Identifying Prognostic Factors for Adverse Outcomes in Adults with Bacteremic Pneumococcal Pneumonia

by

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ABSTRACT

Bacteremic pneumococcal pneumonia (BPP) is a severe form of invasive pneumonia that continues to cause significant morbidity and mortality worldwide, yet large-scale studies identifying prognostic factors for adverse outcomes in patients with BPP is significantly lacking. Furthermore, considerable knowledge gaps and conflicting results exist for even widely known prognostic factors for mortality such as smoking.

Therefore, the first objective of this program of research was to identify prognostic factors associated with mortality and in-hospital complications in adult patients with BPP. This objective was achieved using a population-based cohort study composed of 1636 adults (≥18 years) with BPP hospitalized between 2000-2010 in Northern Alberta, Canada. The results indicated that both acid-suppressing drugs and guideline discordant antibiotic treatments are potentially modifiable prognostic factors. Furthermore, frailty (i.e. elderly, nursing home residents, or dementia patients), pneumonia severity, and high case fatality rate (CFR) serotypes were associated with an increased risk of morbidity and mortality, while prior pneumococcal vaccination was associated with a reduced risk. Paradoxically, current smoking was associated with reduce mortality in patients with BPP.

Building on this result, the second objective of this research program was to examine whether differential acquisition of pneumococcal serotypes in smokers could potentially explain the influence on mortality. The results indicated that current smokers were more

likely to be infected with low CFR pneumococcal serotypes compared to non-smokers, which may fully, or partially, explain the reduced mortality previously reported in studies involving patients with CAP.

Collectively this research suggests that several modifiable prognostic factors exist in patients with BPP. Moreover, additional follow-up in patients who are frail following BPP may also be warranted. As this research is the first to suggest that differential acquisition of low CFR serotypes may explain the reduced mortality in smokers with pneumonia, further research is needed to confirm these findings and determine the usefulness of providing CFR data rapidly at the point of care.

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LIST OF ABBREVIATIONS

ACIP - Advisory Committee on Immunization Practices

ATS – American Thoracic Society

AIDS - Acquired Immune Deficiency Syndrome

ARDS - Acute Respiratory Distress Syndrome

BPP - Bacteremic Pneumococcal Pneumonia

CAP - Community Acquired Pneumonia

CFR - Case Fatality Rate

CI - Confidence Interval

COPD - Chronic Obstructive Pulmonary Disease

CRB-65 - Confusion, Respiratory Rate, Systolic/Diastolic Blood Pressure, Age ≥ 65

CSF - Cerebral Spinal Fluid

CURB-65 – Confusion, Blood Urea Nitrogen, Respiratory Rate, Systolic/Diastolic Blood Pressure, Age ≥ 65

GI - Gastrointestinal

IDSA – Infectious Disease Society of America

ICU - Intensive Care Unit

IPD - Invasive Pneumococcal Disease

MACE - Major Adverse Cardiovascular events

OR - Odds Ratio

PBS – Pitt Bacteremia Score

PCV7 - Pneumococcal Conjugate Vaccine (7 serotypes)

PCV13 - Pneumococcal Conjugate Vaccine (13 serotypes)

PHAC - Public Health Agency of Canada

PPV23 - Pneumococcal Polysaccharide Vaccine (23 serotypes)

PSI - Pneumonia Severity Index

RR - Risk Ratio

CHAPTER 1: INTRODUCTION

1.1 Statement of the Problem

Pneumonia is the seventh leading cause of death in the United States. It accounts for an estimated $9 billion in direct health care costs and 600,000 admissions to hospital each year.[1-3] Similarly, in Canada, pneumonia accounts for over one million doctor visits and 60,000 hospitalizations annually.[4] At least 30-50% of all cases of community-acquired pneumonia (CAP) are believed to be caused by *Streptococcus pneumoniae* (pneumococcus).[5,6]

Pneumococcal infections can be broadly divided into invasive and non-invasive disease. Non-invasive pneumococcal disease includes otitis media, sinusitis, and pneumonia, while invasive pneumococcal disease (IPD), defined as the isolation of *S. pneumoniae* from a normally sterile site, typically manifests as bacteremia alone, meningitis, or most commonly as bacteremic pneumonia.[7] The clinical and economic impact of pneumococcal pneumonia (with or without bacteremia) is substantial. In 2004 alone, pneumococcal pneumonia caused 866,000 illness episodes, and 19,000 deaths in the United States.[1] Additionally, direct medical costs for all pneumococcal diseases totalled $3.5 billion, and pneumococcal pneumonia in particular was responsible for 72% of the total cost.[1]

Bacteremia accompanies pneumonia in 25% of adults with pneumonia.[8,9]Although relatively uncommon, bacteremic pneumococcal pneumonia (BPP) is often a severe life

threatening infection that can result in major adverse outcomes including septic shock, cardiac failure, mechanical ventilation, acute respiratory distress syndrome (ARDS), and death.[10] The case fatality rate of patients with BPP in the pre-antibiotic era was as high as 80%; today approximately 20% of hospitalised patients still die despite appropriate early antibiotic therapy, adjunctive treatments, and intensive supportive care.[11-13] This indicates that other non-therapy related factors are responsible for influencing adverse patient outcomes. Identifying important and potentially modifiable prognostic factors for adverse outcomes would lead to a greater understanding of the natural history of the disease and could potentially alter therapeutic approaches and guide targeted intervention strategies.

1.2 Bacteremic Pneumococcal Pneumonia

1.2.1 Epidemiology

S. pneumoniae is a gram-positive bacterium that normally colonizes the human nasopharynx.[14] Humans are the only natural reservoir for pneumococcus and transmission from person to person is thought to mainly occur through droplets or aerosols.[14] The asymptomatic carriage of pneumococcus begins during infancy with a prevalence rate of 30-60% in infants.[14] As a person ages, the prevalence of pneumococcal carriage decreases where approximately only 1-10% of adults carry pneumococcus.[14] In some instances, *S. pneumoniae* is able to spread past the nasopharynx to cause either non-invasive disease or IPD.

In order to track the global or local spread of pneumococci, it is common to serotype the capsular polysaccharide.[15] The polysaccharide capsule is the main virulence factor for *S. pneumoniae*, primarily by protecting the bacteria from opsonization and phagocytosis.[15] There are currently 93 unique pneumococcal serotypes that have been characterized.[16,17] Most, if not all of these serotypes are capable of causing serious disease in humans, however certain serotypes have been found to be much more likely than others to cause invasive disease.[18] One study by Robbins and colleagues used a total of 13,616 different pneumococcal strains isolated from patients with invasive infections in several countries, to demonstrate that the prevalence of pneumococcal serotypes is uneven.[19] For instance they found that only 30 of the most prevalent types of pneumococcal serotypes accounted for 91.5% of all cases of IPD.[19] Therefore, pneumococcal serotypes vary in their potential to cause invasive disease. Moreover, in a meta-analysis by Bruggemann et al. composed of invasive and carriage pneumococcal isolates from children in different countries showed that the invasive disease potential for each serotype did not vary appreciably temporally or geographically.[20] Multiple studies have also noted that there is an inverse relationship between the invasiveness of a serotype and its carriage prevalence.[20,21]

BPP is estimated to account for 9–18 cases per 100,000 adults per year.[22,23] In 2012, the United States reported 2,101 cases of BPP in a surveillance area representing 30,356,544 persons including children and adults.[24] Incidence rates also depend on age. This was well demonstrated in one American study conducted between 1993-1997 where the annual incidence in the age group 20-29 was 3.4 per 100,000 persons, for those aged 70-79 it was 38.5 per 100,000 persons, and for ages 80 and above it was 76.2 per 100,000

persons.[25] Other factors such as smoking have also been shown to affect incidence rates of BPP. The incidence of BPP for smokers has been shown to be 16.3 (95% CI, 14.6−18.1) cases per 100,000 person-years compared to 5.1 (95% CI, 4.2−6.2) cases per 100,000 person-years for nonsmokers.[26] From a Canadian perspective, one study from Edmonton, Alberta, reported an incidence rate of 9.7/100,000 person years in adults over the age of 17 with BPP.[27]

The case fatality rates among patients with BPP vary widely across studies and region. Case fatality rates have been highest in studies from Chile (33%),[28] Canada (21%),[27]and the US (20.3%),[25] compared with lower rates in Spain (11%) and Sweden (9.3%).[29] Furthermore, the study from the United States reported that the majority of deaths occurred among adults over the age of 50 years.[25] Although the exact reason for the different case fatality rates between countries remains unclear, potential explanations include differences in serotypes, treatment and supportive care, or severity of illness.

1.2.2 Risk Factors

Since BPP is a subgroup of IPD, the majority of studies investigating risk factors for IPD tend to include BPP patients. The main risk factors identified for IPD include extremes of age (<2 years or > 65 years), comorbidities or immunodeficiencies, and certain lifestyle factors (e.g. drug abuse, smoking, and excessive alcohol consumption).[30] According to the Public Health Agency of Canada (PHAC) conditions associated with an increased risk of IPD include: chronic cerebral spinal fluid (CSF) leak, chronic neurologic condition that may impair clearance of oral secretions, cochlear implants, chronic cardiac or

pulmonary disease, diabetes mellitus, chronic kidney disease, chronic liver disease, asthma, sickle cell disease, congenital immunodeficiencies, asplenia, immunocompromising therapy, HIV infection, hematopoietic stem cell transplant, malignant neoplasms including leukemia and lymphoma, nephrotic syndrome, and solid organ or islet transplant.[31] Others have also found that increasing age,[32,33] male sex,[33,34] alcohol abuse,[35,36] cigarette smoking,[36,37] and crowding,[38] are major risk factors for IPD.

Two studies have investigated whether there are risk factors for developing bacteremia in patients with pneumonia. Among 3116 patients hospitalized with CAP, Falguera et al found that the presence of chronic liver disease, pleuritic pain, tachycardia, tachypnea, systolic hypotension, and the absence of prior antibiotic therapy were risk factors for bacteremia in patients with CAP.[39] However, several of these may be manifestations of subclinical disease or markers of the host response to the infection. In the second study, Kang and colleagues found that the use of immunosuppressant drugs, diabetes mellitus, and younger age (<65 years), were independent risk factors associated with the development of bacteremic pneumonia in 981 patients with pneumococcal CAP.[40]

1.2.3 Diagnosis and Treatment

The diagnosis of pneumonia is largely empirical and is initially based on a patient's history, comorbidities, select clinical features (e.g., cough, fever, sputum production, and pleuritic chest pain) and potential radiographic findings.[22] Once a clinician has made a tentative diagnosis of pneumonia, the next step is to assess the severity of illness. This is a crucial step since all major decisions regarding the management of CAP, including

further diagnostic testing and treatment issues, revolve around the initial assessment of severity.[22] Currently, the decision to hospitalize patients with CAP is based on the risk of death, the stability of the patient's clinical condition, and complications.[22] Several severity of illness scoring systems have been developed in order to aid clinicians in assessing the severity of infection and to predict the risk of death. These include the Pneumonia Severity Index (PSI),[41] the CURB-65 scoring system,[42] the CRB-65 scoring system (without the uraemia),[43] the modified-American Thoracic Society (ATS) scoring system,[44] the Infectious Disease Society of America (IDSA)/ATS guidelines,[45] and the Pitt Bacteremia Score (PBS)[46] (**Tables 1-1 and 1-2**). In a study by Feldman et al., the accuracy of each of these severity of illness scores to predict 14-day mortality were evaluated in 844 patients with BPP.[47] The PBS and modified-ATS scoring systems were found to be the most specific in predicting mortality, whereas the PSI and the IDSA/ATS guidelines were the most sensitive.[47] These results were similar to a study by Spindler et al., which found high sensitivity for the PSI (score ≥ 4), CURB-65 (score ≥ 2), and ATS (1 major or > 1 minor criteria), but lower specificity for predicting death in patients with BPP.[48]

Once a clinician has determined that a patient with CAP should be hospitalized, current guidelines on the management of CAP in adults recommend that antibiotic therapy be commenced as soon as possible after the diagnosis of CAP is considered.[22] Therefore, current Canadian guidelines recommend that all patients hospitalized with CAP be initially treated with antibiotics that cover the most common typical (e.g., pneumococcus, *haemophilus influenzae*) and atypical organisms (e.g., mycoplasma, chlamydia), namely,

the combination of a macrolide with a beta-lactam, or monotherapy with a respiratory fluoroquinolone.[9] Importantly, these guidelines are aimed at CAP in general and whether dual therapy is associated with reduced mortality in BPP is uncertain.[25,43,44]

A definitive diagnosis of pneumococcal pneumonia with bacteremia requires that *S. pneumoniae* be isolated from the blood. Blood cultures are recommended in all hospitalized patients in Canada, preferably before antibiotic treatment.[45] However, blood cultures have been estimated to yield positive results for *S. pneumoniae* in less than 10% of patients who have pneumococcal pneumonia.[46] This low rate may be due to the rarity of bacteremia in pneumococcal pneumonia (25%), autolysis of *S. pneumoniae*, pre-antibiotic treatment, or inadequate samples.[46] Therefore, the conventional tests have been questioned for their clinical usefulness, and the number of cases of BPP may be significantly underestimated due to the insufficiency of these standard diagnostic tests.[47] However, new diagnostic techniques such as the serotype-specific urinary antigen test, and polymerase chain reaction (PCR) have been shown to be more promising options for the diagnosis of BPP in the future.[48,49]

1.2.4 Prevention

As important as diagnosis and treatment are, from a public health perspective, prevention through various vaccination strategies is of the utmost import. The current polysaccharide vaccine in Canada called Pneumovax® 23 (PPV23) is manufactured by Merck Frost Canada Ltd. and has been authorized for use in Canada since 1983.[50] The Pneumovax® 23 is composed of 23 pneumococcal strains (1, 2, 3, 4, 5, 6B, 7F, 8, 9N,

10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20 22F, 23F and 33F) which provides protection against approximately 87% of strains causing IPD.[50] Current Canadian guidelines suggest that all adults over the age of 65 or for persons with known risk factors for IPD are vaccinated with the PPV23.[50] The evidence of the effectiveness of PPV23 however remains inconsistent. For instance, the 2 most recently published meta-analyses (a Cochrane Collaboration and a World Health Organization–commissioned meta-analysis) concluded in favour and against vaccine effectiveness, respectively.[51,52] The Cochrane meta-analysis determined a vaccine efficacy of 74% (95% CI, 54%–85%) against IPD (basically bacteremic pneumococcal pneumonia). Moreover, the pooled estimate of vaccine efficacy for all-cause CAP was 28% (95% CI, 7%-44%). Because there were high degrees of heterogeneity ($I^2 = 85\%$, $P < 0.0001$), the authors would not definitively conclude that the PPV prevents all-cause pneumonia in adults.[51]Moreover, their meta-analysis failed to demonstrate any significant evidence for PPV23 effectiveness against mortality (all-cause or pneumococcal-related).[51]

The World Health Organization–commissioned meta-analysis however, reported only a small protective effect against all-cause pneumonia (RR, 0.73; 95% CI, 0.56–0.94) or bacteremic pneumonia (RR, 0.90; 95% CI, 0.46–1.77), and no significant effectiveness against all-cause mortality (RR, 0.97 95% CI 0.87–1.09).[52] In contrast to these analyses however, in a study by Johnstone et al. involving a large population-based cohort of patients hospitalized with pneumonia, previous pneumococcal vaccination was associated with a significant 40% relative reduction in hospital mortality or need for ICU admission.[53] This finding is also consistent with other studies focused on hospitalized

patients with pneumonia.[54,55] As for the effectiveness of the PPV23 against BPP specific mortality little is currently known. A recent 3-year prospective cohort study involving 27 204 hospitalized patients aged ≥ 60 years, attempted to investigate the effectiveness of the PPV23 against mortality in patients with bacteremic pneumococcal CAP. However, the study was underpowered to draw any specific conclusions.[56]

Beyond the PPV23, the seven-valent pneumococcal conjugate vaccine (PCV7), Prevnar, Pfizer Canada Inc, Canada) is also available and was licensed in Canada in 2002, and is indicated for infants and high-risk children.[57] Studies have shown that the vaccination of young children with the PCV7 resulted in a decrease in the incidence of pneumococcal disease in older children and adults, particularly in high-risk and elderly adults.[57] Following the introduction of the PCV7, there was an increase in non-vaccine serotypes colonization and a reduction in colonization of vaccine serotypes in vaccinated populations.[58] However, a review of the evidence suggests that there is a net decline in IPD in young children, even with an increase in non-vaccine serotypes.[58]

The PCV13 (Prevnar 13, Pfizer Canada Inc) was approved in Canada in 2010 and has replaced the PCV7.[59] Recently the Centre for Disease Control and Prevention (CDC) has authorized the use of the new PCV13 containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F among adults over the age of 65 in the United States.[60] Two randomized studies conducted in the United States and Europe have investigated the immunogenicity of the PCV13 in adults. In the first study, the PCV13 elicited statistically significant higher anti-pneumococcal opsonophagocytic activity (OPA)

geometric mean antibody titers (GMTs) than in the PPV23 for 8 of the 12 serotypes common to both vaccines in adults aged 60–64 years with no prior pneumococcal vaccination.[61] However, in the second study, OPA GMTs from the PCV13 were comparable with those elicited by PPV23 for two serotypes and higher for 10 serotypes among adults aged ≥70 years who previously had been immunized with a single dose of PPV23 ≥5 years before enrolment.[62] Furthermore, a more recent study involving the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) composed of 84,496 adults 65 years of age or older, has investigated the efficacy of the PCV13 in adults. The study determined the efficacy of the PCV13 against IPD to be 52% (95% CI, 22%-71%), and against confirmed pneumococcal pneumonia to be 31% (95% CI, 10%-47%).

1.3 Prognostic Factors for Mortality in Adults with BPP

Prognostic factors play a crucial role in risk stratification, patient management and treatment strategies. In general, a prognostic factor is a clinical characteristic that provides information on the likely outcome of an individual with a diagnosed condition in the absence of therapy.[61] Clinicians are often able to use prognostic factors in order to separate patients into risk groups whereby the outcomes can be predicted more readily. In theory, this allows therapy to be more efficiently delivered to patients who would benefit the most, while ensuing that other patients do not undergo unnecessary treatments or procedures.[62]

In patients with BPP, several studies have investigated potential prognostic factors for mortality.[23,28,29,44,63-71] Of these studies (summarized in **Table 1-2**), the vast majority have small sample sizes (n=60 to 300) and have been relatively inconsistent in factors identified. A major limitation of the majority of studies is that these studies may not have sufficient power to identify all important prognostic factors, or the associations may have been due to chance as a result of multiple hypothesis testing. Moreover, adjustments for different variables in the analyses between studies or uncontrolled confounding factors are also a concern.[72] These limitations raise uncertainties about the study conclusions and require replication and confirmatory re-examination of the prognostic value of several factors. Despite these limitations, the following is a summary of the main prognostic factors for mortality in adult CAP patients with and without BPP.

1.3.1 Age

The importance of age as a clinical decision-making factor in the management of patients hospitalized with CAP has been highly debated. Some studies suggest that the higher rates of mortality reflect the higher rates of comorbid conditions, poor functional status, and disability in the elderly. However, other studies have demonstrated that age independently predicts mortality in patients hospitalized with CAP, which suggests that age is an important prognostic factor for mortality.[2,73] In adult patients with BPP, several studies have identified that increasing age is associated with higher mortality.[23,28,29,44,74,75] One study by Naucler et al. also found age to be associated with mortality in patients without recorded comorbidities suggesting that age is important beyond its associations with comorbidities.[29] Additionally, age was also identified to be a significant predictor of

mortality in patients with BPP over the age of 65.[63] Therefore, age appears to be an independent predictor for mortality in patients with BPP.

1.3.2 Sex

Several studies including one meta-analysis have identified males hospitalized with CAP to be at an increased risk of mortality.[6,76-78] Additionally, males are weighted more heavily in the PSI index score for severity based on initial validation work which also indicated males were at higher risk of adverse outcomes.[41] Yet, only one study has identified being male as an important prognostic factor associated with an increased risk of in-hospital BPP mortality.[29] Two studies have found no association between sex and mortality from BPP, while other studies failed to include sex in their multivariate analysis.[28,63] Though BPP is diagnosed more often in men then women, whether sex differences exist in prognosis remains uncertain.

1.3.3 Lifestyle Factors

Multiple studies have shown that smoking is a significant risk factor for acquiring pneumonia including BPP.[26,36,79] Yet, little attention has been given to determining whether smoking is a prognostic factor for mortality, particularly in patients with BPP. In a review study on smoking and the outcomes of infection, Huttunen and colleagues found inconsistent evidence on the relationship between smoking and CAP related mortality.[80] This included two meta-analyses,[6,81] one case-control,[82] and five cohort studies,[83-87] which found either no significant association or a negative association between smoking and pneumonia related death. However, one case-control,[88] three longitudinal cohort

studies,[89-91] and two cohort studies,[92,93] found that smoking increased mortality in patients with pneumonia. Only two studies have investigated smoking specifically in patients with BPP.[29,94] Both studies concluded that tobacco smoke increased the risk of mortality in patients with BPP.[29,94] However, in the study by Naucler et al. smoking status was acquired through the use of a survey, and 20% of respondents failed to indicate their smoking status.[29] Furthermore, in the study by Bello involving adults with pneumococcal CAP where smoking was found to have an increased risk of 30-day mortality was limited by sample size (only 10 of 35 deaths were in current smokers) and was not restricted to BPP.[94] Therefore, much uncertainty remains on whether smoking can influence mortality in patients with BPP.

Alcohol abuse is a known risk factor for CAP, and has recently been accepted as a risk factor for IPD and BPP.[36,79,95] However, there has been little evidence to suggest that alcohol abuse increases the risk of mortality in patients with CAP.[96,97]

Two recent studies have found that alcohol abuse significantly increases the risk of mortality in adults with BPP.[23,29] One study found no association between alcohol abuse and mortality.[65] However, this study included heath care associated pneumonia as a prognostic factor for mortality, which may account for the discrepancy from the previous studies. [65]

1.3.4 Chronic Comorbid Conditions

Comorbid conditions most known to be associated with an increased risk of mortality in patients with CAP are those listed in the PSI index including neoplastic disease, liver

disease, congestive heart failure, cerebrovascular disease, and renal disease.[41] In a meta-analysis by Fine et al., coronary artery disease and a neurological disease were also associated with an increased risk of mortality in patients with CAP.[6] Several comorbid conditions including: liver disease,[29] renal disease,[29] solid tumor,[29] coronary artery disease[67], chronic obstructive pulmonary disease (COPD)[70], and immunocompromising disorders[67], have been shown to be associated with mortality in patients with BPP. The impact of comorbidities was also evaluated by the Charlson comorbidity index in three studies. [23,29,64] One study found that the Charlson comorbidity score was associated with increased mortality[23], while another found that only patients with a score greater than 4 were associated with increased mortality.[29] The last study found no significant association between the Charlson index score and mortality in patients with BPP.[65]

1.3.5 Antibiotic Therapy

For CAP patients admitted to the hospital, guidelines recommend first-line treatment with either a respiratory fluoroquinolone or the combination of a beta-lactam and a macrolide.[22] These recommendations are based primarily on large observational studies using inpatient administrative databases that have demonstrated reduced mortality with recommended antibiotics as compared with other antibiotics or combinations.[98-100] Other studies have also shown that mortality has decreased as adherence to these antibiotic recommendations has increased.[101,102] Increased mortality rates have been reported when initial therapy for pneumococcal bacteremic pneumonia was discordant.[64,70] Moreover, two reports suggest that dual therapy (macrolide and a beta-lactam) within the first 48–72 h decreases the risk of mortality in adult patients with BPP.[69,70] However, in the largest

study by Naucler et al., no significant difference in mortality was seen in the macrolide and a beta-lactam group vs the beta-lactam only group - although this conclusion was based on only 26 patients receiving dual therapy. Another smaller study also noted no significant change in mortality with the addition of a macrolide.[68] Therefore, further studies are needed to determine the impact of guideline concordant antibiotic treatment in patients with BPP.

