Effectiveness of pneumococcal vaccine in preventing hospital admissions for pneumonia among the elderly

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DECLARATION

I, MAROPENG RAPETSOA, declare that the dissertation that I hereby submit for the degree MSc Clinical epidemiology at the University of Pretoria, is my own work and has not previously been submitted by me at another university.

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ABSTRACT

Introduction

Hospitalisations and prolonged hospital stays impose great economic burden especially at the present time when resources are limited. Community-acquired pneumonia (CAP) is a common and costly illness associated with considerable morbidity and mortality. Other than children, the elderly are the most vulnerable to CAP due to reduced immunity and comorbid chronic conditions. *Streptococcus pneumoniae (S. pneumoniae)* has been identified as the most common culprit encountered in cases of CAP with the incidence of CAP peaking during the annual influenza season. There is a known synergistic pathogenesis between the influenza virus and *S. pneumoniae*. Vaccination against invasive pneumococcal disease (IPD) is established in children. However, the burden of pneumonia has remained high in the elderly. This study sought to explore primarily the effectiveness of pneumococcal vaccination, as administered in a South African Medical scheme population, in the elderly who are aged 65 years and older; and secondly to explore the effectiveness of influenza vaccination in the same age group in preventing hospital admissions due to pneumonia (all causes).

Methods

The study population consisted of 34 068 beneficiaries of Medihelp medical aid scheme, and the outcome measures were investigated for years 2017/2018. The researcher has conducted a case-control study using cross-sectional secondary data with 1:1 matching. The sample size consisted of 800 pairs of case and control for primary and secondary exposures (pneumococcal vaccine and influenza vaccine, respectively). ICD-10 (International classification of diseases .10th revision) coding was used to identify study cases based on hospital admission claims and was matched for covariates age, sex and important comorbidities: ischaemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), asthma and diabetes mellitus (DM). For the primary outcome, we adjusted for the use of influenza vaccine and for the secondary outcome, we adjusted for the use of pneumococcal vaccine. McNemar's odds ratio (OR) and its 95% confidence interval (CI) was used to measure the association between vaccination and hospitalisation

for CAP. Sensitivity analyses by means of propensity score matching (PSM) were also performed to estimate the OR. In addition, subgroup analyses were performed by estimating the odds ratios in participants who have used 23-valent pneumococcal polysaccharide vaccine (PPSV-23) and 13-valent pneumococcal conjugate vaccine (PCV-13) respectively for the primary exposure by PSM.

Results

All participants had claimed only one type of pneumococcal vaccine in this study. Vaccine uptake for pneumococcal vaccine and influenza vaccine in the study population were 0.9% and 16.6% respectively. For the primary exposure, 15 (1.9%) cases were exposed to pneumococcal vaccine compared to nine (1.1%) in controls with an OR of 1.67 (95% confidence interval (CI), 0.683 - 4.319) (P= 0.308). Propensity score matching revealed similar estimates, although closer to the null value, with OR of 1.05 (95% CI, 0.991 - 1.121) (P= 0.095). For the secondary exposure, 140 (17.5%) cases were exposed to influenza vaccination compared to 152 (19.0%) controls with an OR of 0.90 (95% CI, 0.683 - 1.178) with a (P= 0.460). Using PSM the OR was 0.99 (95% CI, 0.983 - 0.994) (P<0.001).

Conclusions

In order to enhance the vaccine effectiveness (VE) of pneumococcal vaccine, it is recommended that sequential vaccination with a dose of PCV-13 to be followed by a dose of PPSV-23 one year later in all adults 65 years and older. Once off vaccination with either type of pneumococcal vaccine did not confer a protective benefit in this study. This recommendation is based on guidelines in use for South Africa and other international agencies. Compliance with the guidelines vaccination schedule was found not to be the practice in our study population. For the secondary exposure, our findings reaffirm the significance of seasonal influenza vaccination for the study age cohort. We recommend that programmes to significantly enhance both pneumococcal and influenza vaccine uptake be earnestly addressed in order to address severe uptake deficiencies observed in this study. Both vaccines should be given concurrently in order to enhance compliance and to further reduce the burden of CAP for the study age cohort.

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GLOSSARY

Elderly: According to the United Nations, people aged 60 years and older

Community acquired Pneumonia: An acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community, as distinguished from hospital-acquired (nosocomial) pneumonia (HAP).

ICD-10 coding: A coding system developed by the World Health Organisation that translates the written description of medical and health information into standard codes.

Hospitalisation: Admission to a hospital for medical or surgical treatment.

Vaccination: The process where a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine.

Opsonisation: The process by which a microbe is labeled for removal via complement and/or antibodies, and subsequently phagocytosed.

LIST OF ABBREVIATIONS

CAP	Community-acquired pneumonia
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DM	Diabetes mellitus
GMC	Geometric mean concentration
GP	General Practitioner
ICD-10	International classification of diseases .10th revision
IgG	Immunoglobulin type G
IHD	Ischaemic heart disease
IPD	Invasive pneumococcal disease
IT	Information technology
OR	Odds ratio
PCV-13	13-valent pneumococcal conjugate vaccine
PPSV-23	23-valent pneumococcal polysaccharide vaccine
PSM	Propensity score matching
VE	Vaccine effectiveness
VT	Vaccine-type

CHAPTER 1: INTRODUCTION

1.1 Purpose of the study

The burden and cost of treating community-acquired pneumonia (CAP) continues to be high, especially in high-risk patients with advanced age and comorbid conditions.[1-4] *Streptococcus pneumoniae (S. pneumoniae)* has been identified as the commonest pathogen responsible for infections secondary to annual influenza seasonal circulation.[5] Influenza virus increases the incidence of pneumococcal disease during the annual influenza season.[6]

The use of pneumococcal vaccination is established in the treatment of invasive pneumococcal disease (IPD).[7] In adults, pneumococcal pneumonia constitutes the vast majority of pneumococcal disease.[1] In South Africa, sequential pneumococcal vaccination of 13-valent pneumococcal conjugate vaccine (PCV-13) followed a year later by 23-valent pneumococcal polysaccharide vaccine (PPSV-23) is recommended for all adults 65 years and older who are pneumococcal vaccine naïve. Alternatively, all adults 65 years and older who have received PPSV-23 should receive a single dose of PCV-13 at least one year later.[8] Other countries where pneumococcal vaccination is part of public health policy strategy in the elderly include the United States of America, Germany, Australia and the United Kingdom.[9-11] The addition of a single dose of PCV-13 in those previously recommended to receive PPSV-23 has been validated for potential cost-effectiveness.[12]

Due to the copathogenity of *S. pneumoniae* and influenza virus in the aetiology of pneumonia,[13] the purpose for our study was to investigate primarily the effectiveness of pneumococcal vaccine, as administered to a South African medical scheme's beneficiaries, in preventing hospital admissions due to pneumonia. Secondarily, we aimed to establish the effectiveness of influenza vaccination among elderly patients in preventing hospital admissions due to pneumonia using the same dataset. Hospital treated pneumonia is the most resource-intensive form of treatment for CAP. Our study population consisted of only private health care insured patients belonging to a registered medical aid

scheme operating within the South African borders. The findings from this study have highlighted and measured the impact of pneumococcal and influenza vaccination for this high-risk age group, and have also evaluated vaccination importance, on the high burden of CAP.

CHAPTER 2: LITERATURE REVIEW

2.1 Aetiology and burden of community-acquired pneumonia

As populations worldwide are expanding, life expectancies are also increasing. The more populations age, the more infections and their associated complications become prevalent.[14] This has evidently resulted in increased hospitalisations and fiscal spend. According to the World Health Organization 2016 estimates, lower respiratory tract infections constitute the third-highest cause of death in lower-middle-income countries in the top ten causes of death list for which pneumonia is included.[15] CAP is a common and costly illness associated with considerable morbidity and mortality. CAP confers a high-risk of long-term adverse events compared with the general population who have not experienced it. The elderly experience reduced quality of life post hospitalisation for pneumonia-associated complications.[16-17]

Patients characterised as elderly, typically from ages 60 years and older, experience physiological changes consistent with growing age. In addition to age, associated changes in the lung function impair the respiratory reserve response to combat respiratory insult. Respiratory muscles, both diaphragmatic and skeletal, also weaken with age. The consequences of ageing on the chest wall mechanics and airway clearance impairs the resolution of bacterial seeding of the lungs and allows for progression to pneumonia.[18] These changes make the elderly susceptible to infections as they advance with age. In addition, comorbid conditions that contribute to decreased immunity such as chronic lung disease, diabetes mellitus (DM) , chronic renal disease and ischaemic heart disease (IHD) have also been linked to an increased incidence of CAP.[4] There is also an increased short-term risk of myocardial infarction in association with pneumonia, influenza and other chest infections. The risk of myocardial infarction associated with pneumonia peaks at the onset of the infection and is informed by the severity of the illness.[19]

After hospitalisation for CAP, elderly patients greatly experience worsening of their pre-existing comorbid symptoms and need extended caregiver assistance.[20] In fact, among patients with at-risk conditions, the rate of all-cause pneumonia substantially increases with the accumulation of concurrent at-risk conditions (risk stacking).[21]

Pneumonia, an inflammatory disease of the lung, is predominantly caused by bacteria, fungi, viruses or other organisms. *S .pneumoniae*, a gram-positive bacterium with over 90 serotypes is one of the most commonly identified causative agent.[4-5] Other bacteria that cause CAP include *Staphylococcus aureus*, *Pseudomonas aeruginosa* and other gram-negative bacilli. [22]

Treatments for pneumonia in hospital include empiric antimicrobial therapy and oxygen therapy. However, people with weakened immune systems are more likely to have complications such as respiratory failure, sepsis, lung abscesses and collapse.[23] Therefore, prevention of pneumonia occurrence is vital and alternative prevention strategies, such as vaccination, thus become pivotal.

Although pneumococcus is one of the most identified causes of CAP, the frequency with which it has been implicated has reduced in countries where the use of pneumococcal vaccine use is widespread.[24] During influenza outbreaks, the circulating influenza virus becomes the principal cause of CAP, which is serious enough to require hospitalisation, with secondary bacterial infection as a major contributor.[25-27] In the 2009 influenza pandemic, *S. pneumoniae* was identified as important in the prognosis of H1N1-associated disease, thereby demonstrating synergistic pathogenesis between the influenza virus and *S. pneumoniae*.[28] In a study by Madhi et al.[13] synergistic pathogenesis was also seen where vaccination against *S. pneumoniae* reduced the frequency of pneumonia associated with Influenza A, respiratory syncytial virus and parainfluenza viruses.

Another study found that influenza circulation was moderately associated with annual winter increases in rates of invasive pneumococcal pneumonia during non-pandemic periods in the United States. This study estimated that 11-14% of invasive pneumococcal pneumonia are associated with influenza circulation.[27] It is understood that the damage from the airway epithelial lining caused by influenza facilitates bacterial growth in the elderly. In turn, bacterium-derived proteases enhance viral virulence.[29]

2.2 Composition of pneumococcal vaccine

Immunogenicity is important for the efficacy of any vaccine. Serum antibodies to the polysaccharide mediate protection against pneumococcal infection in a serotype-specific manner. The goal of pneumococcal polysaccharide vaccine preparations is to generate these antibodies.[10,29]

Pneumococcal vaccine is available as PCV-13, which forms part of the expanded programme for immunisation in South Africa for children which was introduced in 2011.[7] PCV-13 replaced 7-valent pneumococcal conjugate vaccine (PCV-7) which was initially used in childhood vaccination. PCV-13 has bacterial polysaccharides covalently conjugated to an immunogenic carrier protein resulting in the formation of memory B-lymphocytes, thus proving long-acting immunologic memory and an anamnestic response. The PCV-13 covers 13 serotypes (1 3 4 5 6A 6B 7F 9V 14 18C 19A 19F 23F), of which one added serotype is unique from 23-valent pneumococcal polysaccharide vaccine (PPSV-23).

