Invasive Pneumococcal Disease and Long-Term Outcomes in Adults and Children in Alberta

by

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Abstract

Despite the introduction of vaccination and surveillance efforts, invasive pneumococcal disease (IPD) remains a disease of great public health concern, in terms of morbidity, mortality, and healthcare burden. The association between increased short-term (30-day) mortality following IPD has been frequently studied, however the relationship between IPD and long-term mortality is largely unknown in both adults and children.

All IPD patients in Alberta, Canada, between 1999-2019 had clinical data collected through chart reviews and were linked to provincial administrative health and vital statistic databases. Cases were age and sex matched to non-IPD general population controls. Using Cox Proportional Hazards modeling, the primary outcome was overall time to all-cause mortality. Additional outcomes were <30-day, 30-90 day, and >90-day mortality compared to matched controls from the general population. In children we also assessed time to all-cause hospitalization as a surrogate marker for overall poor outcomes, and differences in severity of disease based on hospitalization status at IPD diagnosis.

Our first objective was to assess mortality in adults. Incident IPD events were identified in 4,522 patients, with an average follow-up time of 6·0 years (SD 0.05), ranging 1 day to 19 years. The mean age was 55·8 years, with 56·7% being males. There were 1937 deaths in cases compared to 2654 deaths in controls (81 deaths 1000/PY's vs 47 deaths 1000/PY's respectively). Overall all-cause mortality was consistently higher among cases compared to controls, adjusted hazard ratio (aHR) 1.77 (95% CI 1.67 - 1.88), but also higher within 30-day (aHR 3.75 [95% CI 3.29 - 4.28]), 30–90-day (aHR 1.56 [95% CI 1.27 - 1.93]) and greater than 90-day (aHR 1.44 [95%CI 1.34-1.55]) time intervals independently.

Our second objective was to assess mortality and hospitalizations in children. Incident IPD cases were found in 888 children, with a mean age of 3.8 years (SD 4.1) and 56.6% males. There were 49 total deaths in cases and 55 deaths in controls (4.8 deaths/1000 PY's vs 2.7 deaths/1000 PY's respectively).

Risk of mortality was higher only in the short-term interval (aHR 8.78 [95% CI 3.33-23.18]) which ultimately influenced overall mortality to be higher (aHR 1.80 [1.22-2.64]) during the entire follow-up.

An IPD event increases risk of short, intermediate, and long-term mortality regardless of age, sex or comorbidity in adults, while it only primarily increases the risk of short-term mortality in children. Importantly, these studies help recognize the high risk IPD has on mortality, regardless of age. These findings can help clinicians focus efforts on specialized patient plans, to limit short and long-term downstream effects following acute infection.

Preface

This thesis is an original work done by Kristen Versluys. The research project received research ethics approval from the University of Alberta Health Research Ethics Board, Project Name “Long-term health outcomes and health care utilization among patient diagnosed with invasive pneumococcal disease in Alberta”, No. Pro0071271, first approved August 15, 2018. Alberta Health Services granted access to all administrative datasets used for this project. A version of Chapter 2 has been submitted for publication at the time of thesis submission.

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List of Abbreviations

aHR = Adjusted hazard ratio

CI = Confidence interval

CSF = Cerebral spinal fluid

DAD = Discharge abstract database

ICD = International classification of diseases

IPD = Invasive pneumococcal disease

LML = Log-minus log

PCV = Pneumococcal conjugate vaccine

PHN = Personal healthcare number

PY = Person-years

SD = Standard Deviation

uHR = Unadjusted hazard ratio

Chapter 1: Introduction

1.1 Statement of the Problem

As described by the World Health Organization, *Streptococcus pneumoniae* is the leading cause of severe pneumonia worldwide, causing significant morbidity and mortality[1]. This effect is most significant in young children and in the elderly[1]. Worldwide, each year it is estimated that there are 1.6 million deaths from pneumococcal disease, with death estimates upwards of 700,000 occurring in children alone[2]. Not only is the morbidity and mortality burden high, but the resultant burden on healthcare systems are equally significant. Healthcare costs in the US were estimated between $21.7 to $58.5 million per 100,000 person-years at risk - hospital costs that are 8 to 23 times higher than that of a healthy individual without pneumococcal disease[3]. Similarly, in Canada the financial and clinical burden was significant - with a yearly cost of $193 million Canadian dollars and 54,330 life-years lost before the introduction of routine vaccinations[4].

There are a variety of illnesses that can be caused by *Streptococcus pneumoniae* that range in severity from non-invasive otitis media, upper respiratory illnesses, and sinusitis to invasive disease such as meningitis, septicemia, and bacteremic pneumonia[5]. Invasive pneumococcal disease (IPD) occurs when the bacteria is able to invade a sterile body site and due to the severity of illness, is accompanied by high fatality rates - up to 20% for septicemia and 50% for meningitis[1]. Understanding the natural timeline of IPD as it relates to mortality and morbidity, and potential downstream sequelae is important in disease prevention, but also can aid clinicians in patient management. To date, there have been very few studies following IPD patients for long-term mortality outcomes following infection.

1.2 Epidemiology of Invasive Pneumococcal Disease

Streptococcus pneumoniae is an opportunistic pathogen as it can asymptomatically colonize the nasopharynx of individuals, yet cause disease when its virulence factors are able to overpower the host's

defence - particularly in young children (with underdeveloped immune systems) and the elderly (immunocompromised)[6]. Some virulence factors *S. pneumoniae* possess are pneumolysins for host invasion and inducing a proinflammatory response, pili and adhesins to help bind to host cells, but most notably the antiphagocytic polysaccharide capsule[7]. There are 100 different capsular serotypes that have been identified to date, however not all are equally virulent as some are more likely to cause invasive disease[8].

Aside from age, other risk factors that have been shown to influence both IPD incidence and mortality include sex, comorbidities, and living in densely populated areas[9]. Frequently, the male sex has been shown to have higher incidence and mortality following IPD infection[10,11], particularly in adults, however the reasoning is largely unknown[9]. As would be expected, those with chronic conditions involving the lungs, heart, liver, and kidney are at higher risk of acquiring IPD, as are those with immunodeficiency due to HIV/AIDS or asplenia[12]. Lifestyle factors such as smoking, alcohol and drug use have demonstrated an association with increased risk of IPD, in part due to immunosuppressive effects[9]. Lastly, crowded environments provide the perfect opportunity for infectious spread through droplets that remain on surfaces. Case fatality rates in developing countries have been shown to be much higher compared to developed countries, likely a result of densely populated environments and households, along with healthcare inequities and a host of socioeconomic factors[2,13].

Although the impact of IPD affects all countries greatly, there are differences in incidence between high and low-income countries. In Ontario (Canada) the incidence of IPD for all ages was 8.7 per 100,000 individuals[14], similarly in the USA, incidence of IPD in adults was estimated to be 8.0 per 100,000 individuals[15]. In a literature review performed by Maimaiti et al. to assess IPD incidence in lower income countries, they found that IPD incidence was significantly higher in South Asia and Sub-Saharan Africa (rates of 52 and 86/100,000 in Nepal and Bangladesh, rates of 388 and 416/100,000 in Gambia

and Mozambique, respectively)[2]. Regardless of the country, IPD has a significant population burden worldwide, and focused efforts are required to drive down incidence rates.

1.3 IPD Outcomes: Hospitalization and Mortality

In Canada, hospitalization rates in older adults for all-cause pneumococcal pneumonia (invasive and non-invasive) have been declining but remain high (e.g., in 2010 it was 1537 hospitalizations per 100,000 individuals ≥65 years old)[4]. Older adults not only are at higher risk of hospitalization, but also typically have longer hospitalizations requiring more treatment and interventions[4]. In a meta-analysis, it was estimated that the overall case fatality for IPD in adults was between 15-20%, and up to 30-40% in older adults - with most deaths occurring within the first 30 days of hospitalization[16]. In a study of young Argentinian children, it was estimated that there were 33 hospitalizations from IPD per 100,000 admissions, with death being a very rare outcome (1%)[17]. Most data published on childhood mortality and hospitalization compare rates between IPD cases before and after vaccinations were introduced, however there is limited research investigating IPD cases versus general population controls.

1.4 Prevention and Vaccination

Given the severity and prevalence of IPD, focused efforts have been made to produce effective vaccines to protect populations at highest risk. Since the early 2000's there have been three pneumococcal conjugate vaccines (PCV) that have been implemented for routine vaccination in children - covering 7, 10 and 13 pneumococcal serotypes (PCV-7, PCV-10 and PCV-13, covering serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F)[18]. Similarly in adults, a 23-valent vaccine has been developed and is recommended for those over the age of 65, or for those with immunosuppressive or chronic health conditions[3]. As it is not feasible to cover the genetic variability of all pneumococcal serotypes, only the most virulent serotypes have been targeted. By encouraging vaccination in young children and the elderly, it promotes a population and community level protective herd immunity effect

for those serotypes. Since vaccine introduction, IPD rates in children in British Columbia, Canada have dropped significantly (incidence rate ratio (IRR) of 0.84 [95% CI 0.79-0.89]), however non-vaccine serotype IPD rates have seen increases (IRR of 2.12 [95% CI 1.84-2.45])[19].

IPD is a nationally notifiable disease and is under passive surveillance in many countries in the world - such as Canada, USA, Australia, and the European Union, etc.[3,20,21,22]. Continued surveillance, in particular the capsular serotype, is important to monitor changing trends in distribution and help identify needs for current and future vaccine coverage. In addition to monitoring serotype switching, closely observing antimicrobial resistance patterns is important in preventing morbidity and mortality to ensure that effective treatments are available[1]. In an era of vaccinations and antimicrobial therapy, it is imperative that IPD cases are closely monitored to prevent bacterial evolution that increases virulence and escapes treatment.

1.5 Summary

Research studying hospitalization and mortality following IPD has been greatly lacking, with most data framed relative to pre- and post-vaccine eras to assess vaccine effectiveness. Given the incidence and resultant economic and healthcare associated burden of IPD, there is an importance in determining current survivorship and long-term health sequelae following IPD infection to identify high risk individuals so that proactive healthcare interventions and resources can be allocated to these individuals.

1.6 Objectives

Our research has two objectives:

1) To characterize the short, intermediate, and long-term mortality following IPD infections in adults compared to population level age and sex-matched hospitalized controls over a 20-year time-period in Alberta, Canada.

2) To describe the natural history of IPD in children, by observing subsequent mortality and hospitalization events following infection, over a 20-year time span covering PCV-7 and PCV-13 vaccine implementations.

For our first objective, we utilized comprehensive chart reviews to compile all IPD cases in Alberta from 1999-2019. Each case was matched to up to two age and sex-matched population controls (hospitalized when possible), and all cases and controls were followed until they were censored or died using Cox Proportional Hazard Modeling. We used provincially gathered administrative health data to determine mortality, censoring and comorbidity data. We hypothesized that short-term mortality is directly associated with IPD, however we do not know if IPD has continued influence affecting long-term mortality compared to matched controls.

For our second objective, we sought out a similar approach to the first, however modified the analysis slightly. As mortality is an uncommon outcome in children, we also included time to hospitalization in our hazard modelling as a surrogate marker of a poor health outcome. Children are less likely to be hospitalized during IPD diagnosis and many instead experience occult bacteremia. To describe this, we also included a supplementary analysis assessing severity of illness by comparing those who were hospitalized at diagnosis and those who were not. We hypothesized that younger children would have a higher burden of disease.

1.7 References

1. World Health Organization, Vaccine-Preventable Diseases Surveillance and Standards. Pneumococcus. 2018; Available at: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_17_Pneumococcus_R2.pdf?ua=1
2. Maimaiti N, Ahmed Z, Isa ZM, *et al.* Clinical burden of invasive pneumococcal disease in selected developing countries. *Value Health Reg Issues* 2013;**2**(2):259-63.
3. Government of Canada [Internet]. Invasive Pneumococcal Disease. 2019; Available at: Invasive Pneumococcal Disease - Canada.ca
4. McNiel SA, Qizilbash N, Ye J, *et al.* A retrospective study of the clinical burden of hospitalized all-cause and pneumococcal pneumonia in Canada. *Can Resp Journal* 2016;1-10 https://doi.org/10.1155/2016/3605834
5. Centers for Disease Control and Prevention [Internet]. Pneumococcal Disease: Types of Infection. 2020; Available at: https://www.cdc.gov/pneumococcal/about/infection-types.html
6. Brooks LRK and Mias GI. *Streptococcus pneumoniae*'s virulence and host immunity: aging, diagnostics, and prevention. *Front Immunol* 2018;**9**(1366):1-29.
7. Mitchell AM and Mitchell TJ. *Streptococcus pneumoniae:* Virulence factors and variation. *Clin Microbiol Infect* 2010;**16**(5):411-8.
8. Centers for Disease Control and Prevention [Internet]. Pneumococcal Disease: For Laboratorians. 2020; Available at: https://www.cdc.gov/pneumococcal/laboratorians.html
9. Schoenmakers MCJ, Hament JM, Fleer A, *et al.* Risk factors for invasive pneumococcal disease. *Rev Med Microbiol* 2002;**13**(1):29-36.
10. Wagenvoort G, Sanders E, de Melker H, *et al.* Long-term mortality after IPD and bacteremic versus non-bacteremic pneumococcal pneumonia. *Vaccine* 2017;**35**(14)1749-57.
11. Christensen JS, Jensen TG, Kolmos HJ, *et al.* Bacteremia with *Streptococcus pneumoniae*: sepsis and other risk factors of 30-day mortality - a hospital-based cohort study. *Eur J Clin Microbiol Infect Dis* 2012;**31**:2719-25.
12. Centers for Disease Control and Prevention [Internet]. Pneumococcal Disease: Risk Factors. 2020; Available at: https://www.cdc.gov/pneumococcal/clinicians/risk-factors.html
13. Centers for Disease Control and Prevention [Internet]. Travelers' Health. Chapter 4: Travel-Related Infectious Disease: Pneumococcal Disease. 2020; Available at: https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/pneumococcal-disease
14. Public Health Ontario [Internet]. Infectious Disease Trends in Ontario. 2019; Available at: https://www.publichealthontario.ca/data-and-analysis/commonly-used-products/reportable-disease-trends-annually#/52
15. Centers for Disease Control and Prevention [Internet]. Pneumococcal Disease: Surveillance and Reporting. 2020; Available at: https://www.cdc.gov/pneumococcal/surveillance.html
16. Chen H, Matsumoto H, Horita N, *et al.* Prognostic factors for mortality in invasive pneumococcal disease in adults: a system review and meta-analysis. *Sci Rep* 2021;**11**(11865)
17. Lopez EL, Glatstein E, Ezcurra GC, *et al.* Rapid decrease in rates of hospitalization resulting from invasive pneumococcal disease and community-acquired pneumonia in children aged <60 months after 13-valent pneumococcal conjugate vaccine introduction in Argentina. *J. Pediatric Infect. Dis. Soc.* 2018;**7**(1):30-5.