1.3.6 Pneumococcal Serotypes

Certain serotypes have been found to be more likely than other serotypes to be associated with fatal BPP cases. Multiple studies including one meta-analysis by Weinberger et al., have demonstrated that certain pneumococcal serotypes are associated with an increased risk of mortality in BPP patients even after adjustment for confounding factors such as age and comorbidities.[16,23,103] Furthermore, in the same study, the serotypes with the highest case fatality rates (CFR) (i.e. serotypes 1, 4, 5, 7F, 8) were found to have the lowest invasive disease potential, and vice versa for the low CFR serotypes (i.e. 3, 6A, 6B, 9N, 19A, 19F, 23F).[21] One theory for this "paradox" is that serotypes with high CFR are believed to be "opportunistic" pathogens that primarily infect the most vulnerable of individuals including persons with underlying conditions. Low CFR serotypes on the other hand are deemed "primary pathogens" that typically infect non-immunocompromised individuals.[16] However, whether high CFR serotypes are more significant in the prognosis of mortality in patients with BPP than host factors remains up for debate. The study by Naucler et al. found that the effect of serotypes grouped by CFR on mortality in patients with BPP was mitigated after adjusting for host factors.[29] Another

study by Lugan and colleagues, found low invasive disease potential serotypes (i.e. high CFR serotypes) an independent risk factor for 30-day mortality in BPP patients.[23] Therefore, certain serotypes do appear to be associated with increased mortality, however it remains unclear as to whether serotypes with high CFR are more important than host patient factors such as underlying co-morbid conditions or disease severity.

1.4 Prognostic Factors for In-Hospital Complications

A meta-analysis by Fine et al. reported that most complications suffered by patients with CAP could be categorized into four categories including: infection related, pulmonary, cardiovascular, and gastrointestinal (including hepatic).[6] The most commonly reported complications were found to be hepatic abnormalities (12.3% of 463 patients), pleural effusion (10.6% of 3049 patients) renal failure (10.4% of 355 patients), heart failure (8.6% in 232 patients) and respiratory failure (7.8% in 232 patients).[6] However, none of the studies reported in the meta-analysis focused specifically on in-hospital complications. Therefore, very limited research exists on the number of in-hospital complications that occur in patients with CAP. With respect to BPP, a recent study by Blot and colleagues, identified ARDS, cardiac failure, and mechanical ventilation [6% (9/151), 17% (26/151), and 11% (17/151) respectively] as common complications among survivors with BPP.[10] To the best of my knowledge no previous study has investigated the prognostic factors associated with nonfatal complications in patients with BPP.

1.5 Summary

Mortality rates among adults with BPP remain high despite significant advances in antibiotic therapy and supportive therapies. Identifying important prognostic factors for adverse outcomes in patients with BPP is crucial in order to identify patients who might benefit the most from aggressive therapeutic or adjunctive treatments or who might benefit from a higher level of care such as that provided in the intensive care unit. Only a few studies have investigated prognostic factors for mortality in patients with BPP, and the results from these studies are inconsistent. Reasons for the discrepancies between these studies include small sample size, [23,28,44,63-71] missing data, [29] different subgroups within the population, [65] retrospective design, [28,44] and uncontrolled confounders.[68,90,91,93] Additionally, there have been no studies that have investigated potential prognostic factors for in-hospital complications in BPP patients. Therefore, larger prospective population based studies are needed to investigate and validate prognostic factors for morbidity and mortality in patients with BPP in the real world. Moreover, smoking has been investigated as a potential prognostic factor for mortality in patients with BPP. Yet, certain studies have found that smoking is associated with a reduced risk of death.[2,87,104] Thus, studies are needed to confirm the association between smoking and mortality in BPP patients, and to find a potential explanation for a reduction in mortality among smokers compared to non-smokers with BPP.

1.6 Objectives

The three objectives of this program of research were:

1) To identify prognostic factors associated with in-hospital mortality and nonfatal complications in patients with BPP.

2) To determine the independent association between current smoking and in-hospital mortality in patients with BPP.

3) To evaluate the potential role of pneumococcal serotypes on the associations between current smoking and in-hospital mortality in patients with BPP.

Two pre-specified and inter-linked studies were undertaken to achieve the three stated objectives of this research program. The first objective was addressed in a population-based cohort study (Chapter 2) derived from a large clinical dataset of BPP patients from northern Alberta, Canada that was designed to identify prognostic factors for mortality and in-hospital complications. This study, when completed, will be one of the largest and most comprehensive studies completed to date to identify independent prognostic factors for mortality in patients with confirmed BPP and perhaps the first study to assess prognostic factors for in-hospital complications.

The second and third objectives were addressed through a population-based cohort study (Chapter 3) that also utilized the aforementioned population-based clinical dataset populated with detailed information regarding smoking status and pneumococcal serotypes. This study, when completed, will determine the potential impacts of smoking status and the role of serotypes in the outcomes of patients with BPP.

Table 1-1: The PSI algorithm and criteria

Demographic Factor	
Age	
If Male	Age (yr)
If Female	Age (yr) - 10
Nursing home resident	+ 10
Comorbidity	
Neoplastic disease	+ 30
Liver disease	+ 20
Congestive heart failure	+ 10
Cerebrovascular disease	+ 10
Renal disease	+ 10
Physical Exam Findings	
Altered mental status	+ 20
Pulse ≥125/minute	+ 10
Respiratory rate >30/minute	+ 20
Systolic blood pressure <90 mm Hg	+ 20
Temperature <35°C or ≥40°C	+ 15
Lab and Radiographic Findings	
Arterial pH <7.35	+ 30
Blood urea nitrogen ≥30 mg/dl (11 mmol/liter)	+ 20
Sodium <130 mmol/liter	+ 20
Glucose ≥250 mg/dl (14 mmol/liter)	+ 10
Hematocrit <30%	+ 10
Partial pressure of arterial O2 <60mmHg	+ 10
Pleural effusion	+ 10

*No points = Risk Class I, Σ < 70 = Risk Class II, Σ 71-90 Risk Class III, Σ 91-130 = Risk Class IV, Σ > 130 = Risk Class V

Table 1-2: Parameters and criteria for the severity of illness scores: PBS, modified-ATS, CURB-65, and CRB-65

Scoring System	PBS	Modified-ATS	IDSA/ATS	CURB-65	CRB-65
Parameters	- Fever (oral temperature) ≤35°C or ≥40°C (2 points) 35.1–36.0°C or 39.0–39.9°C (1 point) - Hypotension (2 points) (Acute hypotensive event with drop in systolic blood pressure >30 mmHg and diastolic blood pressure >20 mmHg or requirement for intravenous vasopressor agents or Systolic blood pressure <90 mmHg) - Mechanical ventilation (2 points) - Cardiac arrest (4 points) - Mental status Disoriented (1 point) Stuporous (2 points) Comatose (4 points)	<u>Minor criteria</u> - Systolic BP <90 mmHga - Multilobar involvement (>2 lobes) - Pa02/Fi02 ratio (<250) <u>Major criteria</u> - Requirement for mechanical ventilation - Septic shock	<u>Minor criteria</u> - Resp rate ≥30/min - Pa02/Fi02 ratio ≤250 - Multilobar infiltrate - Confusion and/or disorientation - Uraemia (BUN≥20 mg/dL) - Leucopenia (WBC <4000 cells/ mm3) - Thrombocytopenia (platelet< 100 000cells/mm) - Hypothermia (≤36°C) - Hypotension <u>Major criteria</u> - Requirement for mechanical ventilation - Septic shock	- Confusion - Urea (>7 mmol/L), - Respiratory rate (≥30/min), - Blood pressure (systolic <90 or diastolic ≤60 mmHg), and - Age ≥65 years	- Confusion - Respiratory rate (≥30/min) - Blood pressure (systolic <90 or diastolic ≤60 mmHg), and - Age ≥65 years
Criteria for severe illness	>4 points	2 minor or 1 major criteria	Any major or 3 minor criteria	≥3 parameters	≥3 parameters

Table 1-3: Studies focused on in-hospital mortality in patients with bacteremic pneumococcal pneumonia

Author (Year)	N	Study Focus	Study Design	Outcome Measure	Type of analysis	Mortality prognostic Factors	OR and 95% CI
Fica et al.[28] 2014	60	Bacteremic pneumococcal pneumonia patients ≥18 years	Single center (Chile)	In-hospital mortality	Multiple logistic regression	CAP PIRO score > 3	29.7 (4.7–187.0)
						Age ≥ 65 years	42.1 (2.2–796.0)
						Blood platelets < 100,000/μL	10.9 (1.2–96.0)
Naucler et al.[29] 2013	1580	Bacteremic pneumococcal pneumonia patients ≥18 years	Multicenter (Sweden)	30-day mortality	Multiple logistic regression	Age ≥ 65	4.3 (2.8-6.5)
						Male	1.6 (1.1-2.2)
						Smoking	1.8 (1.0-3.1)
						Alcohol abuse	3.8 (1.9-7.9)
						Liver Disease	2.3 (1.0-4.9)
						Renal disease	1.8 (1.0-3.3)
						Solid tumor	2.6 (1.5-4.5)
						Charlson Index ≥ 4	3.2 (1.8-5.9)
Ruiz et al. [63] 2013	399	Bacteremic pneumococcal pneumonia patients	Two hospitals (Spain)	30-day mortality in patients ≥ 65 years	Multiple logistic regression	Age (continuous)	1.2 (1.1–1.3)
						Altered mental status	13.2 (3.7–47.2)
						Respiratory rate ≥30/min	5.8 (1.8–18.6)
						Systolic blood pressure < 90 mmHg	10.9 (1.5–81.9)
						Blood urea nitrogen > 30mg/dL	5.4 (1.0–28.4)
						Bilateral or multilobar involvement	5.2 (1.6–17.8)
Lujan et al.[23] 2010	299	Bacteremic pneumococcal	Single center (Spain)	30-day mortality	Multiple logistic	Serotype L	7.0 (1.7-28.6)
						ATS/IDSA criteria	4.8 (1.9-12.1)

		pneumonia patients ≥18 years			regression with ATS/IDSA criteria	Alcohol	4.0 (11.4)
						Charlson score	1.3 (1.1-1.6)
						Age	1.0 (1.0-1.1)
					Multiple logistic regression with PSI	Serotype L	5.3 (1.3-21.6)
						PSI class V	9.5 (3.1-29.5)
						Alcohol	3.2 (1.2-8.4)
						Charlson score	1.2 (1.0-1.5)
Garnacho-Montero et al.[64] 2010	125	Bacteremic pneumococcal pneumonia patients ≥18 years	Single center (Spain)	In-hospital mortality	Cox proportional regression analysis.	Sepsis severe or septic shock at admission	5.1 (1.6-15.7)
						1st adequate antibiotic dose ≥4 h	2.6 (1.1–6.5)
						Age ≥65	4.0 (1.9-8.6)
Rello et al.[65] 2010	228	Bacteremic pneumococcal pneumonia patients ≥18 years	Single centre (US)	30-day mortality	Multiple logistic regression	HCAP	5.6 (1.9-16.6)
						Need for vasopressors	4.2 (1.4-13.0)
						$PaO_2/FIO_2 < 250$	3.9 (1.4-10.7) 0.47 (0.2-1.0)
Berjohn et al.[66] 2008	363	Bacteremic pneumococcal pneumonia patients ≥18 years	Multicenter (US)	In-hospital mortality	Multiple logistic regression	At least one active antibiotic in < 4 hours	0.47 (0.2-1.0)
Chi et al.[67] 2006	200	Bacteremic pneumococcal pneumonia patients ≥ 65 years	Single center (US)	All-cause mortality within 30 days	Multiple logistic regression	Age ≥ 85	6.6 (1.0-43.1)
						Coronary artery disease	4.6 (1.4-14.5)
						Immunocompromosing conditions	5.0 (1.6-15.7)
Dwyer et al.[68] 2006	340	Bacteremic pneumococcal pneumonia patients	Multicenter (Sweden, Canada, Spain,	In-hospital mortality	Multiple logistic regression	Age >65	2.6 (1.2-5.9)
						> 2 lung lobes affected	2.2 (1.0-4.7)
						APS 8-14	8.3 (2.1-54.9)

			US, UK)			APS 14-17	23.8 (4.8-180.3)
						APS ≥ 18	53.8 (11.8-395.0)
Weiss et al.[69] 2004	95	Bacteremic pneumococcal pneumonia patients ≥18 years	Single centre (Canada)	In-hospital mortality	Miettinen's formula	Septic Shock	6.2 (1.8-21.4)
						Beta-lactam and macrolide treatment within 48 hours	0.2 (0.07-0.7)
						Septic Shock	6.2 (1.8-21.4)
Lujan et al. [70] 2004	100	Patients aged >=18 yrs with diagnosis of CAP where S. pneumonia was documented in blood cultures	Single centre (Spain)	28-day mortality	Multiple logistic regression NCCLS 1999	Previous hospitalization	8.9 (2.0-38.7)
						COPD	6.7 (1.5-29.5)
						Multilobar involvement	8.1 (1.9-35.5)
						Discordant therapy	5.7 (0.72-45.3)
					Multiple logistic regression NCCLS 2002	Previous hospitalization	8.0 (1.5-42.7)
						COPD	9.2 (1.7-49.8)
						Multilobar involvement	14.3 (2.4-85.0)
Martinez et al.[44] 2003	409	Bacteremic pneumococcal pneumonia patients	Single center (Spain)	In-hospital mortality	Multiple logistic regression	Age ≥ 65	2.5 (1.1-5.7)
						Shock	18.3 (7.5-45.0)
						Macrolide therapy	0.4 (0.2-0.9)
						Macrolide + penicillin resistance	3.1 (1.1-9.2)
Mufson et al. [71] 1999	308	Adults (15 years of age and older) and children (14 years of age and younger) with bacteremic pneumococcal pneumonia	Multicenter (US)	In-hospital mortality	Univariate analysis	Chronic renal disease	5.0 (1.9–12.7)
						Arteriosclerotic heart disease	2.4 (1.1–5.2)
						Cancer	2.2 (1.0–5.1)
						≥ 1 of 6 underlying diseases	2.0 (1.0–4.1)

1.7 References

1. Huang SS, Johnson KM, Ray GT, et al. Healthcare utilization and cost of pneumococcal disease in the United States. *Vaccine.* Apr 18 2011;29(18):3398-3412.
2. Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. *Chest.* Apr 2005;127(4):1260-1270.
3. McAlister FA, Majumdar SR, Blitz S, Rowe BH, Romney J, Marrie TJ. The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. *Diabetes care.* Apr 2005;28(4):810-815.
4. Canadian Institute for Health Information. Respiratory Disease in Canada. 2001. URL: https://secure.cihi.ca/free_products/RespiratoryComplete.pdf Acessed on: Jun 24th, 2015.
5. Organization WH. Pneumococcal vaccines. WHO paper - 2012. *Wkly Epidemiol Rec.* 21012;87:129-44.
6. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *Jama.* Jan 10 1996;275(2):134-141.
7. Werno AM, Murdoch DR. Medical microbiology: laboratory diagnosis of invasive pneumococcal disease. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Mar 15 2008;46(6):926-932.
8. Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PloS one.* 2013;8(4):e60273.
9. Feldman C, Anderson R. Recent advances in our understanding of Streptococcus pneumoniae infection. *F1000prime reports.* 2014;6:82.
10. Blot M, Croisier D, Pechinot A, et al. A leukocyte score to improve clinical outcome predictions in bacteremic pneumococcal pneumonia in adults. *Open forum infectious diseases.* Sep 2014;1(2):ofu075.
11. Lujan M, Gallego M, Rello J. Optimal therapy for severe pneumococcal community-acquired pneumonia. *Intensive care medicine.* Jul 2006;32(7):971-980.
12. Tilghman R, Finland M. CLinical significance of bacteremia in pneumococcic pneumonia. *Archives of Internal Medicine.* 1937;59(4):602-619.
13. Austrian R, Gold J. Pneumococcal Bacteremia with Especial Reference to Bacteremic Pneumococcal Pneumonia. *Annals of internal medicine.* May 1964;60:759-776.
14. Song JY, Nahm MH, Moseley MA. Clinical implications of pneumococcal serotypes: invasive disease potential, clinical presentations, and antibiotic resistance. *Journal of Korean medical science.* Jan 2013;28(1):4-15.

15. Henriques-Normark B, Tuomanen EI. The pneumococcus: epidemiology, microbiology, and pathogenesis. *Cold Spring Harbor perspectives in medicine.* Jul 2013;3(7).
16. Sjostrom K, Spindler C, Ortqvist A, et al. Clonal and capsular types decide whether pneumococci will act as a primary or opportunistic pathogen. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Feb 15 2006;42(4):451-459.
17. Henriques-Normark B, Blomberg C, Dagerhamn J, Battig P, Normark S. The rise and fall of bacterial clones: Streptococcus pneumoniae. *Nature reviews. Microbiology.* Nov 2008;6(11):827-837.
18. Kalin M. Pneumococcal serotypes and their clinical relevance. *Thorax.* 1998;53(3):159-162.
19. Robbins JB, Austrian R, Lee CJ, et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *The Journal of infectious diseases.* Dec 1983;148(6):1136-1159.
20. Brueggemann AB, Peto TE, Crook DW, Butler JC, Kristinsson KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. *The Journal of infectious diseases.* Oct 1 2004;190(7):1203-1211.
21. Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2010;51(6):692-699.
22. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Mar 1 2007;44 Suppl 2:S27-72.
23. Lujan M, Gallego M, Belmonte Y, et al. Influence of pneumococcal serotype group on outcome in adults with bacteraemic pneumonia. *The European respiratory journal.* Nov 2010;36(5):1073-1079.
24. Centers for Disease Control and Prevention Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae, 2012. Available at http://www.cdc.gov.login.ezproxy.library.ualberta.ca/abcs/reports-findings/survreports/spneu12.html.
25. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978-1997. *The American journal of medicine.* Jul 26 1999;107(1A):34S-43S.
26. Flory JH, Joffe M, Fishman NO, Edelstein PH, Metlay JP. Socioeconomic risk factors for bacteraemic pneumococcal pneumonia in adults. *Epidemiology and infection.* May 2009;137(5):717-726.
27. Shariatzadeh MR, Huang JQ, Tyrrell GJ, Johnson MM, Marrie TJ. Bacteremic pneumococcal pneumonia: a prospective study in Edmonton and neighboring municipalities. *Medicine.* May 2005;84(3):147-161.

28. Fica A, Bunster N, Aliaga F, et al. Bacteremic pneumococcal pneumonia: serotype distribution, antimicrobial susceptibility, severity scores, risk factors, and mortality in a single center in Chile. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases.* Mar-Apr 2014;18(2):115-123.
29. Naucler P, Darenberg J, Morfeldt E, Ortqvist A, Henriques Normark B. Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia. *Thorax.* Jun 2013;68(6):571-579.
30. Torres A, Blasi F, Dartois N, Akova M. 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.* Jul 28 2015.
31. Public Health Agency of Canada. Canadian Immunization Guide. Part 4 Active Vaccines. Pneumococcal Vaccine. Available online at: http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pneu-eng.php - tab1. Accessed on: Jun 24th, 2015.
32. Kellner JD, Vanderkooi OG, MacDonald J, Church DL, Tyrrell GJ, Scheifele DW. Changing epidemiology of invasive pneumococcal disease in Canada, 1998-2007: update from the Calgary-area Streptococcus pneumoniae research (CASPER) study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jul 15 2009;49(2):205-212.
33. Burman LA, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors, and prognosis. *Reviews of infectious diseases.* Mar-Apr 1985;7(2):133-142.
34. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. *The Journal of infectious diseases.* Jan 15 2001;183(2):239-246.
35. Weisfelt M, de Gans J, van der Ende A, van de Beek D. Community-acquired bacterial meningitis in alcoholic patients. *PloS one.* 2010;5(2):e9102.
36. Cruickshank HC, Jefferies JM, Clarke SC. Lifestyle risk factors for invasive pneumococcal disease: a systematic review. *BMJ open.* 2014;4(6):e005224.
37. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. *The New England journal of medicine.* Mar 9 2000;342(10):681-689.
38. Romney MG, Hull MW, Gustafson R, et al. Large community outbreak of Streptococcus pneumoniae serotype 5 invasive infection in an impoverished, urban population. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2008;47(6):768-774.
39. Falguera M, Trujillano J, Caro S, et al. A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Aug 1 2009;49(3):409-416.
40. Kang CI, Song JH, Kim SH, et al. Risk factors and pathogenic significance of bacteremic pneumonia in adult patients with community-acquired pneumococcal pneumonia. *J Infect.* Jan 2013;66(1):34-40.

41. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *The New England journal of medicine.* Jan 23 1997;336(4):243-250.
42. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *Jama.* Feb 9 2000;283(6):749-755.
43. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med.* Aug 13-27 2001;161(15):1837-1842.
44. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Feb 15 2003;36(4):389-395.
45. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Summary of Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Disease Society and the Canadian Thoracic Society. *The Canadian journal of infectious diseases = Journal canadien des maladies infectieuses.* Sep 2000;11(5):237-248.
46. Song JY, Eun BW, Nahm MH. Diagnosis of pneumococcal pneumonia: current pitfalls and the way forward. *Infection & chemotherapy.* Dec 2013;45(4):351-366.
47. Chalasani NP, Valdecanas MA, Gopal AK, McGowan JE, Jr., Jurado RL. Clinical utility of blood cultures in adult patients with community-acquired pneumonia without defined underlying risks. *Chest.* Oct 1995;108(4):932-936.
48. Huijts SM, Pride MW, Vos JM, et al. Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. *The European respiratory journal.* Nov 2013;42(5):1283-1290.
49. Resti M, Moriondo M, Cortimiglia M, et al. Community-acquired bacteremic pneumococcal pneumonia in children: diagnosis and serotyping by real-time polymerase chain reaction using blood samples. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Nov 1 2010;51(9):1042-1049.
50. Canada PHAo. *Pneumococcal vaccine.* 7 ed. Ottawa: Public Health Agency of Canada2006.
51. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. *The Cochrane database of systematic reviews.* 2013;1:Cd000422.
52. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Jan 6 2009;180(1):48-58.

53. Johnstone J, Eurich DT, Minhas JK, Marrie TJ, Majumdar SR. Impact of the pneumococcal vaccine on long-term morbidity and mortality of adults at high risk for pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jul 1 2010;51(1):15-22.
54. Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *Jama.* Oct 22-29 1997;278(16):1333-1339.
55. Ament A, Baltussen R, Duru G, et al. Cost-effectiveness of pneumococcal vaccination of older people: a study in 5 western European countries. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Aug 2000;31(2):444-450.
56. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged >/= 60 years: 3 years of follow-up in the CAPAMIS study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Apr 2014;58(7):909-917.
57. Lucero MG, Dulalia VE, Nillos LT, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. *The Cochrane database of systematic reviews.* 2009(4):Cd004977.
58. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. *Lancet.* Dec 3 2011;378(9807):1962-1973.
59. Kellner J. Update on the success of the pneumococcal conjugate vaccine. *Paediatrics & child health.* Apr 2011;16(4):233-240.
60. (CDC) CfDCaP. Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults Aged ≥65 Years: Recommendations of the Advisory Committee on Immunization Practices (ACIP). 2014.
61. Italiano A. Prognostic or predictive? It's time to get back to definitions! *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 10 2011;29(35):4718; author reply 4718-4719.
62. N. Lynn Henry DFH. *Clinical Importance of Prognostic Factors. Moving from Scientifically Interesting to Clinically Useful.* 2008.
63. Ruiz LA, Zalacain R, Capelastegui A, et al. Bacteremic pneumococcal pneumonia in elderly and very elderly patients: host- and pathogen-related factors, process of care, and outcome. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Aug 2014;69(8):1018-1024.
64. Garnacho-Montero J, Garcia-Cabrera E, Diaz-Martin A, et al. Determinants of outcome in patients with bacteraemic pneumococcal pneumonia: importance of early adequate treatment. *Scandinavian journal of infectious diseases.* Mar 2010;42(3):185-192.
65. Rello J, Lujan M, Gallego M, et al. Why mortality is increased in health-care-associated pneumonia: lessons from pneumococcal bacteremic pneumonia. *Chest.* May 2010;137(5):1138-1144.