Pneumococcal vaccine is also available as PPSV-23. PPSV covers 23 serotypes, 11 additional to those found in the conjugate vaccine (2 8 9N 10A 11A 12F 15B 17F 20 22F 33F). Some of the serotypes contained have a fair cross-reactivity with serotypes not found in the vaccine (6B, 6A,15B and 15A) this provides potential coverage of more than 23 serotypes, Since PPSV-23 is made of polysaccharide and non-protein antigens, it induces an antibody response independent from T-lymphocytes. These antigens induce type-specific antibodies that enhance opsonisation, phagocytosis and killing of pneumococci by leucocytes.[29] Thus the immune response is considered short-lived and lacks the ability to elicit an anamnestic response.[10,30-31]

The conjugation of the capsular polysaccharide to a protein carrier converts the polysaccharide to a T-cell dependent antigen. Pneumococcal conjugate vaccines establish a state of immunological priming and memory resulting in great enhancement of antibody responses on boosting and imparts longer lasting activity.[32] In children, bacterial polysaccharides protein-conjugate vaccines elicit functional antibody responses which are quantitatively superior to those of elicited by free bacterial polysaccharides however with a smaller coverage of pneumococcal serotypes. Conjugated vaccines are administered first to augment the antipneumococcal response to subsequent administration of the

unconjugated vaccines for the serotypes common to both vaccines. In contrast an initial administration of PPSV-23 results in diminished response to subsequent administration of PCV-13.[33]

2.3 Pneumococcal vaccine antibody response

In most elderly patients, the antibody response to PPSV-23 is adequate. In a study by Sankilampi et al.[34] 23-valent pneumococcal vaccine was assessed in the elderly aged 65 to 91 years and immunoglobulin type G (IgG) antibodies to pneumococcal serotypes 4 6B 9V 14 19F and 23F were measured. The overall percentage of elderly participants with antibody concentrations >1 µg/ml to the six antigens increased by vaccination from 61% - 87% but in females older than 85 years old only to 75%.

Another study evaluated immune response following administration of PPSV-23 for the following serotypes: 10A 11A 15B 17F. IgG geometric mean concentrations (GMC) were measured in participants older than 50 years after a single dose administration of PPSV-23. One month post-vaccination the GMC's for 10A, 11A, 15B, 17F were 9.0, 4.5, 8.4 and 11.5 respectively. The percentage of participants achieving >2-fold increases in IgG GMC's between pre-vaccination and 1 month post-vaccination were 90%,85%,88% and 89%, respectively for the serotypes investigated.[35]

In contrast, a different study measured antibody concentrations and opsonisation titres for multiple serotypes amongst both old and young healthy controls. Antibody concentrations were found to be similar for six out of the seven tested serotypes, while opsonisation titres were significantly higher in six of the seven tested serotypes in the younger population. Antibody potency as measured by the ratio of opsonisation titre to antibody concentration was found to be significantly higher for the younger participants for all serotypes tested. The conclusion was that while all ages of adults make similar concentrations of antibodies in response to pneumococcal vaccine, the effectiveness of those antibodies are reduced in the older population.[36]

In a study by de Roux et al.[32] , the authors compared immunogenicity and safety of PCV-7 vaccine with that of PPSV-23 in adults over the age of 70 years who had not been previously vaccinated with a pneumococcal vaccine. One year later the participants

received a booster dose with either PCV-7 or PPSV-23. Immune response was compared for seven serotypes that were common to both vaccines. They concluded that in adults, an initial dose of PCV-7 is likely to elicit higher and more effective levels of antipneumococcal antibodies compared to PPSV-23. PCV-7 elicits an immunological state that allows subsequent administration of PCV-7 or PPSV-23 to maintain functional antipolysaccharide antibody levels.

In another study, investigators compared vaccine responses to PPSV-23 in previously unvaccinated institutionalised elderly patients (mean age 85.5 years) to healthy younger adults (mean age 37 years) by measuring pre vaccination and post vaccination serum IgG concentrations and functional antibody activity. They found that post vaccination IgG antibody concentrations for two serotypes (6B and 19F) of the five studied (4, 6B, 14, 19F, and 23F) were significantly lower in elderly than in younger adults; however, opsonophagocytic activity was significantly reduced for all serotypes in the elderly. [37]

2.4 Effectiveness of pneumococcal vaccine

The effectiveness of pneumococcal vaccination in paediatrics is well established. In an earlier randomised double-blind study in Soweto, Klugman et al.[38] investigated the efficacy of 9-valent pneumococcal vaccine given together with *H. influenzae* type B conjugate vaccine in human deficiency virus (HIV) infected and HIV non-infected children in the prevention of IPD. In HIV non-infected children, the vaccine reduced the incidence of a first episode of IPD due to serotypes included in the vaccine by 83% (95% confidence interval (CI), 39 to 97; 17 cases among controls and 3 among vaccine recipients). Among HIV-infected children, the efficacy was 65% (95% CI, 24 to 86; 26 and 9 cases, respectively). This vaccine effectiveness (VE) also translated to reductions in antibiotic resistance in IPD.

In South Africa, pneumococcal vaccine was first introduced as PCV-7 in 2009 as part of an expanded programme of immunisation. It was later replaced by PCV-13 in 2011.The rates of IPD were substantially reduced in this age group. These benefits were mediated by reduced nasopharyngeal carriage of vaccine serotypes showing indirect effects that translated into reductions in disease also seen in older children and adults. Additionally, vaccination in this group reduced the rates of antibiotic-resistant IPD. In 2017, the incidence of IPD in children younger than five years was six per 100 000 per population compared to an incidence rate of 30 per 100 000 in 2005 before PCV-13 was introduced.

The incidence of IPD in the elderly who are older than 64 years has been stable at less than 10 per 100 000 per population.[7,39] Therefore it is unequivocal that universal routine vaccination in children aged five years and younger has a substantial benefit on the most severe cases of *S. pneumoniae* in reducing nasopharyngeal carriage. A similar benefit has also been demonstrated elsewhere.[40-41]

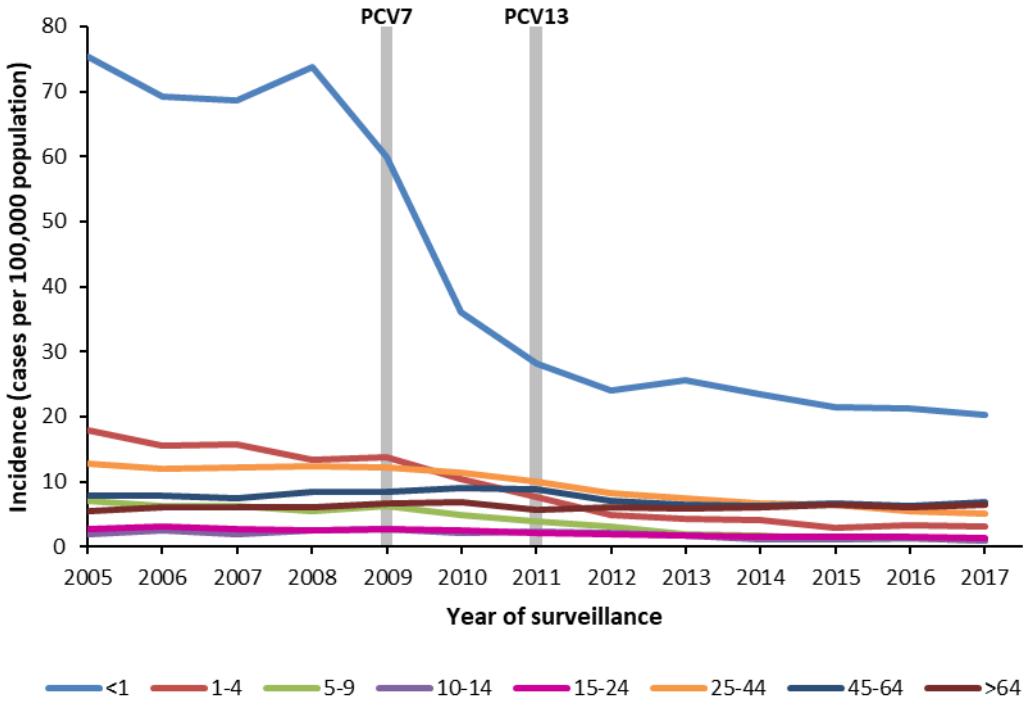

Figure 1: Age-specific incidence rates for laboratory-confirmed invasive pneumococcal disease, reported to GERMS-SA, South Africa, 2005-2017

Source: Communicable diseases surveillance and outbreak investigation in South Africa[42]

The estimated vaccine coverage for accessing the third dose of PCV-13 in South Africa was reported as 73% in 2018.[43] With that being said, unvaccinated adults are still likely to have some residual burden of pneumococcal disease due to serotypes that are included in PCV-13. The herd protection effects are considered to manifest slower in adults in comparison to the vaccinated children population.[44] It is also reported that even with childhood immunisation in place, ten percent of CAP cases in adults 65 years and older are caused by PCV-13 serotypes and are potentially avoidable with the use of pneumococcal vaccination.[45]

Bacteraemic pneumococcal pneumonia confers the most severe disease form of pneumococcal disease but non-bacteraemic pneumonia is the most frequent manifestation of pneumococcal infection in the elderly.[46-48] Given many limitations of diagnostic tests for non-bacteraemic pneumococcal pneumonia, most studies report the incidence of bacteraemic or IPD, and thus, grossly underestimate the true burden of pneumococcal pneumonia. For every case of bacteraemic pneumococcal pneumonia, it is estimated that there are at least three additional cases of non-bacteraemic pneumococcal pneumonia.[1] Despite pneumococcal immunisation in children and adults, the burden of pneumococcal disease in adults has remained high.[49] Recommendations for direct vaccination in adults for pneumococcal disease have been implemented in some countries to address this residual burden of CAP seen in adults.[10] That being said, pneumococcal pneumonia in the elderly represents a clear unmet medical need. There has been inconsistent evidence on the effectiveness of pneumococcal vaccines in reducing the risk of pneumonia treated in hospital.

Jackson et al.[50] in a retrospective cohort study of 47 365 participants investigated the association between pneumococcal vaccination with PPSV-23 for primary outcomes: hospitalisation because of CAP, pneumonia in patients not hospitalised and pneumococcal bacteraemia. The researchers found that receipt of pneumococcal vaccine was associated with a significant reduction in the risk of pneumococcal bacteraemia hazard ratio (HR) of 0.56 (95% CI, 0.33 - 0.93). It also found a slightly increased risk of hospitalisation for pneumonia HR= 1.14 (95% CI, 1.02 - 1.28). Pneumococcal vaccine did not alter the risk of outpatient pneumonia with an HR= 1.04 (95% CI, 0.96 - 1.13) or any case of CAP regardless of whether it required hospitalisation or not, with the HR= 1.07 (95% CI, 0.99 - 1.14). This study was observational from records review and therefore prone to misclassification bias.

Similarly, in retrospective case-control study by Leventer-Roberts et al.[51], nested in a population-based cohort, the investigators investigated the effectiveness of PPSV-23 against IPD and hospital-treated pneumonia in adults aged 65 years and older. Demographic information, laboratory data and diagnosis were extracted from a chronic disease registry from in-patient and outpatient records. The adjusted association between vaccination and IPD were a protective odds ratio (OR) of 0.58 (95% CI, 0.41 - 0.81) this study however, showed no protective effect between vaccination and hospital-treated pneumonia. The OR was 1.01 (95% CI, 0.97 - 1.04).

In contrast, a Spanish study which was a matched case-control study, was conducted in patients aged 65 years and older who were admitted with CAP in five hospitals. The study aimed to assess the effectiveness of the PPSV-23 in preventing hospital admissions due to CAP. Cases were matched to controls by sex, age, date of hospitalisation and underlying disease. Patient information was collected from written hospital medical records and interview of patients for a history of past pneumonia and vaccination status. The overall adjusted OR was 0.76 (95% CI, 0.590 - 0.991). The adjusted OR in immunosuppressed and immunocompetent participants were 0.79 (95% CI, 0.525 - 1.187) and 0.76 (95 % CI, 0.544 - 1.072) respectively.[52]

Another study done which was a population-based cohort study involving 27 204 individuals aged 60 years and older, assessed the clinical effectiveness of using PPSV-23 in preventing CAP. Primary outcomes were hospitalisation for pneumococcal CAP (bacteraemic and non-bacteraemic cases) and all-cause CAP. All CAP cases were radiographically confirmed and validated by checking clinical records. After multivariable adjustments, as compared with those never vaccinated, recent vaccination with PPSV-23 (less than 5 years ago) was associated with reduced risks of bacteraemic pneumococcal CAP (HR, 0.38; 95% CI, 0.09 - 1.68), non-bacteraemic pneumococcal CAP (HR, 0.52; 95% CI, 0.29 - 0.92), overall pneumococcal CAP (HR, 0.49; 95% CI, 0.29 - 0.84), and all-cause CAP (HR, 0.75; 95% CI, 0.58 - 0.98).[53]

In a different study, Wiemken et al.[54] also investigated the effectiveness of PPSV-23 in preventing hospitalisations due to *S. pneumoniae* CAP in a nested case-control study wherein cases were defined as CAP plus *S. pneumoniae* identified in blood, broncho-alveolar lavage, sputum or by testing for urinary antigen. This study also investigated if VE may be influenced by sex. From a total of 2 688 elderly adults (aged 65 years and older) hospitalised with CAP, the overall adjusted VE was 37% (95% CI, 10.1% - 55.4%). For males, the adjusted VE was 34% (95% CI, -1.0% - 57.3%) for females the overall adjusted VE was 68% (95 % CI, 40.3% - 83.0%).

