Invasive Pneumococcal Disease: Still Lots to Learn and a Need for Standardized Data Collection Instruments

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Abstract

Background. Large studies of invasive pneumococcal disease (IPD) are frequently lacking detailed clinical information. Methods. A population-based 15-year study of IPD in Northern Alberta. Results. 2435 patients with a mean age of 54.2 years formed the study group. Males outnumbered females and Aboriginal and homeless persons were overrepresented. High rates of smoking, excessive alcohol use, and illicit drug use were seen. Almost all (87%) had a major comorbidity and 15% had functional limitations prior to admission. Bacteremia, pneumonia, and meningitis were the most common major manifestations of IPD. Almost half of the patients had alteration of mental status at the time of admission and 22% required mechanical ventilation. Myocardial infarction, pulmonary embolism, and new onset stroke occurred in 1.7, 1.3, and 1.1% of the patients, respectively; of those who had echocardiograms, 35% had impaired ventricular function. The overall in-hospital mortality was 15.6%. Conclusions. IPD remains a serious infection in adults. In addition to immunization, preventative measures need to consider the sociodemographic features more carefully. A standard set of data need to be collected so that comparisons can be made from study to study. Future investigations should target cardiac function and pulmonary embolism prevention in this population.

1. Introduction

Streptococcus pneumoniae from the time of its discovery by Louis Pasteur in 1881 to the present day has been an important human pathogen [1]. The capsule of the pneumococcus, composed of polysaccharides, helps it avoid host defenses and hence it is a major virulence factor [2]. Challenges in finding an effective vaccine have been the number of capsular types (of which there are currently 94) and the fact that polysaccharides are not very antigenic [3]. Fortunately most of the cases of pneumococcal disease are caused by a smaller number of capsular serotypes and conjugating the polysaccharide with a protein has led to more effective vaccines [3].

There have been numerous prior studies of invasive pneumococcal disease (IPD) ranging from those with small numbers that are rich in clinical detail to those that are very large and are focused on the intended and unintended consequences of vaccination but lack necessary clinical details [4–7]. We, however, took advantage of the fact that pneumococcal protein conjugate vaccine seven (PCV-7) was introduced in Alberta, Canada, in 2002 and PCV-13 in 2010 to conduct a study of “IPD” in Northern Alberta. We specifically undertook a comprehensive and population-based study from 2000 to 2014 to provide a detailed description of invasive pneumococcal disease in a modern era. We feel this is of utmost importance as it will serve as bench mark for other studies.

2. Methods

2.1. Definitions. Cases of IPD were defined as per the national case definition of isolation of S. pneumoniae from a normally sterile site such as blood, CSF, pleural fluid, biopsy tissue,
Table 1: Sociodemographic and lifestyle features in 2435 adults with invasive pneumococcal disease.

| Feature                                      | Number | Percent |
|----------------------------------------------|--------|---------|
| Number studied                               | 2435   | 100     |
| Number of males                              | 1380   | 56.7    |
| Mean age (SD)                                | 54.2 (17.8) | 12.8 |
| Aboriginal (first nations)                   | 312    | 12.8    |
| To hospital by ambulance                      | 1098   | 45.1    |
| Admission status                             |        |         |
| Never seen at a hospital                     | 3      | 0.1     |
| Outpatient only with visits for IV antibiotics| 10     | 0.4     |
| Emergency Room only                          | 229    | 9.4     |
| Inpatient                                    | 2193   | 90.1    |
| Residence prior to admission                 |        |         |
| Home                                         | 1960   | 80.5    |
| Homeless, no shelter                         | 98     | 4.0     |
| Homeless, shelter                            | 86     | 3.5     |
| Lodge/group home                             | 119    | 4.9     |
| Continuing care facility                     | 60     | 2.5     |
| Subacute care                                | 7      | 0.3     |
| Functional status in the week prior to admission |      |         |
| Fully functional                             | 2078   | 85.4    |
| Walking with assistance                      | 302    | 12.4    |
| Wheelchair                                   | 37     | 1.5     |
| Bedridden                                    | 18     | 0.7     |
| Smoker, current                              | 1104   | 45.3    |
| Alcohol, excess use                          | 620    | 25.5    |
| Illicit drug use                             | 482    | 19.8    |

joint aspiration, pericardial fluid, or peritoneal fluid [8]. IPD is a provincially notifiable disease in Alberta; therefore all invasive pneumococcal isolates are submitted to the Provincial Laboratory for Public Health (PLPH) for further characterization. This allowed us to prospectively identify all cases of IPD in Northern Alberta.