66. Berjohn CM, Fishman NO, Joffe MM, Edelstein PH, Metlay JP. Treatment and outcomes for patients with bacteremic pneumococcal pneumonia. *Medicine.* May 2008;87(3):160-166.
67. Chi RC, Jackson LA, Neuzil KM. Characteristics and outcomes of older adults with community-acquired pneumococcal bacteremia. *Journal of the American Geriatrics Society.* Jan 2006;54(1):115-120.
68. Dwyer R, Ortqvist A, Aufwerber E, et al. Addition of a macrolide to a ss-lactam in bacteremic pneumococcal pneumonia. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology.* Aug 2006;25(8):518-521.
69. Weiss K, Low DE, Cortes L, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic Streptococcus pneumoniae pneumonia in adults. *Canadian respiratory journal : journal of the Canadian Thoracic Society.* Nov-Dec 2004;11(8):589-593.
70. Lujan M, Gallego M, Fontanals D, Mariscal D, Rello J. Prospective observational study of bacteremic pneumococcal pneumonia: Effect of discordant therapy on mortality. *Critical care medicine.* Mar 2004;32(3):625-631.
71. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978-1997. *Am J Med.* 1999;107(1A):34S-43S.
72. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Systematic reviews.* 2013;2:71.
73. Sligl WI, Eurich DT, Marrie TJ, Majumdar SR. Age still matters: prognosticating short- and long-term mortality for critically ill patients with pneumonia. *Critical care medicine.* Nov 2010;38(11):2126-2132.
74. Kalin M, Ortqvist A, Almela M, et al. Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. *The Journal of infectious diseases.* Sep 2000;182(3):840-847.
75. Moroney JF, Fiore AE, Harrison LH, et al. Clinical outcomes of bacteremic pneumococcal pneumonia in the era of antibiotic resistance. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2001;33(6):797-805.
76. Mortensen EM, Kapoor WN, Chang CC, Fine MJ. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Dec 15 2003;37(12):1617-1624.
77. Uematsu H, Kunisawa S, Sasaki N, Ikai H, Imanaka Y. Development of a risk-adjusted in-hospital mortality prediction model for community-acquired pneumonia: a retrospective analysis using a Japanese administrative database. *BMC pulmonary medicine.* 2014;14:203.
78. Daley J, Jencks S, Draper D, Lenhart G, Thomas N, Walker J. Predicting hospital-associated mortality for Medicare patients. A method for patients with stroke, pneumonia, acute myocardial infarction, and congestive heart failure. *Jama.* Dec 23-30 1988;260(24):3617-3624.

79. Grau I, Ardanuy C, Calatayud L, Schulze MH, Linares J, Pallares R. Smoking and alcohol abuse are the most preventable risk factors for invasive pneumonia and other pneumococcal infections. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases.* Aug 2014;25:59-64.
80. Huttunen R, Heikkinen T, Syrjanen J. Smoking and the outcome of infection. *Journal of internal medicine.* Mar 2011;269(3):258-269.
81. Katanoda K, Marugame T, Saika K, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. *Journal of epidemiology / Japan Epidemiological Association.* 2008;18(6):251-264.
82. Jha P, Jacob B, Gajalakshmi V, et al. A nationally representative case-control study of smoking and death in India. *The New England journal of medicine.* Mar 13 2008;358(11):1137-1147.
83. Lange P, Vestbo J, Nyboe J. Risk factors for death and hospitalization from pneumonia. A prospective study of a general population. *The European respiratory journal.* Oct 1995;8(10):1694-1698.
84. LaCroix AZ, Lipson S, Miles TP, White L. Prospective study of pneumonia hospitalizations and mortality of U.S. older people: the role of chronic conditions, health behaviors, and nutritional status. *Public health reports.* Jul-Aug 1989;104(4):350-360.
85. Madeddu G, Porqueddu EM, Cambosu F, et al. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. *Infection.* Jun 2008;36(3):231-236.
86. Yende S, Angus DC, Ali IS, et al. Influence of comorbid conditions on long-term mortality after pneumonia in older people. *Journal of the American Geriatrics Society.* Apr 2007;55(4):518-525.
87. Garau J, Baquero F, Perez-Trallero E, et al. Factors impacting on length of stay and mortality of community-acquired pneumonia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Apr 2008;14(4):322-329.
88. Sitas F, Urban M, Bradshaw D, Kielkowski D, Bah S, Peto R. Tobacco attributable deaths in South Africa. *Tobacco control.* Dec 2004;13(4):396-399.
89. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *Bmj.* Oct 8 1994;309(6959):901-911.
90. Rogot E, Murray JL. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public health reports.* May-Jun 1980;95(3):213-222.
91. Inoue Y, Koizumi A, Wada Y, et al. Risk and protective factors related to mortality from pneumonia among middleaged and elderly community residents: the JACC Study. *Journal of epidemiology / Japan Epidemiological Association.* Nov 2007;17(6):194-202.
92. Andrews J, Chandrasekaran P, McSwiggan D. Lower respiratory tract infections in an acute geriatric male ward: a one-year prospective surveillance. *Gerontology.* 1984;30(5):290-296.

93. Garcia-Vidal C, Ardanuy C, Tubau F, et al. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. *Thorax.* Jan 2010;65(1):77-81.
94. Bello S, Menendez R, Torres A, et al. Tobacco smoking increases the risk for death from pneumococcal pneumonia. *Chest.* Oct 2014;146(4):1029-1037.
95. Samokhvalov AV, Irving HM, Rehm J. Alcohol consumption as a risk factor for pneumonia: a systematic review and meta-analysis. *Epidemiology and infection.* Dec 2010;138(12):1789-1795.
96. Saitz R, Ghali WA, Moskowitz MA. The impact of alcohol-related diagnoses on pneumonia outcomes. *Arch Intern Med.* Jul 14 1997;157(13):1446-1452.
97. de Roux A, Cavalcanti M, Marcos MA, et al. Impact of alcohol abuse in the etiology and severity of community-acquired pneumonia. *Chest.* May 2006;129(5):1219-1225.
98. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. *Arch Intern Med.* Nov 22 1999;159(21):2562-2572.
99. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. *Chest.* May 2003;123(5):1503-1511.
100. Wunderink RG, Waterer GW. Clinical practice. Community-acquired pneumonia. *The New England journal of medicine.* Feb 6 2014;370(6):543-551.
101. Capelastegui A, Espana PP, Quintana JM, et al. Improvement of process-of-care and outcomes after implementing a guideline for the management of community-acquired pneumonia: a controlled before-and-after design study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Oct 1 2004;39(7):955-963.
102. Dean NC, Silver MP, Bateman KA, James B, Hadlock CJ, Hale D. Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. *The American journal of medicine.* Apr 15 2001;110(6):451-457.
103. Pletz MW, Welte T, Klugman KP. The paradox in pneumococcal serotypes: highly invasive does not mean highly lethal. *The European respiratory journal.* Oct 2010;36(4):712-713.
104. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Apr 15 2006;42(8):1093-1101.

CHAPTER 2: PROGNOSTIC FACTORS ASSOCIATED WITH ADVERSE OUTCOMES IN PAITENTS WITH BACTEREMIC PNEUMOCOCCAL PNEUMONIA

2.1 Introduction

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality worldwide [1]. *Streptococcus pneumoniae* (hereafter, "pneumococcus") remains the most commonly identified pathogen in CAP, and is responsible for 30-40% of all diagnostically confirmed cases [2]. It has been estimated that 25% of cases of pneumococcal pneumonia are associated with bacteremia.[3] Complications of bacteremic pneumococcal pneumonia (BPP) are diverse and range from adult respiratory distress syndrome to septic shock and death [4]. Case fatality rates in adults with BPP are 15 to 36% despite continued advances in antibiotic therapy and supportive care.[5-7] Furthermore, major complications (e.g., need for mechanical ventilation, heart failure, acute kidney injury) occur in a large proportion of patients who survive pneumococcal bacteremia.[8] Thus, there is interest in identifying novel prognostic markers to identify those at highest risk of adverse events associated with BPP before they occur.

Several studies have reported prognostic factors associated with mortality in patients with BPP including extremes of age, alcohol abuse, certain comorbidities, severity of presenting illness, late antibiotic treatment, and CAP guideline-discordant therapy.[9-12]

However, the findings from these studies are often contradictory, and the generalizability of 3 of these studies is limited due to small study sample sizes (all less than 150 patients), [9-11] missing data, [12] or uncontrolled confounding. Furthermore, studies examining in-hospital complications in BPP patients are even more limited, [8,13] and to our knowledge prognostic factors associated with in-hospital complications in patients with BPP have yet to be examined in detail.

Therefore, we used a large clinically rich prospective population-based cohort to evaluate potential prognostic factors associated with mortality and major in-hospital complications in adults with BPP.

2.2 Methods

Setting and Subjects

Since 1998, all cases of IPD in the province of Alberta are classified as notifiable diseases and therefore are reported to the Provincial Health Office. As a result of this reporting requirement, identified *S. pneumoniae* isolates from IPD cases in Alberta are forwarded to the Provincial Laboratory for Public Health in Edmonton, Alberta, for serotyping and antimicrobial susceptibility trend analysis.[14,15] The definition of IPD followed the Canadian national case definition: isolation of *S. pneumoniae* from a nonsterile site such as blood, cerebrospinal fluid, pleural fluid, biopsy tissue, joint aspiration, pericardial fluid or peritoneal fluid.[16] The database used for this survey encompassed IPD cases that occurred in Northern Alberta, Canada (population: 2,060,039[17]) between January 1, 2000 and December 31, 2010. From this population, we

restricted our study to adult patients (≥18 years) with clinically diagnosed pneumonia who had pneumococcal bacteremia (**Figure 1**).

Data collection

All identified cases of bacteremic pneumococcal pneumonia (BPP) were reviewed in detail by trained research nurses who have had much prior experience in this field using a data collection tool previously described.[18,19] Information collected included sociodemographic data, pre-existing comorbid conditions, and prescription drug history, lifestyle factors (e.g., smoking status, alcohol intake, illicit drug use), and clinical data (e.g., chest radiograph findings, antibiotic treatments). We classified antibiotic treatments according to whether or not they were concordant or discordant with clinical practice guidelines for the empiric treatment of CAP.[20,21]

S. pneumoniae Characterization

Optochin susceptibility and bile solubility assays were used to confirm that isolates were S. *pneumoniae.*[14,15] Serotyping of all isolates was performed using the Quellung reaction[22] and grouped according to previous literature into: low case fatality rates (CFR) serotypes (1, 4, 5, 7F, 8) vs high CFR serotypes (3, 6A, 6B, 9N, 9V, 12F, 14, 19A, 19F, 22F, 23F).[12,23] All "other" serotypes identified from cases in our survey (2, 7C, 9L, 10A, 10F, 11A, 11B, 11F, 13, 15A, 15B, 15C, 16F, 17F, 18A, 18B, 18C, 18F, 20, 22A, 23A, 23B, 28A, 29, 31, 33A, 33F, 34, 35A, 35B, 35C, 35F, 37, 38, 40, 42) were subsequently classified as high CRF category because there were similar patient characteristics and

nearly identical CFRs as observed with the high CFR serotypes (22% in high CRF serotypes vs 17% in low CRF serotypes).

Outcomes

Our primary outcome of interest was in-hospital mortality. The secondary end-point of interest was any major in-hospital complication, defined as the presence of one or more of: need for mechanical ventilation, adult respiratory distress syndrome (ARDS) not needing mechanical ventilation, major adverse cardiovascular events (MACE, including unstable angina, myocardial infarction, heart failure, or cardiac arrest), liver failure, acute kidney injury, stroke, seizure, or acute aspiration associated with the presenting illness. All outcomes were obtained by detailed chart review and adjudicated by medical experts as previously described.

Statistical Analysis

Descriptive data using appropriate statistical tests were undertaken. Adjusted odd ratios were estimated using multivariable logistic regression. All potential prognostic variables listed in **Table 2-1** were adjusted for in our analysis. The c-statistic (area under the receiver-operating characteristic [ROC]) was used to describe overall predictive model accuracy and the Hosmer-Lemeshow test statistic was used to assess the model's goodness-of-fit. All analyses were performed with Stata SE, version 12.1 (Stata, College Station, Tex).

Sensitivity Analyses

We conducted several sensitivity analyses to evaluate the robustness of our study results. First, we restricted analyses to those 65-years and older because these patients are at a substantially increased risk of mortality.[24] Second, we stratified by sex, because females with IPD have a much higher risk of mortality than males.[25] Third, we stratified our analysis based on low vs high CFR serotypes.[23] Fourth, we reclassified our CFR serotypes as low vs high vs "other" rather than collapsing the latter two categories.

2.3 Results

Our cohort consisted of 1636 adults with BPP; mean age was 54 (SD 18) years, 434 (27%) were over the age of 65 years, and 931 (57%) were male. COPD, mental health disorders, and cardiac disease were the most frequent comorbidities, and in terms of lifestyle factors, 51% of patients were non-smokers and 25% abused alcohol (**Table 2-1**). Overall, 41% had low CFR serotypes and only 4% had been vaccinated with the polysaccharide pneumococcal vaccine prior to presentation.

In-Hospital Mortality

Overall, 226 (14%) patients died in hospital. Compared with those who survived, patients who died were older, more likely to reside in a nursing home, and sicker (e.g., more comorbidities and medications) and they had more severe BPP (e.g., multilobe pneumonia, high CFR serotypes, see **Table 2-1**). Moreover, patients who died were also more likely to have suffered 2 or more major complications than those who survived (41% vs 8%, $P < 0.001$ for difference).

In the multivariable analysis, the most important independent prognostic factors for death were older age, nursing home residence, community-dwelling dementia, alcohol abuse, and the use of acid-suppressing drugs as well as some characteristics of BPP itself and its treatment such as multi-lobe pneumonia and use of CAP guideline-discordant antibiotics (**Table 2-4**). Of note, even though less than 5% of patients were vaccinated, pneumococcal vaccination was independently associated with lower mortality (adjusted odds ratio [aOR], 0.2; 95% CI, 0.05-0.9; $P = 0.03$).

Major In-Hospital Complications

Among the 1410 BPP survivors, most patient-level characteristics were similar to those we noted for mortality (**Table 2-2**). The most common in-hospital complications were need for mechanical ventilation (16%), acute aspiration (6%), and MACE (5%) (**Table 2-3**). In the multivariable analysis, the most important prognostic factors independently associated with in-hospital complications were stroke, alcohol abuse, multilobe pneumonia, and having a high CFR serotype (**Table 2-5**).

Sensitivity analyses with respect to mortality

Restricting analyses to persons 65 years and older, stratifying by sex, categorizing according to high CFR serotypes, or reclassifying CFR as low vs high vs other did not materially alter the strength of association or statistical significance of any of the prognostic factors described in the main analysis for in-hospital mortality or complications (**Figures 2-2, 2-3, & 2-4**).

2.4 Discussion

Using a large clinically rich population based cohort we found that in-hospital mortality and major in-hospital complications associated with BPP are still common (14% and 22%, respectively). Older age and other markers of frailty along with acid suppressing drugs were independently associated with in-hospital mortality while alcohol abuse, pneumonia severity, and guideline-discordant antibiotic treatments were independently associated with both in-hospital mortality and complications. Of note, high CFR serotypes were independently associated with both increased mortality and increased complications. Though fewer than 1-in-20 patients were documented to have received polysaccharide pneumococcal vaccine, it was associated with reduced mortality although it did not affect rates of in-hospital complications.

Previous studies have identified older age,[10] guideline-discordant antibiotic therapy,[9,11] and multilobe pneumonia,[11] as independent factors associated with increased BPP mortality. Our work confirms this and extends these findings to other markers of frailty beyond older age such as nursing home residence and community-dwelling dementia. Though acid-suppressing drugs are associated with an increased risk of pneumonia and an increased risk of recurrent pneumonia,[19] our findings that acid-suppressing drugs are associated with increased mortality was somewhat unexpected. It has been suggested that these medications may intensify the severity of an infection by promoting acid-suppression and bacterial overgrowth, which would increase the risk for mortality particularly among elderly patients.[19]

Our study also highlights the potential role of serotypes on adverse outcomes, which has been a controversial topic.[23,26] Although we found an association between high CFR serotypes and adverse in-hospital events, a recent comparable study involving 1580 adult patients with BPP by Naucler et al. found that the effect of serotypes on mortality was mitigated after adjusting for age, sex and Charlson Index.[12] Conversely, a study by Harboe et al. composed of 18,858 patients with IPD found that specific pneumococcal serotypes increased the risk of IPD associated mortality after adjusting for age and comorbidity.[27] Our study is consistent with the larger study of Harboe et al.[27] and supports the idea that pneumococcal serotypes are an important prognostic factor for in-hospital adverse events in BPP patients. Although knowing the pneumococcal serotype may not necessarily change the antibiotic therapy for a patient, these patients may be worthy of closer and more intensive monitoring and follow-up, and suggests to us that it may be worthwhile to provide serotype information as quickly as possible at the point-of-care.

Despite its strengths, our study is not without limitations. First, we do not have cause-specific mortality. Second, we had little information on the severity of in-hospital complications, only whether they occurred or not. Third, our findings may not be generalizable to patients with pneumococcal bacteremia without pneumonia or cases of non-pneumonia IPD such as meningitis. Fourth, our data represent adults with BPP prior to the era of recommendations to use conjugated vaccines in addition to just pneumococcal polysaccharide vaccine in this patient population.[28,29] Lastly, our serotypes were grouped based on serotype specific CFRs reported by previous meta-analysis and it

is possible that certain serotypes were misclassified.[23] If this were the case, however, it would tend to bias to the null and suggests that, if anything, the associations between serotypes and outcomes are stronger than we reported.

The impact of BPP on mortality and in-hospital complications is substantial. Although we discovered only two potentially modifiable factors (current use of acid-suppressing drugs and treatment with CAP guideline-discordant antibiotics), we have established the importance of recognizing frailty and lifestyle factors and our results suggest that more rapid availability of pneumococcal serotypes might aid frontline clinicians by helping them select out a subgroup of patients destined to have poor outcomes who might benefit from more intense monitoring and more rapid intensification of supportive care and treatments for their pneumonia.

Table 2-1: Characteristics of 1636 adult patients with bacteremic pneumococcal pneumonia, stratified by mortality

Characteristic	Mortality		P-value
	No (n=1410)	Yes (n=226)	
	N (%) or Mean (SD)		
Age, mean (SD)	52 (17)	65 (18)	<0.001
Sex, male	801 (56.8)	130 (57.5)	0.8
Aboriginal	186 (13.2)	26 (11.5)	0.5
Nursing home	22 (1.6)	26 (11.5)	<0.001
Non-smoker	663 (47.0)	164 (72.6)	<0.001
Underlying condition			
Dementia	16 (1.1)	15 (6.6)	<0.001
Mental health disorder	241 (17.1)	40 (17.7)	0.8
Stroke	48 (3.4)	17 (7.6)	0.003
Cardiac disease	205 (14.5)	65 (28.8)	<0.001
Anemia	93 (6.6)	27 (11.9)	0.004
Diabetes	180 (12.8)	38 (16.8)	0.096
Asplenia	11 (0.8)	1 (0.4)	0.6
Auto-immune disorder	147 (10.4)	27 (11.9)	0.6
AIDS	76 (5.4)	9 (4.0)	0.4
Cancer	161 (11.4)	52 (23.0)	<0.001
Immunosuppressive therapy	96 (6.8)	30 (13.3)	0.001
Musculoskeletal disorder	211 (15.0)	51 (22.6)	0.004
Asthma	174 (12.3)	21 (9.3)	0.2
COPD	282 (20.0)	64 (28.3)	0.004
Hepatic cirrhosis	58 (4.1)	19 (8.4)	0.005
GI Bleed	33 (2.3)	12 (5.3)	0.011
Renal disorder	56 (4.0)	25 (11.1)	<0.001
≥ 3 other comorbidities	203 (14.4)	58 (25.7)	<0.001
Alcoholism	346 (24.5)	67 (29.6)	0.1
Illicit drug use	315 (22.3)	35 (15.5)	0.021
Multilobe pneumonia	309 (21.9)	91 (40.3)	<0.001
Guideline-discordant antibiotics	242 (17.2)	91 (40.3)	<0.001
≥ 3 non-antibiotic medications	549 (38.9)	139 (61.5)	<0.001
Acid suppressing drugs	223 (15.8)	72 (31.9)	<0.001
Bronchodilators	270 (19.1)	60 (26.5)	0.01
Bronchioanti-inflammatories	65 (4.6)	15 (6.6)	0.2
Pneumococcal vaccine	69 (4.9)	2 (0.9)	0.006
Serotypes by case fatality rates			
Low	624 (44.3)	44 (19.5)	Ref
High	786 (55.7)	182 (80.5)	<0.001

Table 2-2: Characteristics of 1410 surviving adult patients with bacteremic pneumococcal pneumonia, stratified by in-hospital complications

Characteristic	In-hospital complications: No (n=1095)	In-hospital complications: Yes (n=315)	P-value
	N (%) or Mean (SD)		
Age, mean (SD)	51 (17)	55 (16)	<0.001
Sex, male	614 (56.1)	187 (59.4)	0.3
Aboriginal	137 (12.2)	49 (15.6)	0.2
Nursing home	13 (1.2)	9 (2.9)	0.035
Non-smoker	582 (53.2)	165 (52.4)	0.8
Underlying condition			
Dementia	11 (1.0)	5 (1.6)	0.4
Mental health disorder	174 (15.9)	67 (21.3)	0.025
Stroke	27 (2.5)	21 (6.7)	<0.001
Cardiac disease	128 (11.7)	59 (18.7)	0.001
Anemia	65 (5.9)	28 (8.9)	0.063
Diabetes	129 (11.8)	51 (16.2)	0.039
Asplenia	6 (0.5)	5 (1.6)	0.065
Auto-immune disorder	115 (10.5)	32 (10.2)	0.9
AIDS	61 (5.6)	15 (4.8)	0.6
Cancer	141 (12.9)	20 (6.3)	0.001
Immunosuppressive therapy	70 (6.4)	26 (8.3)	0.248
Musculoskeletal disorder	93 (8.5)	40 (12.7)	0.024
Asthma	142 (13.0)	32 (10.2)	0.182
COPD	187 (17.1)	95 (30.2)	<0.001
Hepatic cirrhosis	38 (3.5)	20 (6.3)	0.023
GI Bleed	23 (2.1)	10 (3.2)	0.266
Renal disorder	38 (3.5)	18 (5.7)	0.072
≥ 3 other comorbidities	134 (12.2)	69 (21.9)	<0.001
Alcoholism	221 (20.2)	125 (39.7)	<0.001
Illicit drug use	244 (22.3)	71 (22.5)	0.9
Multilobe pneumonia	183 (16.7)	126 (40.0)	<0.001
Guideline-discordant antibiotics	174 (15.9)	68 (21.6)	0.018
≥ 3 non-antibiotic medications	391 (35.7)	158 (50.2)	<0.001
Acid suppressing drugs	157 (14.3)	66 (21.0)	0.005
Bronchodilators	207 (18.9)	63 (20.0)	0.7
Bronchioanti-inflammatories	49 (4.5)	16 (5.1)	0.7
Pneumococcal vaccine	55 (5.0)	14 (4.4)	0.7
Serotypes by case fatality rates			
Low	534 (48.8)	90 (28.6)	Ref
High	561 (51.2)	225 (71.4)	<0.001