In a randomised double-blind placebo-controlled trial involving 84 496 adults 65 years and older, Bonten et al.[55] evaluated the efficacy of PCV-13 in preventing the following outcomes: first episodes of vaccine-type strains of pneumococcal CAP, non-bacteremic and non-invasive pneumococcal CAP and IPD. In this study, trivalent influenza vaccine was co-administered with both the PCV-13 preparation and placebo. Vaccine efficacy for PCV-13 was 45.6% (95.2% CI, 21.8 - 62.5, P<0.001) for the first episode of confirmed vaccine-type

CAP. Vaccine efficacy was reported as 45.0% (95.2% CI, 14.2 - 65.3, P<0.007) for the first episode of confirmed episode of non-bacteraemic and non-invasive vaccine-type CAP. Vaccine efficacy was 75.0% (95% CI, 41.4 - 90.8, P<0.001) for first episode of vaccine-type IPD. This study was conducted in the Netherlands where the incidence of pneumococcal disease was considered low. The results of this study led to the recommendation of routine vaccination in adults over the age of 65 in some countries.[56]

In another study done in the USA, PCV-13 VE against hospitalised vaccine-type CAP in adults aged >65 years was conducted. Using a test-negative design, they identified cases and controls from a population-based surveillance study of adults who were hospitalised with CAP. Cases were defined as hospitalised CAP patients with PCV-13 serotypes identified via culture or serotype-specific urinary antigen detection assay. The remaining CAP patients served as test-negative controls. Cases were less likely to have received PCV-13 than controls 3/68 (4.4%) vs 285/1966 (14.5%), unadjusted VE 78.2% [95% CI, 12.8 - 91.5%] this study was done following universal recommendation for use of PCV-13 in the United States of America.[57]

Observational studies that have been conducted to establish the effectiveness of both PCV-13 and PPSV-23 in preventing non-bacteraemic pneumococcal pneumonia have largely been heterogeneous in terms of study design and the results reported. However, studies that were cited in this section highlight that sufficient hypothesis has been generated with pneumococcal vaccination being considered as a viable alternative to curb pneumococcal disease in the elderly at a population level.

2.5 Effectiveness of influenza vaccine

Seasonal influenza vaccination is an established public health intervention in the elderly.[58] In South Africa, it is recommended by the National Institute of Communicable Diseases (NICD) to prevent morbidity of influenza infection in vulnerable groups which include persons aged 65 years and older.[8] According to the NICD South African estimates for the 2018 influenza season, the majority of influenza positive samples (98%) detected by the viral watch surveillance programme have been identified as influenza A (H1N1) and the influenza season was a moderate season compared to previous years.[59]

The overall adjusted VE for the 2017/2018 season in the United States against influenza A and B virus infection associated with medically attended acute respiratory illness was

36% (95% CI, 27% - 44%). Most infections (69%) were caused by Influenza A virus (H3N2). Vaccine effectiveness was reported as 25% (95% CI, 13% - 36%) against illness caused by influenza A virus (H3N2) .67% (95% CI, 54% - 76%) against A (H1N1) and 42% (95% CI, 25% - 56%) against influenza B virus. It is recommended for all persons aged six months and older in order to prevent influenza illness including hospitalisations and death.[60]

2.6 Dual benefit of pneumococcal and influenza vaccines

In a study by Schwarz et al.[61] which was a randomised double-blind study, designed to test whether the immune responses induced by the concomitant administration of PCV-13 plus trivalent inactivated influenza vaccine (TIV) to antigens A/HIN1, A/H3N2 and B are non-inferior to those induced by TIV alone (TIV + Placebo). In this study, the investigators also investigated if the immune responses to PCV-13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by PCV-13 + TIV are non-inferior to those induced by PCV-13 administered one month after TIV. The safety profile of PCV-13 + TIV compared with that of each agent alone was also assessed. They found that slightly lower pneumococcal serotype-specific anticapsular polysaccharide IgG GMC's were observed with PCV-13 + TIV relative to PCV-13. They concluded that concomitant administration of PCV-13 + TIV demonstrated acceptable immunogenicity and safety compared with either agent given alone.

In a Japanese study by Kawakami et al.[62] who conducted an open-label randomised clinical trial, and sought to determine the clinical efficacy and cost-saving effect of PPSV-23 against CAP in participants older than 65 years of age receiving routine influenza vaccine during a two-year period. Study participants were randomly assigned to either a PPSV-23 group or a non PPSV-23 group. The incidence, admission and the medical cost for all-cause pneumonia were compared between these two groups. PPSV-23 vaccination significantly reduced the incidence of admission for all-cause pneumonia between the two groups compared in participants older than 75 years of age (41.5%, P= 0.039)

Christenson et al.[63] in a Swedish study performed a prospective study on individuals older than 65 years of age (n= 258 754) to investigate the effectiveness of influenza and pneumococcal vaccines in reducing the need for hospital treatment and death due to influenza, pneumonia and IPD. Vaccination was performed in 124 702 (48%) participants; 72 107 had both vaccines, 29 346 only had the influenza vaccine and 23 249 only had the pneumococcal vaccine. Compared with the unvaccinated cohort, a lower incidence of hospitalisation for all endpoint diagnoses was seen in vaccinated persons. An additive effectiveness of vaccination was seen when both vaccines were given, with a reduction of hospital admissions for influenza (37%), pneumonia (29%) and IPD (44%). They concluded

that vaccination with influenza and pneumococcal vaccines together was effective in reducing the need for hospital admission for influenza and pneumonia.

Baxter et al.[64] also conducted a study to evaluate the immunogenicity and safety of PCV-13 coadministered with a quadrivalent influenza vaccine (QIV) in adults 50 years and older previously vaccinated with PPSV-23 in a phase-4 randomised placebo-controlled trial. They concluded that immune responses to PCV-13 and QIV were non-inferior to PCV-13 given alone, but were associated with lower PCV-13 responses that were significantly lower for four serotypes. They also concluded that dual PCV-13 and QIV yielded similar hemagglunation inhibition assay responses compared to QIV alone.

2.7 Pneumococcal vaccine uptake

Following recommendations for vaccination in children, vaccination in the elderly has been recommended in some countries as a strategy to reduce the burden of pneumococcal disease. There is considerable variation in the uptake of pneumococcal vaccine in different countries with a general trend for its uptake being low even where it is recommended. It is reported that in Germany the uptake of pneumococcal vaccine in adults aged between 65 and 79 is less than one-third of the population in Germany. In Australia where the vaccine has been provided free of charge under government-funded initiatives or by employers, only just over half of targeted adults have received it. The proportion of adults aged 65 and older that were vaccinated up to and including March 2015 stood at only 35.1% in the UK.[9]

This low uptake is commonly attributed to a perception of non-efficacy, resource constraints, patient unawareness and other reasons. This low vaccine uptake has been demonstrated by various studies. In a Swiss study, researchers investigated general practitioner (GP) attitudes and opinions about pneumococcal vaccination in primary care and why it is so rarely provided in that country. They reported that GPs did know that pneumococcal vaccine is recommended for several risk groups and elderly patients. For this low vaccination rate, GPs mentioned that pneumococcal vaccination had little priority in daily practice, especially in comparison with the importance of other vaccinations, namely influenza. The low level of priority was supported by the fact that the GPs rarely ever experienced a case of severe pneumococcal disease.[65]

In another study done in the United States of America which sought to define variables predicting PPSV-23 uptake in eligible African–American adults. It found that 47.8% of participants were unaware of PPSV-23 existence and that for those who were unaware of the existence of PPSV-23, the odds were 6.5 times less likely to be vaccinated. Provider recommendation was a significant predictor of vaccination. Those without a recommendation were approximately 7.3 times less likely to vaccinate.[66]

Pneumococcal vaccine has shown to be underutilised and inadequately accepted in practice despite the possible benefits vaccination presents. This section has highlighted some of the variables thought to influence the low uptake of pneumococcal vaccine from both the healthcare worker and patient perspective.

2.8 Serotype replacement

Ideally, from a public health perspective, if age-based recommendations were to be made for pneumococcal vaccine in this age group, it is important to establish if the vaccine not only prevents pneumococcal disease in vaccine serotypes but also in other pneumococcal strains. It is unknown how long the herd effect will persist in places it has already been observed. The burden of pneumococcal disease, especially non-bacteraemic CAP in the elderly and those with comorbidities, continues to rise even where the herd effect has been shown.[1,9] Studies that have investigated serotype replacement have been sparse.

A 5-year prospective cohort study of adults hospitalised with predominantly non-bacteraemic CAP was conducted to investigate the impact of PCV-13 on serotypes implicated in pneumococcal disease in the United kingdom. The study was done was after PCV-7 had been replaced with PCV-13 in routine paediatric vaccinations. They found that the incidence of hospitalised pneumococcal pneumonia had been declining over the preceding 5 years of the study, including the years following PCV-13 introduction. They also found that the incidence of CAP due to additional PCV-13 serotypes declined by 30% in the 2 years following the introduction of PCV-13, when compared to pre-PCV-13. Although the incidence of CAP due to serotypes 1, 3 and 5 declined during the study, CAP due to serotype 7F/A increased. National IPD data demonstrated a 22% and 31% increase in non PCV-13 serotypes in adults aged 45 – 64 years and 65 years and older, respectively, between 2008–2010 and 2012–2013.[44]

In South Africa, in a national active laboratory-based surveillance for IPD, Von Gottberg et al.[67] assessed the impact of PCV-13 on IPD in adults over the age of 25 years. They found that non-vaccine serotypes increased by 15% (95% CI, 7% - 23%; rates: 3.5 to 4.0 per 100 000 population). Increases were significant for non-vaccine serotypes 8, 15A, 22F and 35B: 34% (95% CI, 9% - 63%; rates: 0.4 to 0.5), 76% (95% CI, 13% - 169%; rates: 0.07 to 0.1), 66% (95% CI, 15% - 137%; rates: 0.1 to 0.2) and 98% (95% CI, 20% - 221%; rates: 0.05 to 0.1), respectively. Seven years since the introduction of children's vaccination, the herd effects were still relevant but serotype replacement was evident.

In a study done in Kilifi in Kenya which assessed the effect of PCV-10 against nasopharyngeal carriage and IPD in children and adults. They found that in addition to persistent vaccine-type (VT) carriage, they also observed a 71% increase in carriage of non-VT pneumococci (particularly serotype 19A) in children younger than 5 years. Age-standardised adjusted prevalence ratio for non PCV-10 type carriage increased by 1.71, (95% CI, 1.47 - 1.99). It is noted that these increases in non-VT carriage have generally been small in comparison with the decline in VT IPD.[40]

Due to an increase in the incidence of pneumococcal disease caused by non-vaccine serotypes post the introduction of PCV-13 universal vaccination in children,[68] this section sought to highlight trends in serotype replacement seen in a few countries which could possibly explain the hospital admissions we observed in the current study.

CHAPTER 3: METHODS

This chapter summarises the current study's aims, objectives, design, setting, participant selection, how the cases, controls and comorbidities were defined and measured, the sample size, how data were analysed and considerations for ethics for this research.

3.1 Aims and objectives

Hypothesis: Our primary hypothesis was that vaccination with the pneumococcal vaccine will result in reduced hospitalisation events due to pneumonia in adults 65 years and older. Our secondary hypothesis was that vaccination with influenza vaccine will result in reduced hospital events due to pneumonia in adults.