2.2. Clinical Data Collection. Research nurses collected sociodemographic, clinical, functional, and laboratory data using a standardized case report form (CRF). The research nurses received training on data collection prior to the start of the study. In addition to the CRF, standard operating procedures documents, definitions, drug classification, and underlying illness categorization were part of their working documents. With respect to underlying illnesses, if the attending physician recorded such an illness it was accepted as such. From September 2012 through the end of the study December 31, 2014, additional data were collected for a substudy examining cardiac events during the hospital stay. Our study received approval from the institutional research review committees of the Alberta Health Regions as well as the University of Alberta ethics review board.

2.3. Identification and Serotyping of S. pneumoniae Isolates. Streptococcus pneumoniae isolates were received at the Provincial Laboratory of Public Health from diagnostic laboratories in Alberta as per requirements of provincial notifiable disease regulations. The isolates were confirmed as S. pneumoniae based on characteristic morphology and optochin susceptibility [9]. All pneumococcal isolates that exhibited a positive Quellung reaction using commercial type specific antisera obtained from Statens Serum Institute, Copenhagen, Denmark, were assigned a serotype designation. Strains that were susceptible to optochin but which failed to serotype using the Quellung assay were assayed further using AccuProbe™ Streptococcus pneumoniae culture identification test, Gen-Probe, San Diego, CA, to confirm the species identification.

2.4. Comparison with Alberta Population. For comparison purposes some characteristics of the Alberta population were obtained from the Alberta Ministry of Health interactive website [10]. The representation of various occupations constituting the workforce in Alberta was from [11].

3. Results

Two thousand four hundred and thirty-five patients with a mean age of 54.2 years had IPD over the 15 years of the study. Across all age groups, males were more likely to have IPD than females. Other sociodemographic features of the study population are given in Table 1. Noteworthy is that 7.5% were homeless and 15% had some functional limitations in the weeks prior to presentation. The occupations of those
who were working are presented in Table 2. For the most part these are similar to the Alberta population. Construction work is overrepresented and 36% of this group were welders. Teachers and health care workers were not at greater risk than the general population.

Comorbid illnesses were common, being present in 98.9% (Table 3). If all cardiovascular conditions are combined, then, fully 45% of the study population were affected prior to presentation. Individually and apart from hypertension, COPD, recent cancer, and hepatitis C were most common.

The manifestations of IPD are presented in Table 4. Bacteremia and pneumonia were most common and the pneumonia patients by definition were bacteremic. Otherwise, meningitis was the most common manifestation of IPD (4.9%) while endocarditis/pericarditis were least common (<1%).

The complications and outcomes from IPD are shown in Table 5. Almost half the patients had altered mental status at the time of admission. Most (748/1039 [72%]) patients with altered mental status had a Glasgow Coma Score value recorded: only 7.5% had a score of 15 while 40.6% had a value of 10 or less with 200 having a score of 3. One-quarter of patients were admitted to ICU and 88.5% of these patients required mechanical ventilation. Most of the acute complications occurred on hospital day 1 including admission to ICU, 557/618 (90%); peritonitis, 33/39 (84%); cardiac arrest, 51/70 (73%); liver failure, 36/62 (58%); heart failure, 51/90 (57%); myocardial infarction, 44/78 (56%); renal failure requiring dialysis, 47/99 (47%).