Table 2-3: Major in-hospital complications from bacteremic pneumococcal pneumonia according to mortality

	Mortality		
	No	**Yes**	**P-value**
Complication	**n=1410**	**n=226**	
	N (%) or Mean (SD)		
Mechanical ventilation	229 (16.2)	116 (51.3)	<0.001
Acute aspiration	81 (5.7)	46 (20.4)	<0.001
MACE	71 (5.0)	63 (27.9)	<0.001
Acute kidney injury	38 (2.7)	28 (12.4)	<0.001
Seizure	24 (1.7)	14 (6.2)	<0.001
Liver failure	17 (1.2)	15 (6.6)	<0.001
Stroke	4 (0.3)	6 (2.7)	0.001
ARDS without ventilation	3 (0.2)	5 (2.2)	<0.001
Any major complication	315 (22.3)	158 (70.0)	<0.001
≥ 2 complications	111 (7.9)	92 (40.7)	<0.001

Table 2-4: Characteristics independently associated with in-hospital mortality: multivariable logistic regression

Characteristic	Adjusted OR (95% CI)	P-value
Age (per decade)	1.5 (1.3-1.7)	<0.001
Nursing home	3.7 (1.8-7.4)	<0.001
Non-smoker	1.9 (1.3-2.7)	0.002
Alcoholism	2.2 (1.4-3.4)	<0.001
Underlying condition		
Dementia	3.7 (1.6-8.6)	0.003
Cancer	1.5 (1.0-2.3)	0.076
Guideline-discordant antibiotics	3.4 (2.4-4.8)	<0.001
Acid suppressing drugs	1.5 (1.0-2.3)	0.036
Multilobe pneumonia	2.6 (1.8-3.6)	<0.001
High CFR serotype	1.8 (1.2-2.8)	0.003
Pneumococcal vaccine	0.2 (0.05-0.9)	0.033

*Adjusted for all other variables presented in **Table 2-1;** Only those variables with P < 0.1 included in Table; Hosmer Lemeshow goodness-of-fit test P = 0.6 and c-statistic = 0.83

Table 2-5: Characteristics independently associated with suffering any in-hospital complication

Complication	Adjusted OR (95% CI)	P-value
Alcoholism	3.2 (2.3-4.6)	<0.001
Underlying condition		
Stroke	2.3 (1.1-4.6)	0.020
AIDS	0.5 (0.3-1.0)	0.050
Cancer	0.3 (0.2-0.5)	<0.001
COPD	2.0 (1.3-2.9)	0.001
Guideline-discordant antibiotics	1.7 (1.2-2.4)	0.005
≥ 3 other non-antibiotic medications	1.7 (1.2-2.4)	0.006
Multilobe pneumonia	3.9 (2.9-5.4)	<0.001
High CFR serotype	2.8 (2.0-2.9)	<0.001

*Adjusted for all other variables presented in **Table 2-1**; Only those variables with P < 0.1 included in Table; Hosmer Lemeshow goodness-of-fit test P = 0.3 and c-statistic = 0.78

Figure 2-1: Selection of adult patients admitted to northern Alberta hospitals with Bacteremic Pneumococcal Pneumonia (BPP)

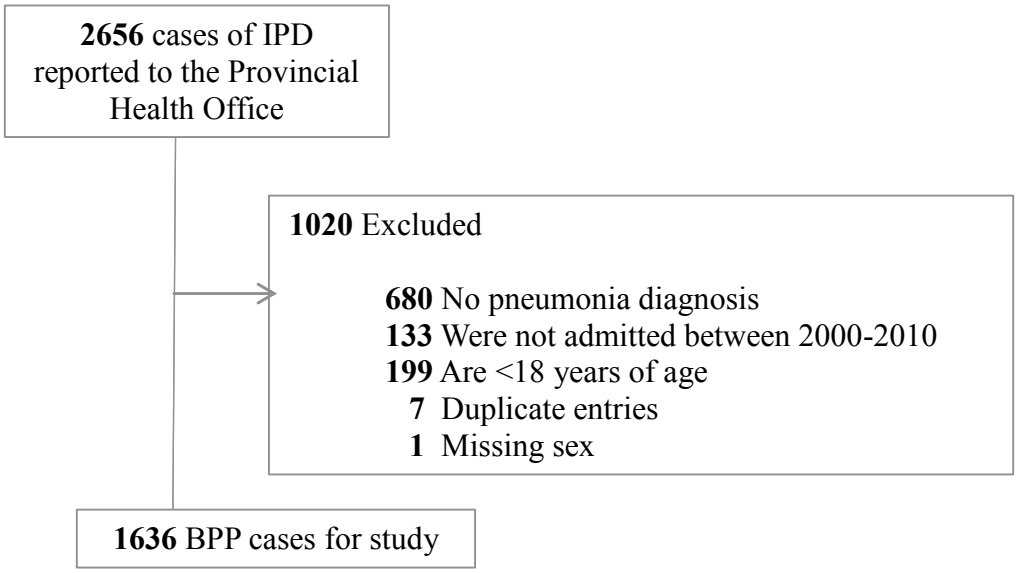


Figure 2-2: Stratified analysis on associations of significant host factors and in-hospital mortality

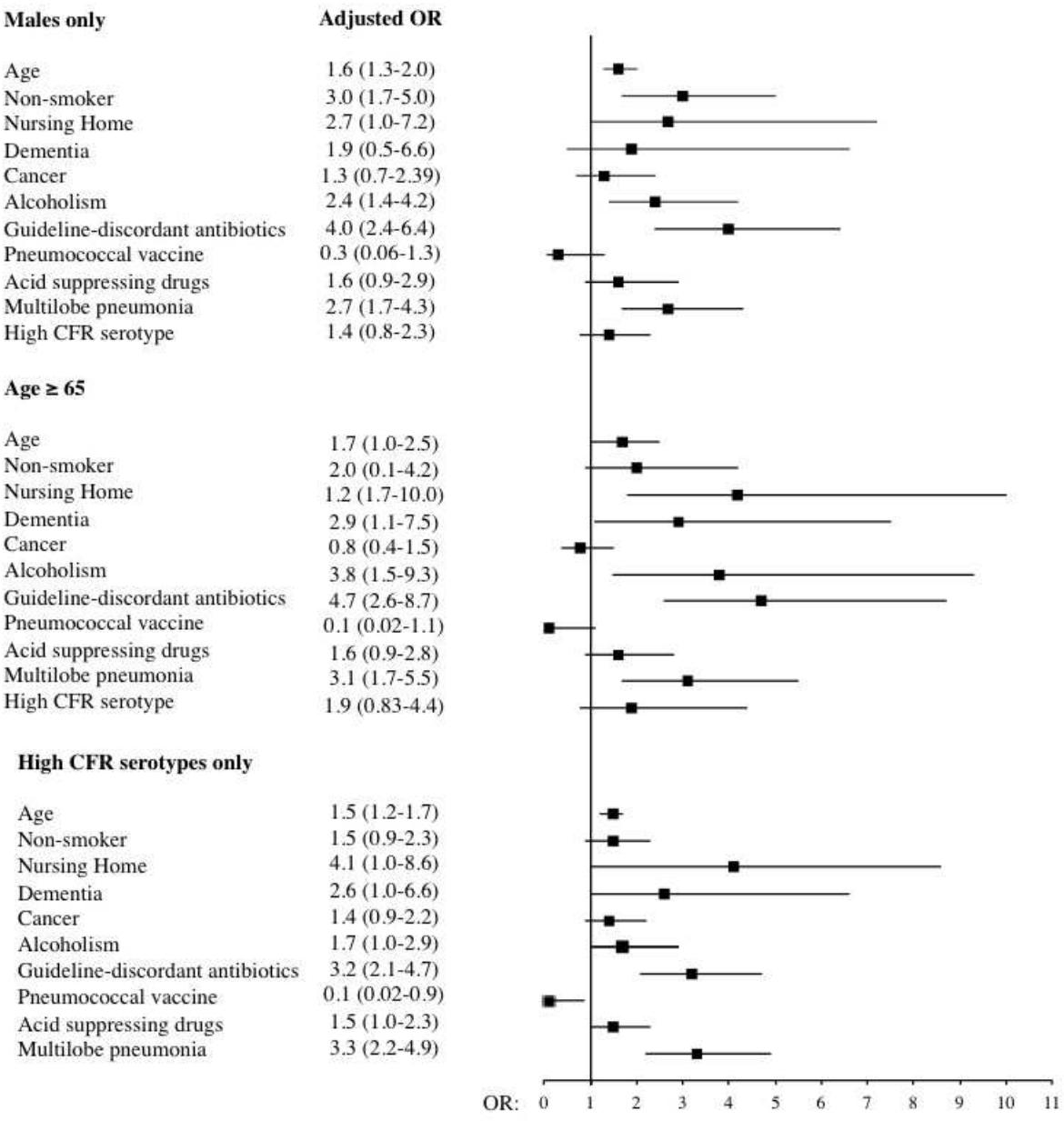


Figure 2-3: Stratified analysis on associations of significant host factors and in-hospital complication

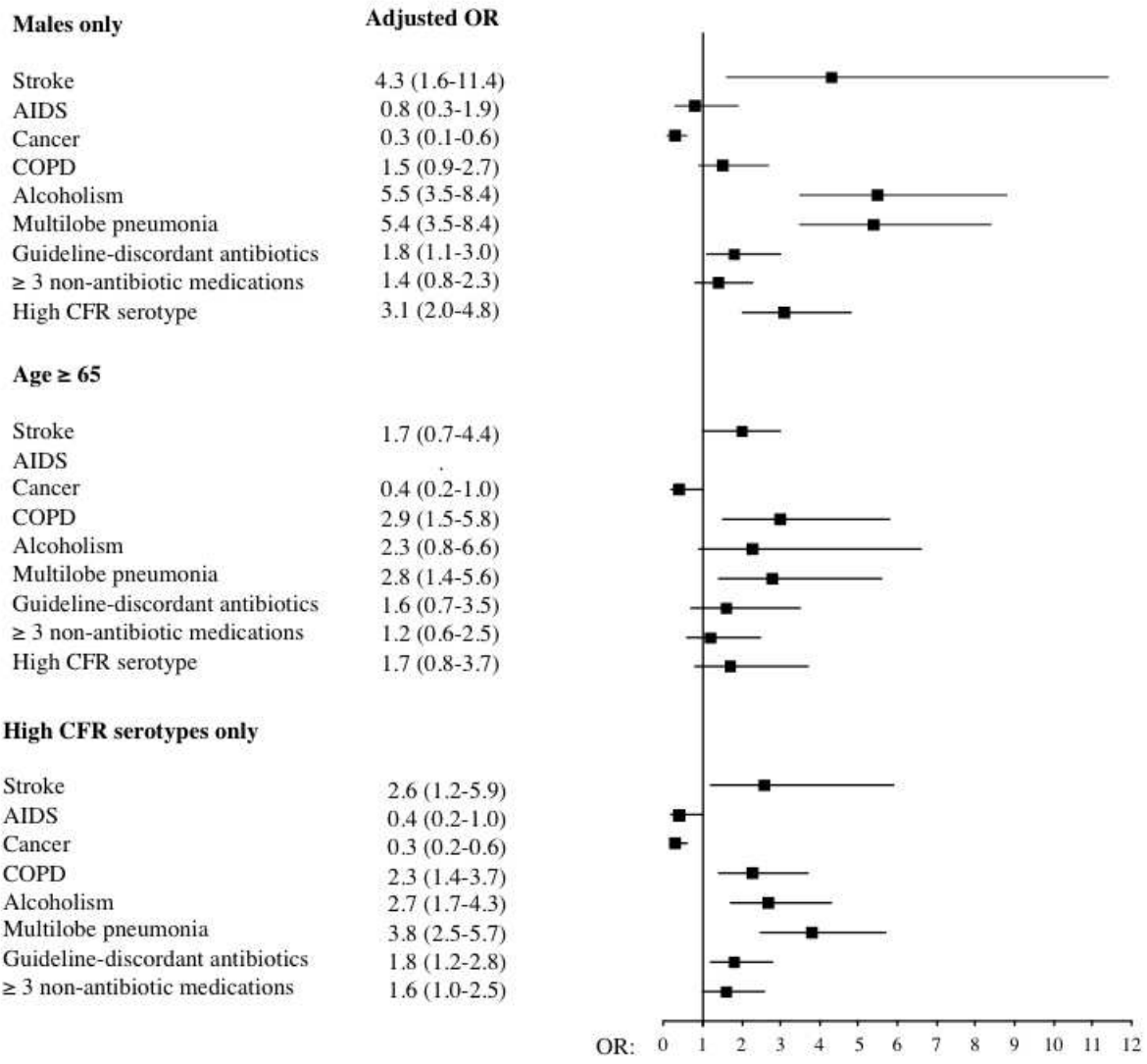
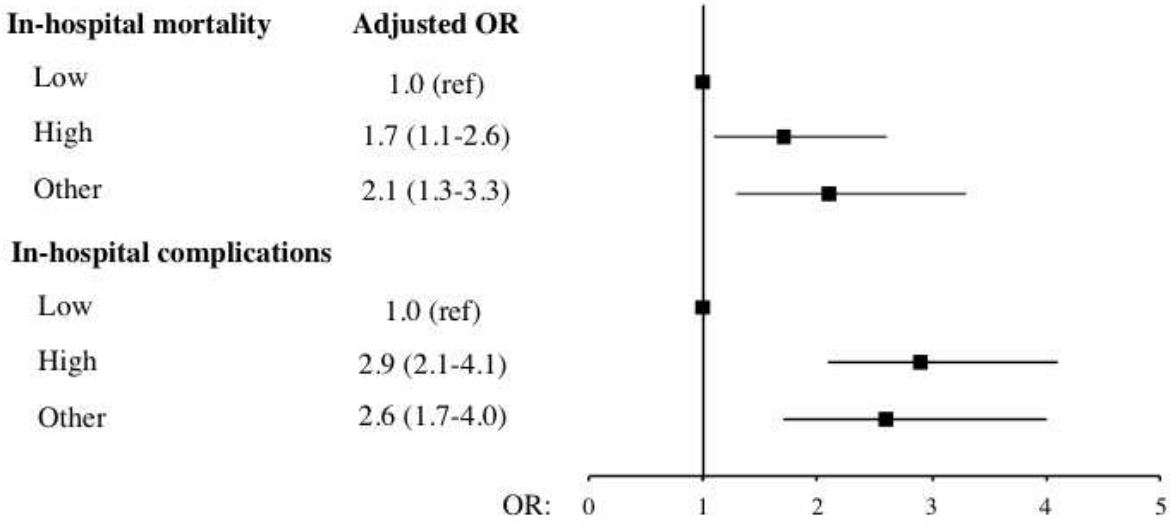


Figure 2-4: Adjusted association between in-hospital mortality or in-hospital complications and pneumococcal serotypes by case fatality rate – using low case fatality rate as the reference category



2.5 References

1. Ortqvist A, Hedlund J, Kalin M. Streptococcus pneumoniae: epidemiology, risk factors, and clinical features. *Seminars in respiratory and critical care medicine.* Dec 2005;26(6):563-574.
2. Jover F, Cuadrado JM, Andreu L, et al. A comparative study of bacteremic and non-bacteremic pneumococcal pneumonia. *European journal of internal medicine.* Jan 2008;19(1):15-21.
3. Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PloS one.* 2013;8(4):e60273.
4. Cremers AJ, Meis JF, Walraven G, Jongh CE, Ferwerda G, Hermans PW. Effects of 7-valent pneumococcal conjugate 1 vaccine on the severity of adult 2 bacteremic pneumococcal pneumonia. *Vaccine.* Jun 30 2014;32(31):3989-3994.
5. Lynch JP, 3rd, Zhanel GG. Streptococcus pneumoniae: epidemiology, risk factors, and strategies for prevention. *Seminars in respiratory and critical care medicine.* Apr 2009;30(2):189-209.
6. Pereira JM, Teixeira-Pinto A, Basilio C, Sousa-Dias C, Mergulhao P, Paiva JA. Can we predict pneumococcal bacteremia in patients with severe community-acquired pneumonia? *Journal of critical care.* Dec 2013;28(6):970-974.
7. Berjohn CM, Fishman NO, Joffe MM, Edelstein PH, Metlay JP. Treatment and outcomes for patients with bacteremic pneumococcal pneumonia. *Medicine.* May 2008;87(3):160-166.
8. Afessa B, Greaves WL, Frederick WR. Pneumococcal bacteremia in adults: a 14-year experience in an inner-city university hospital. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Aug 1995;21(2):345-351.
9. Garnacho-Montero J, Garcia-Cabrera E, Diaz-Martin A, et al. Determinants of outcome in patients with bacteraemic pneumococcal pneumonia: importance of early adequate treatment. *Scandinavian journal of infectious diseases.* Mar 2010;42(3):185-192.
10. Fica A, Bunster N, Aliaga F, et al. Bacteremic pneumococcal pneumonia: serotype distribution, antimicrobial susceptibility, severity scores, risk factors, and mortality in a single center in Chile. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases.* Mar-Apr 2014;18(2):115-123.
11. Lujan M, Gallego M, Fontanals D, Mariscal D, Rello J. Prospective observational study of bacteremic pneumococcal pneumonia: Effect of discordant therapy on mortality. *Critical care medicine.* Mar 2004;32(3):625-631.
12. Naucler P, Darenberg J, Morfeldt E, Ortqvist A, Henriques Normark B. Contribution of host, bacterial factors and antibiotic treatment to mortality in

adult patients with bacteraemic pneumococcal pneumonia. *Thorax.* Jun 2013;68(6):571-579.
13. Blot M, Croisier D, Pechinot A, et al. A leukocyte score to improve clinical outcome predictions in bacteremic pneumococcal pneumonia in adults. *Open forum infectious diseases.* Sep 2014;1(2):ofu075.
14. Tyrrell GJ, Lovgren M, Chui N, et al. Serotypes and antimicrobial susceptibilities of invasive Streptococcus pneumoniae pre- and post-seven valent pneumococcal conjugate vaccine introduction in Alberta, Canada, 2000-2006. *Vaccine.* Jun 2 2009;27(27):3553-3560.
15. Werno AM, Murdoch DR. Medical microbiology: laboratory diagnosis of invasive pneumococcal disease. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Mar 15 2008;46(6):926-932.
16. Case Definitions for Communicable Diseases under National Surveillance - 2009. 2009;35(Suppl 2). http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s2/index-eng.php. Accessed 3-13-2015.
17. Rogot E, Murray JL. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public health reports.* May-Jun 1980;95(3):213-222.
18. Majumdar SR, McAlister FA, Eurich DT, Padwal RS, Marrie TJ. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *Bmj.* Nov 11 2006;333(7576):999.
19. Eurich DT, Sadowski CA, Simpson SH, Marrie TJ, Majumdar SR. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *The American journal of medicine.* Jan 2010;123(1):47-53.
20. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community‐acquired pneumonia in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2007;44 (Suppl 2), pp. S27-S72.
21. Asadi L, Eurich DT, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Guideline adherence and macrolides reduced mortality in outpatients with pneumonia. *Respiratory medicine.* Mar 2012;106(3):451-458.
22. Lund E, Henrichsen J. *Laboratory diagnosis, serology and epidemiology of Streptococcus pneumoniae.* Vol 12. Methods Microbiol.1978.
23. Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2010;51(6):692-699.
24. Ruiz LA, Zalacain R, Capelastegui A, et al. Bacteremic pneumococcal pneumonia in elderly and very elderly patients: host- and pathogen-related factors, process of care, and outcome. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Aug 2014;69(8):1018-1024.
25. Marrie TJ, Tyrrell GJ, Garg S, Vanderkooi OG. Factors predicting mortality in invasive pneumococcal disease in adults in Alberta. *Medicine.* May 2011;90(3):171-179.

26. Alanee SR, McGee L, Jackson D, et al. Association of serotypes of Streptococcus pneumoniae with disease severity and outcome in adults: an international study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jul 1 2007;45(1):46-51.
27. Harboe ZB, Thomsen RW, Riis A, et al. Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. *PLoS medicine.* May 26 2009;6(5):e1000081.
28. Public Health Agency of Canada. Canadian Immunization Guide. Pneumococcal Vaccine. Part 4: Active Vaccines. http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pneu-eng.php. Accessed Oct 07, 2015.
29. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Morbidity and mortality weekly report.* Sep 19 2014;63(37):822-825.

CHAPTER 3: SMOKING AND REDUCED MORTALITY IN BACTEREMIC PNEUMOCOCCAL PNEUMONIA

3.1 Introduction

Streptococcus pneumoniae is the most common cause of community-acquired pneumonia (CAP) and it remains an important cause of morbidity and mortality among adults worldwide.[1] For example, at least one-fifth of all CAP is a result of *S. pneumoniae*, and in 2013, more than 2200 cases of bacteremic pneumococcal pneumonia (BPP) occurred in the United States.[2] The case fatality rate for pneumococcal pneumonia is approximately 5-7% [3] while the case fatality rate for BPP is reportedly as high as 33%.[4] Risk factors for developing CAP in general, and pneumococcal pneumonia (with or without bacteremia) more specifically include older age, immune-compromised status, alcoholism, chronic lung diseases, and current smoking.[1,5]

While it may not be surprising that current smoking is a risk factor for ***developing*** CAP (and specifically pneumococcal pneumonia), three large (~ 70,000 total patients) cohorts studies have also suggested that current smoking is independently associated with a lower risk of mortality among those ***with*** pneumonia.[6-8] Although not all studies demonstrate this finding,[9-13] the fact that current smoking is not always consistently a robust risk factor for increased mortality in patients with CAP is intriguing and warrants further explanation. We hypothesized that one potential mechanism might be related to differential acquisition of low vs high case fatality rate [CFR] pneumococcal serotypes according to whether or not one smokes. This is not implausible – for instance, it is

known that current smokers with invasive pneumococcal disease are more likely to be infected with low CFR serotypes than are non-smokers, although to our knowledge this has not been examined in the setting of (pneumococcal) pneumonia.[14]

To carefully test our hypothesis would require a large population of patients with pneumococcal pneumonia who all had documented smoking data and known pneumococcal serotypes. To achieve this, we examined a clinically-rich prospective population-based cohort of patients with BPP thus ensuring we knew patients had pneumonia and knew which serotypes they were infected with. We had two major objectives. First, we had to demonstrate that current smoking was independently associated with reduced mortality in BPP. Second, we had to undertake stratified and adjusted analyses to explore the relationships between smoking status and the CFR of the serotypes acquired by these patients to test our hypotheses.

3.2 Methods

Subjects and Setting

Since 1998, all cases of IPD (and thus, all cases of BPP) identified in Alberta are classified as a notifiable disease and therefore must be reported to the Provincial Health Office. Subsequently all pneumococcal isolates from cases of IPD are forwarded to the Provincial Laboratory for Public Health in Edmonton Alberta, for serotyping and antimicrobial susceptibility trend analysis.[15,16] The definition of IPD follows the Canadian national case definition: isolation of *S. pneumoniae* from a normally sterile site such as blood, cerebrospinal fluid, pleural fluid, biopsy tissue, joint aspirate, pericardial

fluid or peritoneal fluid.[15] All cases of IPD identified in Northern Alberta between January 1st 2000 to December 31st 2010 (approximate population 2,060,039[17]) were first identified.[18] From this population, we restricted our study to all adults (≥18 years) hospitalized with pneumonia who had documented pneumococcal bacteremia (i.e bacteremic pneumococcal pneumonia) (**Figure 3-1**). This study was approved by each institutional research ethics committee in the province and received a waiver for the need for written informed consent.