Our aim was to compare the effectiveness of pneumococcal vaccination versus no vaccination and to also compare the effectiveness of influenza vaccination versus no vaccination in preventing hospital admissions due to pneumonia in adults over the age of 65. Our hypotheses were linked to the following objectives:

i. To measure the odds of being pre-vaccinated with the pneumococcal vaccine (vs. no such vaccination) among those admitted for pneumonia;

ii. To measure the odds of being pre-vaccinated with the pneumococcal vaccine (vs. no such vaccination) among those not admitted to hospital for pneumonia during the same time period;

iii. To match the non-admitted controls to the admitted cases by means of age, sex, current strain influenza vaccine status and selected comorbidities;

iv. To estimate the adjusted OR by using both McNemar's test and propensity score matching (PSM) for admission given prior vaccine (yes or no) with pneumococcal vaccine;

v. To measure the odds of being pre-vaccinated with influenza vaccine (vs. no such vaccination) among those admitted for pneumonia;

vi. To measure the odds of being pre-vaccinated with the influenza vaccine (vs. no such vaccination) among those not admitted to hospital for pneumonia during the same time period;

v. To estimate the adjusted OR by using both the McNemar's test and PSM for admission given prior vaccine (yes or no) with influenza vaccine.

3.2 Study design

This study was an observational case-control study with a 1:1 matching based on cross-sectional secondary data collected from Medihelp medical aid scheme for years 2017 and 2018. The study population consisted of 34 068 participants. This population comprised 1 604 cases and a pool of 32 464 potential controls. The study sample comprised of 800 cases and 800 controls for investigating the effectiveness of pneumococcal vaccine and 800 cases and 800 controls for investigating the effectiveness of influenza vaccine.

For the primary exposure of interest (pneumococcal vaccine), controls were matched for: influenza vaccine; age; sex; diabetes mellitus (DM); asthma; chronic obstructive pulmonary disease (COPD) and ischaemic heart disease (IHD). For the secondary exposure of interest (influenza vaccine), controls were matched for: pneumococcal vaccine; age; sex; DM; asthma; COPD and IHD.

Matching for age was done at intervals +/- 5 years.

3.3 Study setting

We used secondary data from a licensed South African open medical aid scheme providing private health care insurance within the nine provinces of South Africa. We have used retrospective claims data as collected via real-time stored records for claim submissions from registered pharmacies within South Africa for claims of pneumococcal vaccine and influenza vaccine and pre-approved claims submissions for hospital admissions for pneumonia. Data were stored electronically by the scheme for the research period that it was requested for. In this study, Sixty-four percent of the pneumococcal vaccines claimed were PPSV-23 type and Thirty-six percent were PCV-13 type. There were no cases of claims for more than one pneumococcal vaccine type.

3.4 Study population

3.4.1 Inclusion

Participants were included if they met the following criteria:

For cases

i. If they were 65 years and older as of 31 December 2017 and had an objective hospital admission more than ten days after vaccination based on pre-specified admission ICD-10 codes included in the data collection sheet.

For controls

ii. If they were 65 years and older and have not had an admission to hospital for pneumonia in the last 12 months.

3.4.2 Exclusion

Participants were excluded if they met the following criteria:

i. If the treatment of CAP did not require hospitalisation
ii. If claims were rejected due to unavailability of funds, participants were excluded from the study, as we could not establish if they had reimbursed the pneumococcal or influenza vaccines through cash payments.

3.5 Data collection and sampling

Data were collected from the scheme's information technology (IT) division using their Business Intelligence System. The data are required to be stored for a minimum period of ten years as a legal requirement to comply with the Medical scheme's Act (Act 131 of 1998). The data extraction specification sheet for our study was included with the request to the IT division (attached as appendix III).

The data were extracted in Excel format and were exported into STATA-15 (StataCorp, USA) format for matching and analysis.

For cases, the outcome variable: pneumonia hospitalisation is a binary variable. It was defined by captured records of admissions to private hospitals for study periods 2017 to 2018 validated by the following ICD-10 codes based on the treating doctor's admission pre-authorisation request: J12.0 - J12.9 , J13, J14, J15, J15.0, J15.1 - J15.9, J16, J16.0, J16.8, J17, J17.0, J17.1- J17.3, J17.8, J18, J18.0, J18.1, J18.2, J18.8 and J18.9. The ICD-10 code descriptions are included in appendix III, which contains details of the data extraction tool. The hospital admissions are subject to case management and pre-authorisation criteria. The first hospitalisation event was the only hospital event counted if the participant had more than one hospitalisation for pneumonia as pre-specified for the study period.

For controls, the outcome variable: pneumonia hospitalisation which is a binary variable, was excluded using the following ICD-10 codes that were included in identifying the cases: J12.0 - J12.9, J13, J14, J15, J15.0, J15.1-J15.9, J16, J16.0, J16.8, J17, J17.0, J17.1 - J17.3, J17.8, J18, J18.0, J18.1, J18.2, J18.8 and J18.9.

Only information from paid claims of pneumococcal vaccine and influenza vaccine identified by the NAPPI codes[1] used from pharmacy claims were used.
For pneumococcal vaccine, the following NAPPI codes were used to validate utilisation:

i. 755826 Trade name: Pneumovax vaccine™
ii. 836699 Trade name: Imovax pneumo 23™
iii. 715858 Trade name: Prevenar 13™

For influenza vaccine, the following NAPPI codes were used to validate utilisation:

i. 711737 Trade name: Fluarix™
ii. 711345 Trade name: Fluvax™
iii. 732826 Trade name: Influvac™
iv. 813338 Trade name: Vaxigrip™
v. 702733 Trade name: X-flu™

[1] NAPPI code: A unique identifier for a given ethical, surgical or consumable product, which enables electronic transfer of information throughout the health care delivery chain.

The identified comorbidities were collected for participants who had a registration for the following diagnoses and were claiming monthly chronic medicine:

COPD registered with any of the following ICD-10 codes: J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.8 and J44.9

IHD registered with any of the following ICD-10 codes: I20.0, I20.1, I20.8, I20.9, I25.0, I25.1, I25.2, I25.3, I25.4, I25.5, I25.6, I25.8 and I25.9

DM registered with any of the following ICD-10 codes: E10.0 - E10.9, E11.0 - E11.9, E13.0 - E19 and O24.1 - O24.9

Asthma registered with the following ICD-10 codes: J45.0, J45.1, J45.8, J45.9 and J46

From the 1 604 cases collected, 800 cases were randomly sampled using STATA-15 using the following command: *sample 800, count*

The following age groups were used for matching cases and controls for the covariate age: 65-69 years, 70-74 years, 75-79 years, 80-84 years, 85-89 years, 90-94 years and 95-200 years. These age groups were in intervals of 5 years. The age groups were labelled in STATA-15 as age groups 1 through to age group 7, respectively. In the matching process for cases where a matching control could not be found for a particular age group, we relaxed the control age group to one age group above or one age group below the age group that could not be matched to the case.

In addition to age, we also matched for sex and comorbidities IHD, COPD, DM and asthma. For the primary outcome measure, we assessed pneumococcal VE and adjusted for influenza vaccine use and for our secondary outcome measure, we assessed influenza VE and adjusted for pneumococcal vaccine use. In the matching process where pneumococcal vaccine was the predictor, if for example we wanted to match a case to a control who is a 70 year old female (sex= 0) with IHD (ihd= 1) and asthma (asthma= 1) who vaccinated against influenza (flu_vac= 1), the following STATA-15 commands were used:

Keep if age group==2 & sex==0 & ihd==1 & asthma==1 & copd==0 & dm==0 & flu_vac=1

STATA-15 would then exclude all controls, which were not identical to this covariate, then we would use the following command for STATA-15 to randomly choose one control from the pool of controls generated:

Sample 1, count

This process was repeated for all the 800 cases. A pool of 32 464 controls were available to be matched with the 800 cases.

For the secondary exposure, where influenza vaccine was the predictor, if for example we wanted to match a case who is a 70 year old female (sex=0) with IHD (ihd=1) and asthma (asthma=1) who vaccinated against pneumococcal vaccine (pneumo_vac=1), the following STATA-15 commands were used :

Keep if age group==2 & sex==0 & ihd==1 & asthma==1 & copd==0 & dm==0 & pneumo_vac=1

STATA-15 would then exclude all controls, which were not identical to this covariate, and then we would use the following command for STATA-15 to randomly choose one control from the pool of available controls:

Sample 1, count

This process was also repeated for all the 800 cases with a pool of 32 464 controls available to be matched randomly with these 800 cases.

This study in its entirety matched 1600 cases to randomly selected controls to measure the study outcomes.

3.5.1 Sample size

The following power analysis performed using PS Sample size software was used to determine the study sample size (assuming we wished to detect a protective effectiveness of 50% or higher and that 5% of controls will be vaccinated; and that there will be 0.6 correlation between the vaccine exposure status of cases and their matched controls):

Sample size (controls)	**Power to detect VE** >=50%
600	72.7
700	79.1
800	84.1

The selected sample size comprised 800 cases and 800 controls for each outcome measured.

3.6 Data analysis and management

3.6.1 Data security

All data sourced from the IT department from the scheme were received in MS Excel format. These data were extracted by personnel who had authority and delegation to do so by the scheme's principal officer. The scheme's claims records are stored by the scheme as a legal requirement. The data received were exported into STATA-15 format for the process of sampling, matching and analysis. The data are currently stored in a cloud which is password-protected.

3.6.2 Baseline data management

Relevant baseline variables for cases as well as the matched controls for variables age, sex, vaccination status for both influenza, pneumococcal vaccine and comorbidities IHD, COPD, DM and asthma were coded in Exel format and exported to STATA-15. They have

been described using appropriate statistical analytic methods as described in section 3.7.1 to follow.

3.6.3 Matched data management

The matched pairs as described in section 3.7.2 were allocated a number identifying each pair starting from pair number 1 to pair number 800. The individual case and the individual control were also allocated identical participant pair identification numbers starting from 1 to 800 for the analysis of exposure with pneumococcal vaccine. This was repeated for the influenza vaccine exposure analysis.

This means that for each data set (primary exposure data set and secondary exposure data set) pair number 1 will consist of case number 1 and control number 1 and the numbering system continues for the entire randomly selected sample of 800 cases and controls. These data sets have also been stored and analysed using analytic statistical methods as described in section 4.5 to follow.

3.7 Data analysis

3.7.1 Baseline data analysis

The sample characteristics were described and summarised using means and standard deviation for continuous data for which the only variable in this study was variable: age. Histograms were used to assess normality of distribution and where it was considered not normally distributed, we also reported the interquartile range. We have also described the allocation of the age groups that were used in the matching for randomly allocated cases and controls. Inherently as the cases and the controls were meant to be similar through the matching process except for the predictor variable measured for, we have not analysed the differences between the groups but only described them as a result.

Comorbidities across the study population to show that the study population was an at-risk population were also described. The proportions of the distribution of comorbidities between cases and controls and the entire population were also described.

Vaccination status across the entire study population has been described in order to illustrate vaccine uptake for both the influenza and pneumococcal vaccines as the predictors of our study outcome.

3.7.2 Matched pairs data analysis

For the matched pairs in the primary analysis we have modelled using McNemar's OR with its 95% CI. Our study had 1:1 matching of case to control. For an analysis using an alternative matching method, we have employed PSM to estimate the odds ratios between cases who have vaccinated against pneumococcal vaccine first and then secondly cases who have vaccinated against influenza vaccine as compared to controls. A P value of <0.05 was considered as statistically significant. For the McNemar's OR analysis, we reported the McNemar's OR with its 95% CI and for the PSM analysis we also estimated the OR with its 95% CI with pneumococcal vaccine as the predictor variable. In addition, we performed analysis with both forms of matching for influenza vaccine as the exposure of interest. For sensitivity analysis, we performed subgroup analysis by estimating the OR for vaccination exposure in cases who have used PPSV-23 only and cases who have used PCV-13 only compared to vaccination exposure in controls by PSM.

3.8 Ethical considerations

Approval to conduct our study was received from the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria. Ethics approval certificate number 152/2019 is included as appendix I.

Informed consent: As information stored on claims data belong to the scheme, permission has been sought and granted from the principal officer, executive of health care

and the executive of Information systems of Medihelp medical scheme to use this secondary data as included in the appendix section

Confidentiality: In accordance with Medical Scheme's Act,[69] the data extracted and availed to the researcher do not contain any information that can be used to identify any of the participants in the study, and this has ensured that confidentiality of the participants personal information was not violated. Each study participant was allocated an arbitrary participant number for identification. The extracted data only contained variables pre-specified in the data collection sheet supplied by the principal investigator before data extraction was initiated. There were no risks to participants as this was a record review based on retrospectively collected data.