18. Centers for Disease Control and Prevention [Internet]. Vaccines and Preventable Diseases: About Pneumococcal Vaccines. 2020; Available at: https://www.cdc.gov/vaccines/vpd/pneumo/hcp/about-vaccine.html
19. Vadlamudi NK, Patrick DM, Hoang L, *et al.* Incidence of invasive pneumococcal disease after introduction of the 13-valent conjugate pneumococcal vaccine in British Columbia: a retrospective cohort study. *PLoS One* 2020;**15**(9)e0239848. doi: 10.1371/journal.pone.0239848
20. Australian Government Department of Health [Internet]. Invasive pneumococcal disease in Australia, 2003. 2005; Available at: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-2004-cdi2804a.htm
21. Centers for Disease Control and Prevention [Internet]. Nationally Notifiable Infectious Diseases and Conditions, United States: Annual Tables. 2019; Available at: https://wonder.cdc.gov/nndss/nndss_annual_tables_menu.asp
22. European Centre for Disease Prevention and Control: An Agency of the European Union [Internet]. Invasive pneumococcal disease. 2021; Available at: https://www.ecdc.europa.eu/en/invasive-pneumococcal-disease

Chapter 2: Invasive Pneumococcal Disease and Long-Term Mortality in Adults

2.1 Introduction

Despite the introduction of the capsular polysaccharide pneumococcal vaccines over the past number of decades, *Streptococcus pneumoniae* is still a cause of significant morbidity and mortality worldwide [1,2]. The most serious manifestation of infection is invasive pneumococcal disease (IPD), which is characterized by bacteria invading a normally sterile body site such as the blood, lungs, or cerebrospinal fluid. In Canada there are on average 3,000 IPD cases per year[3], with an incidence of around 8·8 to 9·9 cases per 100,000 individuals[4]. Incidence is consistently higher in those over 60 years. In 2018, IPD incidence in Canadians over 60 was 27·1 cases per 100,000 in males and 20·2 cases per 100,000 in females, despite public vaccination programs targeted at this higher risk age group[5].

Short-term 30-day mortality following IPD has been frequently studied - with an estimated case fatality within 30 days ranging from 13-21%[6,7]. Increasing age and comorbidities such as chronic pulmonary and cardiovascular diseases are associated with increased case fatality rates [6,7]. However, literature on long-term mortality following IPD has been largely deficient, despite being a notifiable disease in Canada since 2000[8]. Two studies performed in Norway and the Netherlands investigated 1 and 5-year mortality following IPD compared to age and sex-matched controls in the general population[6,9]. In those who survived initial hospitalization or survived 30 days following acute infection, IPD mortality was significantly higher in cases compared to controls (1-year mortality 10-30% vs 1-3%; 5-year mortality 35-42% vs 7-15%, respectively)[6,9]. However, it was noted in the Dutch study that most deaths occurred within the first 30 days (case mortality of 17%)[6], thus, it remains unclear whether IPD increases long-term mortality. Moreover, these were highly selected samples as both studies used data from only one hospital in a large urban center and is unlikely to be representative of the broader IPD population, particularly those in rural areas [6,9].

Widespread pneumococcal vaccination has seen major success[10], however with an aging population at risk of IPD, and pneumococcal serotypes changing to evade current vaccinations, IPD remains a disease of public health concern[11]. Indeed, we have previously shown a change in serotypes and associated potential increases in severity of disease among IPD patients in Alberta, Canada[12]. To better understand how IPD is impacting mortality, we investigated short, intermediate, and long-term mortality outcomes of individuals with IPD compared to age and sex-matched controls over a 20-year period.

2.2 Methods

IPD Cases

Cases of IPD were defined by laboratory confirmed isolation of *Streptococcus pneumoniae* from a sterile site, including blood, cerebrospinal fluid (CSF), and pleural fluid[13]. In Alberta (Canada), all IPD cases are notifiable to Alberta Health, thus case procurement is accurate and complete. Data was collected on all adult IPD patients (≥18 years) in Alberta from 1999-2019. Alberta's population was estimated at 2·9 million at the start of follow-up and 4·3 million by the end of follow-up[14], with cases residing in both rural and urban settings. Data was collected using standardized case reports, including demographic information, comorbidities, pharmacy data, laboratory results, diagnostic imaging, and vitals for the entirety of their hospital stay. Clinically significant comorbidities for IPD patients have been previously described[15]. This study was given approval by the University of Alberta Health Ethics Research Board (Pro00071271) and a data disclosure agreement with Alberta Health Services was obtained (RA88876).

Matched Controls

Cases were age and sex-matched with up to two population controls, who did not have a history of IPD. As cases were hospitalized, where possible, hospital controls were preferred as both groups likely

have poorer underlying health compared to non-hospitalized controls. Hospitalized controls were defined as being alive at the time of the index case, the same age (+/-1 year), sex and hospitalized within +/- 3-month time frame as the case IPD index date. Overall, 4357 (96·4%) IPD cases had a least 1 hospitalized control; in some IPD cases (n=165, 3·6%), no suitable hospitalized controls were available thus, non-hospitalized age-sex controls were selected from Alberta's general population registry.

Linkage to Administrative Data

Using provincially designated unique lifetime personal health care numbers (PHN's), patients were linked to the administrative health databases routinely collected by Alberta Health/Alberta Health Services. This included Alberta Vital statistics to determine mortality (the provincial registry system which captures all migration within the province), and all hospitalizations, ambulatory visits, and physician claims. Standardized International Classification of Diseases, Ninth and Tenth revisions (ICD-9 and 10) were used for diagnostic coding preceding IPD date, hospitalization date for controls or pseudo-index date for non-hospitalized controls, for up to 5 years to identify comorbidities.

Outcome Measures

The primary outcome was overall time to all-cause mortality following IPD index date. We assessed short-term (<30 days following IPD), intermediate-term (30-90 days) and long-term (>90 days) mortality to try understand the relationship between infection and survival. Mortality within 30 days is expected to be directly associated with acute IPD infection as others have noted[6,7], 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

To describe the relationship between IPD patients and short, intermediate, and long-term mortality, survival analysis was performed. Time zero was defined as date of IPD diagnosis, or pseudo-

date for matched controls. Patients were followed until death, censoring (individual left the province) or March 31, 2019 if the individual was alive at the end of the follow-up period. The maximum total follow-up time possible was 20 years (1999-2019). If death or censoring preceded the start of the intermediate or long-term follow-up (for 30-90 day and >90-day analyses), these individuals were subsequently excluded so as to observe the effects of IPD on these outcomes among those who survived to these time periods. By completing the segmented analysis, a clearer picture of long-term mortality can be understood after removing the shorter mortality from the estimates. Finally, an analysis was completed to look at overall survival over the entire potential 20 years of follow-up (i.e. 30-day, 30-90, and >90 daytime periods were not assessed). If multiple IPD episodes occurred, only the first event was used. This was observed in 142 (3·1%) patients.

Kaplan-Meier survival curves and log-rank tests were used to describe mortality over time and were stratified by age and sex. Age categories were broken down into <45, 45-60, 60-75, and >75 years. To characterize the population, all relevant diagnostic codes (ICD-9 and ICD-10 classifications) in the administrative databases including hospitalization, ambulatory, and physicians claims before each individual's respective index date were identified and the Elixhauser Comorbidity index was calculated[16]. Three additional cardiovascular risk factors (hyperlipidemia, prior stroke, and prior ischemic heart disease) were also included with the Elixhauser score as cardiovascular disease is associated with increased risk of IPD. Scores were categorized into two groups – 0-1 comorbidity, or ≥2 comorbidities. Cox proportional hazard modeling was used to calculate hazard ratios comparing cases to controls. Adjusted analysis was performed using models with case/control status, age categories, and Elixhauser comorbidity index scores. Stratified analysis was performed by age, comorbidity scores and sex. In addition, to determine if mortality trends have changed over time, we stratified IPD cases occurring >10 years ago, 5-10 years ago, and within the last 5 years of analysis. Cox proportional hazards assumption was tested using log-minus-log (LML) plots for the overall full model and no violations were noted. A p-

value of <0·05 was considered significant in modeling. All analyses were performed using STATA statistical software version 15 (StataCorp, College Station TX).

In a sensitivity analysis, we excluded all IPD cases (and their controls) if no hospitalized controls were identified for the IPD case (n=164, 3·6%). In addition, we also excluded all IPD cases who had more than one IPD event (n=142, 3·1%) to ensure these events were not influencing our mortality estimates.

2.3 Results

Patient Characteristics

Out of 5671 IPD events, the first IPD event for each individual was used leaving 5471 unique study subjects. 61 individuals could not be linked to the administrative data (i.e. out of province patients, unknown PHN, etc.) and were excluded. Lastly, there were 888 cases <18 years of age that were removed from analysis (Figure 1). Thus, our study included 4522 IPD case subjects which were matched to 8837 controls (4315 [95%] with 2 control subjects per case). Overall, the mean age was 55.8 (SD 17·7) years, with 56·7% males. Data on site of infection was only available in patients from 1999-2014. Of these subjects, 67% had *S. pneumoniae* identified in more than one sterile body site. There were 2008 (44·4%) cases of invasive pneumonia (of which 1959 (97·7%) also had a positive blood culture), 116 (2·6%) cases of meningitis, 2315 (51·2%) cases of bacteremia/sepsis, and 646 (14·3%) from an unspecified/other sterile source (not mutually exclusive). The most frequent comorbidities in cases respectively were hypertension (39·6%), arrhythmias (36·8%), other immunosuppressive conditions (32·2%), and chronic obstructive pulmonary disease (26·4%). Lifestyle factors were also examined, and it was found that 43·5% of cases had harmful use of alcohol and 20·1% of cases were described as chronic smokers. Controls had higher or equal representation of comorbidities preceding the index date of event in nearly every category, with the exception of HIV infection (Table 1).

All-Cause Mortality within 30 Days

Within 30 days of the IPD index date (or pseudo-date for controls), there were 614 deaths among IPD cases (1915 deaths/1000 PY's) compared to 348 deaths in the control group (510 deaths/1000 PY's) (Figure 2A): unadjusted hazard ratio (uHR) comparing cases to controls of 3·65 (95% CI 3·20 - 4·17). After adjusting for any residual confounding by age (due to our 1-year age bands) and Elixhauser comorbidity scores, IPD cases were still significantly associated with increased risk of 30-day mortality: adjusted hazard ratio (aHR) 3·75 (95% CI 3·29 - 4·28) compared to controls (Table 2).

Stratified by Elixhauser comorbidity scores, no major differences were noted. aHR was 6·41 (95% CI 4·01 - 10·24) in those with a score of 0-1, and 3·55 (95% CI 3·10 - 4·08) in those with multimorbidities (≥2), with both groups showing elevated risk. Significantly increased risk of mortality in IPD cases was also observed in every age category. Comparing cases to controls, observed aHR's for respective age categories was 8·88 (95% CI 5·46 - 14·42) in those <45 years, 4.66 (95% CI 3·56 - 6·09) in those 45-60 years, 3·85 (95% CI 3·00 - 4·95) in those 60-75 years, and 2·54 (95% CI 2·05 - 3·15) in those over 75 years. Lastly, analyses by sex showed that female and male cases had similar increased risk compared to their controls; female aHR 4·02 (95% CI 3·29 - 4·91) and male aHR 3·57 (95% CI 3·00 - 4·25). No interactions with age categories nor Elixhauser scores were noted.