Data collection

Upon reporting of *S. pneumoniae* isolates, an extensive chart review of all identified cases was conducted by trained research nurses.[19,20] Optochin susceptibility and bile solubility assays were used to confirm that isolates were *S. pneumoniae.*[15,16] Serotyping of all isolates was performed by the Quellung reaction using serotype-specific antisera from Statens Serum Institute (Denmark) as previously described [21]. Additional information collected included demographics, pre-existing comorbid conditions, prescription drug history, lifestyle factors, and antibiotic treatments. We classified empiric antibiotic treatments according to whether or not they were concordant or discordant with current clinical practice guidelines for the empiric treatment of hospitalized patients with CAP.[22,23]

Exposures and Outcomes

Our exposure of interest was current smoking. Smoking status was classified as follows: current (i.e. active) smokers, former smokers, and those who never smoked. For analysis

purposes, as others have done,[5,14] those who never smoked as well as those who were former smokers were collectively considered "non-smokers". We did not collect the number of cigarettes per day or pack-years of exposure, and only definitely know that patients were current smokers or not. Our primary outcome of interest was all-cause in-hospital mortality.

Classification of Serotypes According to Case Fatality Rates

Pneumococcal serotypes were grouped according to published literature reviews and classified as low CFR (serotypes 1, 4, 5, 7F, and 8) vs high CFR (serotypes 3, 6A, 6B, 9N, 19A, 19F, 23F).[24,25] The remaining "other" serotypes identified in the study, (2, 7C, 9L, 9V, 10A, 10F, 11A, 11B, 11F, 12F, 13, 14, 15A, 15B, 15C, 16F, 17F, 18A, 18B, 18C, 18F, 20, 22A, 22F, 23A, 23B, 28A, 29, 31, 33A, 33F, 34, 35A, 35B, 35C, 35F, 37, 38, 40, 42) were classified as high CFR because preliminary analyses indicated these serotypes had similar patient characteristics and in-hospital mortality rates as observed with the high CFR serotypes (22% (78/358) in high CRF compared with 17% (104/610) in the other non-low non-high serotypes).

Statistical analysis

We undertook descriptive statistics using tests appropriate to the data (e.g. chi-squared and Student's t-test). To evaluate the independent association between current smoking and in-hospital mortality we used multivariable logistic regression analyses and adjusted for all of the demographic, clinical, and pneumonia-related variables presented in **Table 3-1**. Then we evaluated the interplay between current smoking (vs not) and low CFR

serotypes (vs not) by directly testing this interaction term. The c-statistic (area under the receiver-operating characteristic [ROC]) was used to describe overall predictive model accuracy and the Hosmer-Lemeshow test statistic was used to assess the model's goodness-of-fit.

Sensitivity analysis

To assess the robustness of our results, first we repeated the entire analysis after excluding patients under the age of 65-years, since older patients are already at increased risk of mortality.[26] Second, we restricted our analysis to males, because they are known to have a lower risk of mortality than females.[25] Third, we excluded former smokers rather than group them with never-smokers, and re-ran all analyses. Fourth, we excluded all of the "other" CFR (that is, non-high non-low) serotypes rather than group them with high CFR and re-ran all analyses. Fifth, in Alberta, outbreaks of low CFR serotype 8 (2005) and low CFR serotype 5 (2006) were known to have occurred.[27] Therefore, to ensure that these two outbreaks did not affect our analysis we excluded all patients with serotypes 5 and 8, and re-ran all analyses. Sixth, we repeated our analysis including the variable of any major in-hospital complication to determine its affect on the association between smoking and in-hospital mortality. Seventh, a recent study has demonstrated an association between high CFR serotypes and individuals who are immunocompromised,[28] and therefore we excluded patients with immunocompromising conditions according to the recent Advisory Committee on Immunization Practices (ACIP) guidelines for adult pneumococcal vaccination and re-ran our analysis.[29] Lastly, to ensure differences in comorbidities were not driving our results, we further adjusted our analyses for the

Charlson index score.[30] All analyses were performed with Stata SE, version 12.1 (Stata, College Station, TX).

3.3 Results

The final study cohort consisted of 1636 adults hospitalized with BPP. Average age was 54 (SD 18) years, 434 (27%) patients were over the age of 65 years, 931 (57%) patients were male, and almost half (n=809, 49%) the cohort were current smokers. Relative to non-smokers, current smokers tended to be younger, more likely male, and to be homeless (**Table 3-1**). Of note, although current smokers were more likely to abuse alcohol or illicit drugs, they also had fewer comorbidities and used fewer medications than non-smokers (**Table 3-1**). Overall, 226 (14%) patients with BPP died in hospital.

3.3.1 Smoking and Mortality

Overall, 62 current smokers died compared with 164 non-smokers (8% vs 20% mortality for non-smokers, $P<0.001$). After adjusting for all the variables presented in **Table 3-1**, current smoking was independently associated with reduced in-hospital mortality (adjusted odds ratio (aOR), 0.52; 95% CI, 0.36-0.77; $P = 0.001$ and see **Table 3-2**).

Serotypes and Mortality

Overall, 668 (41%) patients were infected with low CFR serotypes while 968 (59%) were infected with high CFR serotypes (**Table 3-3**). After adjustment for all the variables in **Table 3-1**, the low CFR serotype group was independently associated with decreased

mortality relative to the high CFR group (7% vs 19% mortality for high CFR, aOR. 0.54; 95% CI, 0.36-0.82; *P* = 0.003) **(Table 3-4).**

Interplay of Smoking, Serotypes, and Mortality

Current smokers were more likely to be infected with low CFR serotypes than were non-smokers (429 (53%) current smokers vs 239 (29%) non-smokers, aOR, 1.67; 95%CI, 1.31-2.12, P<0.001 and **Figure 3-2**). In particular, current smokers were more likely to be infected with low CFR serotypes 5 and 8, while non-smokers were more likely to be infected with high CFR serotypes 6A, 6B, 14, 19A, 19F, 22F, and 23F (**Figure 3-2**, **Table 3-5**). In the same mortality models that were presented earlier, adjustment for CFR serotype did not eliminate the independent association between current smoking and mortality (aOR, 0.52; 95% CI, 0.36-0.77; *P* = 0.001) (**Table 3-4**) and the interaction term testing current smoking (vs not) X low CFR (vs not) was not statistically significant (adjusted *P*-value = 0.12).

Sensitivity analysis

The results of sensitivity analyses are displayed in **Figure 3-3**. Restricting analyses to patients 65-years and older or to males did not substantially change the adjusted odds ratio for current smoking and in-hospital mortality, although the findings were no longer statistically significant for the former. Similarly, excluding former smokers and "other" CFR serotypes did not materially change our findings. Excluding 'other' CFR serotypes altogether or the low CFR serotypes associated with outbreaks did not change our findings. Addition of major in-hospital complication to our model did not significantly

change our findings. Moreover, exclusion of immunocompromised individuals further decreased the risk of in-hospital mortality in current smokers with BPP. Lastly, adding the Charlson Comorbidity Index as a covariate in the model did not materially change our results (**Figure 3-3**).[23,31]

3.4 Discussion

In this population-based cohort study of 1636 patients hospitalized with BPP, we found that current smoking was independently associated with a nearly 50% reduction of in-hospital mortality. Similar to other studies, we found that current smokers tended to be younger with fewer comorbid conditions, but that they were also more likely to abuse alcohol or illicit drugs when compared to non-smokers.[9,14] However, these differences in patient-level characteristics could not explain the mortality reduction in BPP that we observed. Moreover, while our data showed differential infection with low vs high CFR pneumococcal serotypes by smoking status, serotype differences alone could also not explain the association between current smoking and lower mortality in BPP that we observed.

The results of this study are broadly consistent with three previous studies that have suggested that mortality is decreased in current smokers with pneumonia.[6-8] One large study, involving 62,918 adults hospitalized with CAP found that smoking was significantly associated with a reduced risk of in-hospital mortality (adjusted hazard ratio 0.90 overall, 95% CI 0.68-0.91 and 0.79 in those who were vaccinated against pneumococcus, 95% CI 0.82-0.99)[7] while another study (n=3233) similarly found a

significant reduction in mortality among current smokers with CAP (adjusted OR 0.5; $P < 0.05$).[8]

Conversely, in a prospective cohort study by Bello *et al.* composed of adults with pneumococcal CAP, smokers were found to have an increased risk of 30-day mortality (aOR, 5.0; 95% CI, 1.8-13.5; $P = .001$).[9] However, this study was limited by sample size (only 10 of 35 deaths were in current smokers) and was not restricted to BPP. Similarly, Naucler et al. evaluated 1580 adult patients with BPP and found that smokers had an increased risk of 30-day mortality (aOR, 1.79, 95% CI, 1.02-3.14).[25] This study, however is difficult to interpret as 1 in 5 patients had missing data for smoking status – and it is more than likely that missingness for smoking status would be associated with adverse events. By examining a clinically rich and complete population based cohort of patients with BPP, we think we have overcome some of the limitations of these prior studies.

Why should current smoking be associated with lower mortality in BPP? We have demonstrated that a potentially likely explanation is a predilection for infection with low CFR serotypes. Indeed, we found that low CFR serotypes (especially serotypes 5 and 8) were more common in current smokers than non-smokers. One previous study also supports the idea that smokers may be predisposed to serotype 8 and other low CFR serotypes.[14] The biological mechanism for this is unknown, although it has been hypothesized that current smokers may have a different environmental niche in their nasopharynx, allowing for increased adhesion by certain specific pneumococcal serotypes.[32] This could also partially explain why current smokers are at an increased risk

for developing IPD on the one hand but at lower risk of IPD-related mortality on the other.[33] Alternately, our results may be related to residual confounding, particularly since CFR of serotypes did not explain the entire mortality advantage with current smoking that we observed.

Our study has important limitations. It is important to note that a seven valent pneumococcal conjugated vaccination (PCV7) program was begun in Alberta in 2002. The PCV7 includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, but not serotypes 5 and 8.[15] Some studies have shown that the prevalence of certain pneumococcal serotypes in adults decreased over time after the introduction of the PCV7.[34,35] Furthermore, providers may have been more likely to vaccinate children at the start of the program if they knew they had second-hand smoke exposure (i.e. another adult current smoker in the household), which may have affected heard immunity. Whether this pediatric vaccination program resulted in a shift in IPD in adults in Alberta or could have potentially affected our study results is unknown but it is difficult to explain why such shifts would only affect current smokers. Ideally, although we could not do this, we would attempt to compare our results to patients hospitalized with non-pneumococcal bacteremic pneumonia and demonstrate that current smokers do not have a mortality advantage in that setting – fulfilling "specificity" in the Bradford-Hill criteria.

Second, we had little information about the current amount or total duration of current smoking, and therefore we could not investigate a dose-response relationship. Third, and *a priori*, we relied on previous literature to classify our pneumococcal serotypes and then

collapsed 56 different types into two categories. Therefore, it is possible certain serotypes may have been classified incorrectly, although this would tend to bias to the null. Fourth, our study may have been influenced by collider-stratification bias.[36-38] Collider bias is a type of selection bias that can be inadvertently introduced into observational studies by adjusting, restricting, or stratifying on a common "effect" related to both the exposure and outcome.[36,38] For example, studies have shown an inverse association between low birth weight and neonatal mortality in women who smoke.[38] Birth weight was found to be a collider, which created associations between factors affecting birth weight that are normally independent (e.g. maternal smoking, [39] or multiple pregnancies, [40]) but appeared correlated within the different strata of birth weight.[38] The result of the collider-stratification was a potentially biased estimate of neonatal mortality in low birthweight babies of mothers who smoked.[38] The consequence of collider bias in our study, if it existed, might lead to a spurious association between smoking and mortality although we could not even predict the direction of bias. Last, although our data was collected from a large geographical region in Canada, some may be concerned that our results cannot be generalized to other settings.

In summary, our findings suggest that current smokers with (bacteremic) pneumococcal pneumonia have a decreased risk of in-hospital mortality when compared with non-smokers, and we believe that this finding may be partly explained by the observation that current smokers are more likely to be infected with low CFR serotypes. Elucidating the mechanisms for this differential acquisition of pneumococcal serotypes would be important from both a research and public health perspective.

Table 3-1: Characteristics of 1636 adult patients with bacteremic pneumococcal pneumonia (BPP) by smoking status

Characteristic	Current smoker: No (n=827)	Current smoker: Yes (n=809)	*P*-value
Age (years)	59.4 ± 19.2	48.3 ± 14.5	<0.001
Male sex	444 (53.7)	487 (60.2)	0.008
Aboriginal	84 (10.2)	128 (15.8)	0.001
Nursing home	44 (5.3)	4 (0.49)	<0.001
Homeless	45 (5.4)	117 (14.5)	<0.001
Underlying condition			
Dementia	25 (3.0)	6 (0.7)	<0.001
Stroke	42 (5.1)	23 (2.8)	0.021
Cardiac disease	161 (19.5)	58 (7.2)	<0.001
Diabetes	129 (15.6)	89 (11.0)	0.006
AIDS	28 (3.4)	57 (7.0)	0.001
Asplenia	7 (0.85)	5 (0.62)	0.6
Auto-immune disorder	107 (12.9)	67 (8.3)	0.002
Immunosuppressed	91 (11.0)	35 (4.3)	<0.001
Cancer	141 (17.0)	72 (8.9)	<0.001
Asthma	92 (11.1)	103 (12.7)	0.3
COPD	172 (20.8)	174 (21.5)	0.7
Hepatic cirrhosis	38 (4.6)	39 (4.8)	0.8
Alcoholism	128 (15.5)	285 (35.2)	<0.001
Illicit drug use	89 (10.8)	261 (32.3)	<0.001
≥ 3 other comorbidities	257 (31.1)	173 (21.4)	<0.001
≥ 3 medications	490 (59.3)	272 (33.6)	<0.001
Pneumococcal vaccine	33 (4.0)	38 (4.7)	0.5
Multilobe pneumonia	197 (23.8)	203 (25.1)	0.6
Guideline-discordant antibiotics	202 (24.4)	131 (16.2)	<0.001

Table 3-2: Characteristics of 1636 adult patients with bacteremic pneumococcal pneumonia (BPP) by serotype-specific case fatality rate group

Characteristic	CFR group Low (n=668)	High (n=968)	*P*-value
Age (years)	48.4 ± 15.2	59.0 ± 17.8	<0.001
Male sex	431 (64.5)	500 (51.6)	<0.001
Aboriginal	115 (17.2)	97 (10.0)	<0.001
Nursing home	4 (0.60)	44 (4.5)	<0.001
Homeless	109 (16.3)	53 (5.5)	<0.001
Underlying condition			
Dementia	7 (1.0)	24 (2.5)	<0.001
Stroke	9 (1.3)	47 (4.9)	<0.001
Cardiac disease	38 (5.7)	181 (18.7)	<0.001
Diabetes	52 (7.8)	166 (17.1)	<0.001
AIDS	33 (4.9)	52 (5.4)	0.7
Asplenia	1 (0.15)	11 (1.1)	0.022
Auto-immune disorder	37 (5.5)	137 (14.2)	<0.001
Immunosuppressed	18 (2.7)	108 (11.2)	<0.001
Cancer	42 (6.3)	171 (17.7)	<0.001
Asthma	81 (12.1)	114 (11.8)	0.8
COPD	106 (15.9)	240 (24.8)	<0.001
Hepatic cirrhosis	18 (2.7)	59 (6.1)	0.001
Alcoholism	206 (30.8)	207 (21.4)	<0.001
Illicit drug use	207 (31.0)	143 (14.8)	<0.001
≥ 3 other comorbidities	101 (15.1)	329 (34.0)	<0.001
≥ 3 medications	199 (29.8)	563 (58.2)	<0.001
Pneumococcal vaccine	24 (3.6)	47 (4.9)	0.2
Multilobe pneumonia	158 (23.7)	242 (25.0)	0.5
Guideline-discordant antibiotics	112 (16.8)	221 (22.8)	0.003

Table 3-3: In-hospital mortality model without CFR serotypes

Characteristic	Adjusted OR (95% CI)	*P*-value
Current smoker	0.51 (0.35-0.75)	0.001
Age (per decade)	1.47 (1.29-1.67)	<0.001
Nursing home	3.40 (1.72-6.70)	0.001
Underlying conditions		
Dementia	3.19 (1.38-7.35)	0.007
Cancer	1.51 (0.99-2.31)	0.056
Hepatic cirrhosis	1.99 (1.07-3.72)	0.031
Alcoholism	2.30 (1.50-3.72)	<0.001
Pneumococcal vaccine	0.19 (0.04-0.80)	0.028
Multilobe pneumonia	2.53 (1.80-3.54)	<0.001
Guideline-discordant antibiotics	3.29 (2.33-4.64)	<0.001

*Adjusted for all variables presented in **Table 3-1;** Only those variables with p<0.1 included in Table; Hosmer Lemeshow goodness-of-fit test p= 0.98 and c-statistic = 0.82

Table 3-4: In-hospital mortality model including low and high CFR serotypes

Characteristic	Adjusted OR (95% CI)	*P*-value
Current smoker	0.52 (0.36-0.77)	0.001
Age (per decade)	1.42 (1.24-1.62)	<0.001
Nursing home	3.34 (1.69-6.60)	0.001
Underlying conditions		
Dementia	3.27 (1.42-7.53)	0.005
Cancer	1.47 (0.96-2.24)	0.076
Hepatic cirrhosis	1.79 (0.95-3.34)	0.070
Alcoholism	2.32 (1.51-3.56)	<0.001
Pneumococcal vaccine	0.19 (0.04-0.80)	0.024
Multilobe pneumonia	2.53 (2.29-4.57)	<0.001
Guideline-discordant antibiotics	3.24 (2.29-4.57)	<0.001
Low CFR serotype	0.54 (0.36-0.82)	0.003

*Adjusted for all variables presented in **Table 3-1;** Only those variables with p<0.1 included in Table; Hosmer Lemeshow goodness-of-fit test p= 0.81 and c-statistic = 0.82

Table 3-5: Comparison of pneumococcal serotypes acquired by smokers and non-smokers

		All patients			Deaths only		
	Serotype	**Non-smokers (n=809)**	**Smokers (n=827)**	***P*-value**	**Non-Smokers (n=164)**	**Smokers (n=62)**	***P*-value**
Low CFR serotypes	1	11 (1.3)	17 (2.1)	0.2	1 (0.6)	0	1.00
	4	72 (8.7)	92 (11.4)	0.073	8 (4.9)	9 (14.5)	0.022
	5	68 (8.2)	179 (22.1)	<0.001	7 (4.3)	1 (1.6)	0.451
	7F	36 (4.4)	41 (5.1)	0.5	7 (4.3)	0	0.19
	8	52 (6.3)	100 (12.4)	<0.001	7 (4.3)	4 (6.5)	0.5
High CFR serotypes	3	62 (7.5)	54 (6.7)	0.5	19 (11.6)	13 (21.0)	0.087
	6A	25 (3.0)	10 (1.2)	0.013	10 (6.1)	2 (3.2)	0.5
	6B	25(3.0)	7 (0.9)	<0.001	6 (3.7)	1 (1.6)	0.7
	9N	22 (2.7)	18 (2.2)	0.6	4 (2.4)	0	0.6
	9V	57 (4.2)	42 (3.0)	0.1	4 (2.4)	0	0.6
	12F	17 (2.1)	34 (4.2)	0.012	2 (1.2)	3 (4.8)	0.13
	14	63 (7.6)	22 (2.7)	<0.001	6 (3.7)	2 (3.2)	1.00
	19A	65 (5.2)	38 (3.5)	0.008	6 (3.7)	3 (4.8)	0.7
	19F	22 (2.7)	10 (1.2)	0.038	5 (3.0)	1 (1.6)	1.00
	22F	58 (7.0)	34 (4.2)	0.014	11 (6.7)	5 (8.1)	0.7
	23F	22 (2.7)	10 (1.2)	0.038	7 (4.3)	1 (1.6)	0.5
	*Other	194 (23.5)	129 (16.0)	<0.001	54 (32.9)	17 (26.6)	0.5

Figure 3-1: Selection of adult patients admitted to northern Alberta hospitals with bacteremic pneumococcal pneumonia (BPP)