The substudy (N = 811) related to cardiovascular complications is presented in Table 6. The most common complication was atrial fibrillation, which occurred in more than one in ten patients. What was surprising was that 24% had echocardiograms done, 87% of which were transthoracic, and 8.9% had severely impaired left ventricular function with ejection fractions <30–35%.

Table 7 shows the serotypes in PCV-7, PCV-13, and PPV-23 vaccines. These accounted for 22.7%, 52.3%, and 82.9% of isolates, respectively. An additional five serotypes rounded out those that accounted for 1% or more of the isolates but were not present in the first 23 serotypes listed. Overall these 28 serotypes accounted for 90.3% of the isolates.

### Table 2: Occupations of 581 patients with IPD compared with Alberta population 2015 working in these occupations.

| Occupation                        | IPD Number | IPD % | Alberta population, % |
|-----------------------------------|------------|-------|-----------------------|
| Accommodation, food services      | 37         | 6.3   | 6.5                   |
| Agriculture                       | 22         | 3.7   | 2.2                   |
| Business                          | 17         | 2.9   | 3.4                   |
| Construction                      | 147        | 25.3  | 11.0                  |
| Education                         | 35         | 6.0   | 6.7                   |
| Finance, real estate              | 79         | 13.5  | 4.4                   |
| Forestry, mining, oil, and gas    | 44         | 7.5   | 6.4                   |
| Health care                       | 20         | 3.4   | 11.7                  |
| Professional, science, teacher    | 15         | 2.4   | 7.8                   |
| Transportation                    | 30         | 5.1   | 5.9                   |
| Utilities                         | 3          | 0.5   | 0.7                   |

### Table 3: Comorbid illnesses in 2435 patients with invasive pneumococcal disease.

| Disease                                | Number | Percent |
|----------------------------------------|--------|---------|
| Any underlying disease                 | 2409   | 98.9    |
| Selected underlying diseases           |        |         |
| Epilepsy                               | 136    | 5.6     |
| Alzheimer’s disease                    | 83     | 3.4     |
| Stroke                                 | 106    | 4.4     |
| Hypertension                           | 622    | 25.5    |
| Heart failure                          | 156    | 6.4     |
| Previous myocardial infarction         | 168    | 6.9     |
| Atrial fibrillation                    | 128    | 5.3     |
| Anemia                                 | 167    | 6.9     |
| Insulin dependent diabetes mellitus    | 87     | 3.6     |
| Hepatitis C                            | 307    | 12.6    |
| Cirrhosis                              | 151    | 6.2     |
| HIV/AIDS                               | 117    | 4.8     |
| Asplenia                               | 37     | 1.5     |
| Rheumatoid arthritis                   | 56     | 2.3     |
| Asthma                                 | 266    | 10.9    |
| Chronic obstructive pulmonary disease  | 441    | 18.6    |
| Cancer within the past 5 years         | 307    | 12.6    |
| Lung cancer                            | 53     | 2.1     |
| Multiple myeloma                       | 42     | 1.7     |
| Chronic lymphocytic leukemia           | 19     | 0.7     |
| Lymphoma                               | 17     | 0.7     |
| Acute leukemia                         | 5      | 0.2     |
| Solid organ transplant                 | 14     | 0.6     |
| No underlying disease                  | 26     | 1.1     |
| One underlying disease                 | 2121   | 87.1    |
| Two underlying diseases                | 256    | 10.5    |
| Three underlying diseases              | 32     | 1.3     |

### Table 4: Manifestations of invasive pneumococcal disease among 2435 patients.

| Manifestation     | Number | Percent |
|-------------------|--------|---------|
| Bacteremia        | 2325   | 95.5    |
| Bacteremia source unknown | 316  | 12.9    |
| Pneumonia         | 2009   | 82.2    |
| Meningitis        | 120    | 4.9     |
| Cellulitis        | 65     | 2.7     |
| Sinusitis         | 44     | 1.8     |
| Septic arthritis  | 40     | 1.6     |
| Peritonitis       | 39     | 1.6     |
| Otitis media      | 38     | 1.6     |
| Endocarditis      | 26     | 1.0     |
| Pericarditis      | 20     | 0.8     |
4. Discussion

The percentage of males with IPD at 56.7% was higher than the percentage of females. Despite the introduction of pneumococcal conjugate vaccines the rate of IPD among males remains higher than that among females especially in children and in adults aged 40–64 and >74 years [12]. Most of the patients with IPD had pneumonia and in studies of pneumonia in general males tend to be predominate [13].