When stratified on year of IPD occurrence, overall mortality differences narrowed over time. Among IPD cases originating >10 years ago (1999-2009), aHR of 4·66 (3·75 - 5·78) was observed relative to controls; aHR of 4·07 (3·09 - 5·35) for cases 5-10 years ago (2009 – 2014), and aHR of 2·88 (2·33 - 3·56) within the last 5 years (2014 – 2019), p<0·001 for trend.

All-Cause Mortality between 30-90 Days

After removing IPD cases (and controls) who died or were censored within 30 days, 3888 cases (86·0%) and 8459 (95·7%) controls remained. Compared to age and sex-matched controls where 220 deaths (107 deaths/1000 PY's) were observed, cases had 149 total deaths (158 deaths/1000 PY's)

between 30 to 90 days following index date (Figure 2B). Both unadjusted and adjusted models for age and comorbidities demonstrated an increased risk of mortality for those with IPD (uHR 1·49 [95% CI 1·21 - 1·83], aHR 1·56 [95% CI 1·27 - 1·93]) (Table 2).

Stratified by Elixhauser comorbidity score, observed aHR's for cases vs. controls were significant in both groups (0-1 comorbidity aHR 16·73 [95% CI 5·09 - 55·06] and ≥ 2 comorbidities aHR 1·32 [95% CI 1·06 - 1·65]); however, few events occurred in patients with only 0-1 comorbidities (n=31, 1·2%). When stratified by age groups, elevated risk of mortality was only observed in those greater than 75 years of age (<45 years aHR 1·75 [95% CI 0·88 - 3·47], 45-60 years aHR 1·44 [95% CI 0·94 - 2·21], 60-75 years aHR 1·36 [95% CI 0·92 - 2·00], and greater than 75 years aHR 1·79 [95% CI 1·28 - 2·50]). Adjusted models stratified by sex revealed similar effects in males and females (female aHR 1·71 [95% CI 1·24 - 2·35] and male aHR 1·48 [95% CI 1·12 - 1·94]). No significant interactions with age or comorbidities were noted.

Cases entering the study >10 years ago had higher observed rates of mortality when compared to controls, than cases entering the study later. Compared to controls, cases > 10 years ago had an aHR of 2·12 (95% CI 1·55 - 2·92), while cases identified between 5-10 years ago had an aHR of 1·40 (95% CI 0·84 - 2·33), and those <5 years ago had an aHR of 1·19 (95% CI 0·85 - 1·66), p<0·001 for trend.

All-Cause Mortality after 90 Days

After removing IPD cases (and controls) who had an event within 90 days, those that survived and were not censored before 90 days were followed-up until March 31, 2019. The average follow-up in this group was 6·7 (SD 0·05) years. At the end of this follow-up period, 1174 cases (49 deaths/1000 PY's) case and 2086 controls (37 deaths/1000 PY's) died (Figure 2C). Again, there was a significant difference observed in mortality between cases and controls, even after adjusting for age and comorbidities (uHR 1·32 [95% CI 1·23 - 1·42], aHR 1·44 [95% CI 1·34 - 1·55]) (Table 2).

Both the groups with 0-1 and ≥2 comorbidities demonstrated higher mortality rates in cases compared to controls (1·72 [95% CI 1·47 - 2·02] and 1·36 [95% CI 1·26 - 1·48] respectively). Every age

group also experienced higher risk of death, with the exception of those older than 75 (<45 years aHR 2·41 [95% CI 1·97 - 2·95], 45-60 years aHR 1·64 [95% CI 1·43 - 1·89], 60-75 years aHR 1·36 [95% CI 1·19 - 1·55], >75 years aHR 1·10 [95% CI 0·97 - 1·26]). Again, both female and male cases had similar increased risk compared to controls. No interactions were noted.

Compared to controls, cases identified >10 years ago had an aHR of 1·50 (95% CI 1·37 - 1·64), cases from 5-10 years ago had an aHR of 1·41 (95% CI 1·20 - 1·67), and cases from <5 years ago had an aHR of 1·26 (95% CI 1·06 - 1·51), p <0·001 for trend. Over each time interval, cases were associated with poorer survival times compared to controls after 90 days following IPD index date.

All-Cause Mortality Overall

Observing the entire follow-up period of 20 years, the average follow-up was 6·0 (SD 0·05) years. Overall, 1937 cases died (81 deaths/1000 PY's) compared to 2654 controls (47 deaths/1000 PY's) (Figure 2). Unadjusted and adjusted models provided similar HR's, with both observing higher mortality in cases vs. controls; uHR 1·66 (95% CI 1·56 - 1·76), aHR 1·77 (95% CI 1·67 - 1·88) (Table 2).

Models stratified by comorbidity score, age group and sex showed cases had increased mortality compared to controls (p < 0·01). Case aHR's stratified by 0-1 and ≥ 2 comorbidities were 2·16 (1·87 - 2·49) and 1·70 (1·59 - 1·81) respectively. The largest relative increased risk was in those <45 years of age: aHR's of 2·97 (95% CI 2·49 - 3·53) in those <45 years, 2·02 (95% CI 1·80 - 2·27) in those 45-60 years, 1·69 (95% CI 1·51 - 1·89) in those 60-75 years, and 1·41 (95% CI 1·27 - 1·56) in >75 years. By sex, female aHR was 1·86 (95% CI 1·71 - 2·04) and male aHR was 1·71 (95% CI 1·58 - 1·85). Interaction models were tested, and none noted.

No significant overall trend in mortality over time was observed with cases identified >10 years ago (aHR 1·80 [95% CI 1·66 - 1·94]), 5-10 years ago (aHR 1·85 [95% CI 1·62 - 2·11]), and the most recent 5 years 1·67 (1·48 - 1·89) (p<0·01) having similar estimates over time (Figure 3).

Sensitivity Analysis

In a sensitivity analysis, after excluding all IPD cases (and their controls) if no hospitalized controls were identified for the case (n=164, 3·6%), our results were unchanged (<30 days aHR 3·71 [95% CI 3·24 - 4·24]; 30-90 days aHR 1·43 [95% CI 1·16 - 1·78]; >90 days aHR 1·37 [95% CI 1·27 - 1·47]; overall mortality aHR 1·70 [95% CI 1·61 - 1·81]). In addition, after we excluded IPD cases (and their matched controls) who had more than one IPD event (n = 142, 3·1%) to ensure these events were not influencing our mortality estimates, similar results were observed (<30 days aHR 3·92 [95% CI 3·43 - 4·48]; 30-90 days aHR 1·59 [95% CI 1·29 - 1·97]; >90 days aHR 1·39 [95% CI 1·29 - 1·49]; overall mortality aHR 1·75 [95% CI 1·65 - 1·86]).

2.4 Discussion

This study showed that having an episode of IPD increases risk of mortality not only in the short-term, which is expected, but is also a prognostic marker of mortality in the intermediate and long-term periods compared to those without IPD. The observed aHR for 30-day mortality was the highest estimate, as acute infection is believed to be directly associated with mortality. As time after infection increases, risk of death is thought to be influenced by lasting sequalae following acute infection - which this study showed remains substantial[17]. Indeed, although the absolute difference in events/PY's between cases and controls was nearly 4-fold higher in the initial 30-day period, the absolute event rate remained almost 50% higher throughout the entire follow-up period, irrespective of age or comorbidity level.

Compared to previously reported IPD mortality data, we found similar results (30-day mortality of 14% vs. 13-21% published, >90-day mortality of 31% compared to 10-42% published)[6,7,9]. Importantly, our data includes a wide population-based estimate of risk. In terms of specific risk groups, like others, we observed a higher absolute rate difference in cases with multimorbidities compared to those

without, irrespective of time frame[6,7,18]; however, the relative hazard ratios compared to controls were highest in those without comorbidity. A similar trend was seen with increasing age. Although those <45 years of age had the lowest absolute rate difference in terms of events/PY's, the relative increase in mortality compared to controls was the highest among those <45 years of age, with the relative difference decreasing with increasing age. Literature frequently describes male sex as being a risk factor for increased incidence and mortality from IPD[6,7], however our findings differ. We observed few differences in sex with respect to short or long-term mortality.

As our study spans a wide period of time, it is important to recognize advancements in medicine and preventative care, particularly in treatment and management of IPD. Indeed, the aHR's decrease with time, with the gap between cases and controls narrowing particularly in the last 5 years. Although the exact mechanisms as to why this is occurring is unknown, some possible explanations are increased use of vaccinations in vulnerable populations, herd immunity protection and advances in antibiotic usage and supportive care[1].

Despite the novelty of our study in evaluating outcomes up to 20 years in a cohort of IPD patients, the large sample size of subjects that were identified from both rural and urban areas and, a case ascertainment that is complete as a result of the provincial surveillance system and notifiable requirements of IPD, there are several limitations to our study that should be recognized. Importantly, there are many potential factors that could influence the risk of mortality following IPD. First, due to the nature of the data, we were unable to account for some clinical differences (e.g., clinical markers such as blood pressure) that may have existed between patients with IPD and control subjects. However, we did adjust for a well-known and validated Elixhauser comorbidity index, and control subjects were matched on site of care. Although it is not possible to adjust for every variable, our control matching on sex and age and adjustments for comorbidities provide a good understanding of IPD mortality. Secondly, the source of infection was not investigated for this study. It is hypothesized that those with nosocomial

infections have worse outcomes compared to those with community acquired infections[7]. Third, the statistical power was low in some stratum analyses where there were fewer deaths, in particular those with limited comorbidities. As a result, confidence intervals were wide and should be interpreted with caution. Last, enrollment was limited to a single province in Canada, which may limit generalizability of our findings, however, with a population of over 4 million people we do not see this as a major concern.

In conclusion, IPD confers increased short, intermediate, and long-term mortality, irrespective of age or comorbidity. In particular, short-term mortality outcomes are most noticeable compared to controls, however those who survive past 30 days are still at elevated risk of mortality. In our aging populations at risk, combined with increasing pneumococcal serotype switching and antibiotic resistance[11,12], IPD remains an important disease so focused efforts on prevention of IPD and how best to prevent downstream sequalae are required. This study suggests that an episode of IPD is associated with a high risk of long-term mortality, irrespective of age or comorbidity level. We believe our findings may help front-line clinicians in recognizing the high-risk nature of IPD patients, even after the acute event has been managed and may assist in long-term post-discharge care plans and preventive strategies to mitigate the risk of longer-term adverse events in these patients.

Table 1: Demographic information comparing cases to controls – sex, age, type of invasive pneumococcal disease (IPD), and comorbidities

	Cases	Controls
Totals, n (%)	4522 (100%)	8837 (100%)
Male	2565 (56·7%)	4994 (56·5%)
Female	1957 (43·3%)	3843 (43·5%)
< 45 years	1324 (29·3%)	2579 (29·2%)
45 - 60 years	1388 (30·7%)	2735 (30·9%)
60-75 years	1054 (23·3%)	2060 (23·3%)
≥ 75 years	756 (16·7%)	1463 (16·6%)
Mean Age, (SD)	55.8 (17·7)	55.8 (17·7)
Type of IPD:		
Pneumonia	2008 (44·4%)	
Positive Blood Culture	1961 (97·7%)	
Positive Pleural Fluid	16 (0·8%)	
Positive Pericardial Fluid	3 (0·1%)	
Positive Peritoneal Fluid	2 (0·1%)	
Unknown	26 (1·3%)	
Meningitis	116 (2·6%)	
Bacteremia/Sepsis	2315 (51·2%)	
Unspecified type	646 (14·3%)	
Unknown	1496 (33·0%)	
Comorbidities, n (%)		
Asplenia	25 (0·6%)	22 (0·5%)
Solid Organ Transplant	113 (2·5%)	187 (4·2%)
HIV Infection	136 (3·0%)	41 (0·9%)
Other Immunosuppression Conditions*	1456 (32·2%)	2252 (50·0%)
Malignancies	1052 (23·3%)	1889 (41·9%)
Chronic Obstructive Pulmonary Disease	1193 (26·4%)	1469 (32·6%)
Other Respiratory Diseases**	771 (17·1%)	1139 (25·3%)
Asthma	1045 (23·1%)	1506 (33·4%)
Chronic Renal Disease	502 (11·1%)	881 (19·6%)

Hypertension	1790 (39·6%)	2744 (60·9%)
Ischemic Heart Disease	990 (21·9%)	1925 (42·7%)
Arrhythmias	1662 (36·8%)	2785 (61·8%)
Valvular Heart Disease	244 (5·4%)	512 (11·4%)
Congestive Heart Failure	645 (14·3%)	1207 (26·8%)
Chronic Liver Disease	806 (17·8%)	863 (19·2%)
Diabetes	1057 (23·4%)	1768 (39·2%)
Smoking	907 (20·1%)	1136 (25·2%)
Harmful Alcohol Use* **	1968 (43·5%)	2503 (55·6%)

*Neutropenia, leukopenia, leukocyte disease not otherwise specified (NOS), functional and genetic white blood cell abnormalities, myelofibrosis, disorders of immune mechanism

**Acute bronchitis, pneumoconiosis, pneumonitis, pulmonary embolism, and other pulmonary circulation disorders

***Alcohol related disorders, toxic effects of alcohol, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic fatty liver disease, alcoholic cirrhosis, alcoholic liver disease, alcohol abuse counseling and surveillance

Table 2: Mortality outcomes of invasive pneumococcal disease (IPD) patients compared to age and sex-matched controls