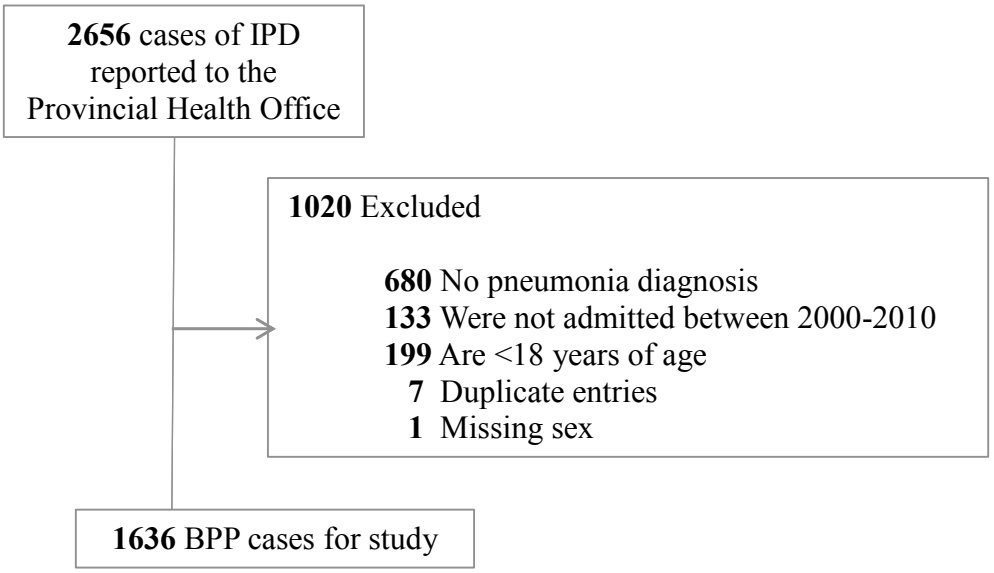
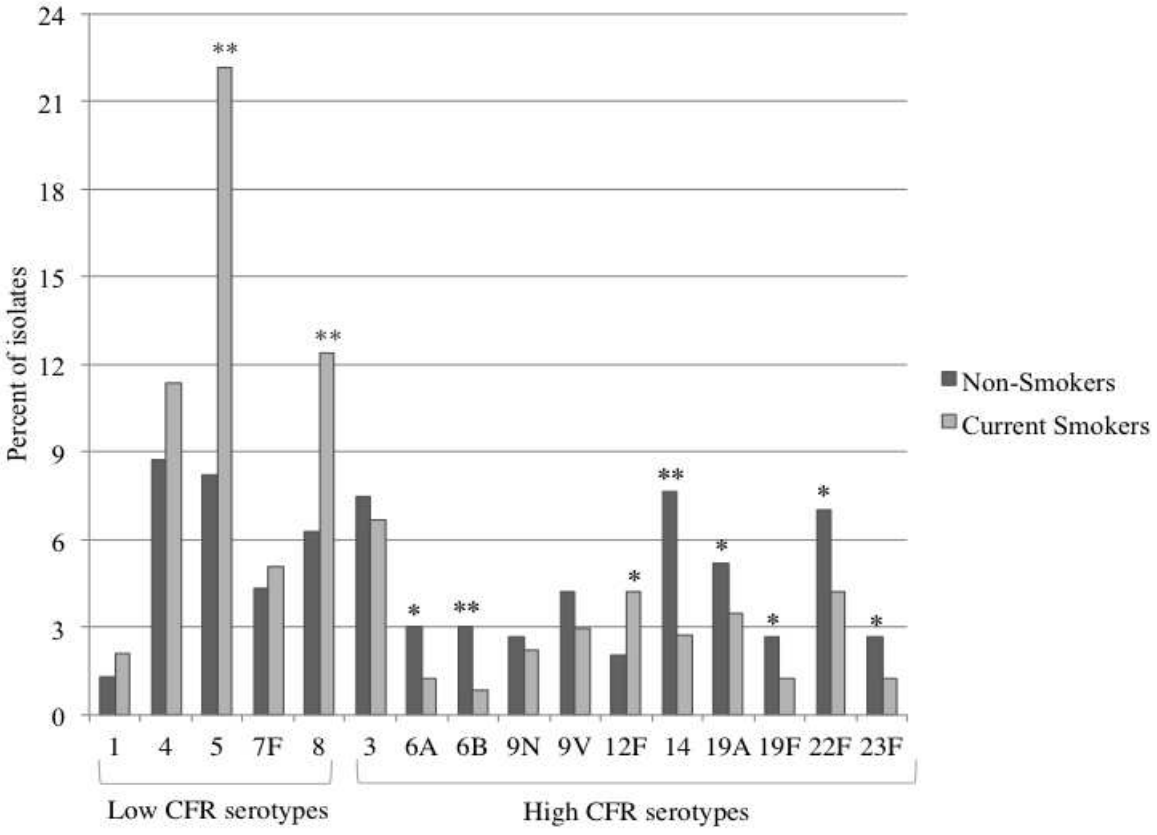
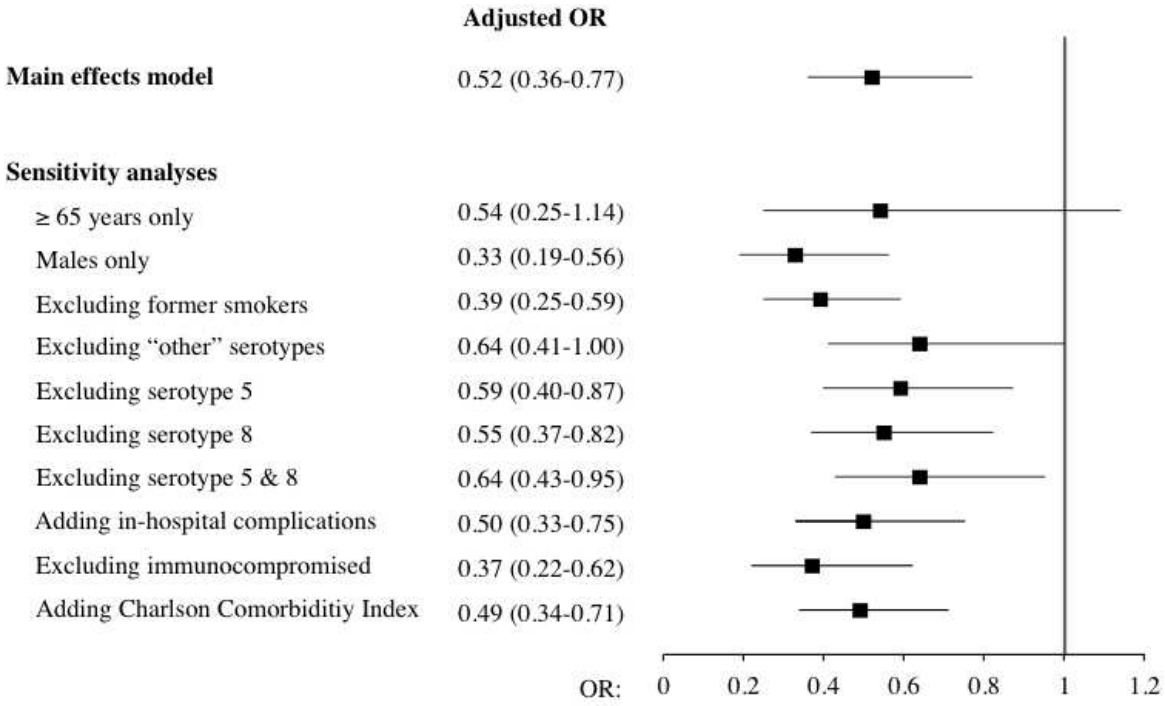


Figure 3-2: Distribution of pneumococcal serotypes according to low and high case fatality rates stratified by smoking status



* P<0.05; ** P<0.001

Figure 3-3: Adjusted ORs and 95% CIs for smoking exposure and in-hospital mortality for the main model and sensitivity analyses



3.5 References

1. Lynch JP, 3rd, Zhanel GG. Streptococcus pneumoniae: epidemiology, risk factors, and strategies for prevention. *Seminars in respiratory and critical care medicine.* Apr 2009;30(2):189-209.
2. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae. 2013. Available at: http://www.cdc.gov/abcs/reportsfindings/survreports/spneu13.pdf. Accessed Sep 4 2015. http://www.cdc.gov/abcs/reportsfindings/survreports/spneu13.pdf.
3. Hamborsky J, Kroger A, Wolfe S. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Washington D.C. Public Health Foundation. 2015;eds. 13th ed.
4. Fica A, Bunster N, Aliaga F, et al. Bacteremic pneumococcal pneumonia: serotype distribution, antimicrobial susceptibility, severity scores, risk factors, and mortality in a single center in Chile. *Braz J Infect Dis.* Mar-Apr 2014;18(2):115-123.
5. Flory JH, Joffe M, Fishman NO, Edelstein PH, Metlay JP. Socioeconomic risk factors for bacteraemic pneumococcal pneumonia in adults. *Epidemiology and infection.* May 2009;137(5):717-726.
6. Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. *Chest.* Apr 2005;127(4):1260-1270.
7. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Apr 15 2006;42(8):1093-1101.
8. Garau J, Baquero F, Perez-Trallero E, et al. Factors impacting on length of stay and mortality of community-acquired pneumonia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Apr 2008;14(4):322-329.
9. Bello S, Menendez R, Torres A, et al. Tobacco smoking increases the risk for death from pneumococcal pneumonia. *Chest.* Oct 2014;146(4):1029-1037.
10. Inoue Y, Koizumi A, Wada Y, et al. Risk and protective factors related to mortality from pneumonia among middleaged and elderly community residents: the JACC Study. *Journal of epidemiology / Japan Epidemiological Association.* Nov 2007;17(6):194-202.
11. Lange P, Vestbo J, Nyboe J. Risk factors for death and hospitalization from pneumonia. A prospective study of a general population. *The European respiratory journal.* Oct 1995;8(10):1694-1698.
12. Katanoda K, Marugame T, Saika K, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. *Journal of epidemiology / Japan Epidemiological Association.* 2008;18(6):251-264.

13. Huttunen R, Heikkinen T, Syrjanen J. Smoking and the outcome of infection. *Journal of internal medicine.* Mar 2011;269(3):258-269.
14. Grau I, Ardanuy C, Calatayud L, Schulze MH, Linares J, Pallares R. Smoking and alcohol abuse are the most preventable risk factors for invasive pneumonia and other pneumococcal infections. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases.* Aug 2014;25:59-64.
15. Tyrrell GJ, Lovgren M, Chui N, et al. Serotypes and antimicrobial susceptibilities of invasive Streptococcus pneumoniae pre- and post-seven valent pneumococcal conjugate vaccine introduction in Alberta, Canada, 2000-2006. *Vaccine.* Jun 2 2009;27(27):3553-3560.
16. Werno AM, Murdoch DR. Medical microbiology: laboratory diagnosis of invasive pneumococcal disease. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Mar 15 2008;46(6):926-932.
17. Surveillance & Assessment Branch AH. Interactive Health Data Application: Population Estimates. Available at: http://www.ahw.gov.ab.ca/IHDA_Retrieval/ihdaData.do. Accessed Sep 4 2015.
18. Johnstone J, Tyrrell GJ, Marrie TJ, Garg S, Kellner JD, Streptococcus pneumoniae Alberta Team g. Streptococcus pneumoniae meningitis in Alberta pre- and postintroduction of the 7-valent pneumococcal conjugate vaccine. *The Canadian journal of infectious diseases & medical microbiology = Journal canadien des maladies infectieuses et de la microbiologie medicale / AMMI Canada.* Winter 2011;22(4):137-141.
19. Majumdar SR, McAlister FA, Eurich DT, Padwal RS, Marrie TJ. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *Bmj.* Nov 11 2006;333(7576):999.
20. Eurich DT, Sadowski CA, Simpson SH, Marrie TJ, Majumdar SR. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *The American journal of medicine.* Jan 2010;123(1):47-53.
21. Lund E, Henrichsen J. *Laboratory diagnosis, serology and epidemiology of Streptococcus pneumoniae.* Vol 12. Methods Microbiol.1978.
22. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community‐acquired pneumonia in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2007;44 (Suppl 2), pp. S27-S72.
23. Asadi L, Eurich DT, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Guideline adherence and macrolides reduced mortality in outpatients with pneumonia. *Respiratory medicine.* Mar 2012;106(3):451-458.
24. Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2010;51(6):692-699.

25. Naucler P, Darenberg J, Morfeldt E, Ortqvist A, Henriques Normark B. Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia. *Thorax.* Jun 2013;68(6):571-579.
26. Ruiz LA, Zalacain R, Capelastegui A, et al. Bacteremic pneumococcal pneumonia in elderly and very elderly patients: host- and pathogen-related factors, process of care, and outcome. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Aug 2014;69(8):1018-1024.
27. Vanderkooi OG, Church DL, MacDonald J, Zucol F, Kellner JD. Community-based outbreaks in vulnerable populations of invasive infections caused by Streptococcus pneumoniae serotypes 5 and 8 in Calgary, Canada. *PLoS One.* 2011;6(12):e28547.
28. Shigayeva A, Rudnick W, Green K, et al. Invasive Pneumococcal Disease Among Immunocompromised Persons: Implications for Vaccination Programs. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 9 2015.
29. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Morbidity and mortality weekly report.* Sep 19 2014;63(37):822-825.
30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases.* 1987;40(5):373-383.
31. Bell TM, Bayt DR, Zarzaur BL. "Smoker's Paradox" in Patients Treated for Severe Injuries: Lower Risk of Mortality After Trauma Observed in Current Smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Feb 2 2015.
32. Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infect Dis.* Mar 2004;4(3):144-154.
33. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. *The New England journal of medicine.* Mar 9 2000;342(10):681-689.
34. Meichtry J, Born R, Kuffer M, et al. Serotype epidemiology of invasive pneumococcal disease in Swiss adults: a nationwide population-based study. *Vaccine.* Sep 8 2014;32(40):5185-5191.
35. Regev-Yochay G, Paran Y, Bishara J, et al. Early impact of PCV7/PCV13 sequential introduction to the national pediatric immunization plan, on adult invasive pneumococcal disease: A nationwide surveillance study. *Vaccine.* Feb 25 2015;33(9):1135-1142.
36. Cole SR, Platt RW, Schisterman EF, et al. Illustrating bias due to conditioning on a collider. *International journal of epidemiology.* Apr 2010;39(2):417-420.
37. VanderWeele TJ, Robins JM. Directed acyclic graphs, sufficient causes, and the properties of conditioning on a common effect. *American journal of epidemiology.* Nov 1 2007;166(9):1096-1104.

38. Whitcomb BW, Schisterman EF, Perkins NJ, Platt RW. Quantification of collider-stratification bias and the birthweight paradox. *Paediatric and perinatal epidemiology.* Sep 2009;23(5):394-402.
39. Wilcox AJ. Birth weight and perinatal mortality: the effect of maternal smoking. *American journal of epidemiology.* May 15 1993;137(10):1098-1104.
40. Buekens P, Wilcox A. Why do small twins have a lower mortality rate than small singletons? *American journal of obstetrics and gynecology.* Mar 1993;168(3 Pt 1):937-941.

CHAPTER 4: SUMMARY

4.1 Overview of Research

One of the most common infections necessitating hospitalization is community-acquired pneumonia (CAP).[1] Approximately 1 million episodes of CAP occur annually in Canada with over 60,000 hospitalizations directly attributed to CAP.[2] The highest incidence (4200 per 100,000 population) occurs among adults 65 years and older.[1] However, morbidity and mortality from CAP are appreciably higher irrespective of age compared to the general population. Although CAP is still considered 'the old man's friend, the relative impact in younger CAP patients (17-25 years) is also substantial with a 2 fold increase in absolute risk of death and the highest relative risk of death compared to the general population among all age groups.[3] Not surprisingly, the economic impact of CAP is substantial with an estimated $9 billion US in direct health care costs consumed each year.[4-6]

Although CAP can be caused by numerous pathogens, *S. pneumoniae* (pneumococcus) is the most commonly identified pathogen, and is responsible for at least 30-50% of all hospitalized cases.[7] Typically, pneumococcal CAP presents as a non-invasive disease, and thus 75% of cases represent non-bacteraemic pneumonia.[8] Invasive pneumococcal disease (IPD) is defined as the isolation of *S. pneumoniae* from a normally sterile body site, where typical presentations include meningitis, bacteremia (source not identified), and bacteremic pneumonia.[9] In the USA, approximately 40,000 cases of IPD occur annually, of which 13,500 occur in adults 65 years of age.[10] Furthermore, the most

common manifestation of IPD is bacteremic pneumonia, which is responsible for 70% of all episodes of IPD in adults.[8] The case-fatality rate in BPP has been shown to differ significantly (9-33%) between different countries, which may in part be explained by differences of disease severity and underlying conditions in the studied population.[11-14] Moreover, mortality rates for adults with BPP have not declined significantly over the past few decades.[15]

The prognosis of patients with BPP ranges from rapid recovery of symptoms without functional impairments to serious complications and death. The case-fatality rate in BPP has been shown to range between 9-33% depending on the population and origin of study.[11-14] Moreover, mortality rates for adults with BPP have not declined significantly over the past few decades.[15] With respect to overall complications of BPP, in one study by Brandenburg et al., 63.3% (n=100/158) of patients with pneumococcal pneumonia developed a complication within 30 days of presentation.[16] Complications associated with pneumococcal pneumonia included respiratory failure, heart failure, renal failure, and shock.[16] In patients specifically with BPP, Berjohn and colleagues found that 25% of patients developed at least one major in-hospital complication.[15] However, very few studies have evaluated the number of complications among patients who survive their initial hospitalization. In a recent study by Blot and colleagues, ARDS, heart failure, and mechanical ventilation [6% (9/151), 17% (26/151), and 11% (17/151) respectively] were found to be common complications among survivors with BPP.[17] Yet, no study has examined prognostic factors for in-hospital complications among patients with BPP.

4.1.1 Previous Literature on Prognostic Factors for Poor Outcomes in Patients with BPP

As discussed in detail in Chapter 1, there are 13 papers that have examined factors associated with mortality in patients with BPP.[11,13-15,18-27] These studies have reported that mortality in patients with BPP is dependent on multiple factors including host factors such as age, sex and comorbidities; lifestyle factors such as tobacco smoking, and alcohol; bacterial factors such as serotype; and management factors such as antibiotic treatment.

In terms of host, 6 articles demonstrated a positive correlation between increasing age and mortality.[11,14,19,26,28,29] Yet, inconclusive results were reported by three studies when investigating the predictive value of sex and mortality.[11,14,18] Several comorbid conditions including: liver disease,[14] renal disease,[14] solid tumor,[14] coronary artery disease,[22] chronic obstructive pulmonary disease (COPD),[25] and immunocompromising disorders,[22] have also been shown to be associated with mortality in patients with BPP. Inconclusive results have been reported on the association of multimorbidity and mortality in patients with BPP.[19,30]

In terms of lifestyle, 7 studies focused on the association of tobacco smoking and alcohols on mortality in patients with CAP have yielded contradictory results.[31-38] For instance, one case-control,[39] and three longitudinal cohort studies,[36-38] found that smoking reduced the risk of mortality in patients with CAP, while 4 other studies have found an

increased risk or no association between smoking and mortality.[31-35] Furthermore, only one study by Naucler et al. examined the effect of smoking on mortality in patients with BPP, in which smoking was found to increase the risk of mortality.[14] In two separate studies, alcohol abuse was shown to be associated with mortality in patients with BPP.[40]

In terms of bacterial factors, a meta-analysis by Weinberger et al. found that high CFR serotypes are associated with an increased risk of mortality in BPP patients even after adjustment for confounding factors such as age and comorbidities.[41] Yet, the findings by the recent study by Naucler et al. contradicted the study by Weinberger and colleagues.[14,41]

Lastly, increased mortality rates have been reported when initial therapy for BPP was discordant.[20,25] Yet, whether guideline-concordant antibiotic therapy reduces mortality in patients with BPP remains uncertain.

4.1.2 Limitations of Prior Literature Regarding Prognosis of BPP

As detailed in Chapter 1 (Table 1), the majority of the 13 studies that have investigated prognostic factors for mortality in patients with BPP have had insufficient sample sizes (all <500 patients, ranging from 60-409), which would limit their ability to produce reliable findings.[11,15,18-27] Further limitations of these studies include missing data, [14] different subgroups within the population, [21] retrospective design, [11,26] and uncontrolled or poorly controlled confounding.[22-24] Therefore, research into which factors influence mortality in patients with BPP is currently needed.

4.2 Objectives

To overcome some of the previous limitations, we aimed to gather further information on a wider range of prognostic factors in patients with BPP. To that end, we evaluated 1636 patients with BPP in Northern Alberta to identify prognostic factors associated with in-hospital mortality and nonfatal complications in adult patients with BPP using a clinically rich population based cohort. Furthermore, building on the results of the first study, we further explored the paradoxical relationship between current smoking and reduced mortality in patients with BPP that we uncovered and that has been reported in some[5,35,42] but not all studies[31,38,43-45]. We paid particular attention to the potential role of pneumococcal serotypes because these data have not been available to others looking at this topic. These objectives were accomplished using two different, but inter-related, studies.

4.3 Summary of Findings

4.3.1 Prognostic Factors for Mortality

Our first study (Chapter 2) shows that in-hospital nonfatal complications and mortality are still very high in patients with BPP (14% and 22%, respectively). In our first study, we noted three independent prognostic factors, older age, nursing home resident, and community-dwelling dementia (which are often associated with 'frailty'), which increased in-hospital mortality among adults with BPP. The finding that increasing age is

a significant prognostic factor for mortality is in line with previous literature.[11,14,19,26,28,29] Nursing home resident however, has only been examined in one previous study by Dwyer et al. [23], which found no significant association between nursing home resident and mortality in patients with BPP.[23] However, this study only included 26 nursing home patients (vs 48 in our study) and was not powered sufficiently to look at this subgroup perhaps accounting for the discrepant findings from ours.[23] No other prognostic study investigating mortality in patients with BPP has included community-dwelling dementia although this finding is consistent with CAP patients overall where community-dwelling dementia has been associated with increased mortality.[46,47]

With respect to modifiable prognostic factors, our results suggested two factors for in-hospital mortality in patients with BPP. First, as previously stated in Chapter 2, acid-suppressing medication was an unexpected predictive factor for mortality, as it has only been demonstrated to be associated with the reoccurrence of CAP.[48] The reason behind this observed relationship is not known but acid suppressing drugs may serve as a marker for additional comorbidity or frailty or, as it has been speculated in CAP, may increase gastric bacteria colonization potentially resulting in more severe infections.[48] Further studies are needed to confirm the association of acid-suppressing medications on mortality in patients with BPP and to further elucidate the potential mechanism to this relationship. Second, we found that guideline-discordant antibiotic therapy is a significant predictor of in-hospital mortality in BPP patients. This result is supported by a previous study by Martinez et al, which found discordant therapy to be independently associated with an increased risk of 28-day mortality in adult patients with BPP.[15] Further

support for our finding comes from two additional studies that reported a decreased risk of mortality in BPP patients receiving adequate antibiotic treatment in less than 4 hours after admission.[15,24] However, two studies by Naucler et al. and Lugan et al. found no significant association between discordant antibiotic therapy and mortality.[14,26] Although, both studies had very small numbers of deaths in the concordant antibiotic treatment groups (n=1 and 5 respectively).

We also confirmed a number of previously documented non-modifiable risk factors for mortality. Of particular note, we determined that high CFR serotypes are independently associated with in-hospital mortality. This finding contradicts the results of a recent study by Naucler et al., which found that the effect of serotype on mortality was mitigated after adjustment for host factors.[14] However, Naucler et al. categorized serotypes into three categories according to low, medium and high CFR, instead of in two categories, which may account for the discrepancy from our results; however reclassifying CFR as low vs high vs other did not materially alter the strength of association of any of our prognostic factors for in-hospital mortality. In a study by Lugan et al., low invasive disease potential serotypes (3, 6A, 6B, 8, 19F, and 23F) were found to have a seven-fold increase in mortality compared with high invasive serotypes (e.g. 1, 5 and 7F) and a four-fold increase compared with other serotypes in patients with BPP.[14] Since as discussed in Chapter 1, pneumococcal serotypes with a low invasive potential are known to be associated with a high case fatality rate, the results of the Lugan et al. study are similar to ours. Furthermore, our results are in line with a study by Harboe et al. composed of

18,858 patients with IPD, which found that high CFR serotypes (e.g. 3, 10A, 11A, 15B, 16F, 17F, 19F, 31, 35F) were associated with increased mortality (aOR ≥ 3, P < 0.001).[49]

4.3.2 Prognostic Factors for In-Hospital Complications

In our first study we also noted that the most common in-hospital complications among surviving patients with BPP were need for mechanical ventilation (16%), acute aspiration (6%), and MACE (5%). In a recent study by Blot and colleagues, cardiac failure and mechanical ventilation [17% (26/151), and 11% (17/151) respectively] were also found to be two most common complications among survivors with BPP.[17] We also determined that similar prognostic factors associated with in-hospital mortality were related to in-hospital complications, although only the use of guideline discordant antibiotics was modifiable (OR, 1.7; 95% CI, 1.2-2.4). Just as with mortality, high CFR serotypes were also associated with increased risk of in-hospital complications (OR, 2.8; 95% CI, 2.0-2.9).

4.3.3 Smoking, Mortality and Role of Serotypes

An unexpected finding from our research related to smoking and mortality. Although smoking is known to be a risk factor for CAP in general, its impact on mortality has been more controversial.[45] For instance, several studies involving patients with CAP have shown either no significant association or a negative association between smoking and pneumonia related death.[31-35,40,44,50] In BPP specifically, one recent study found an increased risk between smoking and mortality[14], although our results (Chapter 2) do not

support this. Indeed, we found a reduced risk of mortality for current smokers. It should be noted that the previous study by Naucler et al., had a significant limitation relating to missing data (1 in 5 patients had missing data for smoking status).[14] Furthermore, our results are also not consistent with the study by Bello et al. involving adults with pneumococcal CAP where smoking was found to have an increased risk of 30-day mortality. This study was limited by sample size (only 10 of 35 deaths were in current smokers) and was not specifically restricted to BPP.[43] However, our result is consistent with three previous studies involving patients with CAP including one large study, composed of 62,918 hospitalized adult patients where smoking was significantly associated with a reduced risk of in-hospital mortality while the other two studies (n=3233 and n=3043 respectively) similarly found a significant reduction in mortality among current smokers with CAP.[5,35,42]

To the best of our knowledge, no study has provided evidence as to why current smokers may have a reduced risk of mortality. In our second study (Chapter 3), we found that serotypes 5 and 8 were significantly more common in smokers than non-smokers with BPP. Furthermore, the low CFR serotype group was independently associated with decreased mortality relative to the high CFR group (7% vs 19%, respectively). In a similar study by Grau et al., serotype 8 was found to be significantly more prevalent among smokers compared to non-smokers with IPD[51] and our study is the first to show that current smokers with BPP are more likely to have low CFR isolates which may partially, or fully, explain the results. It should be acknowledge however that these

results could also be due to selection bias (collider bias), which if present, might lead to a spurious association between smoking and mortality.