CHAPTER 4: RESULTS

The study population consisted of 1 604 cases and 32 464 potential controls. The final sample for each exposure measured consisted of randomly selected 800 cases and 800 controls, with pairs of 463 females and 337 males and a mean±SD age of 77.5 ± 7.7 years. Sixty-four percent (207 participants) of the pneumococcal vaccine claimed from the study population was the PPSV-23 type and Thirty-six percent (116 participants) was for the PCV-13 type. There were no reported observations for participants who had claimed both PPSV-23 and PCV-13 in the duration of the study period. Both descriptive and analytical results are presented in this chapter according to the primary and secondary exposures i.e. pneumococcal vaccine as the exposure variable and influenza vaccine as the exposure variable.

4.1 Descriptive statistics

4.1.1 Overview

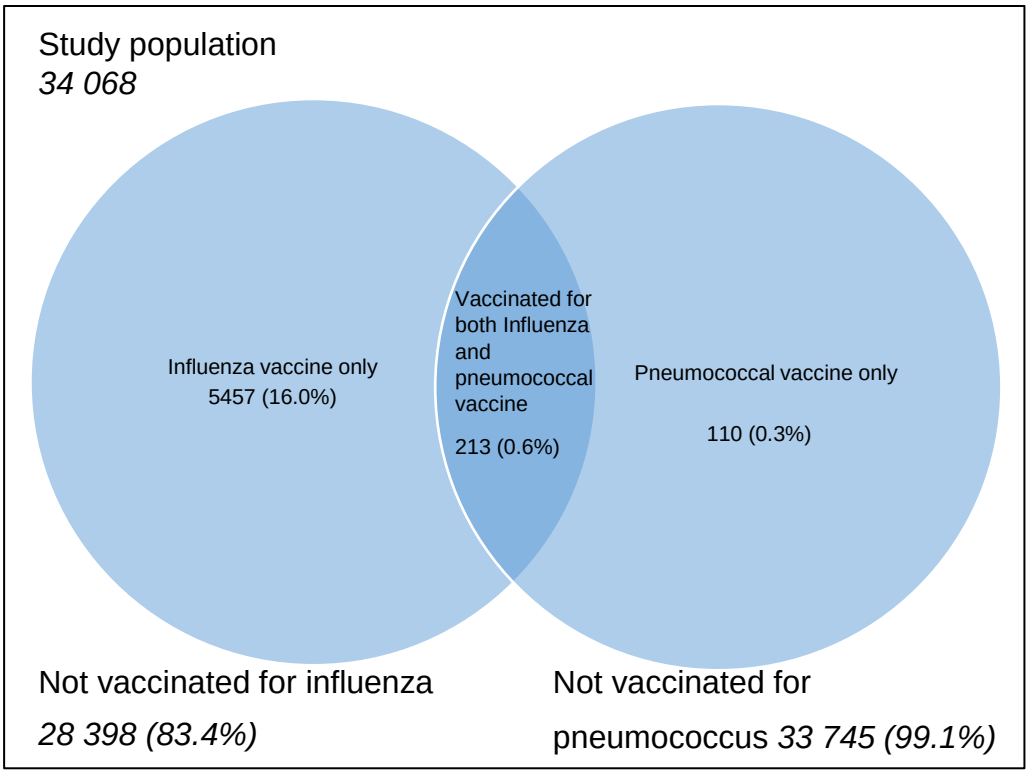

Figure 2: Vaccine uptake in the study population

Our study population was an “at-risk” population. Table 1 describes the prevalence of comorbidities in the study population, cases and pool of controls before the matching was performed. Pneumococcal vaccine uptake in the study population was 0.9% and influenza vaccine uptake in the study population was 16.6%. IHD was the most prevalent comorbidity followed by DM. Table 2 details how pneumococcal and influenza vaccines were claimed according to the listed comorbidities.

Table 1: Distribution of comorbidities across the study population

N= 34068	**Study population n (%)**	**Cases n (%)**	**Controls n (%)**
COPD	585 (1.72)	138 (0.41)	447 (1.31)
ASTHMA	999 (2.93)	108 (0.32)	891 (2.62)
DM	3975 (11.67)	281 (0.82)	3694 (10.84)
IHD	5521 (16.21)	416 (1.22)	5105 (14.98)
COPD + DM	95 (0.28)	23 (0.07)	72 (0.21)
COPD + ASTHMA	102 (0.30)	22 (0.06)	80 (0.23)
COPD + IHD	196 (0.58)	46 (0.14)	150 (0.44)
IHD + DM	1288 (3.78)	107 (0.31)	1181 (3.47)
COPD + IHD + DM	42 (0.12)	10 (0.03)	32 (0.09)
COPD + IHD + ASTHMA	45 (0.13)	8 (0.02)	37 (0.11)
DM + ASTHMA	159 (0.47)	16 (0.05)	143 (0.42)
IHD + ASTHMA	250 (0.73)	31 (0.09)	219 (0.64)
COPD + DM + ASTHMA	24 (0.07)	6 (0.02)	18 (0.05)

COPD= Chronic obstructive pulmonary disease; IHD= Ischaemic heart disease;
DM= Diabetes mellitus

Table 2: Vaccine uptake according to comorbidity

N= 34068	Study population		Cases		Controls	
Comorbidity	**Influenza vaccine n (%)**	**Pneumococcal vaccine n (%)**	**Influenza vaccine n (%)**	**Pneumococcal vaccine n (%)**	**Influenza vaccine n (%)**	**Pneumococcal vaccine n (%)**
COPD	150 (0.44)	16 (0.05)	34 (0.10)	4 (0.01)	116 (0.34)	12 (0.04)
ASTHMA	289 (0.85)	29 (0.09)	33 (0.10)	3 (0.01)	256 (0.75)	26 (0.08)
DM	754 (2.21)	38 (0.11)	54 (0.16)	3 (0.01)	700 (2.05)	35 (0.10)
IHD	1230 (3.61)	71 (0.21)	77 (0.23)	6 (0.02)	1153 (3.38)	65 (0.19)
COPD + DM	24 (0.07)	2 (0.01)	8 (0.02)	1 (0.002)	16 (0.05)	1 (0.002)
COPD + IHD	54 (0.16)	7 (0.02)	13 (0.04)	1 (0.002)	41 (0.12)	6 (0.02)
COPD + ASTHMA	40 (0.12)	5 (0.01)	7 (0.02)	0	33 (0.10)	5 (0.01)
IHD + DM	281 (0.82)	12 (0.04)	24 (0.07)	3 (0.01)	257 (0.75)	9 (0.03)
COPD + IHD + DM	11 (0.03)	2 (0.01)	4 (0.01)	1 (0.002)	7 (0.02)	1 (0.002)
COPD + IHD + ASTHMA	19 (0.06)	4 (0.01)	3 (0.01)	0	16 (0.05)	4 (0.01)
DM + ASTHMA	48 (0.14)	5 (0.01)	6 (0.02)	0	42 (0.12)	5 (0.01)
IHD + ASTHMA	81 (0.24)	10 (0.03)	9 (0.03)	1 (0.002)	72 (0.21)	9 (0.03)
COPD + DM + ASTHMA	8 (0.02)	0	2 (0.01)	0	6 (0.02)	0

COPD= Chronic obstructive pulmonary disease; IHD= Ischaemic heart disease;
DM= Diabetes mellitus

4.2 Characteristics for continuous variables

After exact characteristic matching was performed, the characteristics of the pairs of case and control are detailed below:

4.2.1 Pneumococcal vaccine as the predictor variable

The only continuous variable: age was not normally distributed. The mean ± SD age was 77.5 ± 7.7 years. The summary is presented below:

Table 3: Age distribution where pneumococcal vaccine is the predictor variable

Pairs= 800		**Cases**				**Controls**		
	Mean	**± SD**	**Median**	**Interquartile range**	**Mean**	**± SD**	**Median**	**Interquartile range**
Age	77.5	7.7	77	71 to 83	77.4	7.5	77	71 to 83

Distribution of the paired matched age groups after exact characteristic matching was done were as follows:

Table 4: Distribution of matched pairs according to age groups (pneumococcal vaccine as the predictor variable)

Pairs= 800		
Age group (Age)	**n**	**%**
1 (65-69)	135	16.88
2 (70-74)	176	22.00
3 (75-79)	173	21.63
4 (80-84)	158	19.75
5 (85-89)	97	12.13
6 (90-94)	53	6.63
7 (95-200)	8	1.00

4.2.2 Influenza vaccine as the predictor variable

Similarly for the secondary exposure, Age was not normally distributed. The distribution was as follows.

Table 5: Age distribution where influenza vaccine is the predictor variable

Pairs= 800		**Cases**				**Controls**		
	Mean	**± SD**	**Median**	**Interquartile range**	**Mean**	**±SD**	**Median**	**Interquartile range**
Age	77.5	7.7	77	71 to 83	77.4	7.5	77	72 to 83

Distribution of the paired age groups after exact characteristic matching was done is described as follows:

Table 6: Distribution of matched pairs according to age groups (influenza vaccine as the predictor variable)

Pairs= 800		
Age group (Age)	**n**	**%**
1 (65-69)	134	16.75
2 (70-74)	176	22.00
3 (75-79)	176	22.00
4 (80-84)	156	19.50
5 (85-89)	99	12.38
6 (90-94)	52	6.50
7 (95-200)	7	0.88

4.3 Characteristics for binary variables

After the matching was performed, the characteristics are detailed below:

4.3.1 Pneumococcal vaccine as the predictor variable

Table 7: Sample characteristics (pneumococcal vaccine as the predictor variable)

Pairs= 800		**Cases n (%)**	**Controls n (%)**
Sex	Female	463 (57.88)	463 (57.88)
	Male	337 (42.13)	337 (42.13)
Pneumococcal vaccination status	Vaccinated	15 (1.88)	9 (1.13)
	Unvaccinated	785 (98.13)	791 (98.88)
Influenza vaccination status	Vaccinated	140 (17.50)	140 (17.50)
	Unvaccinated	660 (82.50)	660 (82.50)
Asthma		53 (6.63)	53 (6.63)
COPD		71 (8.88)	71 (8.88)
DM		144 (18.00)	144 (18.00)
IHD		202 (25.25)	202 (25.25)

COPD= Chronic obstructive pulmonary disease; IHD= Ischeamic heart disease;
DM= Diabetes mellitus

4.3.2 Influenza vaccine as the predictor variable

Table 8: Sample characteristics (influenza vaccine as the predictor variable)

Pairs= 800		**Cases n (%)**	**Controls n (%)**
Sex	Female	463 (57.88)	463 (57.88)
	Male	337 (42.13)	337 (42.13)
Influenza vaccination status	Vaccinated	140 (17.50)	152 (19.00)
	Unvaccinated	660 (82.50)	648 (81.00)
Pneumococcal vaccination status	Vaccinated	15 (1.88)	15 (1.88)
	Unvaccinated	785 (98.13)	785 (98.13)
Asthma		53 (6.63)	53 (6.63)
COPD		71 (8.88)	71 (8.88)
DM		144 (18.00)	144 (18.00)
IHD		202 (25.25)	202 (25.25)

COPD= Chronic obstructive pulmonary disease; IHD= Ischaemic heart disease;
DM= Diabetes mellitus

During the matching stage , if an exact characteristic matching control was not found in the same age group as the case,we either relaxed the matching to one age group above or one age group below and so forth until a match was found and matches all the variables except for age. Only the variable age was relaxed and other variables in the matching remained identical for the matched pairs.

When pneumococcal vaccine was the predictor variable , there were a total of five cases where a matching control for the allocated case could not be found in the same age group.For the secondary exposure where influenza vaccine was the predictor,there were a total of six cases for which a matching control in the same age group could not be found.A

summary of controls that were matched with these cases and the age groups that they were eventually relaxed to is shown in Tables 9 and 10 .