People of Aboriginal descent were overrepresented in this study population at 12.8% whereas they constitute about 5.2% of the population of Alberta [10]. It has been noted that among resource poor populations a gap in rates of IPD remains compared with other populations in the same geographic area, a gap that will not be solved by vaccination alone [13, 14].

Almost half the patients with IPD required an ambulance to come to hospital. This is similar to what is observed at a tertiary care hospital in Halifax where 45% of the patients with all-cause pneumonia arrive by ambulance (Petrie D, personal communication). However 90% of our patients were admitted to hospital in sharp contrast to the rate of 47% admission rate for all-cause pneumonia in the Edmonton area but not surprising since most of these patients were bacteremic [15]. The 90% admission rate for patients with IPD is similar to that seen in the USA at 93% prior to introduction of PCV-13 and 95% afterwards [16] but is higher than the 66.9% admission rate among adults of 65 years of age and over with IPD in Ontario [17].

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**Table 5: Complications/outcomes of invasive pneumococcal disease among 2435 patients.**

| Complication                              | Number | Percent |
|-------------------------------------------|--------|---------|
| Altered mental status                     | 1039   | 42.7    |
| Intensive care admission                  | 618    | 25.4    |
| Respiratory failure requiring mechanical ventilation | 547   | 22.5    |
| Pleural effusion                          | 846    | 34.7    |
| Chest tube                                | 255    | 10.5    |
| Aspiration                                | 179    | 7.4     |
| Empyema                                   | 175    | 7.2     |
| Renal failure requiring dialysis          | 99     | 4.1     |
| Congestive heart failure                  | 90     | 3.7     |
| Myocardial infarction                     | 78     | 3.2     |
| Cardiac arrest                            | 70     | 2.8     |
| New onset seizures                        | 67     | 2.8     |
| Upper GI bleed                            | 64     | 2.6     |
| Liver failure                             | 62     | 2.5     |
| Lower GI bleed                            | 31     | 1.2     |
| New onset stroke                          | 28     | 1.1     |
| Pulmonary embolus                         | 11     | 1.3     |
| **Died (in hospital)**                    | 379    | 15.6    |
| Transferred to another acute care facility after admission | 275   | 11.6    |
| Remained in acute care facility after infection cured | 149   | 6.1     |
| Discharged home on antibiotics             | 1370   | 56.3    |
| Home care following discharge             | 288    | 11.8    |

An additional 31 serotypes were represented among the remaining 11.5% of the isolates.

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**Table 6: Cardiac events and investigations 871 patients with IPD.**

| Event or investigation                  | Number | Percent |
|-----------------------------------------|--------|---------|
| Atrial fibrillation                     | 109    | 12.5    |
| Myocardial infarction                   | 15     | 1.7     |
| Asystole                                | 13     | 1.5     |
| Ventricular tachycardia > 30 sec        | 5      | 0.5     |
| Cardiology consultation                 | 60     | 6.8     |
| Coronary angiogram                      | 9      | 1       |
| Echocardiogram                          | 210    | 24.1    |
| Tricuspid regurgitation                 | 114    | 54.3    |
| Mitral regurgitation                    | 112    | 53.3    |
| Aortic regurgitation                    | 25     | 11.9    |
| Valve vegetation                        | 5      | 2.3     |
| Ejection fraction                       |        |         |
| ≥50%                                     | 170    | 80.7    |
| 40–45%                                   | 23     | 10.9    |
| 30–35%                                   | 6      | 2.8     |
| 20–25%                                   | 5      | 2.3     |
| <20%                                     | 8      | 3.8     |
The high rates of tobacco use among homeless persons in Toronto was 273/100,000 per year [19]. One of the reasons for this high rate is crowding, increasing the rate of IPD in this population. Vaccination and other intervention programs should have a high benefit in this population.