The exact biological mechanism for why smokers would have an increased likelihood of acquiring a low CFR isolate is currently unknown. However, serotypes with a high CFR are known to have a thicker polysaccharide capsule compared to serotypes with low CFR.[41] Thus, one could speculate that exposure to tobacco smoke may decrease the ability of respiratory phagocytic cells to detect and subsequently destroy low CFR serotypes compared to high CFR serotypes.[52] Or perhaps exposure to tobacco smoke changes the environmental niche in the nasopharynx, allowing for increased adhesion by certain specific pneumococcal serotypes.[52] It may also be possible that smokers, particularly homeless smokers, often share cigarettes or smoke previously used discarded cigarettes, which could lead to increased transmission of specific serotypes among the smoking population.[53] Indeed, homeless people are 5 times more likely to be infected with pneumococcal disease.[54]

4.4 Implications for Practice

Accurate prognostication of patients with CAP can allow physicians to make informed decision on the most appropriate site of treatment, the extent of diagnostic testing, the intensity of management (outpatient vs. medical floor vs. ICU) and the type and intensity of antibiotic treatment.[55] Current clinical guidelines recommend that clinicians' use validated clinical prediction indices such as the PSI or CURB-65 for determining the initial prognosis of patients with CAP.[55] Current clinical guidelines recommend that

clinicians' use validated clinical prediction indices such as the PSI, CURB-65, CRB-65, modified ATS scoring system, IDSA/ATS guidelines, or the PBS for determining the initial prognosis of patients with CAP. Each of these severity of illness scores have also been validated in patients with BPP.[56,57]

Our results have shown, markers of frailty such as age, nursing home resident, and community dwelling-dementia are significant predictors of in-hospital mortality in patients with BPP. Since only age and nursing home resident are predictors included in the PSI, our results suggest that the addition of other markers of frailty including community dwelling dementia may be beneficial in predicting in-hospital mortality in patients with CAP or BPP. Furthermore, we identified alcohol abuse, and previous pneumococcal vaccination as important predictors of in-hospital mortality, yet neither of these are included in any severity of illness scores. Thus, these factors should be taken into account by physicians alongside the results of severity scores in order to more accurately predict in-hospital mortality in patients with BPP. An awareness of the factors identified in our study in patients with BPP may enable a greater discussion between patients and families about the risks and benefits of complex interventions, or the possibility of death. More practically, identification of these prognostic factors may help frontline clinicians make informed decisions on the management of BPP patients including the intensity of management and follow-up.

The results of this study may also provide some insight into the potential benefits of pneumococcal vaccination. Our research has demonstrated that pneumococcal

vaccination reduces in-hospital mortality among patients with BPP. This finding therefore supports the application of pneumococcal vaccination in adults. Current guidelines recommend vaccinating adults with the PPV23, however support for this recommendation has largely come from studies examining the effectiveness of the vaccination in reducing the incidence of disease, as opposed to the outcome of disease.[57,58] Therefore, compliance with existing recommendations for vaccination may result in a marked decrease in death from BPP. Furthermore, the US Advisory Committee on Immunization Practices (ACIP) updated the 2014/2015 adult pneumococcal vaccination guidelines to recommend routine use of PCV13 alongside the PPV23 in all adults 65 years and older.[59] Therefore the effectiveness of the PCV13 on reducing the incidence of BPP in adults and its effects on poor outcomes has yet to be established. However, one could speculate that if the PCV13 is more effective against BPP in adults than the PPV23, mortality rates in patients with BPP should begin to decrease.

Furthermore, recent changes to the guidelines of pneumococcal vaccination in Canada now call for all tobacco smokers to be vaccinated with the PPV23.[57] Our findings indicated that smokers with BPP are more likely to have low CFR isolates (1, 4, 5, 7F, and 8), which are all included in the PPV23.[60] Therefore, our results provide further support to promote pneumococcal vaccination in smokers. Additionally, the new PCV13 does not contain serotype 8, which we found to be statistically more prevalent in smokers with BPP compared to nonsmokers.[59] This finding suggests that future conjugate vaccines aimed towards adults should consider the addition of serotype 8.

4.5 Limitations

This research represents one the largest, clinically rich, population based studies of patients with BPP conducted to date. The results of our studies are not without limitations and highlight some of the knowledge gaps currently surrounding prognostication for patients with BPP. First, since our study was conducted in only one region, our study requires external validation in order for our results to be generalizable. Therefore, further large prognostic studies in a hospitalized setting using the same clinical factors in this study are needed in replicating and validating our results for in-hospital mortality and complications. Once key prognostic factors are validated through further prognostic research, an outcome prediction study would be helpful in identifying the combination of factors most strongly associated with in-hospital mortality and complications in patients with BPP.

Secondly, we lacked detailed information on smoking intensity and duration. Due to this limitation we were unable to potentially examine a dose-response relationship (e.g. packs per day) between smoking and in-hospital mortality in patients with BPP. Therefore, in order to further refine the relationship between smoking and in-hospital mortality in patients with BPP, future studies should include detailed smoking information including thee number of cigarettes per day, years of smoking, and/or pack-years of smoking.

Thirdly, we did not have access to any information pertaining to previous treatments received prior to hospital admission. Several studies have suggested that outpatient antibacterial therapy for CAP may be associated with hospital complications and

increased disease severity.[61,62] Although, in a study by van de Garde, prior antibiotic therapy was determined not to be a significant prognostic factor for mortality in hospitalized patients with CAP.[62] Moreover, we did not have enough data to produce a severity of illness index. Nor did we know the duration of illness before a patient was hospitalized which may have influenced our results.

Lastly, the results of our study may have been influenced by a change in the prevalence of certain serotypes caused by the introduction of the PCV7. Following the introduction of the PCV7 there was a decrease in the incidence of IPD caused by vaccine serotypes.[63] However, several groups reported an increase in the incidence of infections caused by non-PCV7 serotypes, mainly serotypes 19A, 7F, and 6A.[63] To overcome this problem, the new PCV13 was introduced to cover the serotypes included in the PCV7 and six additional serotypes 1, 3, 5, 6A, 7F, and 19A.[63] Although no evidence of replacement serotypes due to the PCV13 has been observed to date, it remains a possible concern. Thus, continuous monitoring of *S. pneumoniae* serotypes is essential since it has been shown that the incidence of types responsible for invasive disease can change over time.[63] Furthermore, more studies such as the meta-analysis by Weinberger et al., are needed to determine whether other serotypes not currently included in the PPV23 can increase or decrease mortality in patients with BPP.[41]

4.6 Implications for Future Research

Current guidelines for the treatment and diagnosis of patients with CAP do not currently recommend serotyping as a diagnostic tool in patients with BPP. Based on our findings, knowing the infecting pneumococcal serotype could provide useful information for predicting in-hospital mortality in patients with BPP. Therefore, future efforts should be put into the development of new techniques such as serotype-specific antigen tests, which could accurately and reliably detect and serotype *S. pneumonia* in a timely manner for frontline clinicians.[64]

Additionally, our study suggests that taking acid-suppressing drugs at the time of BPP can increase the risk of mortality in patients. Thus, additional studies in other populations of patients with BPP are needed to validate this finding. Moreover, randomized control trials could also be conducted. This could involve comparing mortality rates of hospitalized adult patients with BPP that continue to receive acid-suppressing drugs to patients that would discontinue the usage of any acid-suppressing drugs. If mortality rates decrease in the group that discontinued acid-suppressing drugs compared to the group that continued to use acid-suppressing drugs, this would provide strong evidence to decision makers to reduce the usage of acid-suppressing drugs in hospitalized patients with BPP. Furthermore, longer-term effects of stopping acid-suppressing drugs compared to not stopping acid-suppressing drugs on future rates of recurrent CAP and BPP could also be assessed and would add to the evidence base.

4.7 Conclusions

BPP morbidity and mortality remain very high. In this program of research we investigated potential prognostic factors for in-hospital mortality and complications in

patients with BPP. We identified two potentially modifiable factors (current use of acid-suppressing drug and treatment with CAP guideline-discordant antibiotics), and we also established the importance of recognizing frailty in predicting in-hospital mortality and compilations in patients with BPP. Furthermore, we have shown that current smokers with BPP have a decreased risk of in-hospital mortality and we believe that this finding is partly explained by the observation that current smokers are more likely to be infected with low CFR serotypes. Therefore, our work has highlighted important prognostic factors in predicting poor outcomes in patients with BPP and in elucidating a mechanism for differential acquisition of pneumococcal serotypes in smokers compared with nonsmokers. This research could enhance clinician decision-making on the management of patients hospitalized with BPP, which we hope in turn will improve outcomes in these patients.

4.8 References

1. Rozenbaum MH, Mangen MJ, Huijts SM, van der Werf TS, Postma MJ. Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: A nationwide retrospective claims database analysis. *Vaccine.* Jun 22 2015;33(28):3193-3199.
2. Canadian Institute for Health Information. Respiratory Disease in Canada. 2001. URL: https://secure.cihi.ca/free_products/RespiratoryComplete.pdf Acessed on: Jun 24th, 2015.
3. Eurich DT, Marrie TJ, Minhas-Sandhu JK, Majumdar SR. Ten-Year Mortality after Community-acquired Pneumonia. A Prospective Cohort. *American journal of respiratory and critical care medicine.* Sep 1 2015;192(5):597-604.
4. Huang SS, Johnson KM, Ray GT, et al. Healthcare utilization and cost of pneumococcal disease in the United States. *Vaccine.* Apr 18 2011;29(18):3398-3412.
5. Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. *Chest.* Apr 2005;127(4):1260-1270.
6. McAlister FA, Majumdar SR, Blitz S, Rowe BH, Romney J, Marrie TJ. The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. *Diabetes care.* Apr 2005;28(4):810-815.
7. Johnstone J, Eurich DT, Minhas JK, Marrie TJ, Majumdar SR. Impact of the pneumococcal vaccine on long-term morbidity and mortality of adults at high risk for pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jul 1 2010;51(1):15-22.
8. Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PloS one.* 2013;8(4):e60273.
9. Plosker GL. 13-Valent Pneumococcal Conjugate Vaccine: A Review of Its Use in Adults. *Drugs.* Sep 2015;75(13):1535-1546.
10. Kim DK, Bridges CB, Harriman KH. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older--United States, 2015. *MMWR. Morbidity and mortality weekly report.* Feb 6 2015;64(4):91-92.
11. Fica A, Bunster N, Aliaga F, et al. Bacteremic pneumococcal pneumonia: serotype distribution, antimicrobial susceptibility, severity scores, risk factors, and mortality in a single center in Chile. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases.* Mar-Apr 2014;18(2):115-123.
12. Shariatzadeh MR, Huang JQ, Tyrrell GJ, Johnson MM, Marrie TJ. Bacteremic pneumococcal pneumonia: a prospective study in Edmonton and neighboring municipalities. *Medicine.* May 2005;84(3):147-161.

13. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978-1997. *The American journal of medicine.* Jul 26 1999;107(1A):34S-43S.
14. Naucler P, Darenberg J, Morfeldt E, Ortqvist A, Henriques Normark B. Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia. *Thorax.* Jun 2013;68(6):571-579.
15. Berjohn CM, Fishman NO, Joffe MM, Edelstein PH, Metlay JP. Treatment and outcomes for patients with bacteremic pneumococcal pneumonia. *Medicine.* May 2008;87(3):160-166.
16. Brandenburg JA, Marrie TJ, Coley CM, et al. Clinical presentation, processes and outcomes of care for patients with pneumococcal pneumonia. *Journal of general internal medicine.* Sep 2000;15(9):638-646.
17. Blot M, Croisier D, Pechinot A, et al. A leukocyte score to improve clinical outcome predictions in bacteremic pneumococcal pneumonia in adults. *Open forum infectious diseases.* Sep 2014;1(2):ofu075.
18. Ruiz LA, Zalacain R, Capelastegui A, et al. Bacteremic pneumococcal pneumonia in elderly and very elderly patients: host- and pathogen-related factors, process of care, and outcome. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Aug 2014;69(8):1018-1024.
19. Lujan M, Gallego M, Belmonte Y, et al. Influence of pneumococcal serotype group on outcome in adults with bacteraemic pneumonia. *The European respiratory journal.* Nov 2010;36(5):1073-1079.
20. Garnacho-Montero J, Garcia-Cabrera E, Diaz-Martin A, et al. Determinants of outcome in patients with bacteraemic pneumococcal pneumonia: importance of early adequate treatment. *Scandinavian journal of infectious diseases.* Mar 2010;42(3):185-192.
21. Rello J, Lujan M, Gallego M, et al. Why mortality is increased in health-care-associated pneumonia: lessons from pneumococcal bacteremic pneumonia. *Chest.* May 2010;137(5):1138-1144.
22. Chi RC, Jackson LA, Neuzil KM. Characteristics and outcomes of older adults with community-acquired pneumococcal bacteremia. *Journal of the American Geriatrics Society.* Jan 2006;54(1):115-120.
23. Dwyer R, Ortqvist A, Aufwerber E, et al. Addition of a macrolide to a ss-lactam in bacteremic pneumococcal pneumonia. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology.* Aug 2006;25(8):518-521.
24. Weiss K, Low DE, Cortes L, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic Streptococcus pneumoniae pneumonia in adults. *Canadian respiratory journal : journal of the Canadian Thoracic Society.* Nov-Dec 2004;11(8):589-593.
25. Lujan M, Gallego M, Fontanals D, Mariscal D, Rello J. Prospective observational study of bacteremic pneumococcal pneumonia: Effect of discordant therapy on mortality. *Critical care medicine.* Mar 2004;32(3):625-631.

26. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Feb 15 2003;36(4):389-395.
27. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978-1997. *Am J Med.* 1999;107(1A):34S-43S.
28. Kalin M, Ortqvist A, Almela M, et al. Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. *The Journal of infectious diseases.* Sep 2000;182(3):840-847.
29. Moroney JF, Fiore AE, Harrison LH, et al. Clinical outcomes of bacteremic pneumococcal pneumonia in the era of antibiotic resistance. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2001;33(6):797-805.
30. Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *The New England journal of medicine.* Apr 2 2015;372(14):1312-1323.
31. Lange P, Vestbo J, Nyboe J. Risk factors for death and hospitalization from pneumonia. A prospective study of a general population. *The European respiratory journal.* Oct 1995;8(10):1694-1698.
32. LaCroix AZ, Lipson S, Miles TP, White L. Prospective study of pneumonia hospitalizations and mortality of U.S. older people: the role of chronic conditions, health behaviors, and nutritional status. *Public health reports.* Jul-Aug 1989;104(4):350-360.
33. Madeddu G, Porqueddu EM, Cambosu F, et al. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. *Infection.* Jun 2008;36(3):231-236.
34. Yende S, Angus DC, Ali IS, et al. Influence of comorbid conditions on long-term mortality after pneumonia in older people. *Journal of the American Geriatrics Society.* Apr 2007;55(4):518-525.
35. Garau J, Baquero F, Perez-Trallero E, et al. Factors impacting on length of stay and mortality of community-acquired pneumonia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Apr 2008;14(4):322-329.
36. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *Bmj.* Oct 8 1994;309(6959):901-911.
37. Rogot E, Murray JL. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public health reports.* May-Jun 1980;95(3):213-222.
38. Inoue Y, Koizumi A, Wada Y, et al. Risk and protective factors related to mortality from pneumonia among middleaged and elderly community residents: the JACC Study. *Journal of epidemiology / Japan Epidemiological Association.* Nov 2007;17(6):194-202.

39. Sitas F, Urban M, Bradshaw D, Kielkowski D, Bah S, Peto R. Tobacco attributable deaths in South Africa. *Tobacco control.* Dec 2004;13(4):396-399.
40. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *Jama.* Jan 10 1996;275(2):134-141.
41. Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2010;51(6):692-699.
42. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Apr 15 2006;42(8):1093-1101.
43. Bello S, Menendez R, Torres A, et al. Tobacco smoking increases the risk for death from pneumococcal pneumonia. *Chest.* Oct 2014;146(4):1029-1037.
44. Katanoda K, Marugame T, Saika K, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. *Journal of epidemiology / Japan Epidemiological Association.* 2008;18(6):251-264.
45. Huttunen R, Heikkinen T, Syrjanen J. Smoking and the outcome of infection. *Journal of internal medicine.* Mar 2011;269(3):258-269.
46. Wesemann T, Nullmann H, Pflug MA, Heppner HJ, Pientka L, Thiem U. Pneumonia severity, comorbidity and 1-year mortality in predominantly older adults with community-acquired pneumonia: a cohort study. *BMC infectious diseases.* 2015;15:2.
47. Sachs GA, Carter R, Holtz LR, et al. Cognitive impairment: an independent predictor of excess mortality: a cohort study. *Annals of internal medicine.* Sep 6 2011;155(5):300-308.
48. Eurich DT, Sadowski CA, Simpson SH, Marrie TJ, Majumdar SR. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *The American journal of medicine.* Jan 2010;123(1):47-53.
49. Harboe ZB, Thomsen RW, Riis A, et al. Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. *PLoS medicine.* May 26 2009;6(5):e1000081.
50. Jha P, Jacob B, Gajalakshmi V, et al. A nationally representative case-control study of smoking and death in India. *The New England journal of medicine.* Mar 13 2008;358(11):1137-1147.
51. Grau I, Ardanuy C, Calatayud L, Schulze MH, Linares J, Pallares R. Smoking and alcohol abuse are the most preventable risk factors for invasive pneumonia and other pneumococcal infections. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases.* Aug 2014;25:59-64.
52. Bagaitkar J, Demuth DR, Scott DA. Tobacco use increases susceptibility to bacterial infection. *Tobacco induced diseases.* 2008;4:12.

53. Aloot CB, Vredevoe DL, Brecht ML. Evaluation of high-risk smoking practices used by the homeless. *Cancer nursing.* Apr 1993;16(2):123-130.
54. Marrie TJ. Pneumococcal pneumonia: epidemiology and clinical features. *Seminars in respiratory infections.* Sep 1999;14(3):227-236.
55. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Mar 1 2007;44 Suppl 2:S27-72.
56. Feldman C, Alanee S, Yu VL, et al. Severity of illness scoring systems in patients with bacteraemic pneumococcal pneumonia: implications for the intensive care unit care. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Sep 2009;15(9):850-857.
57. Public Health Agency of Canada. Invasive Pneumococcal Disease. Treatment. http://www.phac-aspc.gc.ca/im/vpd-mev/pneumococcal-pneumococcie/treatment-traitement-eng.php. Accessed October 8, 2015.
58. Vila-Corcoles A. Is the pneumococcal polysaccharide vaccine effective in preventing pneumonia? *The Lancet. Infectious diseases.* Jul 2008;8(7):405-406.
59. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Morbidity and mortality weekly report.* Sep 19 2014;63(37):822-825.
60. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. *The Cochrane database of systematic reviews.* 2013;1:Cd000422.
61. Simonetti AF, Viasus D, Garcia-Vidal C, et al. Impact of pre-hospital antibiotic use on community-acquired pneumonia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Sep 2014;20(9):O531-537.
62. van de Garde EM, Souverein PC, van den Bosch JM, Deneer VH, Goettsch WG, Leufkens HG. Prior outpatient antibacterial therapy as prognostic factor for mortality in hospitalized pneumonia patients. *Respiratory medicine.* Aug 2006;100(8):1342-1348.
63. Tromp KM, Campbell MW, Vazquez A. Recent Developments and Future Directions of Pneumococcal Vaccine Recommendations. *Clinical therapeutics.* May 1 2015;37(5):928-934.
64. Huijts SM, Pride MW, Vos JM, et al. Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. *The European respiratory journal.* Nov 2013;42(5):1283-1290.

BIBLIOGRAPHY

1. Huang SS, Johnson KM, Ray GT, et al. Healthcare utilization and cost of pneumococcal disease in the United States. *Vaccine.* Apr 18 2011;29(18):3398-3412.
2. Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. *Chest.* Apr 2005;127(4):1260-1270.
3. McAlister FA, Majumdar SR, Blitz S, Rowe BH, Romney J, Marrie TJ. The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. *Diabetes care.* Apr 2005;28(4):810-815.
4. Canadian Institute for Health Information. Respiratory Disease in Canada. 2001. URL: https://secure.cihi.ca/free_products/RespiratoryComplete.pdf Acessed on: Jun 24th, 2015.
5. Organization WH. Pneumococcal vaccines. WHO paper - 2012. *Wkly Epidemiol Rec.* 21012;87:129-44.
6. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *Jama.* Jan 10 1996;275(2):134-141.
7. Werno AM, Murdoch DR. Medical microbiology: laboratory diagnosis of invasive pneumococcal disease. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Mar 15 2008;46(6):926-932.
8. Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PloS one.* 2013;8(4):e60273.
9. Feldman C, Anderson R. Recent advances in our understanding of Streptococcus pneumoniae infection. *F1000prime reports.* 2014;6:82.
10. Blot M, Croisier D, Pechinot A, et al. A leukocyte score to improve clinical outcome predictions in bacteremic pneumococcal pneumonia in adults. *Open forum infectious diseases.* Sep 2014;1(2):ofu075.
11. Lujan M, Gallego M, Rello J. Optimal therapy for severe pneumococcal community-acquired pneumonia. *Intensive care medicine.* Jul 2006;32(7):971-980.
12. Tilghman R, Finland M. CLinical significance of bacteremia in pneumococcic pneumonia. *Archives of Internal Medicine.* 1937;59(4):602-619.
13. Austrian R, Gold J. Pneumococcal Bacteremia with Especial Reference to Bacteremic Pneumococcal Pneumonia. *Annals of internal medicine.* May 1964;60:759-776.
14. Song JY, Nahm MH, Moseley MA. Clinical implications of pneumococcal serotypes: invasive disease potential, clinical presentations, and antibiotic resistance. *Journal of Korean medical science.* Jan 2013;28(1):4-15.

15. Henriques-Normark B, Tuomanen EI. The pneumococcus: epidemiology, microbiology, and pathogenesis. *Cold Spring Harbor perspectives in medicine.* Jul 2013;3(7).
16. Sjostrom K, Spindler C, Ortqvist A, et al. Clonal and capsular types decide whether pneumococci will act as a primary or opportunistic pathogen. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Feb 15 2006;42(4):451-459.
17. Henriques-Normark B, Blomberg C, Dagerhamn J, Battig P, Normark S. The rise and fall of bacterial clones: Streptococcus pneumoniae. *Nature reviews. Microbiology.* Nov 2008;6(11):827-837.
18. Kalin M. Pneumococcal serotypes and their clinical relevance. *Thorax.* 1998;53(3):159-162.
19. Robbins JB, Austrian R, Lee CJ, et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *The Journal of infectious diseases.* Dec 1983;148(6):1136-1159.
20. Brueggemann AB, Peto TE, Crook DW, Butler JC, Kristinsson KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. *The Journal of infectious diseases.* Oct 1 2004;190(7):1203-1211.
21. Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2010;51(6):692-699.
22. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Mar 1 2007;44 Suppl 2:S27-72.
23. Lujan M, Gallego M, Belmonte Y, et al. Influence of pneumococcal serotype group on outcome in adults with bacteraemic pneumonia. *The European respiratory journal.* Nov 2010;36(5):1073-1079.
24. Centers for Disease Control and Prevention Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae, 2012. Available at http://www.cdc.gov.login.ezproxy.library.ualberta.ca/abcs/reports-findings/survreports/spneu12.html.
25. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978-1997. *The American journal of medicine.* Jul 26 1999;107(1A):34S-43S.
26. Flory JH, Joffe M, Fishman NO, Edelstein PH, Metlay JP. Socioeconomic risk factors for bacteraemic pneumococcal pneumonia in adults. *Epidemiology and infection.* May 2009;137(5):717-726.
27. Shariatzadeh MR, Huang JQ, Tyrrell GJ, Johnson MM, Marrie TJ. Bacteremic pneumococcal pneumonia: a prospective study in Edmonton and neighboring municipalities. *Medicine.* May 2005;84(3):147-161.