	Controls		Cases		Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
	n/N (%)	Events /1000 PY	n/N (%)	Events /1000 PY			
<30 Days	348/8837 (3·9%)	510	614/4522 (13·6%)	1915	3·65 (3·20 - 4·17)	3·75 (3·29 - 4·28)	<0·001
30-90 Days	220/8459 (2·6%)	107	149/3888 (3·8%)	158	1·49 (1·21 - 1·83)	1·56 (1·27 - 1·93)	<0·001
>90 Days	2086/8236 (25·3%)	37	1174/3733 (31·4%)	49	1·32 (1·23 - 1·42)	1·43 (1·33 - 1·54)	<0·001
Overall	2654/8837 (30·0%)	47	1937/4522 (42·8%)	81	1·66 (1·56 - 1·76)	1·77 (1·67 - 1·88)	<0·001

Figure 1: Flow chart diagram of invasive pneumococcal disease (IPD) case inclusion

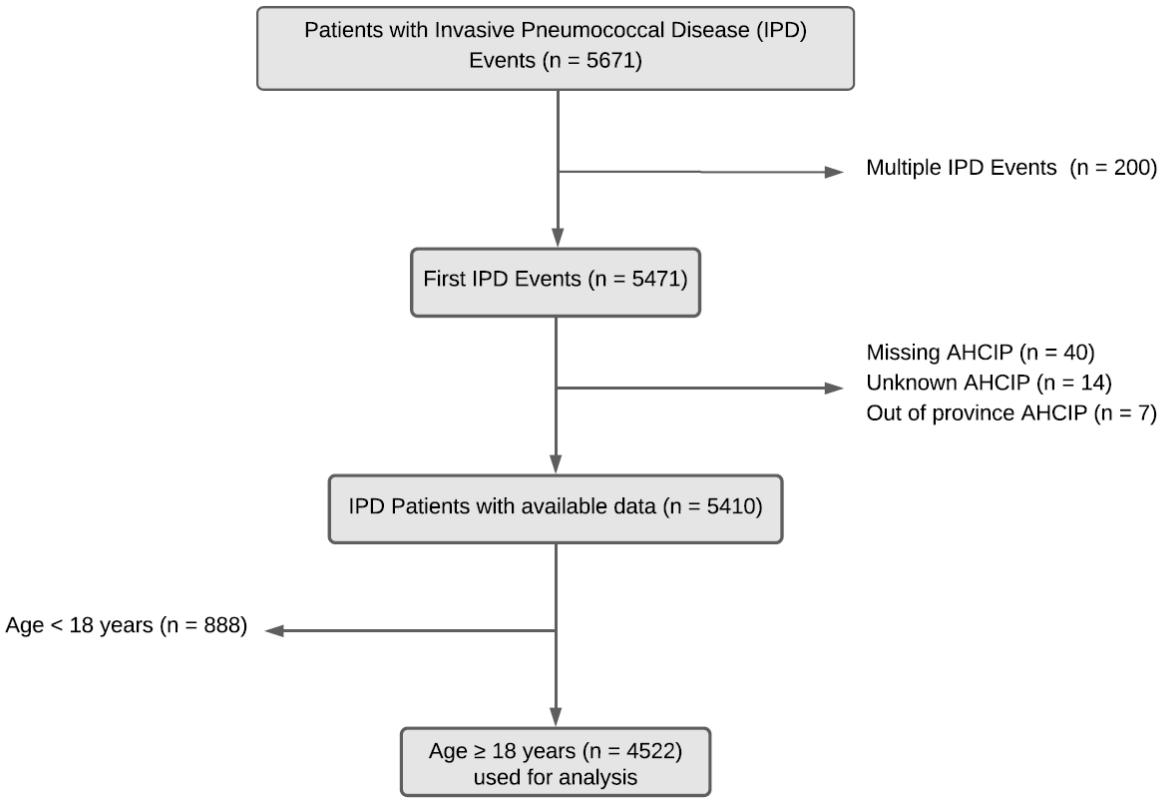
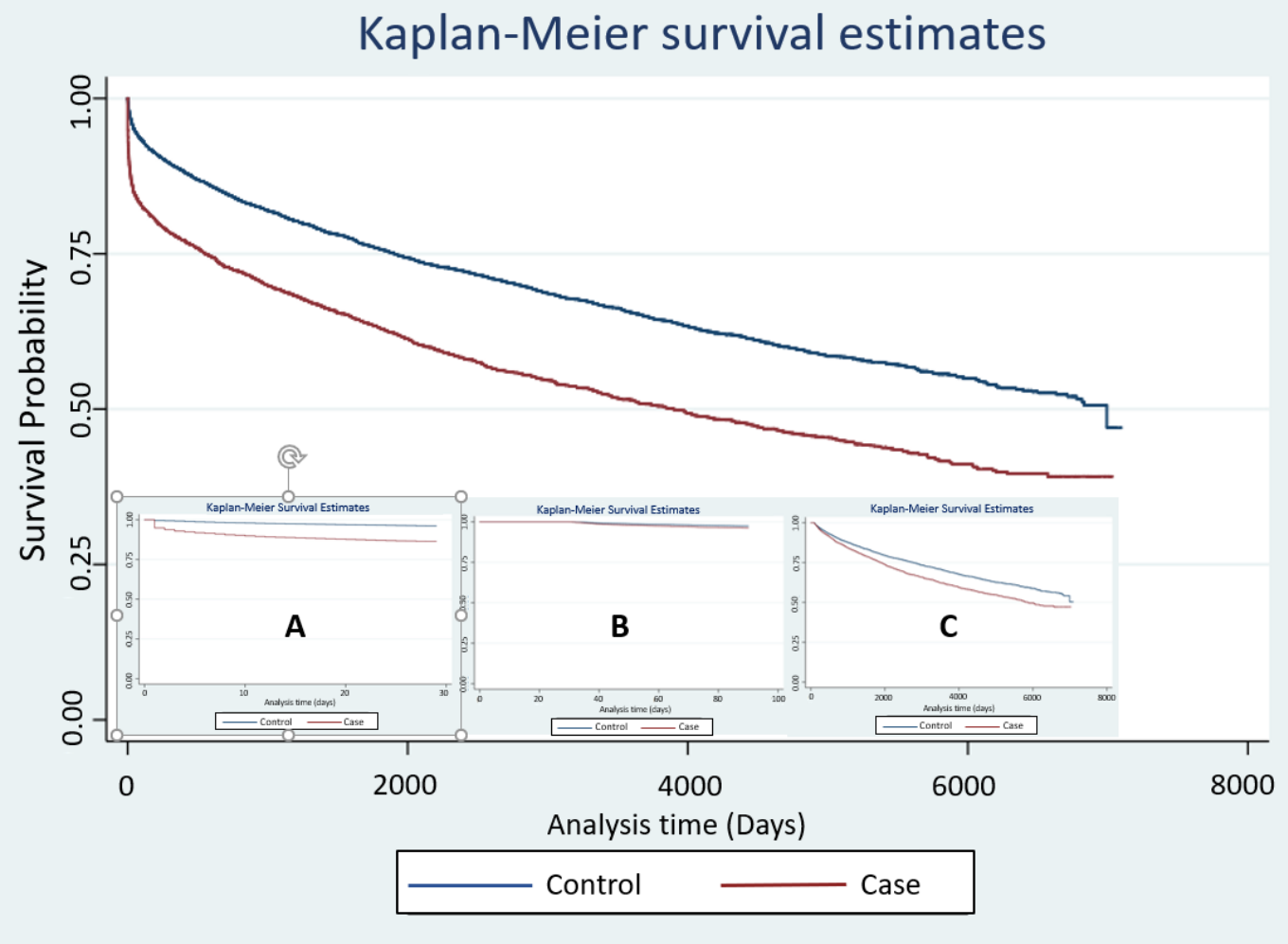
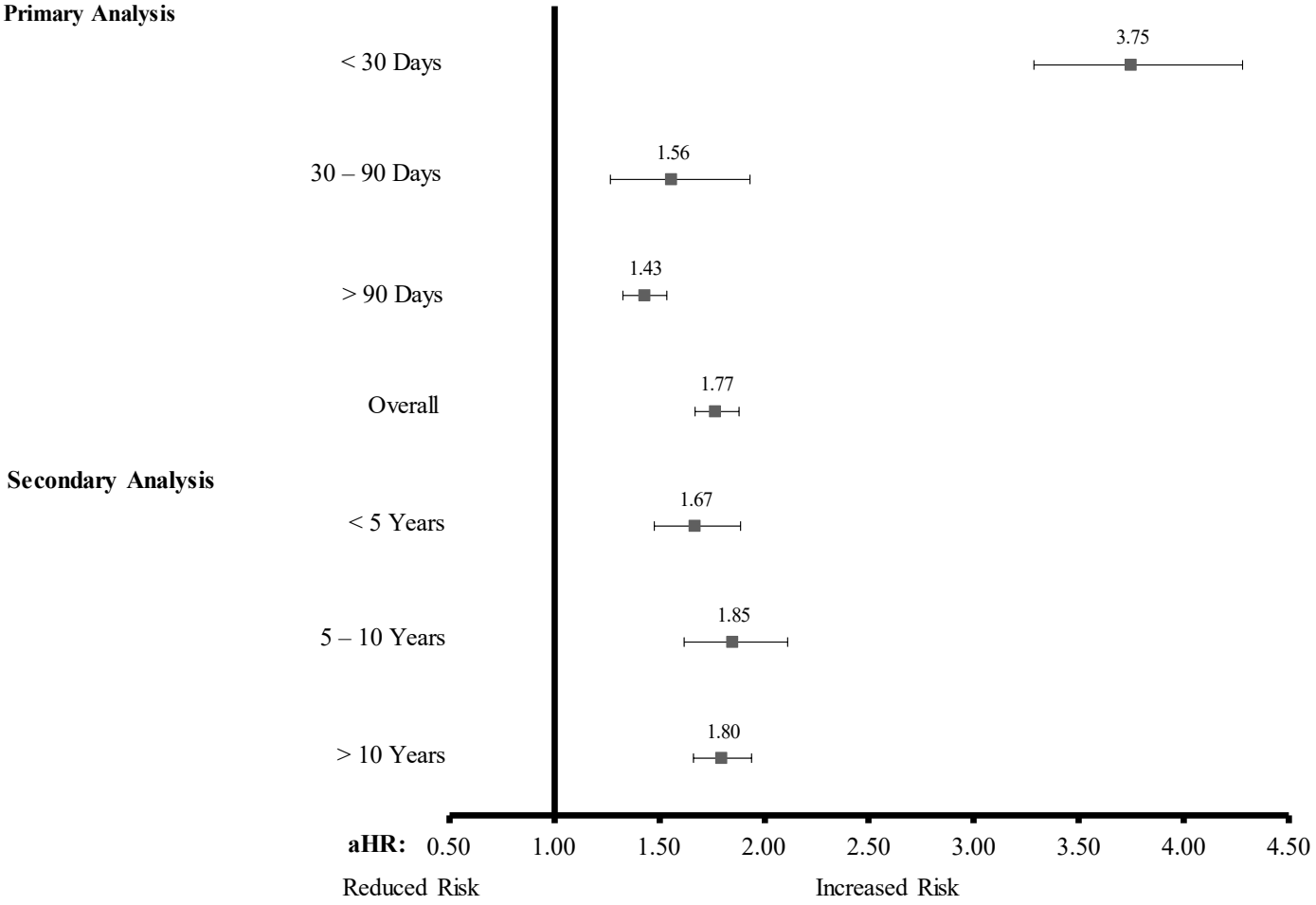


Figure 2: Overall Kaplan-Meier (KM) survival estimates comparing invasive pneumococcal disease (IPD) cases to population controls



a. Less than 30-day KM survival estimates
b. 30 to 90-day KM survival estimates
c. Greater than 90-day KM survival estimates

Figure 3: Adjusted hazard ratios (aHR's) describing mortality risk comparing invasive pneumococcal disease (IPD) cases versus controls after adjusting for age and Elixhauser comorbidity scores.



Primary analysis: Short (less than 30 days), intermediate (30 to 90 days) and long term (greater than 90 days) and overall (entire time-period) follow-up.

Secondary analysis: Invasive pneumococcal disease (IPD) cases (and matched controls) identified less than 5 years ago, between 5 to 10 years ago, and greater than 10 years ago.