In terms of common lifestyle risk factors for IPD, almost half of the patients in our cohort were tobacco smokers. This contrasts with 28.3% of those with all-cause pneumonia in Edmonton requiring hospitalization and with a 28% smoking rate in the general population of Alberta [18, 22]. Smoking is a well-known risk factor for IPD with odds ratio of 4.1 when compared with those without IPD [23]. There is a dose-response relationship with the number of cigarettes smoked per day and those exposed to second-hand smoke are also affected [23]. Furthermore, 25% of our patients self-reported abuse of alcohol, and alcohol abuse is well known to increase both the risk for and the severity of IPD [24–27].

Occupation may also be a risk factor for acquisition of IPD. Previously we found that welders were at increased risk for IPD with a rate of 22.7/100,000 versus 8.7/100,000 in the general adult population [28]. These findings are extended in this study. There were 53 cases among welders, accounting for 36% of all construction workers. Exposure to welding fumes promotes lung inflammation and has been shown in animal models to predispose to pneumonia [28]. Several populations with increased exposure to pneumococcal disease such as health care workers and teachers were not overrepresented. Our classification of occupation was done without reference to the National Occupational Classification Statistics Canada 2011 so some of the occupations are likely misclassified. This applies mostly to business and construction categories.

The vast majority (98.9%) of our patients had one or more comorbid illnesses. Moore et al. found that 76% of the adults with IPD in the USA had an indication for pneumococcal vaccination [16]. While comorbidities that are risk factors for IPD are well recognized and are for the most part indications for vaccination what is not readily recognized is the concept of risk factor stacking [29]. For example, when smoking is added to diabetes, chronic obstructive lung disease, and chronic heart disease the odds ratio for acquisition of IPD increases from 8.5 to >40 [29]. The highest rates of IPD are seen among those who are immunocompromised either by underlying disease or by treatment. In a Toronto study of IPD, 27.8% of the patients were immunocompromised and those with multiple myeloma had a rate of IPD of 847/100,000, for those with acute leukemia it was 220/100,000, and immunosuppressive therapy led to a rate of 20/100,000 [30]. From 2000 to 2004 we used data on IPD Alberta-wide and cancer registry data and found that compared with a rate of 11/100,000 in the general population patients with multiple myeloma had a rate of IPD of 673/100,000 and rates for those with chronic lymphocytic leukemia, acute myelogenous/acute lymphoblastic leukemia, Hodgkin’s disease, and non-Hodgkin’s lymphoma were 124; 129; 47; 63/100,000, respectively [31]. We also found a high rate of IPD disease in patients with lung cancer at 143.6/100,000 [31]. A finding unique to the current study is the overrepresentation of patients with hepatitis C. The implication is that hepatitis C

| Serotype | Number | Percent |
|----------|--------|---------|
| 1        | 28     | 1.1     |
| 3        | 161    | 6.6     |
| 4*       | 219    | 9.0     |
| 5        | 242    | 9.9     |
| 6A       | 51     | 2.1     |
| 6B*      | 42     | 1.7     |
| 7F       | 129    | 5.3     |
| 9V*      | 64     | 2.6     |
| 14*      | 92     | 3.8     |
| 18C*     | 39     | 1.6     |
| 19A      | 113    | 4.6     |
| 19F*     | 53     | 2.2     |
| 23F*     | 45     | 1.8     |
| 2        | 1      | 0.04    |
| 8        | 193    | 7.9     |
| 9N       | 65     | 2.7     |
| 10A      | 17     | 0.7     |
| 11A      | 80     | 3.3     |
| 12F      | 70     | 2.9     |
| 15B      | 15     | 0.6     |
| 17F      | 27     | 1.1     |
| 20       | 93     | 3.8     |
| 22F      | 176    | 7.2     |
| 32F      | 0      | 0       |
| 33F      | 45     | 1.8     |
| 16F      | 33     | 1.4     |
| 23A      | 39     | 1.6     |
| 23B      | 30     | 1.2     |
| 16F      | 33     | 1.4     |