4.4 Cases with no matching controls in the same age group

4.4.1 Pneumococcal vaccine as the predictor variable

Table 9: Cases with no matching controls (pneumococcal vaccine as the predictor variable)

	Cases			Controls	
Case id#	**Age**	**Age group^**	**Control id#**	**Age**	**Age group***
795	78	3	795	81	**4**
797	74	2	797	77	**3**
798	80	4	798	76	**3**
799	96	7	799	91	**6**
800	89	5	800	84	**4**

= Identical number identifier given to a matched case and control pair

^ = The case age group for which no matching control could be found

* = The relaxed age group finally matched with the case

4.4.2 Influenza vaccine as the predictor variable

Table 10: Cases with no matching controls (influenza vaccine as the predictor variable)

	Cases			Controls	
Case id#	**Age**	**Age group^**	**Control id#**	**Age**	**Age group***
438	96	7	438	87	**5**
446	80	4	446	75	**3**
454	74	2	454	77	**3**
457	82	4	457	74	**2**
458	69	1	458	75	**3**
459	97	7	459	90	**6**

= Number identifier given to a matched case and control pair

^ = The case age group for which no matching control could be found

* = The relaxed age group finally matched with the case

4.5 Analytic statistics

4.5.1 Pneumococcal vaccine as the predictor variable

For our primary exposure, using pneumococcal vaccine as the predictor and adjusting for influenza vaccination and comorbidities, we found that there were 15 (1.9%) vaccinations observed in cases compared to nine vaccinations (1.1%) observed in controls. The overall exact McNemar's OR was found to be 1.67 with a 95% CI of (0.683 - 4.319) with a P value of 0.308. When stratified according to sex, in men, McNemar's OR was 3.00 with a 95% CI of (0.536 - 30.393) with a P value of 0.289. In females the McNemar's OR was found to be 1.29 with a 95% CI of (0.426 - 4.062) with a P value of 0.804.

We also performed a stratified analysis for the odds ratios according to the matched seven age groups. We did not record any odds ratios for age groups 5, 6 and 7, as there were no cases that were exposed to pneumococcal vaccine in those age groups. The odds ratios and their associated CI's are summarised in Table 11.

Table 11: Odds ratios stratified by age group (pneumococcal vaccine as the predictor variable)

Age group (Age)	Odds ratio**	95% CI	P value
1 (65-69)	1.00	0.013 to 78.497	1.000
2 (70-74)	2.00	0.287 to 22.110	0.688
3 (75-79)	3.00	0.241 to 157.492	0.625
4 (80-84)	1.25	0.269 to 6.300	1.000

** *McNemar's odds ratio*

4.5.1.1 Sensitivity analysis using propensity score matching

In observational studies, treatment selection is often influenced by participants characteristics. One must account for systematic differences in the baseline characteristics presenting between participants that were treated and those that were not treated. Propensity score matching has been used to reduce or eliminate the effects of confounding when using observational studies of a case-control nature. The propensity score is the probability of exposure given measured baseline variables.[70]

Burden et al.[71] investigated the difference between exact characteristic matching and PSM in a comparative effectiveness study of inhaled corticosteroids in asthma. They found that If the exact characteristic matching is used, the calculation of a propensity score could be useful in identifying variables that require balancing, thereby informing the choice of matching criteria together with clinical considerations.

In the present study, PSM was employed for estimating the association between vaccination and hospital events. We found that the association between once off vaccination with pneumococcus and hospital treated pneumonia yielded a non-protective OR of 1.05 with a CI of (0.991 - 1.121) and a P value of 0.095. For subgroup analysis, we also estimated the odds ratios by using PSM in patients who used PPSV-23 and PCV-13 amongst the cases and controls. The odds ratios estimated with their 95% CI were an OR of 1.01 with 95% CI (0.945 - 1.079) with a P value of 0.766 for PPSV-23 and OR of 1.00 with 95% CI (0.952 - 1.043) with P value of 0.879 for the use of PCV-13.

4.5.2 Influenza vaccine as the predictor variable

For our secondary exposure, influenza vaccine, we estimated for the odds of pneumonia hospitalisation for our cases and controls with influenza vaccine as the predictor and adjusted for pneumococcal vaccine use and the selected comorbidities. There were 140 (17.5%) influenza vaccinations in cases compared to 152 (19.0%) vaccinations of influenza in controls. The overall OR for hospitalisation was found to be 0.90 with a 95% CI of (0.683 - 1.178) and P value of 0.460.When stratified according to sex, in males the OR was found to be 0.84 with an associated 95% CI of (0.539 - 1.293) with a corresponding P value of 0.461. For women the OR for hospitalisation due to pneumonia was 0.94 with a 95% CI of (0.658 - 1.344) with a P value of 0.794.

We also stratified the odds ratios according to the case and control matched age groupings. The odds ratios are reported in Table 12.

Table 12: Odds ratios stratified by age group (influenza vaccine as the predictor variable)

Age group (Years)	Odds ratio**	95% CI	P value
1 (65-69)	0.47	0.161 to 1.216	0.134
2 (70-74)	1.83	0.869 to 4.064	0.121
3 (75-79)	0.89	0.500 to 1.588	0.784
4 (80-84)	0.78	0.418 to 1.428	0.471
5 (85-89)	1.17	0.592 to 2.323	0.749
6 (90-94)	0.53	0.196 to 1.340	0.210
7 (95-200)	0.50	0.008 to 9.605	1.000

** McNemar’s odds ratio

For the secondary exposure, we have applied PSM as well to investigate the odds of hospitalisation in addition to the exact characteristic matching that was performed. It was found that the OR for hospitalisation for pneumonia in those that vaccinated against influenza compared to those that did not vaccinate when influenza vaccination was the predictor, was found to be 0.99 with a 95% CI of (0.983 – 0.994) and a P value < 0.001. This changed our result to reflect a statistically significant finding for the secondary

outcome for measuring the effectiveness of influenza vaccine in preventing hospital admissions due to CAP.

Table 13 summarises the odds ratios estimated by McNemar's test and PSM for the primary and secondary outcomes.

Table 13: Summary of results

	Cases vaccinated n/N (%)	Controls vaccinated n/N (%)	McNemar's odds ratio (95% CI)	P value	PSM odds ratio (95% CI)	P value
Pneumococcal vaccine	15/800 (1.9)	9/800 (1.1)	1.67 (0.683 to 4.319)	0.308	1.05 (0.991 to 1.121)	0.095
Influenza vacccine	140/800 (17.5)	152/800 (19.0)	0.90 (0.683 to 1.178)	0.460	0.99 (0.983 to 0.994)	<0.001

PSM= Propensity score matching

CHAPTER 5: DISCUSSION

The present study assessed the effectiveness of pneumococcal vaccine in preventing hospital admissions due to pneumonia in the elderly after matching for influenza vaccine; and, secondly assessed the effectiveness of influenza vaccine in preventing hospital admissions due to pneumonia in the elderly after matching for pneumococcal vaccine. For this study, secondary data from beneficiaries of a private health insurance company with its beneficiaries spread throughout the nine provinces of South Africa was used. Successful matching was done between cases and controls for important covariates. This chapter will discuss the principal findings of the current study.

5.1 Primary exposure (pneumococcal vaccine)

We have found that a once-off vaccination with either PPSV-23 or PCV-13 did not confer any protection against hospital admissions due to CAP using exact characteristic matching. This present study did not find any association between once-off pneumococcal vaccination and reduced odds for hospitalisation due to CAP. In the sensitivity analysis using PSM to evaluate the same outcome, we found consistent results to when we used exact characteristic matching. The odds for hospitalisation using PSM were however slightly reduced compared to the odds when exact characteristic matching was used. The odds ratios were 1.05 (PSM) and 1.67 (exact characteristic matching), respectively.

Although there has been conflicting evidence regarding the effectiveness of pneumococcal vaccine in preventing CAP, our findings were consistent with the findings from Leventer-Roberts et al.[51] who conducted a case-control study using secondary data, found that there was no demonstrated protective effect between vaccination and hospital treated pneumonia. They found an OR of 1.01 with a CI of (0.97 - 1.04). In our study, the odds for hospitalisation were slightly increased but the trend is similar.

Jackson et al.[50] also found a slightly increased risk of hospitalisation for pneumonia with a HR of 1.14 with a 95 % CI of (1.02 - 1.28).This study was similar to our study because it was a retrospective review of hospital data in elderly patients admitted for CAP. For our study we investigated the association of vaccination and hospital admissions using odds ratios, but they have utilised hazard ratios in their study which assume that the exposure

effect is consistent over time, which would be unlikely as VE with pneumococcal vaccine is known to wane over time.[31] The trends were however similar in terms of association of vaccination and increased risk of hospitalisation. Methodological heterogeneity that exists in previous observational studies that were conducted to assess the effectiveness of pneumococcal vaccine especially PPSV-23, have led to inconsistency amongst results with respect to the protectiveness of pneumococcal vaccine against hospital treated CAP. Other observational studies have also reported results consistent to findings from this present study.[51,72] In contrast, some observational studies have reported protective effectiveness from pneumococcal vaccination with PPSV-23.[52-54] We are not aware of any randomised controlled trials conducted to test the efficacy of PPSV-23 in preventing hospital admissions due to pneumonia.

Of interest is a randomised, double-blind controlled study conducted by Bonten et al.[55] in the Netherlands, which was able to show significant efficacy of PCV-13 for the prevention of vaccine-type non-bacteraemic and non-invasive pneumococcal CAP. Following this study, another real-world VE study was performed in the United States of America. This study evaluated PCV-13 VE against hospitalised VT CAP following the universal recommendation of pneumococcal vaccine in all adults older than 65 years. This American study found that PCV-13 was protective against hospitalised VT CAP with an adjusted VE of 71.1% – 73.3%. From a study population of 2 034, 21% had received PPSV-23 in the previous 5 years.[57]

As our study considered the use of either PPSV-23 or PCV-13 as being vaccinated for pneumococcal vaccine, the effectiveness of either vaccine might have been diluted and resulted in the odds ratios moving towards the null value. On subgroup analysis the odds ratios were different and were trending lower when analysed using PSM with OR of 1.01 and OR of 1.00 for PPSV-23 and PCV-13 ,respectively compared to the OR of 1.7 and OR of 1.5 using exact characteristic matching when the outcome measure was a combined estimate of the two types of vaccines. We are currently not aware of any randomised controlled studies, which have been performed to assess the efficacy of PPSV-23 for non-bacteraemic VT CAP in this age group thus far, but PCV-13 has been validated in randomised controlled trials for this indication. This gives credence to the notion that dilution of effectiveness could have occurred in our current study.

Although we did not demonstrate protective effectiveness for pneumococcal vaccination in reducing hospitalisations for CAP in our study, we however noted that the odds of hospitalisation were lower in females compared to males. The OR in women was 1.29 compared to an OR of 3.00 in men. This finding is consistent with a study done by Wiemken et al.[54] who assessed whether sex had an influence on pneumococcal VE.They found that pneumococcal vaccine protected elderly patients from CAP and the effectiveness was driven by female sex. The OR for females was 0.32 compared to 0.66 in men. This study by Wiemken et al. was also a nested case-control study and suggested that sex is an effect modifier of the odds ratio.

In this present study, we have observed that the uptake for pneumococcal vaccination is critically low. In a study population of 34 068 participants, we only observed an uptake of less than one percent. The study period for our study was over a period of two years. The current South African guidelines for the prevention of CAP recommend that PCV-13 must be administered in all adults 65 years older followed by PPSV-23 after one year. We did not report any observations where participants had claimed both types of pneumococcal vaccines and therefore conclude that pneumococcal vaccine was only used once-off with the majority of participants (64.1%) claiming PPSV-23 and 36.0% claiming PCV-13. The study period would have accommodated for the use of both vaccines. Structural concerns with the medical scheme's benefit design and allocation of claim limits were interrogated to this effect. We established that benefits for PPSV-23 were available from a core benefit (100% of the scheme tariff or medicine price) for adults 55 years and older who had a chronic registration for COPD and asthma. For those who did not meet this requirement, PPSV-23 was available from day-to-day acute limits. PCV-13 is only funded from the day-to-day limits. In the current study, participants who had either COPD or asthma were in total 1 584 and therefore had access to a benefit to claim pneumococcal vaccine. Compliance with the guidelines of the vaccination schedule was not found to be the practice in our study population. We also considered the possibility that some beneficiaries who opted to self-finance for the vaccinations could have contributed to the low uptake.

Clinician recommendation of vaccination could have played a great role in vaccination proportions in our study. Our study was limited to adults 65 years and older who are inherently at high risk for infection in view of age. In addition to age, our study has shown that even in instances where participants had the presence of a combination of comorbidities as indicated in Table 1, vaccination uptake with pneumococcal vaccine was

still undesirably low as reported by 0.9% uptake from the study population. We could only deduce that participants who were vaccinated were thought to be at very high-risk of pneumococcal disease by their treating doctors.