2.5 References

1. Feldman C, Anderson R. Recent advances in the epidemiology and prevention of *Streptococcus pneumoniae* infections. *F1000Research* 2020;**9**(F1000 Faculty Rev):338.
2. Mook-Kanamori BB, Geldhoff M, van der Poll T, *et al.* Pathogenesis and pathophysiology of pneumococcal meningitis. *Clin Microbiol Rev* 2011;**24**(3):557-91.
3. Desai S, Policarpio ME, Wong K, *et al.* The epidemiology of invasive pneumococcal disease in older adults from 2007 to 2014 in Ontario, Canada: a population-based study. *CMAJ Open* 2016;**4**(3):E545-50.
4. Public Health Agency of Canada [Internet]. Vaccine Preventable Disease: Surveillance Report to December 31, 2015. 2017; Available at: vaccine-preventable-disease-eng.pdf (canada.ca).
5. Public Health Agency of Canada [Internet]. Reported cases by age group in Canada, grouped by sex: Notifiable diseases on-line. Pneumococcal Disease, Invasive, 2018. 2021; Available at: Reported cases by age group in Canada, grouped by sex - Notifiable diseases on-line (phac-aspc.gc.ca).
6. Wagenvoort G, Sanders E, de Melker H, *et al.* Long-term mortality after IPD and bacteremic versus non-bacteremic pneumococcal pneumonia. *Vaccine* 2017;**35**(14)1749-57.
7. Christensen JS, Jensen TG, Kolmos HJ, *et al.* Bacteremia with *Streptococcus pneumoniae*: sepsis and other risk factors of 30-day mortality - a hospital-based cohort study. *Eur J Clin Microbiol Infect Dis* 2012;**31**:2719-25.
8. Government of Canada [Internet]. Invasive Pneumococcal Disease. 2019; Available at: Invasive Pneumococcal Disease - Canada.ca
9. Floeystad HK, Holm A, Sandvik L, *et al.* Increased long-term mortality after survival of invasive pneumococcal disease: a population-based study. *Infectious Diseases* 2017;**49**(5):365-72.
10. Wijayasri S, Hillier K, Lim GH, *et al.* The shifting epidemiology and serotype distribution of invasive pneumococcal disease in Ontario, Canada, 2007-2017. *PLOS ONE* 2019;**14**(12):e0226353. doi: 10.1371/journal.pone.0226353
11. Golden AR, Adam HJ, Karlowsky JA, *et al.* Molecular characterization of predominant *Streptococcus pneumoniae* serotypes causing invasive infections in Canada: the SAVE study, 2011-15. *J Antimicrob Chemother* 2018;**73**(7):vii20-31.
12. Marrie TJ, Tyrrell GJ, Majumdar SR, *et al.* Invasive pneumococcal disease in Northern Alberta, not a Red Queen but a dark horse. *Vaccine* 2018;**36**(21):2985-90.
13. Government of Alberta, Ministry of Health [Internet]. Alberta Public Health Disease Management Guidelines: Pneumococcal Disease, Invasive (IPD). 2019; Available at: health-phdmg-pneumococcal-disease-invasive-2019-12.pdf (alberta.ca).
14. Government of Alberta [Internet]. Alberta Population Estimates - Data Tables: Quarterly Alberta total population estimates: 1951-2021 (updated March 18, 2021). 2021; Available at: https://open.alberta.ca/dataset/alberta-population-estimates-data-tables#summary
15. Marrie TJ, Tyrrell GJ, Majumdar SR *et al.* Invasive Pneumococcal Disease: Still Lots to Learn and a Need for Standardized Data Collection Instruments. *Can Respir J.* 2017;**2017**:2397429. doi: 10.1155/2017/2397429.
16. Li B, Evans D, Faris P, *et al.* Risk adjustment performance of Charlson and Elixhauser comorbidities in ICD-9 and ICD-10 administrative databases. *BCM Health Serv Res* 2008;**8**:12. doi: 10.1186/1472-6963-8-12
17. Hughes GJ, Wright LB, Chapman KE, *et al.* Serotype-specific differences in short- and longer-term mortality following invasive pneumococcal disease. *Epidemiol Infect.* 2016;**114**(12):2654-69.
18. Torres A, Blasi F, Dartois N, *et al.* Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. *Thorax* 2015;**70**:984-9.

Chapter 3: Invasive Pneumococcal Disease and Long-Term Outcomes in Children: A 20-Year Population Cohort Study

3.1 Introduction

Streptococcus pneumoniae is an organism commonly found in the upper respiratory tract that typically does not cause infection. However, it is opportunistic in its ability to become a pathogen when provided with the conditions to invade a normally sterile body site and can cause serious illness such as invasive pneumococcal disease (IPD). Less than 10% of adults are carriers of the bacteria, but it is estimated that between 27-64% of children carry the bacteria in their nasopharynx[1]. Young children (<5 years old) are believed to be particularly susceptible to both colonization and infection as they do not yet have a fully developed immune system and have frequent exposures to asymptomatic spread from other colonized children - particularly in crowded places such as daycares[2,3].

Prior to implementation of childhood pneumococcal vaccination, the number of global deaths attributed to pneumococcal disease in children between 1 month to 5 years of age was estimated to be around 1.8 to 2.0 million - representing 11% of all deaths in this age group[4,5]. To combat this high disease mortality in children, in 2000 and 2001, the Food and Drug Agency in the United States and Health Canada, respectively, approved a 7-valent pneumococcal conjugate vaccine (PCV) that targeted the most virulent and commonly occurring serotypes[6,7]. This was implemented as a part of routine childhood immunization schedules in many countries around the world and was later replaced by more comprehensive 10 and 13-valent vaccines. The PCV-10 vaccine was approved and used in select Canadian provinces starting in 2009[8], while the 13-valent vaccine was approved in 2010 in both the United States and Canada[6,9]. Widespread vaccination led to an 80% decrease in IPD caused by PCV-7 covered serotypes, and a 94% decrease in PCV-13 covered serotypes in the most vulnerable children <2 years of age[10]. Studies have also shown that vaccination has led to reduced rates of hospitalization following IPD infection[11], particularly in otherwise healthy children[12].

Despite availability and coverage of vaccines, IPD remains a disease of public health concern and therefore it is important to understand disease severity and outcomes for children who are still being infected. While standardized immunization schedules for children have resulted in decreased prevalence of IPD by vaccine-covered serotypes, prevention remains difficult because of pneumococcal serotype switching, vaccine hesitancy and inequitable vaccine distribution particularly in lower income countries[13]. Furthermore, understanding the changing trends of IPD and it's impacts in children is often difficult. Indeed, research investigating short and long-term mortality in children with IPD have been limited to date, due to low statistical power from a low absolute number of events observed in this population[10,14]. Therefore, historically the primary research objective of those investigating IPD in children has been on prevention and vaccine effectiveness. As a result, there are limited publications investigating the long-term adverse health events following IPD infection that may arise downstream and affect quality of life, especially in children older than 5 years. To fill this knowledge gap and to better understand how IPD impacts children of all ages, thus, we assembled a representative population-based cohort of children with IPD and age and sex-matched population control subjects without IPD to better understand the natural history of an episode of IPD and its relative impact on short, intermediate and long-term hospitalization and mortality outcomes following IPD infection. IPD remains a disease of public health concern and therefore it is important to study disease severity and outcomes for children who are still being infected.

3.2 Methods

IPD Cases

Between 1999 to 2019 all cases of IPD occurring in children <18 years of age were identified and collected in Alberta, Canada (children population ~ 1 million in 2016[15]). 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 bacteremia (septicemia), bacteremic pneumonia and meningitis in children <18 years of age. Standardized patient reporting forms were used by trained healthcare professionals to collect supplementary data on IPD cases identified from 1999-2014 including in vital signs, laboratory results, antibiotic usage, comorbidities, pneumococcal serotype, specimen source and demographic information such as age and sex; however data collected on cases identified from 2015-2019 were more limited in scope (only included IPD date, gender 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. Ethics approval was granted by the University of Alberta Health Ethics Research Board (Pro00071271) and a data disclosure agreement with Alberta Health Services was obtained (RA88876).

Matched Controls

To better understand the negative impacts of IPD in children, each IPD case was matched to two controls, when available. Controls were matched on sex, age (+/- 1 year), had to be alive at the same time as the case, and have no prior history of IPD. Hospitalized controls admitted +/- 3 months from the case were preferentially selected, as they likely have poorer health status and therefore more representative of the IPD population (n=1348, 76.8%). If no matched hospitalized control was available in this time frame, matched controls were pulled from the provincial general population registry (n=408, 23.2%) using the same matching criteria.

Linkage to Administrative Data

All individuals living in Alberta have a provincially assigned 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. In addition, all healthcare services are collected within the province as part of Alberta's

universal healthcare system. Thus, all hospitalization outcomes were identified by linkage to the Discharge Abstract Database (DAD). Lastly, comorbidities of interest were identified from the administrative data 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. As Alberta's healthcare system is integrated provincially, linkage to administrative datasets is robust and complete and the quality and validity of these databases are routinely checked both provincially and federally[16,17].

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 hospitalization following index date. This was defined as the time to first hospitalization for children who were not initially hospitalized at the time of their IPD diagnosis or time to re-hospitalization in those patients initially hospitalized at the time of their 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) - to determine if infection with IPD has lasting consequences on overall health in children.

Statistical Analysis

Survival analyses were performed to establish time to mortality and time to hospitalization following index date, in the <30-day, 30-90 day, >90 day and overall (0 to >90 days) time 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 as they were no longer at risk of an event. 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 important patient characteristics of sex, age, and Elixhauser comorbidity score, 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, as historically a majority of IPD cases occur in children <5 years[3]. Elixhauser 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). Clinical research and healthcare improvements continually advance over time, so a segmented analysis was further performed separating cases and their matched controls identified in 1999-2004, 2004-2009, 2009-2014 and 2014-2019. Lastly, as not all IPD cases are hospitalized at IPD diagnosis, there may be differences in illness severity that is important to capture. Thus, additional models were run comparing hospitalized IPD cases to non-hospitalized IPD cases.

Cox proportional hazard assumptions for mortality and hospitalization 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).

3.3 Results

Patient Demographics

From 1999 to 2019, there were a total of 888 unique primary IPD events in children < 18 years in Alberta, Canada (Figure 1) who were subsequently age and sex matched to 1756 controls (868 [97.7%] cases had two matched controls). 56.6% of cases were males, and the mean age was 3.8 years (standard deviation (SD) 4.1) - with a majority of cases (76.6%) occurring in those less than 5 years of age. Of the

patients who had data available on site of pneumococcal infection, bacteremia was the most identified infection (57.3%), followed by bacteremic pneumonia (28.8%), meningitis (8.2%) and unspecified or other source (13.0%). These sites are not mutually exclusive as cases can have multiple infected sites. Cases from 2015-2019 did not have source data available and accounted for 18% of total cases. Relative comorbidities between cases and controls were generally comparable - the most prevalent comorbidities in cases were neurological disorders (29.5%, excluding paralysis), chronic pulmonary disease (18.4%), fluid and electrolyte disorders (13.5%) and congenital heart disease (6.6%). The top 4 most common serotypes identified were 14, 19A, 19F and 6B (Table 1).

Time to Mortality (Primary Outcome):

Overall, 49 deaths in cases and 55 in controls occurred over the entire follow-up period (4.8 deaths/1000 PY and 2.7 deaths/1000 PY respectively). Of IPD cases that died, 25 were female (N=385, 6.5%) and 24 were male (N=503, 4.8%). In IPD cases, there were 11 deaths in children 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 10-18 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).

Broken down by time interval, there were 22 deaths in cases <30 days after index date (319 deaths/1000 PY), 3 deaths between 30-90 days (14 deaths/1000 PY), and 24 deaths >90 days (2.4 deaths/1000 PY). Among controls, there were 5 deaths in the first 30 days (36 deaths/1000 PY), 3 between 30-90 days (7 deaths/1000 PY) and 47 deaths >90 days (2.3 deaths/1000 PY). Adjusted hazard ratio's (aHR's) comparing cases to controls for <30-day, 30-90 day, >90 days and overall time periods were 8.78 (95% CI 3.33-23.18), 2.03 (95% CI 0.41-10.04), 1.03 (95% CI 0.63-1.69) and 1.80 (95% CI 1.22-2.64), respectively (Table 2). Due to the low number of deaths, the resulting confidence intervals are

wide - nevertheless the first 30 days demonstrate statistical significance ($p<0.001$) with cases having poorer short term survival rates compared to controls (Figure 3).

With respect to the timing of deaths in the first 30 days following IPD index date, 14 cases that were in hospital during IPD diagnosis (+/- 7 days from IPD index) died (N=34, 41.2%). 8 cases that were not admitted to hospital died (N=15, 53.3%), but of those, 7 occurred within the first two days following diagnosis. 3 of the 7 died in the emergency department and therefore were not formally admitted before death. Conversely, there were 5 deaths in the control group within the first 30 days following index date (N=55, 9.1%), with most deaths occurring after 30 days (50/55 control deaths, 90.9%).

Stratified models by age, sex and Elixhauser comorbidity score for mortality are shown in Table 3. Few statistical differences were noted among many of the strata due to low or no events within the stratum. Of note, 30-day mortality in cases showed significance in the 2-5 year age group (aHR 7.93 [95% CI 1.68-37.33]), in males (aHR 5.47 [95% CI 1.74-17.18]) and in females (aHR 22.12 [95% CI 2.86-171.32]). Overall time to mortality in cases was significant for those with an Elixhauser score <2 (aHR 3.65 [95% CI 1.95-6.80]), <1 year old's (aHR 2.47 [95% CI 1.02-5.96]), 2-5 year old's (aHR 3.11 [95% CI 1.46-6.64]) and females (aHR 1.93 [95% CI 1.12-3.35]). No significance was found in any strata in the intermediate or long-term follow-up periods.

In cases between 1999-2004, there were 21 (4.9%) deaths, between 2004-2009 there were 10 (5.7%) deaths, between 2009-2014 there were 11 (9.7%) deaths, and 2014-2019 had 7 (4.0%) deaths. Mortality rates in IPD 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 trend = 0.569.