The first 13 serotypes are in PCV-13 and first 23 in PPV-23. * denotes serotypes in PCV-7. The final four serotypes represent the remaining serotypes that accounted for ≥1% of the isolates beyond those in the 23-valent vaccine.
should be added to the list of indications for pneumococcal vaccination [32].

From 1935 to present, pneumonia has remained the major manifestation of IPD [33–35]. Meningitis has been the second most common manifestation [34, 35] and endocarditis has remained uncommon at about 1% [33, 35]. Although the clinical presentation of IPD has not changed much over time, the mortality rate from IPD has declined from 77.5% in the preantibiotic era to 24.7% in the early antibiotic era to 16.9% at the turn of the 21st century and in-hospital mortality remains too high at 15.6% in our study [33–35]. Austrian and Gold noted in patients with IPD that deaths within the first 5 days

Pulmonary embolism occurred in 1.3% of our patients. From 2.2 to 17% of all strokes have onset during hospitalization for a diagnosis or procedure other than stroke [39]. In a systematic review of trigger factors for ischemic stroke, Guiraud et al. found that infection within the previous week was such a trigger factor with odds ratio of 2.91 (1.41–6) and respiratory tract infection had odds ratio of 2.4 (1.2–4.8) [40]. Hospitalization for infection within 14 days was associated with an increased risk of stroke, OR 8 (1.6–77.3). In a cohort of 5639 patients followed for a median of 12.2 years, 889 developed a stroke within 14 days of hospitalization for some other illness. Twenty-nine of these patients had at least one hospitalization for infection during the preceding 90 days [41]. The infections were mainly of the respiratory or urinary tracts [41].

Pulmonary embolism occurred in 1.3% of our patients. Investigators from Taiwan found that patients with pneumococcal pneumonia were 1.97 times more likely to have a pulmonary embolus than age and sex matched controls without pneumonia [42]. There are likely several factors that predispose to pulmonary embolism in this population, namely, bed-ridden state for 3 or more days and procoagulant effect of infection [43, 44]. In a retrospective review of 1180 medical inpatients, 0.3% of those at low risk for venous thromboembolism (VTE) developed a pulmonary embolus versus 7.5% for those at high risk [45]. Thus the overall population of adult patients with IPD is at intermediate risk and should be evaluated for known risk factors for VTE and if present receive prophylaxis [46]. Clearly this is another area in need of further study.

Several of the complications that occurred were pneumonia specific. Thus decortication was necessary because of late stage empyema. Bronchopleural fistula is an uncommon complication that occurs because cavitating pneumonia results in a pneumothorax [47]. Necrotizing pneumococcal pneumonia resulting in cavitation is more common than previously appreciated. With the widespread use of computed tomographic scanning in patients with pneumococcal pneumonia 15/136 (11%) were found to have such changes [48].

While necrotizing fasciitis is more commonly associated with Group A Streptococcus it does occur with S. pneumoniae [49]. Sixty-five (2.7%) of our patients had cellulitis of whom 2 had necrotizing fasciitis. Streptococcus pneumoniae is secondary only to the meningococcus as a cause of purpura fulminans [50]; however to 1997 only 43 such cases had been described [51]. In contrast to meningococemia patients with pneumococcal induced purpura fulminans are often not hypotensive and 51% to 63% are asplenic [51]. The mortality rate was 60% [49]. Our experience of 1 such case among 2435 adult patients suggests that it is uncommon but may be more common than reported in the literature.

