) from April 2019-2022, unpaid. No other conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100341.

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