Sub-Analysis of Mortality Data among Hospitalized and Non-Hospitalized IPD cases

Investigation of deaths in cases who were hospitalized (n=34) vs. not in hospital (n=15) at IPD diagnosis showed no difference in mortality in the first 30 days: 400 deaths/1000 PY in cases in hospital and 236 deaths/1000 PY in cases not in hospital (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-hospitalized cases (3 deaths in hospitalized cases). After 90 days following IPD, cases hospitalized at index date experienced higher mortality compared to cases that were not (4.1 deaths/1000 PY vs 1.2 deaths/1000 PY; aHR 2.96 [95% CI 1.21-7.26]), leading to an overall aHR of 2.45 (95% CI 1.33-4.53) during the entire follow-up. 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.

Time to Hospitalization (Secondary Outcome)

With respect to hospitalizations, there were 205 hospitalizations in cases <30 days following IPD index date (3728 events/1000 PY), 30 between 30-90 days (186 events/1000 PY), 173 >90 days (27 events/1000 PY), and overall, 408 (45.9%) total hospitalizations (63 events/1000 PY). Comparatively, there were 135 hospitalizations in controls <30 days after index date (1020 events/1000 PY), 92 between 30-90 days (236 events/1000 PY), 475 >90 days (33 events /1000 PY) and 702 (40.0%) total hospitalizations (49 events/1000 PY). Comparing hospitalizations in cases vs. controls, aHR's for <30 days, 30-90 days, >90 days and overall follow-up periods were 3.38 (95% CI 2.72-4.20), 0.78 (95% CI 0.52-1.17), 0.82 (95% CI 0.69-0.98), and 1.31 (95% CI 1.16-1.48) respectively (Table 4). Statistically significant differences were found in all time intervals except for 30-90 day-time interval. IPD cases had higher rates of hospitalization within the <30 day and overall models, while controls had slightly higher rate of hospitalizations >90 days following index date.

Short-term stratified models for time to hospitalization revealed statistical significance for every strata ($p \leq 0.001$), with cases being hospitalized more frequently than controls within the first 30 days (Table 5). Time to hospitalization in the intermediate and long-term follow-up periods showed no statistically significant differences, with the exception of 1-2 year old's in 30-90 day interval (aHR: 0.20 [95% CI 0.06-0.66]); or those with an Elixhauser score ≥2 (aHR: 0.64 [95% CI 0.46-0.87]), 2-5 year old's (aHR: 0.63 [95% CI 0.45-0.89]) or males (aHR: 0.72 [95% CI 0.56-0.91]) in the >90 days follow-up (cases having fewer hospitalizations compared to controls). Lastly, stratified models demonstrate that the overall rate of hospitalization in cases was higher in those with Elixhauser scores <2, those <1 year or 5-10 years of age, and both males and females (aHR's: 1.54 [95% CI 1.31-1.80], 2.01 [95% CI 1.53-2.65], 1.54 [95% CI 1.10-2.15], 1.23 [95% CI 1.04-1.45] and 1.43 [95% CI 1.19-1.72], respectively).

In cases between 1999-2004, there were 169 (39.5%) hospitalizations, between 2004-2009 there were 92 (52.9%) hospitalizations, between 2009-2014 there were 52 (46.0%) hospitalizations, and 2014-2019 had 95 (54.9%) hospitalizations. Over time, hospitalization 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 trend = 0.277.

3.4 Discussion

This 20 year study shows that IPD continues to negatively impact children, with the majority of children IPD cases in those <5 years of age, and of male sex, as others have also observed[3,14]. Considering our primary outcome of mortality, although over the entire follow-up period the absolute number of deaths observed was small, the relative number of deaths in cases was nearly double that of deaths seen in controls. As there are no observable differences between cases and controls in the intermediate and long-term follow-up periods, this overall effect is influenced primarily by the short-

term deaths occurring as a result of acute infection – findings that differ from what we have previously observed in adults. Interestingly, the relative rates of death compared to controls remained stable over time with no discernable decrease in trend observed over the time-period of study.

By age strata, the overall relative number of deaths in children between 0-1, 2-5 and 10-18 years of age were two to three times higher compared to matched controls, while no difference was observed in children between 1-2 and 5-10 years. Although males are commonly described as being at higher risk of acquiring IPD, both male and female cases have poorer short-term survival compared to controls. As others have noted, low statistical power due to few deaths led to uninterpretable strata or strata with extremely wide confidence intervals - particularly in the intermediate and short-term outcomes[10,14]. Overall, cases with a comorbidity score of 0 or 1 were at higher risk of death compared to controls (aHR 3.65 [95% CI 1.95-6.80]). The reason behind this is unknown, but one possible explanation is that they had comorbidities not yet formally identified, or not included for the purpose of this study, that put them at higher risk of acquiring IPD and subsequently dying from it. That said, these confidence intervals should be interpreted with caution and additional studies are required to further explore differences in children by age groups, sex and comorbidities.

The secondary outcome of time to hospitalization was used as a supplementary marker of poor health outcomes. In every strata, the risk of children being admitted to hospital within 30-days is significantly higher in cases compared to controls, suggesting that despite the majority being initially managed in the hospital, that short-term downstream sequalae are common. Some of the intermediate and long-term strata show that risk of hospitalization in these time periods are lower in cases compared to matched controls. Further investigation is needed to explore this trend but could 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.

The objective of our study differs from those previously performed, as our focus was on mortality and hospitalization in cases versus controls, in children of all ages, and irrespective of serotype or vaccination status. Others have described improved rates of hospitalization 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 13 vaccines, and we did not find significant improvements in hospitalization or mortality rates when comparing cases and controls. Indeed, the proportion of hospitalizations in IPD children increased from 2004-2009 and 2014-2019. That said, with vaccine implementation, it is possible that the incidence rate of IPD decreased at the population level.

To our knowledge, a long-term IPD study of this duration, wide geographical area, and in children of all ages has not been previously performed. Although unique, there are limitations to consider and address in future studies. Identification of hospitalization status at IPD diagnosis is difficult to determine, which is important as deaths that occur in the Emergency Department prior to being officially admitted are not included in hospitalized cases. Despite this, most IPD case deaths still occur in those hospitalized at diagnosis, indicating that there are differences in case severity to be further evaluated. For instance, otherwise healthy children presenting with occult bacteremia and not requiring hospitalization may not be appropriate to group with cases with severe illness needing intensive medical interventions. In addition to not knowing case severity, vaccination status of cases was not known. As the most frequently recorded serotypes were those covered by vaccines, it would be useful to know if these were breakthrough infections or infections occurring in unvaccinated children. As mentioned previously, in much of the mortality data, statistical power is limited; however, this is unlikely to change as our study was in an extremely large geographical population and captured all IPD cases in children over a 20-year time span. All this considered, this study is novel in that it spanned over the introduction of two PCV vaccines and provides information on changes in childhood IPD mortality and hospitalization outcomes over time.

In conclusion, short-term mortality in children with IPD is significant given the invasive nature of disease. However, cases have similar survival rates compared to matched population controls in the intermediate and long-term time periods, indicating that the lasting effects of IPD infection may not be substantial on long-term survival which is reassuring. If a child survives the acute effects of infection, their long-term prognosis does not differ substantially from matched population controls. These findings emphasize the importance of prevention and vaccination, while also stressing to clinicians that focus and close follow-up of children immediately following an IPD event are warranted to prevent poor downstream health outcomes.

Table 1: Demographic Information for Cases and Controls

	Cases	Controls
Totals, n (%)	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%)
Type of IPD		
Pneumonia	256 (28.8%)	
Positive Blood Culture	181 (70.7%)	
Positive Pleural Fluid	6 (2.3%)	
Positive Peritoneal Fluid	1 (0.4%)	
Unknown	68 (26.6%)	
Meningitis	73 (8.2%)	
Bacteremia/Septicemia	509 (57.3%)	
Unspecified	115 (13.0%)	
Unknown	160 (18.0%)	
Serotype (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	

Elixhauser Comorbidities, n (%)	Cases	Controls
Congestive Heart Failure	23 (2.6%)	29 (1.7%)
Cardiac Arrhythmia	56 (6.3%)	108 (6.2%)
Valvular Heart Disease	25 (2.8%)	33 (1.9%)
Pulmonary Circulation Disorders	11 (1.2%)	18 (1.0%)
Peripheral Vascular Disorders	14 (1.6%)	20 (1.1%)
Hypertension	25 (2.8%)	40 (2.3%)
Paralysis	14 (1.6%)	61 (3.5%)
Other Neurological Disorders	262 (29.5%)	536 (30.5%)
Chronic Pulmonary Disease	163 (18.4%)	402 (22.9%)
Diabetes	7 (0.8%)	25 (1.4%)
Hypothyroidism	7 (0.8%)	14 (0.8%)
Renal Failure	27 (3.0%)	44 (2.5%)
Liver Disease	25 (2.8%)	36 (2.1%)
Peptic Ulcer Disease	5 (0.6%)	7 (0.4%)
HIV/AIDS	1 (0.1%)	0 (0%)
Lymphoma	5 (0.6%)	14 (0.8%)
Solid Tumor Cancer	26 (2.9%)	66 (3.8%)
Rheumatoid Arthritis	42 (4.7%)	89 (5.1%)
Coagulopathy	27 (3.0%)	42 (2.4%)
Obesity	6 (0.7%)	17 (1.0%)
Weight Loss	65 (7.3%)	130 (7.4%)
Fluid & Electrolyte Disorders	120 (13.5%)	216 (12.3%)
Blood Loss Anemia	1 (0.1%)	2 (0.1%)
Deficiency Anemia	32 (3.6%)	71 (4.0%)
Drug Abuse	17 (1.9%)	59 (3.4%)
Psychoses	2 (0.2%)	17 (1.0%)
Depression	34 (3.8%)	95 (5.4%)
Prior Ischemic Heart Disease	8 (0.9%)	8 (0.5%)
Prior Stroke	5 (0.6%)	20 (1.1%)
Hyperlipidemia	4 (0.5%)	11 (0.6%)
Congenital Heart Disease	59 (6.6%)	85 (4.8%)

Table 2: Mortality Outcomes of Patients with IPD Relative to Matched Controls

	Cases		Controls		Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
	n/N (%)	Events /1000 PY	n/N (%)	Events /1000 PY			
<30 Days	22/888 (2.5%)	318.8	5/1756 (0.3%)	36.0	8.78 (3.33 - 23.19)	8.78 (3.33 - 23.18)	<0.001
30-90 Days	3/864 (0.3%)	14.1	3/1745 (0.2%)	7.0	2.02 (0.41 - 10.01)	2.03 (0.41 - 10.04)	0.387
>90 Days	24/860 (2.8%)	2.4	47/1739 (2.7%)	2.3	1.03 (0.63 - 1.69)	1.03 (0.63 - 1.69)	0.904
Overall	49/888 (5.5%)	4.8	55/1756 (3.1%)	2.7	1.80 (1.22 - 2.64)	1.80 (1.22 - 2.64)	0.003

Table 3: Case vs. Control Adjusted Hazard Ratios for Age Categories by Time Interval - Time to Mortality

	Short Term (<30 days)		Intermediate (30-90 days)		Long Term (>90 days)		Overall Mortality	
	aHR (95% CI)	**p-value**	**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)	0.387	1.03 (0.63-1.69)	0.904	1.80 (1.22-2.64)	0.003
Elixhauser Groups								
Elix < 2	N/A	N/A	1.97 (0.12-31.58)	0.631	1.50 (0.68-3.30)	0.316	3.65 (1.95-6.80)	<0.001
Elix ≥ 2	2.38 (0.69-8.23)	0.171	2.31 (0.32-16.49)	0.402	0.89 (0.47-1.70)	0.730	1.15 (0.67-1.97)	0.616
Age Groups								
< 1 y/o	N/A	N/A	2.06 (0.13-32.88)	0.610	1.01 (0.30-3.36)	0.984	2.47 (1.02-5.96)	0.044
1-2 y/o	N/A	N/A	2.01 (0.13-32.08)	0.622	0.47 (0.13-1.66)	0.242	1.02 (0.41-2.52)	0.969
2-5 y/o	7.93 (1.68-37.33)	0.009	2.01 (0.13-32.14)	0.621	2.03 (0.76-5.41)	0.156	3.11 (1.46-6.64)	0.003
5-10y/o	2.00 (0.13-31.98)	0.624	N/A	N/A	0.66 (0.21-2.04)	0.470	0.76 (0.27-2.13)	0.604
10-18 y/o	4.04 (0.74-22.04)	0.107	N/A	N/A	1.74 (0.53-5.70)	0.361	2.32 (0.90-6.02)	0.083
Sex								
Female	22.12 (2.86-171.32)	0.003	0.68 (0.07-6.50)	0.734	1.18 (0.59-2.34)	0.636	1.93 (1.12-3.35)	0.019
Male	5.47 (1.74-17.18)	0.004	N/A	N/A	0.89 (0.44-1.81)	0.753	1.67 (0.97-2.86)	0.064