This low vaccine uptake is consistent with estimates given by Blasi et al.[9] who have described some reasons postulated to be associated with it. Some include a perception of no effectiveness, patient refusal or simple lack of time. The low pneumococcal vaccine uptake observed in the present study could be consistent with findings from other studies, which found that some general practitioners attach low priority to pneumococcal vaccination, as they had not encountered severe pneumococcal disease in their daily practice. They recommended that a feasible way to raise awareness of pneumococcal vaccination was to give it concurrently with influenza vaccine when it is due to be given.[65-66] An older study in the United Kingdom had already observed as early as the year 2008 that there is an association between pneumococcal vaccine uptake and existence of vaccination policy in care homes.[73] Pneumococcal vaccination is now offered routinely in the United Kingdom.[74] We are not aware of a study in the South African context, which addresses reasons for the low vaccination uptake as observed in this study. It is also noteworthy that the South African guidelines were published in the Journal of Thoracic Diseases, an overseas journal that may not be widely read by South African general practitioners and non- pulmonologist specialists.

In the present study we also noted that the distribution of comorbidities as well as vaccinations for pneumococcus and influenza were lower in the cases compared to controls as shown in Tables 1 and 2. The matching for comorbidities between cases and controls could not be done according to severity of disease, as the medical scheme could not stratify the information provided to the primary investigator. We deduced that there is a likelihood that cases that were admitted might have had more severe comorbid disease than the controls for which we could not match.

In our study, due to no information regarding the serotypes of *S. pneumoniae* involved in the hospitalisations reported, some patients might have been infected with serotypes other than those included in the pneumococcal vaccines claimed. According to Von Gottberg et al.[67] the impact of PCV-13 on IPD since inception of PCV-13 from 2005-2016, they have noted that IPD rates declined from 10.8 to 5.9 per 100 000 population. In addition, non-

vaccine serotypes increased by 15%, from rates of 3.5 to 4.0 per 100 000 population. Increases were significant for non-vaccine serotypes 8,15A, 22F and 35B.

This was further examined in a recent study by Lo et al.[68] who investigated pneumococcal lineages behind the predominant non-vaccine serotypes, the mechanism of serotype replacement in disease, as well as the major pneumococcal lineages contributing to IPD in the post-vaccine era and their antibiotic resistant traits. They concluded that globally spreading lineages expressing invasive serotypes have an important role in serotype replacement, and that local antibiotic-selective pressures in different countries might explain emerging non-vaccine serotypes associated with different pneumococcal lineages. This study also noted that the invasive disease potential of serotypes is not the only determinant of disease replacement, and that serotypes with low invasive disease potential can still cause disease among individuals with comorbid conditions. In clinical practice, reporting for blood culture susceptibility when presenting with pneumonia, is generally non-representative and inadequate.[75] Apart from known serotypes of pneumococcus associated with IPD, it is equally essential to establish serotypes associated with all hospitalised cases of CAP and to monitor changes in terms of serotype replacement associated with severe disease caused by pneumococcus other than IPD, which result in hospitalisation.

Finally, our study may have been underpowered to detect the protective effectiveness, given the very low uptake of pneumococcal vaccine, especially among those hospitalised with pneumonia. As well as the fact that our study was designed to detect a protective effectiveness of 50% or greater.

5.2 Secondary exposure (influenza vaccine)

For our secondary exposure, we assessed the effectiveness of influenza vaccination in preventing hospital admissions due to pneumonia and found that the association between vaccination with influenza vaccine and hospital treated CAP is protective .This protective effect was not statistically significant and did not differ between sexes. However on sensitivity analyses when PSM was used, the use of influenza vaccine showed statistically significant protection in preventing hospital admissions due to pneumonia. The OR reflected with exact characteristic matching was 0.90 compared to 0.99 when PSM was used, the CI's were (0.683 – 1.178) and (0.983 – 0.994), respectively. The use of influenza

vaccination is an established public health intervention, which is currently recommended in high-risk groups by the NICD to prevent the severity of influenza infection. With improved influenza vaccine formulations better protection for severe disease is likely to be achieved.[76]

The present study found that the proportion vaccinated in our study population for influenza was 16.6%. and according to the NICD viral watch surveillance programme, the influenza season in our study period was reported as moderate.[77] Our findings in the South African context were similar to a nested case-control study done 11 years ago in a large medical database of elderly patients over the age of 65 from a cohort of 45 422 participants.[78] They reported an unadjusted OR of 1.01 with a 95% CI of (0.85 - 1.19) and an adjusted OR for combined end-points of OR of 0.81 with a 95% CI of (0.67 - 0.97). In their study, the rate of influenza vaccination was 15.4% .Compared to our study this is an endorsement that vaccine uptake has not increased at a high rate for this high-risk population. For this current study we reported a McNemar's OR of 0.90 with a CI (0.683 - 1.178) however with PSM our OR was 0.99 with a CI of (0.983 - 0.994). It is important to note that influenza vaccine uptake reported in this current study of 16.6% where influenza vaccine is currently recommended for routine use is in stark contrast to a recent study, which reported influenza vaccine uptake of 68% also in a setting where influenza vaccination is given routinely.[57] In another study, the uptake was as high as 74.6%.[79] This also highlights clear gaps in compliance to the recommendation of annual influenza vaccinations for high-risk groups in South Africa. Some notable enablers for influenza vaccine uptake on a micro-level were reported in a systematic review by Schmid et al.[80] as positive attitude towards influenza vaccines, high perceived utility of vaccination, cues to action and previous vaccinations with influenza. It is noted that Influenza vaccine access in our study population was not restricted by the medical aid scheme. According to the scheme rules, all beneficiaries of the scheme are entitled to 100% of the scheme tariff/medicine price for influenza vaccination annually. We are not aware of any studies, which have described the barriers to influenza vaccination in the South African context. It is important to understand these gaps in compliance in order to reduce missed opportunities presented by this low uptake.

CHAPTER 6: CONCLUSIONS

6.1 Strengths and limitations

Our study had a large control repository (n= 32 464) from where we could randomly select matching controls to the cases. We also had enough cases to randomly select an adequately powered sample of cases (n= 800) for each study outcome from the study population of 1 604 cases. There were also no missing data for any of the variables included in our study. However, we had a very low level of vaccine uptake which has diminished the power of our study. In addition, it is possible that those admitted with pneumonia had more severe levels of comorbidity than those not admitted.

The effectiveness estimates for our study were based on early effectiveness of the vaccines as our study period was for two years. As pneumococcal VE is known to wane over time, [31,53] the fact that our study focused on early vaccination outcomes is considered a strength. Our study setting was a population of medical aid beneficiaries from all the nine provinces of South Africa therefore, it was geographically and ethnically heterogeneous which strengthens the study's external validity.

In this study, we did not have the ability to adequately distinguish the types of pneumonia involved and therefore we were unable to correlate the type of pneumonia to the vaccine serotypes included in the claimed vaccines for our cases. This ambiguity of not knowing the disease-causing agent aptly reflects what occurs in real life practice and is a definite reflection of the severity of disease and not only about the effectiveness of vaccine in preventing infection.

Our study had several limitations. It was an observational study and therefore we could not adjust for residual bias due to inherent differences between those who were vaccinated and those who did not receive vaccination hence residual confounding could not be completely excluded. We tried to minimise the impact of this bias by randomly matching our cases to controls on important variables such as sex, age and selected important comorbidities. We however did not have information on the smoking status, which is one of the important predictors for CAP.[81]

ICD-10 coding in our study was used as a proxy to identify the diagnoses for the captured pneumonia admissions cases and as such may be subject to misclassification as this information was captured by hospital staff based on the admitting doctor's given ICD-10 code prior to submission of claims from the admitting hospitals to the scheme.

Finally, our observational study has evaluated the effect of a single vaccination with a single type of vaccine. Compliance with the guidelines of the vaccination schedule was not found to be the practice in our study population. It is important that practitioners and patients are made aware of the international and local guidelines so that the immunisation efforts would be more likely to show benefit for this use of medical scheme funds. The decrease in the healthcare burden such as severe complications and in-hospital mortality, longer hospital stays together with reduced economic burden are the most likely benefits for increased compliance and uptake in pneumococcal and influenza vaccines in the elderly for both the public and private sectors.

6.2 Conclusions

The characteristics for cases and controls indicated obvious similarities as they were matched according to the important covariates age, sex, influenza vaccination or pneumococcal vaccination (depending on the exposure variable), COPD, IHD, DM and asthma. For the primary exposure, the use of once-off pneumococcal vaccination with either PCV-13 or PPSV-23 did not confer any protectiveness in preventing hospital admissions for our target group. We also noted that the odds for hospitalisation due to pneumonia were lower in women than in men. For our secondary exposure, our study has shown that vaccination with influenza vaccine is protective in preventing hospital events due to pneumonia. This protective effect did not reflect a statistically significant result when we performed McNemar's OR with exact characteristic matching, however when our VE was adjusted by PSM the protectiveness of influenza vaccine showed statistically significant benefit in preventing hospital admissions due to pneumonia.

6.3 Recommendations

According to the findings from this present study, in order to maximise protection against hospital treated CAP the following recommendations are made:

- Pneumococcal vaccine should be administered sequentially with PCV-13 followed by PPSV-23 a year later for all adults who are 65 years and older as recommended in South Africa and by international agencies in order to reduce the burden of pneumococcal disease. Further studies are recommended to establish pneumococcal serotypes that are causing disease serious enough to warrant hospital admission for CAP in the current environment where IPD has been contained.
- Other vaccination strategies such as high valency conjugate vaccines and future protein based vaccines with serotype independent protection should also be investigated to reduce the burden of CAP.
- To significantly improve pneumococcal vaccine uptake and compliance to the vaccination regime recommended, publicity and financial support around pneumococcal vaccination must be greatly enhanced. From the private sector perspective, publicity in the form of vaccination campaigns involving service providers such as retail pharmacies and the usage of digital platforms such as short message service (sms) and email reminders when the influenza season approaches in order to drive up vaccine uptake and improve compliance.
- Influenza vaccine to be offered to all adults who are 65 years and older sufficiently early before the start of the annual influenza season in order to reduce the severity of CAP and to prevent hospital admissions.
- To significantly improve influenza vaccine uptake and compliance, publicity and financial support around influenza vaccination must be greatly enhanced.
- In order to improve compliance, simultaneous administration of pneumococcal and influenza vaccines to be given at the scheduled intervals.
- Further studies to investigate the low uptake of both pneumococcal and influenza vaccinations to improve understanding of the knowledge, attitudes and behaviours regarding the perception of these vaccines in the South African context.

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CHAPTER 8: APPENDICES

Appendix I Ethics approval letter

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

10 April 2019

Approval Certificate
New Application

Ethics Reference No.: 152/2019
Title: Effectiveness of pneumococcal vaccine in preventing hospital admissions for pneumonia among the elderly

Dear Ms MIK Rapetsoa

The **New Application** as supported by documents received between 2019-03-26 and 2019-04-10 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 2019-04-10.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year and needs to be renewed annually by 2020-04-10.
- Please remember to use your protocol number (152/2019) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed (Int) MPharmMed PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health)

Research Ethics Committee
Room 4-60, Level 4, Tswelopele Building
University of Pretoria, Private Bag X323
Arcadia 0007, South Africa
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Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

Appendix II Permission to collect secondary data

medihelp
medical scheme

	Your reference	Date
TO WHOM IT MAY CONCERN	Our reference	Date 2019-03-05
	Enquiries	Tel. No.
	HEYN VAN ROOYEN	012 334 2081

STUDENT/EMPLOYEE: MS MAROPENG RAPETSOA
STUDENT NUMBER: 17245372

This serves to confirm that the above mentioned, as an employee of Medihelp, has been granted permission to use secondary data sourced from the Scheme's database which includes claims and hospitalisation data to be used in research purposes for attaining her Masters degree.

She has been approved to access this data for investigating the effectiveness of Pnemococcal vaccine in the population aged 65 years and older for the years 2017/2018.

The following conditions are attached to this approval in agreement with the student/employee:

- The data that she will receive will not contain any member details or any detail that will jeopardise the confidentiality agreement with our members.
- Results of this research will be reported to the Scheme on completion of the study.