Because of a growing literature on the cardiovascular sequelae of sepsis in general [52–57] and pneumococcal infection in particular [52–57, 58], we undertook a substudy of cardiovascular complications and risk factors part way through the study (from 2012 to 2014). Acute myocardial infarction is not uncommon following pneumonia with rates ranging from 1.5% to 15% [52, 53, 58]. However the 15% rate was in patients with severe pneumonia [53]. Rhythm disorders are also common, with 12% having a new diagnosis of cardiac arrhythmia within 90 days of admission for pneumonia [54]. Atrial fibrillation is most common, but other dysrhythmias do occur as in this study where 1.5% of patients had one or more episodes of asystole and 0.3% had ventricular tachycardia. A striking finding from our study was that 35% of patients who had an echocardiogram performed had an ejection fraction of <50% indicating systolic dysfunction. Myocardial dysfunction in sepsis has been recognized for some time and this dysfunction may be systolic or diastolic [59–61]. While several factors may play a role in the pathogenesis of cardiovascular complications during the course of IPD the pneumococcus does play a direct role. In both animal models and humans, translocation of S. pneumoniae into the myocardium has been observed during pneumococcal sepsis [55]. It has also been shown that pneumolysin causes microscopic lesions in the myocardium [55]. Some interventions may be beneficial; thus aspirin resulted in lower 30-day mortality following pneumonia in one study [56] and vaccination with pneumococcal polysaccharide vaccine was associated with fewer acute coronary syndrome events in another [57].

Table 7 shows selected serotyping data. Fifty-two percent of the isolates had serotypes that are in the current PCV-13 formulation. While 59 serotypes were present overall, 28 accounted for 90.3% of all cases of IPD over the 14 years of the study. The serotype shifts over the course of the study are not shown but it is apparent that more effective control of
IPD in adults will require new vaccine strategies. Indeed a 15-valent PCV which contains serotypes 22F and 33F in addition to the PCV-13 serotypes is currently undergoing clinical trials [62]. Serotype 22F accounted for 7.2% of the isolates in our study about the same as the 9.8% reported Canada-wide from 2011 to 2014 [63]. Serotype 33F accounted for 3% of isolates in Canada and 1.8% in our study. The Canada-wide study included children and adults [62].

A strength of this study is the detailed collection of data which allow for a full appreciation of the various epidemiological and clinical factors in IPD. This strength is also a weakness in that in some areas necessary data were not collected. However what the study does do is allow for the development of a standardized data collection instrument which can be used in all future such studies so that comparisons from study to study can be made. There are also several noteworthy limitations to our study. First and foremost, we do not have detailed immunization data for these patients. Second, comorbidities and complications were based on physician records and not necessarily standardized definitions. For example, serial troponins were not collected on all IPD patients nor were echocardiograms done on all patients. Third, biomarkers and measures of inflammatory response were not routinely collected. Fourth, we did not gather data on the few IPD patients that may not have been admitted to hospital. Last, our cohort, though population based, was drawn from the northern half of one province in Canada and some may be concerned that our results are not generalizable to other jurisdictions or nations.

In conclusion, IPD remains a serious infection in adults. Preventative measures to improve vaccination rates especially in the elderly and groups at higher risk that may be harder to reach as shown in this study are needed [63]. Addressing sociodemographic factors that put individuals at higher risk for IPD is also necessary. A standard set of data should be collected so that comparisons can be made from study to study. Future investigations should focus on further elucidation of the cardiovascular effects of IPD and what can be done to ameliorate these effects.

Disclosure

The funders had no role in the design of the study or data analysis and they have not seen the manuscript.

Conflicts of Interest

Other than the two research grants mentioned in the Acknowledgments, authors declare no conflicts of interest.

Authors’ Contributions

T. J. Marrie and G. J. Tyrrell designed the study, organized the data collection, and had full access to all of the data in the study. Dean T. Eurich conducted all analyses and had full access to the data. T. J. Marrie, G. J. Tyrrell, Dean T. Eurich, and Sumit R. Majumdar wrote the manuscript. All authors contributed to the interpretation of data, revising the manuscript for intellectual content, and approving the manuscript to be published.

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