*N/A = not enough deaths to interpret

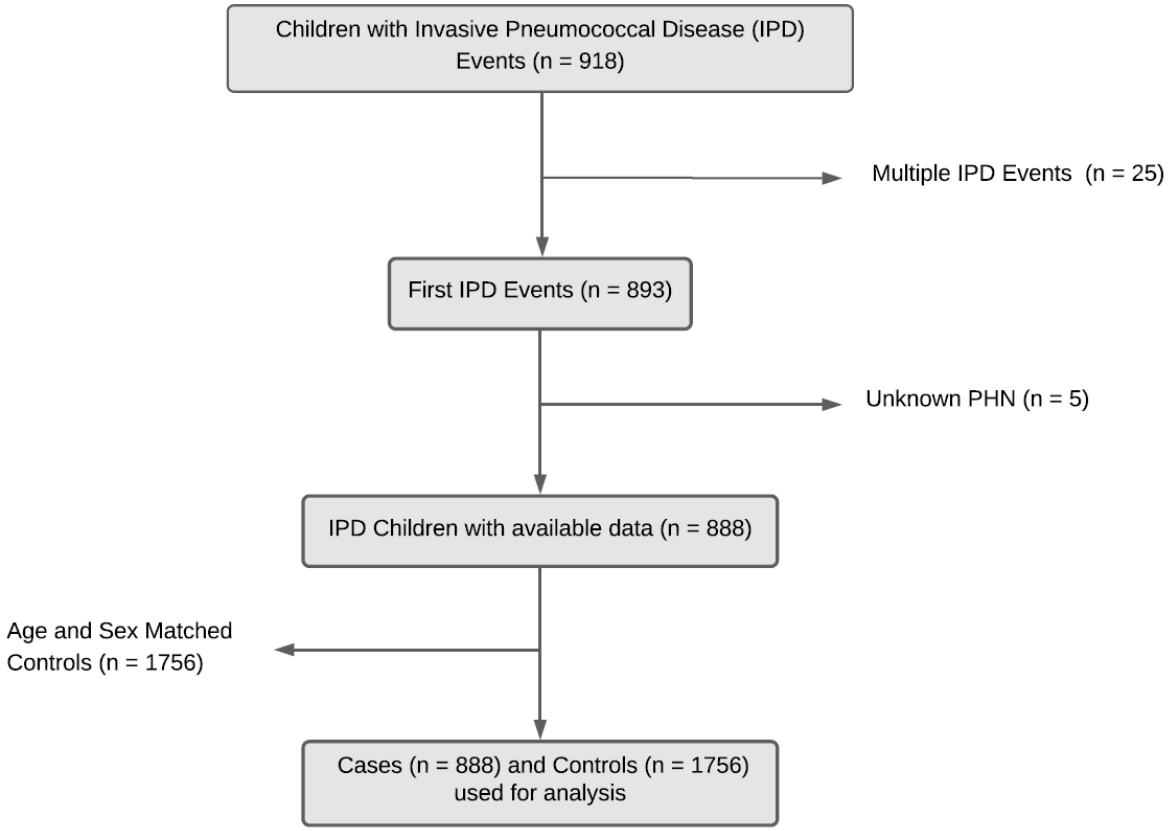
Table 4: First Hospitalization Outcomes of Patients with IPD Relative to Matched Controls

	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)	0.232
>90 Days	173/629 (27.5%)	27	475/1514(31.4%)	33	0.82 (0.69 - 0.98)	0.82 (0.69 - 0.98)	0.025
Overall	408/888 (45.9%)	63	702/1756(40.0%)	49	1.31 (1.16 - 1.49)	1.31 (1.16 - 1.48)	<0.001

Table 5: Case vs. Control Adjusted Hazard Ratios for Age Categories by Time Interval - Time to First Hospitalization

	Short Term (<30 days)		Intermediate (30-90 days)		Long Term (>90 days)		Overall Hospitalization	
	aHR (95% CI)	**p-value**	**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)	0.232	0.82 (0.69-0.98)	0.025	1.31 (1.16-1.48)	<0.001
Elixhauser Groups								
Elix < 2	4.59 (3.38-6.24)	<0.001	0.47 (0.22-1.01)	0.054	1.00 (0.81-1.23)	0.996	1.54 (1.31-1.80)	<0.001
Elix ≥ 2	2.55 (1.84-3.52)	<0.001	1.18 (0.72-1.94)	0.516	0.64 (0.46-0.87)	0.005	1.16 (0.95-1.41)	0.135
Age Groups								
< 1 y/o	6.28 (3.66-10.77)	<0.001	1.23 (0.47-3.24)	0.675	1.13 (0.76-1.67)	0.546	2.01 (1.53-2.65)	<0.001
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)	0.072	1.10 (0.86-1.40)	0.446
2-5 y/o	2.94 (1.93-4.47)	<0.001	1.01 (0.53-1.94)	0.974	0.63 (0.45-0.89)	0.009	1.10 0.87-1.38)	0.441
5-10 y/o	2.54 (1.49-4.31)	0.001	1.20 (0.30-4.79)	0.799	1.09 (0.68-1.75)	0.721	1.54 (1.10-2.15)	0.011
10-18 y/o	2.75 (1.47-5.14)	0.001	1.34 (0.45-4.01)	0.597	0.85 (0.54-1.35)	0.495	1.27 (0.90-1.78)	0.174
Sex								
Female	3.30 (2.38-4.57)	<0.001	0.73 (0.39-1.37)	0.329	0.97 (0.75-1.25)	0.809	1.43 (1.19-1.72)	<0.001
Male	3.45 (2.57-4.62)	<0.001	0.81 (0.47-1.40)	0.452	0.72 (0.56-0.91)	0.006	1.23 (1.04-1.45)	0.013

Figure 1: Flow Diagram of Case and Control Inclusion



*PHN: Provincial Healthcare Number

Figure 2: Relative (%) Deaths in Cases versus Controls by Age Category

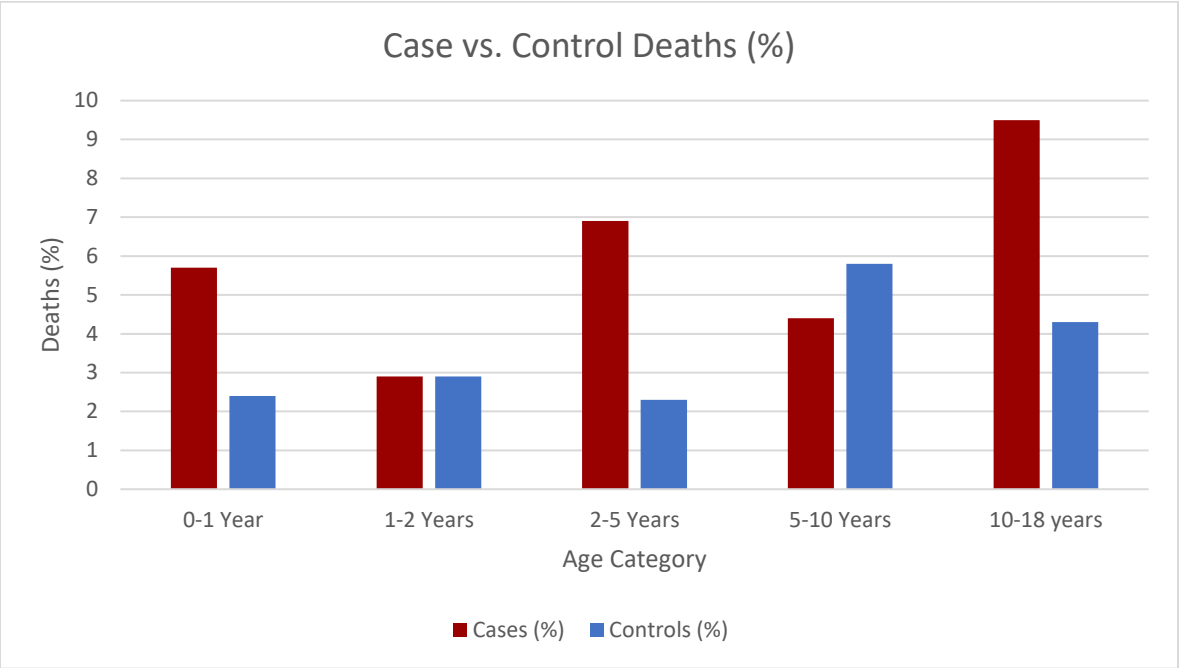
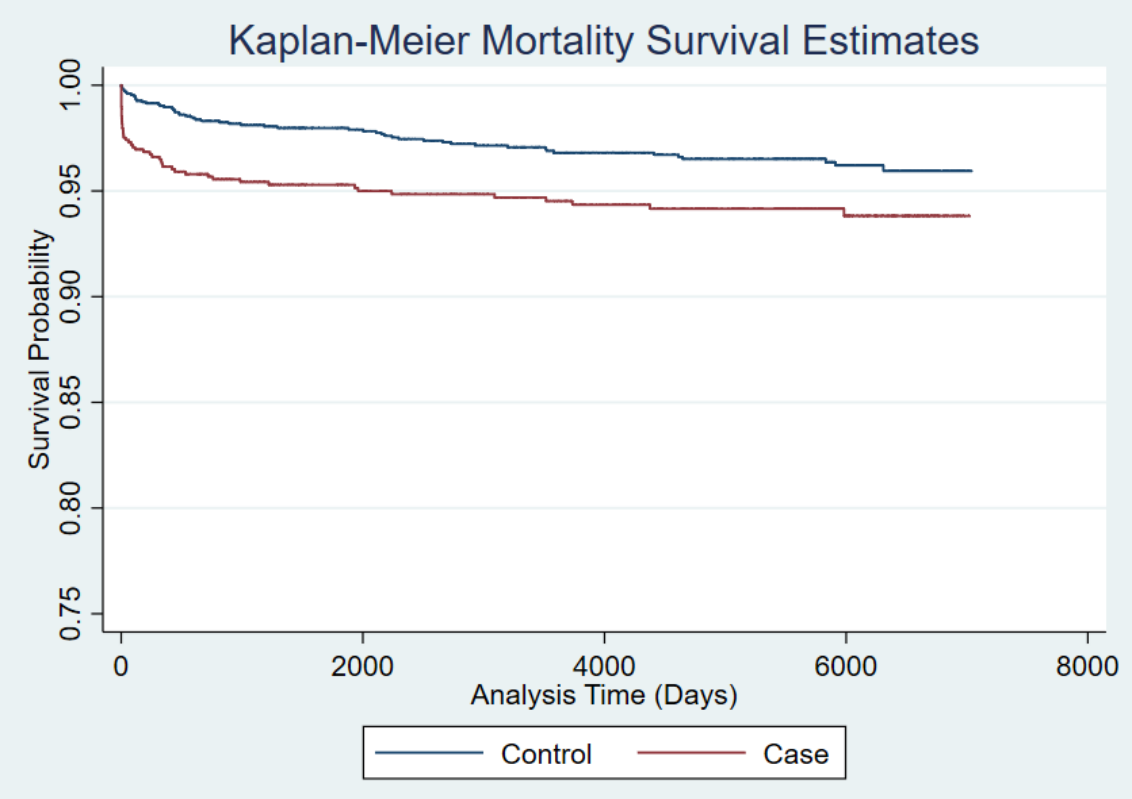


Figure 3: Overall Mortality Kaplan-Meier Survival Estimates Curve Comparing Cases to Controls



3.5 References

1. Weiser JN, Ferreira DM, Paton JC. Streptococcus pneumoniae: transmission, colonization and invasion. *Nat Rev Microbiol*. 2018;**16**(6):355-367. doi:10.1038/s41579-018-0001-8
2. Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infect Dis*. 2004;**4**(3):144-54. doi: 10.1016/S1473-3099(04)00938-7
3. Tan TQ. Pediatric invasive pneumococcal disease in the United States in the era of pneumococcal conjugate vaccines. *Clin Microbiol Rev*. 2012;**25**(3):409-419. doi:10.1128/CMR.00018-12
4. Williams BG, Gouws E, Boschi-Pinto C, *et al*. Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis.* 2002;**2**(1):25-32. doi: 10.1016/s1473-3099(01)00170-0
5. O'Brien KL, Wolfson LJ, Watt JP, *et al*. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *Lancet*. 2009;**374**(9693):893-902. doi: 10.1016/S0140-6736(09)61204-6
6. Centers for Disease Control and Prevention [Internet]. Vaccines and Preventable Diseases. Pneumococcal Vaccination: What Everyone Should Know. 2020; Available at: Pneumococcal Vaccination: What Everyone Should Know | CDC.
7. McClure CA, Ford MW, Wilson JB, *et al*. Pneumococcal conjugate vaccination in Canadian infants and children younger than five years of age: Recommendations and expected benefits. *Can J Infect Dis Med Microbiol*. 2006;**17**(1):19-26. doi:10.1155/2006/835768.
8. Public Health Agency of Canada [Internet]. An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI): Update on the use of pneumococcal vaccines in adults 65 years of age and older – A Public Health Perspective. 2018: Available at: Update on the use of pneumococcal vaccines in adults 65 years of age and older – A Public Health Perspective - Canada.ca
9. Wijayasri S, Hillier K, Lim GH, *et al.* The shifting epidemiology and serotype distribution of invasive pneumococcal disease in Ontario, Canada, 2007-2017. PLoS ONE. 2019;**14**(12): e0226353. https://doi.org/10.1371/journal.pone.0226353
10. Harboe ZB, Dalby T, Weinberger DM, *et al.* Impact of 13-valent Pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. *Clin Infect Dis.* 2014;**59**(8):1066-73. https://doi.org/10.1093/cid/ciu524
11. López EL, Glatstein E, Ezcurra GC, *et al*. Rapid decrease in rates of hospitalization resulting from invasive pneumococcal disease and community-acquired pneumonia in children aged <60 months after 13-valent pneumococcal conjugate vaccine introduction in Argentina. *J Pediatric Infect Dis Soc*. 2018;**7**(1):30-35. doi: 10.1093/jpids/piw089
12. Dreyzin A, McCormick M, Zullo J, *et al*. Impact of PCV-13 vaccine on invasive pneumococcal disease in hospitalised children: A multi-institutional analysis. *Acta Paediatr*. 2021;**110**(2):624-630. doi: 10.1111/apa.15594
13. Navarro-Torné A, Dias J, Hruba F, *et al.* Risk factors for Death from Invasive Pneumococcal Disease, Europe, 2010. *Emerg. Infect. Dis.* 2015;**21**(3):417-25. doi:10.3201/eid2103.140634.
14. Hughes GJ, Wright LB, Chapman KE, *et al.* Serotype-specific differences in short- and longer-term mortality following invasive pneumococcal disease. *Epidemiol Infect.* 2016;**144**(22):2654-69. doi: 10.1017/S0950268816000856
15. Statistics Canada [Internet]. Census Profile, 2016 Census: Alberta and Canada (updated August 9, 2019). 2019; Available at: Census Profile, 2016 Census - Alberta [Province] and Canada [Country] (statcan.gc.ca)