28. Fica A, Bunster N, Aliaga F, et al. Bacteremic pneumococcal pneumonia: serotype distribution, antimicrobial susceptibility, severity scores, risk factors, and mortality in a single center in Chile. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases.* Mar-Apr 2014;18(2):115-123.
29. Naucler P, Darenberg J, Morfeldt E, Ortqvist A, Henriques Normark B. Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia. *Thorax.* Jun 2013;68(6):571-579.
30. Torres A, Blasi F, Dartois N, Akova M. 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.* Jul 28 2015.
31. Public Health Agency of Canada. Canadian Immunization Guide. Part 4 Active Vaccines. Pneumococcal Vaccine. Available online at: http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pneu-eng.php - tab1. Accessed on: Jun 24th, 2015.
32. Kellner JD, Vanderkooi OG, MacDonald J, Church DL, Tyrrell GJ, Scheifele DW. Changing epidemiology of invasive pneumococcal disease in Canada, 1998-2007: update from the Calgary-area Streptococcus pneumoniae research (CASPER) study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jul 15 2009;49(2):205-212.
33. Burman LA, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors, and prognosis. *Reviews of infectious diseases.* Mar-Apr 1985;7(2):133-142.
34. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. *The Journal of infectious diseases.* Jan 15 2001;183(2):239-246.
35. Weisfelt M, de Gans J, van der Ende A, van de Beek D. Community-acquired bacterial meningitis in alcoholic patients. *PloS one.* 2010;5(2):e9102.
36. Cruickshank HC, Jefferies JM, Clarke SC. Lifestyle risk factors for invasive pneumococcal disease: a systematic review. *BMJ open.* 2014;4(6):e005224.
37. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. *The New England journal of medicine.* Mar 9 2000;342(10):681-689.
38. Romney MG, Hull MW, Gustafson R, et al. Large community outbreak of Streptococcus pneumoniae serotype 5 invasive infection in an impoverished, urban population. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2008;47(6):768-774.
39. Falguera M, Trujillano J, Caro S, et al. A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Aug 1 2009;49(3):409-416.
40. Kang CI, Song JH, Kim SH, et al. Risk factors and pathogenic significance of bacteremic pneumonia in adult patients with community-acquired pneumococcal pneumonia. *J Infect.* Jan 2013;66(1):34-40.

41. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *The New England journal of medicine.* Jan 23 1997;336(4):243-250.
42. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax.* May 2003;58(5):377-382.
43. Capelastegui A, Espana PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. *The European respiratory journal.* Jan 2006;27(1):151-157.
44. Angus DC, Marrie TJ, Obrosky DS, et al. Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. *American journal of respiratory and critical care medicine.* Sep 1 2002;166(5):717-723.
45. Liapikou A, Ferrer M, Polverino E, et al. Severe community-acquired pneumonia: validation of the Infectious Diseases Society of America/American Thoracic Society guidelines to predict an intensive care unit admission. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Feb 15 2009;48(4):377-385.
46. Paterson DL, Ko WC, Von Gottberg A, et al. International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections. *Annals of internal medicine.* Jan 6 2004;140(1):26-32.
47. Feldman C, Alanee S, Yu VL, et al. Severity of illness scoring systems in patients with bacteraemic pneumococcal pneumonia: implications for the intensive care unit care. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Sep 2009;15(9):850-857.
48. Spindler C, Ortqvist A. Prognostic score systems and community-acquired bacteraemic pneumococcal pneumonia. *The European respiratory journal.* Oct 2006;28(4):816-823.
49. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med.* Aug 13-27 2001;161(15):1837-1842.
50. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Feb 15 2003;36(4):389-395.
51. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Summary of Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Disease Society and the Canadian Thoracic Society. *The Canadian journal of infectious diseases = Journal canadien des maladies infectieuses.* Sep 2000;11(5):237-248.

52. Song JY, Eun BW, Nahm MH. Diagnosis of pneumococcal pneumonia: current pitfalls and the way forward. *Infection & chemotherapy.* Dec 2013;45(4):351-366.
53. Chalasani NP, Valdecanas MA, Gopal AK, McGowan JE, Jr., Jurado RL. Clinical utility of blood cultures in adult patients with community-acquired pneumonia without defined underlying risks. *Chest.* Oct 1995;108(4):932-936.
54. Huijts SM, Pride MW, Vos JM, et al. Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. *The European respiratory journal.* Nov 2013;42(5):1283-1290.
55. Resti M, Moriondo M, Cortimiglia M, et al. Community-acquired bacteremic pneumococcal pneumonia in children: diagnosis and serotyping by real-time polymerase chain reaction using blood samples. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Nov 1 2010;51(9):1042-1049.
56. Canada PHAo. *Pneumococcal vaccine.* 7 ed. Ottawa: Public Health Agency of Canada2006.
57. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. *The Cochrane database of systematic reviews.* 2013;1:Cd000422.
58. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Jan 6 2009;180(1):48-58.
59. Johnstone J, Eurich DT, Minhas JK, Marrie TJ, Majumdar SR. Impact of the pneumococcal vaccine on long-term morbidity and mortality of adults at high risk for pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jul 1 2010;51(1):15-22.
60. Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *Jama.* Oct 22-29 1997;278(16):1333-1339.
61. Ament A, Baltussen R, Duru G, et al. Cost-effectiveness of pneumococcal vaccination of older people: a study in 5 western European countries. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Aug 2000;31(2):444-450.
62. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged >/= 60 years: 3 years of follow-up in the CAPAMIS study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Apr 2014;58(7):909-917.
63. Lucero MG, Dulalia VE, Nillos LT, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. *The Cochrane database of systematic reviews.* 2009(4):Cd004977.

64. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. *Lancet.* Dec 3 2011;378(9807):1962-1973.
65. Kellner J. Update on the success of the pneumococcal conjugate vaccine. *Paediatrics & child health.* Apr 2011;16(4):233-240.
66. (CDC) CfDCaP. Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults Aged ≥65 Years: Recommendations of the Advisory Committee on Immunization Practices (ACIP). 2014.
67. Italiano A. Prognostic or predictive? It's time to get back to definitions! *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 10 2011;29(35):4718; author reply 4718-4719.
68. N. Lynn Henry DFH. *Clinical Importance of Prognostic Factors. Moving from Scientifically Interesting to Clinically Useful.* 2008.
69. Ruiz LA, Zalacain R, Capelastegui A, et al. Bacteremic pneumococcal pneumonia in elderly and very elderly patients: host- and pathogen-related factors, process of care, and outcome. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Aug 2014;69(8):1018-1024.
70. Garnacho-Montero J, Garcia-Cabrera E, Diaz-Martin A, et al. Determinants of outcome in patients with bacteraemic pneumococcal pneumonia: importance of early adequate treatment. *Scandinavian journal of infectious diseases.* Mar 2010;42(3):185-192.
71. Rello J, Lujan M, Gallego M, et al. Why mortality is increased in health-care-associated pneumonia: lessons from pneumococcal bacteremic pneumonia. *Chest.* May 2010;137(5):1138-1144.
72. Berjohn CM, Fishman NO, Joffe MM, Edelstein PH, Metlay JP. Treatment and outcomes for patients with bacteremic pneumococcal pneumonia. *Medicine.* May 2008;87(3):160-166.
73. Chi RC, Jackson LA, Neuzil KM. Characteristics and outcomes of older adults with community-acquired pneumococcal bacteremia. *Journal of the American Geriatrics Society.* Jan 2006;54(1):115-120.
74. Dwyer R, Ortqvist A, Aufwerber E, et al. Addition of a macrolide to a ss-lactam in bacteremic pneumococcal pneumonia. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology.* Aug 2006;25(8):518-521.
75. Weiss K, Low DE, Cortes L, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic Streptococcus pneumoniae pneumonia in adults. *Canadian respiratory journal : journal of the Canadian Thoracic Society.* Nov-Dec 2004;11(8):589-593.
76. Lujan M, Gallego M, Fontanals D, Mariscal D, Rello J. Prospective observational study of bacteremic pneumococcal pneumonia: Effect of discordant therapy on mortality. *Critical care medicine.* Mar 2004;32(3):625-631.
77. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978-1997. *Am J Med.* 1999;107(1A):34S-43S.

78. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Systematic reviews.* 2013;2:71.
79. Sligl WI, Eurich DT, Marrie TJ, Majumdar SR. Age still matters: prognosticating short- and long-term mortality for critically ill patients with pneumonia. *Critical care medicine.* Nov 2010;38(11):2126-2132.
80. Kalin M, Ortqvist A, Almela M, et al. Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. *The Journal of infectious diseases.* Sep 2000;182(3):840-847.
81. Moroney JF, Fiore AE, Harrison LH, et al. Clinical outcomes of bacteremic pneumococcal pneumonia in the era of antibiotic resistance. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 15 2001;33(6):797-805.
82. Mortensen EM, Kapoor WN, Chang CC, Fine MJ. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Dec 15 2003;37(12):1617-1624.
83. Uematsu H, Kunisawa S, Sasaki N, Ikai H, Imanaka Y. Development of a risk-adjusted in-hospital mortality prediction model for community-acquired pneumonia: a retrospective analysis using a Japanese administrative database. *BMC pulmonary medicine.* 2014;14:203.
84. Daley J, Jencks S, Draper D, Lenhart G, Thomas N, Walker J. Predicting hospital-associated mortality for Medicare patients. A method for patients with stroke, pneumonia, acute myocardial infarction, and congestive heart failure. *Jama.* Dec 23-30 1988;260(24):3617-3624.
85. Grau I, Ardanuy C, Calatayud L, Schulze MH, Linares J, Pallares R. Smoking and alcohol abuse are the most preventable risk factors for invasive pneumonia and other pneumococcal infections. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases.* Aug 2014;25:59-64.
86. Huttunen R, Heikkinen T, Syrjanen J. Smoking and the outcome of infection. *Journal of internal medicine.* Mar 2011;269(3):258-269.
87. Katanoda K, Marugame T, Saika K, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. *Journal of epidemiology / Japan Epidemiological Association.* 2008;18(6):251-264.
88. Jha P, Jacob B, Gajalakshmi V, et al. A nationally representative case-control study of smoking and death in India. *The New England journal of medicine.* Mar 13 2008;358(11):1137-1147.
89. Lange P, Vestbo J, Nyboe J. Risk factors for death and hospitalization from pneumonia. A prospective study of a general population. *The European respiratory journal.* Oct 1995;8(10):1694-1698.
90. LaCroix AZ, Lipson S, Miles TP, White L. Prospective study of pneumonia hospitalizations and mortality of U.S. older people: the role of chronic conditions, health behaviors, and nutritional status. *Public health reports.* Jul-Aug 1989;104(4):350-360.

91. Madeddu G, Porqueddu EM, Cambosu F, et al. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. *Infection.* Jun 2008;36(3):231-236.
92. Yende S, Angus DC, Ali IS, et al. Influence of comorbid conditions on long-term mortality after pneumonia in older people. *Journal of the American Geriatrics Society.* Apr 2007;55(4):518-525.
93. Garau J, Baquero F, Perez-Trallero E, et al. Factors impacting on length of stay and mortality of community-acquired pneumonia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Apr 2008;14(4):322-329.
94. Sitas F, Urban M, Bradshaw D, Kielkowski D, Bah S, Peto R. Tobacco attributable deaths in South Africa. *Tobacco control.* Dec 2004;13(4):396-399.
95. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *Bmj.* Oct 8 1994;309(6959):901-911.
96. Rogot E, Murray JL. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public health reports.* May-Jun 1980;95(3):213-222.
97. Inoue Y, Koizumi A, Wada Y, et al. Risk and protective factors related to mortality from pneumonia among middleaged and elderly community residents: the JACC Study. *Journal of epidemiology / Japan Epidemiological Association.* Nov 2007;17(6):194-202.
98. Andrews J, Chandrasekaran P, McSwiggan D. Lower respiratory tract infections in an acute geriatric male ward: a one-year prospective surveillance. *Gerontology.* 1984;30(5):290-296.
99. Garcia-Vidal C, Ardanuy C, Tubau F, et al. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. *Thorax.* Jan 2010;65(1):77-81.
100. Bello S, Menendez R, Torres A, et al. Tobacco smoking increases the risk for death from pneumococcal pneumonia. *Chest.* Oct 2014;146(4):1029-1037.
101. Samokhvalov AV, Irving HM, Rehm J. Alcohol consumption as a risk factor for pneumonia: a systematic review and meta-analysis. *Epidemiology and infection.* Dec 2010;138(12):1789-1795.
102. Saitz R, Ghali WA, Moskowitz MA. The impact of alcohol-related diagnoses on pneumonia outcomes. *Arch Intern Med.* Jul 14 1997;157(13):1446-1452.
103. de Roux A, Cavalcanti M, Marcos MA, et al. Impact of alcohol abuse in the etiology and severity of community-acquired pneumonia. *Chest.* May 2006;129(5):1219-1225.
104. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. *Arch Intern Med.* Nov 22 1999;159(21):2562-2572.
105. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. *Chest.* May 2003;123(5):1503-1511.

106. Wunderink RG, Waterer GW. Clinical practice. Community-acquired pneumonia. *The New England journal of medicine.* Feb 6 2014;370(6):543-551.
107. Capelastegui A, Espana PP, Quintana JM, et al. Improvement of process-of-care and outcomes after implementing a guideline for the management of community-acquired pneumonia: a controlled before-and-after design study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Oct 1 2004;39(7):955-963.
108. Dean NC, Silver MP, Bateman KA, James B, Hadlock CJ, Hale D. Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. *The American journal of medicine.* Apr 15 2001;110(6):451-457.
109. Pletz MW, Welte T, Klugman KP. The paradox in pneumococcal serotypes: highly invasive does not mean highly lethal. *The European respiratory journal.* Oct 2010;36(4):712-713.
110. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Apr 15 2006;42(8):1093-1101.
111. Ortqvist A, Hedlund J, Kalin M. Streptococcus pneumoniae: epidemiology, risk factors, and clinical features. *Seminars in respiratory and critical care medicine.* Dec 2005;26(6):563-574.
112. Jover F, Cuadrado JM, Andreu L, et al. A comparative study of bacteremic and non-bacteremic pneumococcal pneumonia. *European journal of internal medicine.* Jan 2008;19(1):15-21.
113. Cremers AJ, Meis JF, Walraven G, Jongh CE, Ferwerda G, Hermans PW. Effects of 7-valent pneumococcal conjugate 1 vaccine on the severity of adult 2 bacteremic pneumococcal pneumonia. *Vaccine.* Jun 30 2014;32(31):3989-3994.
114. Lynch JP, 3rd, Zhanel GG. Streptococcus pneumoniae: epidemiology, risk factors, and strategies for prevention. *Seminars in respiratory and critical care medicine.* Apr 2009;30(2):189-209.
115. Pereira JM, Teixeira-Pinto A, Basilio C, Sousa-Dias C, Mergulhao P, Paiva JA. Can we predict pneumococcal bacteremia in patients with severe community-acquired pneumonia? *Journal of critical care.* Dec 2013;28(6):970-974.
116. Afessa B, Greaves WL, Frederick WR. Pneumococcal bacteremia in adults: a 14-year experience in an inner-city university hospital. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Aug 1995;21(2):345-351.
117. Tyrrell GJ, Lovgren M, Chui N, et al. Serotypes and antimicrobial susceptibilities of invasive Streptococcus pneumoniae pre- and post-seven valent pneumococcal conjugate vaccine introduction in Alberta, Canada, 2000-2006. *Vaccine.* Jun 2 2009;27(27):3553-3560.

118. Case Definitions for Communicable Diseases under National Surveillance - 2009. 2009;35(Suppl 2). http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s2/index-eng.php. Accessed 3-13-2015.
119. Majumdar SR, McAlister FA, Eurich DT, Padwal RS, Marrie TJ. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *Bmj.* Nov 11 2006;333(7576):999.
120. Eurich DT, Sadowski CA, Simpson SH, Marrie TJ, Majumdar SR. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *The American journal of medicine.* Jan 2010;123(1):47-53.
121. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community‐acquired pneumonia in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2007;44 (Suppl 2), pp. S27-S72.
122. Asadi L, Eurich DT, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Guideline adherence and macrolides reduced mortality in outpatients with pneumonia. *Respiratory medicine.* Mar 2012;106(3):451-458.
123. Lund E, Henrichsen J. *Laboratory diagnosis, serology and epidemiology of Streptococcus pneumoniae.* Vol 12. Methods Microbiol.1978.
124. Marrie TJ, Tyrrell GJ, Garg S, Vanderkooi OG. Factors predicting mortality in invasive pneumococcal disease in adults in Alberta. *Medicine.* May 2011;90(3):171-179.
125. Alanee SR, McGee L, Jackson D, et al. Association of serotypes of Streptococcus pneumoniae with disease severity and outcome in adults: an international study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jul 1 2007;45(1):46-51.
126. Harboe ZB, Thomsen RW, Riis A, et al. Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. *PLoS medicine.* May 26 2009;6(5):e1000081.
127. Vila-Corcoles A, Salsench E, Rodriguez-Blanco T, et al. Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: a matched case-control study. *Vaccine.* Mar 4 2009;27(10):1504-1510.
128. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Morbidity and mortality weekly report.* Sep 19 2014;63(37):822-825.
129. Ruiz M, Ewig S, Marcos MA, et al. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *American journal of respiratory and critical care medicine.* Aug 1999;160(2):397-405.
130. Hamborsky J, Kroger A, Wolfe S. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Washington D.C. Public Health Foundation. 2015;eds. 13th ed.

131. Johnstone J, Tyrrell GJ, Marrie TJ, Garg S, Kellner JD, Streptococcus pneumoniae Alberta Team g. Streptococcus pneumoniae meningitis in Alberta pre- and postintroduction of the 7-valent pneumococcal conjugate vaccine. *The Canadian journal of infectious diseases & medical microbiology = Journal canadien des maladies infectieuses et de la microbiologie medicale / AMMI Canada.* Winter 2011;22(4):137-141.
132. Vanderkooi OG, Church DL, MacDonald J, Zucol F, Kellner JD. Community-based outbreaks in vulnerable populations of invasive infections caused by Streptococcus pneumoniae serotypes 5 and 8 in Calgary, Canada. *PLoS One.* 2011;6(12):e28547.
133. Shigayeva A, Rudnick W, Green K, et al. Invasive Pneumococcal Disease Among Immunocompromised Persons: Implications for Vaccination Programs. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Sep 9 2015.
134. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases.* 1987;40(5):373-383.
135. Bell TM, Bayt DR, Zarzaur BL. "Smoker's Paradox" in Patients Treated for Severe Injuries: Lower Risk of Mortality After Trauma Observed in Current Smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Feb 2 2015.
136. Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infect Dis.* Mar 2004;4(3):144-154.
137. Meichtry J, Born R, Kuffer M, et al. Serotype epidemiology of invasive pneumococcal disease in Swiss adults: a nationwide population-based study. *Vaccine.* Sep 8 2014;32(40):5185-5191.
138. Regev-Yochay G, Paran Y, Bishara J, et al. Early impact of PCV7/PCV13 sequential introduction to the national pediatric immunization plan, on adult invasive pneumococcal disease: A nationwide surveillance study. *Vaccine.* Feb 25 2015;33(9):1135-1142.
139. Cole SR, Platt RW, Schisterman EF, et al. Illustrating bias due to conditioning on a collider. *International journal of epidemiology.* Apr 2010;39(2):417-420.
140. VanderWeele TJ, Robins JM. Directed acyclic graphs, sufficient causes, and the properties of conditioning on a common effect. *American journal of epidemiology.* Nov 1 2007;166(9):1096-1104.
141. Whitcomb BW, Schisterman EF, Perkins NJ, Platt RW. Quantification of collider-stratification bias and the birthweight paradox. *Paediatric and perinatal epidemiology.* Sep 2009;23(5):394-402.
142. Wilcox AJ. Birth weight and perinatal mortality: the effect of maternal smoking. *American journal of epidemiology.* May 15 1993;137(10):1098-1104.
143. Buekens P, Wilcox A. Why do small twins have a lower mortality rate than small singletons? *American journal of obstetrics and gynecology.* Mar 1993;168(3 Pt 1):937-941.

144. Rozenbaum MH, Mangen MJ, Huijts SM, van der Werf TS, Postma MJ. Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: A nationwide retrospective claims database analysis. *Vaccine.* Jun 22 2015;33(28):3193-3199.
145. Eurich DT, Marrie TJ, Minhas-Sandhu JK, Majumdar SR. Ten-Year Mortality after Community-acquired Pneumonia. A Prospective Cohort. *American journal of respiratory and critical care medicine.* Sep 1 2015;192(5):597-604.
146. Plosker GL. 13-Valent Pneumococcal Conjugate Vaccine: A Review of Its Use in Adults. *Drugs.* Sep 2015;75(13):1535-1546.
147. Kim DK, Bridges CB, Harriman KH. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older--United States, 2015. *MMWR. Morbidity and mortality weekly report.* Feb 6 2015;64(4):91-92.
148. Brandenburg JA, Marrie TJ, Coley CM, et al. Clinical presentation, processes and outcomes of care for patients with pneumococcal pneumonia. *Journal of general internal medicine.* Sep 2000;15(9):638-646.
149. Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *The New England journal of medicine.* Apr 2 2015;372(14):1312-1323.
150. Wesemann T, Nullmann H, Pflug MA, Heppner HJ, Pientka L, Thiem U. Pneumonia severity, comorbidity and 1-year mortality in predominantly older adults with community-acquired pneumonia: a cohort study. *BMC infectious diseases.* 2015;15:2.
151. Sachs GA, Carter R, Holtz LR, et al. Cognitive impairment: an independent predictor of excess mortality: a cohort study. *Annals of internal medicine.* Sep 6 2011;155(5):300-308.
152. Bagaitkar J, Demuth DR, Scott DA. Tobacco use increases susceptibility to bacterial infection. *Tobacco induced diseases.* 2008;4:12.
153. Aloot CB, Vredevoe DL, Brecht ML. Evaluation of high-risk smoking practices used by the homeless. *Cancer nursing.* Apr 1993;16(2):123-130.
154. Marrie TJ. Pneumococcal pneumonia: epidemiology and clinical features. *Seminars in respiratory infections.* Sep 1999;14(3):227-236.
155. Public Health Agency of Canada. Invasive Pneumococcal Disease. Treatment. http://www.phac-aspc.gc.ca/im/vpd-mev/pneumococcal-pneumococcie/treatment-traitement-eng.php. Accessed October 8, 2015.
156. Vila-Corcoles A. Is the pneumococcal polysaccharide vaccine effective in preventing pneumonia? *The Lancet. Infectious diseases.* Jul 2008;8(7):405-406.
157. Simonetti AF, Viasus D, Garcia-Vidal C, et al. Impact of pre-hospital antibiotic use on community-acquired pneumonia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Sep 2014;20(9):O531-537.
158. van de Garde EM, Souverein PC, van den Bosch JM, Deneer VH, Goettsch WG, Leufkens HG. Prior outpatient antibacterial therapy as prognostic factor for

mortality in hospitalized pneumonia patients. *Respiratory medicine.* Aug 2006;100(8):1342-1348.
159. Tromp KM, Campbell MW, Vazquez A. Recent Developments and Future Directions of Pneumococcal Vaccine Recommendations. *Clinical therapeutics.* May 1 2015;37(5):928-934.