16. Canadian Institute for Health Information [Internet]. Discharge Abstract Database metadata (DAD). 2021; Available at: Discharge Abstract Database metadata (DAD) | CIHI
17. Canadian Institute for Health Information. National Ambulatory Care Reporting System – Open-Year Data Quality Test Specifications, 2019-2020. 2020; Available from: National Ambulatory Care Reporting System Open-Year Data Quality Test Specifications, 2019–2020 (cihi.ca)

Bibliography

1) Australian Government Department of Health [Internet]. Invasive pneumococcal disease in Australia, 2003. 2005; Available at: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-2004-cdi2804a.htm
2) Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infect Dis*. 2004;**4**(3):144-54. doi: 10.1016/S1473-3099(04)00938-7
3) Brooks LRK and Mias GI. *Streptococcus pneumonia*e's virulence and host immunity: aging, diagnostics, and prevention. *Front Immunol* 2018;**9**(1366):1-29.
4) Canadian Institute for Health Information [Internet]. Discharge Abstract Database metadata (DAD). 2021; Available at: Discharge Abstract Database metadata (DAD) | CIHI
5) Canadian Institute for Health Information. National Ambulatory Care Reporting System – Open-Year Data Quality Test Specifications, 2019-2020. 2020; Available from: National Ambulatory Care Reporting System Open-Year Data Quality Test Specifications, 2019–2020 (cihi.ca)
6) Centers for Disease Control and Prevention [Internet]. Nationally Notifiable Infectious Diseases and Conditions, United States: Annual Tables. 2019; Available at: https://wonder.cdc.gov/nndss/nndss_annual_tables_menu.asp
7) Centers for Disease Control and Prevention [Internet]. Pneumococcal Disease: For Laboratorians. 2020; Available at: https://www.cdc.gov/pneumococcal/laboratorians.html
8) Centers for Disease Control and Prevention [Internet]. Pneumococcal Disease: Risk Factors. 2020; Available at: https://www.cdc.gov/pneumococcal/clinicians/risk-factors.html
9) Centers for Disease Control and Prevention [Internet]. Pneumococcal Disease: Surveillance and Reporting. 2020; Available at: https://www.cdc.gov/pneumococcal/surveillance.html
10) Centers for Disease Control and Prevention [Internet]. Pneumococcal Disease: Types of Infection. 2020; Available at: https://www.cdc.gov/pneumococcal/about/infection-types.html
11) Centers for Disease Control and Prevention [Internet]. Travelers' Health. Chapter 4: Travel-Related Infectious Disease: Pneumococcal Disease. 2020; Available at: https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/pneumococcal-disease
12) Centers for Disease Control and Prevention [Internet]. Vaccines and Preventable Diseases: About Pneumococcal Vaccines. 2020; Available at: https://www.cdc.gov/vaccines/vpd/pneumo/hcp/about-vaccine.html
13) Centers for Disease Control and Prevention [Internet]. Vaccines and Preventable Diseases. Pneumococcal Vaccination: What Everyone Should Know. 2020; Available at: Pneumococcal Vaccination: What Everyone Should Know | CDC.
14) Chen H, Matsumoto H, Horita N, *et al.* Prognostic factors for mortality in invasive pneumococcal disease in adults: a system review and meta-analysis. *Sci Rep* 2021;**11**(11865)
15) Christensen JS, Jensen TG, Kolmos HJ, *et al.* Bacteremia with *Streptococcus pneumoniae*: sepsis and other risk factors of 30-day mortality - a hospital-based cohort study. *Eur J Clin Microbiol Infect Dis* 2012;**31**:2719-25.
16) Desai S, Policarpio ME, Wong K, *et al.* The epidemiology of invasive pneumococcal disease in older adults from 2007 to 2014 in Ontario, Canada: a population-based study. *CMAJ Open* 2016;**4**(3):E545-50.
17) Dreyzin A, McCormick M, Zullo J, *et al*. Impact of PCV-13 vaccine on invasive pneumococcal disease in hospitalised children: A multi-institutional analysis. *Acta Paediatr*. 2021;**110**(2):624-630. doi: 10.1111/apa.15594

18) European Centre for Disease Prevention and Control: An Agency of the European Union [Internet]. Invasive pneumococcal disease. 2021; Available at: https://www.ecdc.europa.eu/en/invasive-pneumococcal-disease
19) Feldman C, Anderson R. Recent advances in the epidemiology and prevention of *Streptococcus pneumoniae* infections. *F1000Research* 2020;**9**(F1000 Faculty Rev):338.
20) Floeystad HK, Holm A, Sandvik L, *et al.* Increased long-term mortality after survival of invasive pneumococcal disease: a population-based study. *Infectious Diseases* 2017;**49**(5):365-72.
21) Golden AR, Adam HJ, Karlowsky JA, *et al.* Molecular characterization of predominant *Streptococcus pneumoniae* serotypes causing invasive infections in Canada: the SAVE study, 2011-15. *J Antimicrob Chemother* 2018;**73**(7):vii20-31.
22) Government of Alberta [Internet]. Alberta Population Estimates - Data Tables: Quarterly Alberta total population estimates: 1951-2021 (updated March 18, 2021). 2021; Available at: https://open.alberta.ca/dataset/alberta-population-estimates-data-tables#summary
23) Government of Alberta, Ministry of Health [Internet]. Alberta Public Health Disease Management Guidelines: Pneumococcal Disease, Invasive (IPD). 2019; Available at: health-phdmg-pneumococcal-disease-invasive-2019-12.pdf (alberta.ca).
24) Government of Canada [Internet]. Invasive Pneumococcal Disease. 2019; Available at: Invasive Pneumococcal Disease - Canada.ca
25) Harboe ZB, Dalby T, Weinberger DM, *et al.* Impact of 13-valent Pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. *Clin Infect Dis.* 2014;**59**(8):1066-73. https://doi.org/10.1093/cid/ciu524
26) Hughes GJ, Wright LB, Chapman KE, *et al.* Serotype-specific differences in short- and longer-term mortality following invasive pneumococcal disease. *Epidemiol Infect.* 2016;**144**(22):2654-69. doi: 10.1017/S0950268816000856
27) Li B, Evans D, Faris P, *et al.* Risk adjustment performance of Charlson and Elixhauser comorbidities in ICD-9 and ICD-10 administrative databases. *BCM Health Serv Res* 2008;**8**:12. doi: 10.1186/1472-6963-8-12
28) López EL, Glatstein E, Ezcurra GC, *et al*. Rapid decrease in rates of hospitalization resulting from invasive pneumococcal disease and community-acquired pneumonia in children aged <60 months after 13-valent pneumococcal conjugate vaccine introduction in Argentina. *J Pediatric Infect Dis Soc*. 2018;**7**(1):30-35. doi: 10.1093/jpids/piw089
29) Maimaiti N, Ahmed Z, Isa ZM, *et al.* Clinical burden of invasive pneumococcal disease in selected developing countries. *Value Health Reg Issues* 2013;**2**(2):259-63.
30) Marrie TJ, Tyrrell GJ, Majumdar SR, *et al.* Invasive pneumococcal disease in Northern Alberta, not a Red Queen but a dark horse. *Vaccine* 2018;**36**(21):2985-90.
31) Marrie TJ, Tyrrell GJ, Majumdar SR *et al.* Invasive Pneumococcal Disease: Still Lots to Learn and a Need for Standardized Data Collection Instruments. *Can Respir J.* 2017;**2017**:2397429. doi: 10.1155/2017/2397429.
32) McClure CA, Ford MW, Wilson JB, *et al*. Pneumococcal conjugate vaccination in Canadian infants and children younger than five years of age: Recommendations and expected benefits. *Can J Infect Dis Med Microbiol*. 2006;**17**(1):19-26. doi:10.1155/2006/835768.
33) McNeil SA, Qizilbash N, Ye J, *et al.* A retrospective study of the clinical burden of hospitalized all-cause and pneumococcal pneumonia in Canada. *Can Resp Journal* 2016;1-10 https://doi.org/10.1155/2016/3605834
34) Mitchell AM and Mitchell TJ. *Streptococcus pneumoniae:* Virulence factors and variation. *Clin Microbiol Infect* 2010;**16**(5):411-8.
35) Mook-Kanamori BB, Geldhoff M, van der Poll T, *et al.* Pathogenesis and pathophysiology of pneumococcal meningitis. *Clin Microbiol Rev* 2011;**24**(3):557-91.

36) Navarro-Torné A, Dias J, Hruba F, *et al.* Risk factors for Death from Invasive Pneumococcal Disease, Europe, 2010. *Emerg. Infect. Dis.* 2015;**21**(3):417-25. doi:10.3201/eid2103.140634.
37) O'Brien KL, Wolfson LJ, Watt JP, *et al*. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *Lancet*. 2009;**374**(9693):893-902. doi: 10.1016/S0140-6736(09)61204-6
38) Public Health Agency of Canada [Internet]. An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI): Update on the use of pneumococcal vaccines in adults 65 years of age and older – A Public Health Perspective. 2018: Available at: Update on the use of pneumococcal vaccines in adults 65 years of age and older – A Public Health Perspective - Canada.ca
39) Public Health Agency of Canada [Internet]. Reported cases by age group in Canada, grouped by sex: Notifiable diseases on-line. Pneumococcal Disease, Invasive, 2018. 2021; Available at: Reported cases by age group in Canada, grouped by sex - Notifiable diseases on-line (phac-aspc.gc.ca).
40) Public Health Agency of Canada [Internet]. Vaccine Preventable Disease: Surveillance Report to December 31, 2015. 2017; Available at: vaccine-preventable-disease-eng.pdf (canada.ca).
41) Public Health Ontario [Internet]. Infectious Disease Trends in Ontario. 2019; Available at: https://www.publichealthontario.ca/data-and-analysis/commonly-used-products/reportable-disease-trends-annually#/52
42) Schoenmakers MCJ, Hament JM, Fleer A, *et al.* Risk factors for invasive pneumococcal disease. *Rev Med Microbiol* 2002;**13**(1):29-36.
43) Statistics Canada [Internet]. Census Profile, 2016 Census: Alberta and Canada (updated August 9, 2019). 2019; Available at: Census Profile, 2016 Census - Alberta [Province] and Canada [Country] (statcan.gc.ca)
44) Tan TQ. Pediatric invasive pneumococcal disease in the United States in the era of pneumococcal conjugate vaccines. *Clin Microbiol Rev*. 2012;**25**(3):409-419. doi:10.1128/CMR.00018-12
45) Torres A, Blasi F, Dartois N, *et al.* Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. *Thorax* 2015;**70**:984-9.
46) Vadlamudi NK, Patrick DM, Hoang L, *et al.* Incidence of invasive pneumococcal disease after introduction of the 13-valent conjugate pneumococcal vaccine in British Columbia: a retrospective cohort study. *PLoS One* 2020;**15**(9)e0239848. doi: 10.1371/journal.pone.0239848
47) Wagenvoort G, Sanders E, de Melker H, *et al.* Long-term mortality after IPD and bacteremic versus non-bacteremic pneumococcal pneumonia. *Vaccine* 2017;**35**(14)1749-57.
48) Weiser JN, Ferreira DM, Paton JC. Streptococcus pneumoniae: transmission, colonization and invasion. *Nat Rev Microbiol*. 2018;**16**(6):355-367. doi:10.1038/s41579-018-0001-8
49) Wijayasri S, Hillier K, Lim GH, *et al.* The shifting epidemiology and serotype distribution of invasive pneumococcal disease in Ontario, Canada, 2007-2017. *PLOS ONE* 2019;**14**(12):e0226353. doi: 10.1371/journal.pone.0226353
50) Williams BG, Gouws E, Boschi-Pinto C, *et al*. Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis.* 2002;**2**(1):25-32. doi: 10.1016/s1473-3099(01)00170-0
51) World Health Organization, Vaccine-Preventable Diseases Surveillance and Standards. Pneumococcus. 2018; Available at: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_17_Pneumococcus_R2.pdf?ua=1