Yours faithfully

Heyn van Rooyen
Principal Officer

Customer Care: 086 0100 678 | www.medihelp.co.za
410 Steve Biko Road, Arcadia, Pretoria, 0083 | Medihelp is an authorised financial services provider (FSP No. 15738)

Appendix III Data collection sheet

Patient ID	Date of birth	Date of admission	Age at admission	sex	Influenza vaccine claimed	Influenza vaccine claim date	Pneumocccal vaccine claimed	Pneumococcal vaccine claim date	Admission for Pneumonia in the past 12 months	COPD	IHD	DM	Asthma
				Male=1 Female=0	Yes=1 No=0	Please only capture the first paid claim if there is more than 1 claim.	Yes=1 No=0		Yes=1 No=0	Yes=1 No=0	Yes=1 No=0	Yes=1 No=0	Yes=1 No=0

Validation ICD-10 codes to be used

1. Hospitalisation any time between 2017/01/01 and 2018/12/31 for the following Pneumonia ICD-10 codes:
   J12.0=ADENOVIRAL PNEUMONIA
   J12.1=RESPIRATORY SYNCYTIAL VIRUS PNEUMONIA
   J12.2=PARAINFLUENZA VIRUS PNEUMONIA
   J12.3=HUMAN METAPNEUMOVIRUS PNEUMONIA
   J12.8=OTHER VIRAL PNEUMONIA
   J12.9=VIRAL PNEUMONIA, UNSPECIFIED

J13=PNEUMONIA DUE TO STREPTOCOCCUS PNEUMONIAE
J14=PNEUMONIA DUE TO HAEMOPHILUS INFLUENZAE
J15=BACTERIAL PNEUMONIA, NOT ELSEWHERE CLASSIFIED
J15.0=PNEUMONIA DUE TO KLEBSIELLA PNEUMONIAE
J15.1=PNEUMONIA DUE TO PSEUDOMONAS
J15.2=PNEUMONIA DUE TO STAPHYLOCOCCUS
J15.3=PNEUMONIA DUE TO STREPTOCOCCUS, GROUP B
J15.4=PNEUMONIA DUE TO OTHER STREPTOCOCCI
J15.5=PNEUMONIA DUE TO ESCHERICHIA COLI
J15.6=PNEUMONIA DUE TO OTHER AEROBIC GRAM-NEGATIVE BACTERIA
J15.7=PNEUMONIA DUE TO MYCOPLASMA PNEUMONIAE
J15.8=OTHER BACTERIAL PNEUMONIA
J15.9=BACTERIAL PNEUMONIA, UNSPECIFIED
J16=PNEUMONIA DUE TO OTHER INFECTIOUS ORGANISMS, NOT ELSEWHERE CLASSIFIED
J16.0=CHLAMYDIAL PNEUMONIA
J16.8=PNEUMONIA DUE TO OTHER SPECIFIED INFECTIOUS ORGANISMS
J17=PNEUMONIA IN DISEASES CLASSIFIED ELSEWHERE
J17.0=PNEUMONIA IN BACTERIAL DISEASES CLASSIFIED ELSEWHERE
J17.1=PNEUMONIA IN VIRAL DISEASES CLASSIFIED ELSEWHERE
J17.2=PNEUMONIA IN MYCOSES
J17.3=PNEUMONIA IN PARASITIC DISEASES
J17.8=PNEUMONIA IN OTHER DISEASES CLASSIFIED ELSEWHERE
J18=PNEUMONIA, ORGANISM UNSPECIFIED
J18.0=BRONCHOPNEUMONIA, UNSPECIFIED
J18.1=LOBAR PNEUMONIA, UNSPECIFIED
J18.2=HYPOSTATIC PNEUMONIA, UNSPECIFIED
J18.8=OTHER PNEUMONIA, ORGANISM UNSPECIFIED
J18.9=PNEUMONIA, UNSPECIFIED

2. Pneumoccocal vaccine with the following NAPPI codes
   755826=PNEUMOVAX VACCINE
   836699=IMOVAX PNEUMO 23
   715858=PREVENAR 13 PRE-FILL SYRINGE 28MCG/0.5ML

   Influenza vaccine with the following NAPPI codes
   711737=FLUARIX PREFILL SYRINGE 0.5ML
   732826=INFLUVAC 0.5ML
   813338=VAXIGRIP SINGLE DOSE 0.5ML PRE-FILL
   702733=X-FLU PREFILLED 0.5ML SYRINGE

3. Diabetes registration for the following codes:
   E10.0=TYPE 1 DIABETES MELLITUS WITH COMA
   E10.1=TYPE 1 DIABETES MELLITUS WITH KETOACIDOSIS

E10.2=TYPE 1 DIABETES MELLITUS WITH RENAL COMPLICATIONS
E10.3=TYPE 1 DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
E10.4=TYPE 1 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
E10.5=TYPE 1 DIABETES MELLITUS WITH PERIPHERAL CIRCULATORY COMPLICATIONS
E10.6=TYPE 1 DIABETES MELLITUS WITH OTHER SPECIFIED COMPLICATIONS
E10.7=TYPE 1 DIABETES MELLITUS WITH MULTIPLE COMPLICATIONS
E10.8=TYPE 1 DIABETES MELLITUS WITH UNSPECIFIED COMPLICATIONS
E10.9=TYPE 1 DIABETES MELLITUS WITHOUT COMPLICATIONS
E11=TYPE 2 DIABETES MELLITUS
E11.0=TYPE 2 DIABETES MELLITUS WITH COMA
E11.1=TYPE 2 DIABETES MELLITUS WITH COMA
E11.2=TYPE 2 DIABETES MELLITUS WITH RENAL COMPLICATIONS
E11.3=TYPE 2 DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
E11.4=TYPE 2 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
E11.5=TYPE 2 DIABETES MELLITUS WITH PERIPHERAL CIRCULATORY
E11.6=TYPE 2 DIABETES MELLITUS WITH OTHER SPECIFIED COMPLICATIONS
E11.7=TYPE 2 DIABETES MELLITUS WITH MULTIPLE COMPLICATIONS
E11.8=TYPE 2 DIABETES MELLITUS WITH UNSPECIFIED COMPLICATIONS
E11.9=TYPE 2 DIABETES MELLITUS WITHOUT COMPLICATIONS
E13=OTHER SPECIFIED DIABETES MELLITUS
E13.0=OTHER SPECIFIED DIABETES MELLITUS WITH COMA
E13.1=OTHER SPECIFIED DIABETES MELLITUS WITH KETOACIDOSIS
E13.2=OTHER SPECIFIED DIABETES MELLITUS WITH RENAL COMPLICATIONS
E13.3=OTHER SPECIFIED DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
E13.4=OTHER SPECIFIED DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
E13.5=OTHER SPECIFIED DIABETES MELLITUS WITH PERIPHERAL CIRCULATORY COMPLICATIONS
E13.6=OTHER SPECIFIED DIABETES MELLITUS WITH OTHER SPECIFIED COMPLICATIONS
E13.7=OTHER SPECIFIED DIABETES MELLITUS WITH MULTIPLE COMPLICATIONS
E13.8=OTHER SPECIFIED DIABETES MELLITUS WITH UNSPECIFIED COMPLICATIONS
E13.9=OTHER SPECIFIED DIABETES MELLITUS WITHOUT COMPLICATIONS
O24.1=PRE-EXISTING TYPE 2 DIABETES MELLITUS
O24.2=PRE-EXISTING MALNUTRITION-RELATED DIABETES MELLITUS
O24.3=PRE-EXISTING DIABETES MELLITUS, UNSPECIFIED
O24.4=DIABETES MELLITUS ARISING IN PREGNANCY
O24.9=DIABETES MELLITUS IN PREGNANCY, UNSPECIFIED

4. COPD registration for the following codes:
   J43.0=MACLEOD'S SYNDROME
   J43.1=PANLOBULAR EMPHYSEMA
   J43.2=CENTRILOBULAR EMPHYSEMA
   J43.8=OTHER EMPHYSEMA
   J43.9=EMPHYSEMA, UNSPECIFIED
   J44=OTHER CHRONIC OBSTRUCTIVE PULMONARY DISEASE
   J44.0=CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ACUTE LOWER RESPIRATORY INFECTION
   J44.1=CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ACUTE EXACERBATION, UNSPECIFIED
   J44.8=OTHER SPECIFIED CHRONIC OBSTRUCTIVE PULMONARY DISEASE
   J44.9=CHRONIC OBSTRUCTIVE PULMONARY DISEASE, UNSPECIFIED

5. Asthma registration with the following codes:
   J45=ASTHMA
   J45.0=PREDOMINANTLY ALLERGIC ASTHMA
   J45.1=NONALLERGIC ASTHMA
   J45.8=MIXED ASTHMA
   J46=STATUS ASTHMATICUS

6. Ischaemic heart disease registration with the following codes:
   I20.0=UNSTABLE ANGINA
   I20.1=ANGINA PECTORIS WITH DOCUMENTED SPASM
   I20.8=OTHER FORMS OF ANGINA PECTORIS
   I20.9=ANGINA PECTORIS, UNSPECIFIED
   I25.0=ATHEROSCLEROTIC CARDIOVASCULAR DISEASE, SO DESCRIBED
   I25.1=ATHEROSCLEROTIC HEART DISEASE
   I25.2=OLD MYOCARDIAL INFARCTION
   I25.3=ANEURYSM OF HEART
   I25.4=CORONARY ARTERY ANEURYSM
   I25.5=CORONARY ARTERY ANEURYSM
   I25.6=SILENT MYOCARDIAL ISCHAEMIA
   I25.8=OTHER FORMS OF CHRONIC ISCHAEMIC HEART DISEASE
   I25.9=CHRONIC ISCHAEMIC HEART DISEASE, UNSPECIFIED

Data collection specification sheet for controls

Patient ID	Date of birth	Age at 20181231	sex	Influenza vaccine claim	Influenza vaccine claim date	Pneumococcal vaccine claim	Pneumococcal vaccine claim date	COPD	IHD	DM	Asthma
			Male =1 Female=0	Yes=1 No=0	Please only capture the first paid claim if there is more than 1.	Yes=1 No=0		Yes=1 No=0	Yes= 1 No=0	Yes= 1 No=0	Yes=1 No=0

Validation ICD-10 codes to be used

1. Exclude hospitalisation for any of these codes between 2017/01/01-2018/12/31:
   J12.0=ADENOVIRAL PNEUMONIA
   J12.1=RESPIRATORY SYNCYTIAL VIRUS PNEUMONIA
   J12.2=PARAINFLUENZA VIRUS PNEUMONIA
   J12.3=HUMAN METAPNEUMOVIRUS PNEUMONIA
   J12.8=OTHER VIRAL PNEUMONIA
   J12.9=VIRAL PNEUMONIA, UNSPECIFIED

J13=PNEUMONIA DUE TO STREPTOCOCCUS PNEUMONIAE
J14=PNEUMONIA DUE TO HAEMOPHILUS INFLUENZAE
J15=BACTERIAL PNEUMONIA, NOT ELSEWHERE CLASSIFIED
J15.0=PNEUMONIA DUE TO KLEBSIELLA PNEUMONIAE
J15.1=PNEUMONIA DUE TO PSEUDOMONAS
J15.2=PNEUMONIA DUE TO STAPHYLOCOCCUS
J15.3=PNEUMONIA DUE TO STREPTOCOCCUS, GROUP B
J15.4=PNEUMONIA DUE TO OTHER STREPTOCOCCI
J15.5=PNEUMONIA DUE TO ESCHERICHIA COLI
J15.6=PNEUMONIA DUE TO OTHER AEROBIC GRAM-NEGATIVE BACTERIA
J15.7=PNEUMONIA DUE TO MYCOPLASMA PNEUMONIAE
J15.8=OTHER BACTERIAL PNEUMONIA
J15.9=BACTERIAL PNEUMONIA, UNSPECIFIED
J16=PNEUMONIA DUE TO OTHER INFECTIOUS ORGANISMS, NOT ELSEWHERE CLASSIFIED
J16.0=CHLAMYDIAL PNEUMONIA
J16.8=PNEUMONIA DUE TO OTHER SPECIFIED INFECTIOUS ORGANISMS
J17=PNEUMONIA IN DISEASES CLASSIFIED ELSEWHERE
J17.0=PNEUMONIA IN BACTERIAL DISEASES CLASSIFIED ELSEWHERE
J17.1=PNEUMONIA IN VIRAL DISEASES CLASSIFIED ELSEWHERE
J17.2=PNEUMONIA IN MYCOSES
J17.3=PNEUMONIA IN PARASITIC DISEASES
J17.8=PNEUMONIA IN OTHER DISEASES CLASSIFIED ELSEWHERE
J18=PNEUMONIA, ORGANISM UNSPECIFIED
J18.0=BRONCHOPNEUMONIA, UNSPECIFIED
J18.1=LOBAR PNEUMONIA, UNSPECIFIED
J18.2=HYPOSTATIC PNEUMONIA, UNSPECIFIED
J18.8=OTHER PNEUMONIA, ORGANISM UNSPECIFIED
J18.9=PNEUMONIA, UNSPECIFIED

2. Pneumoccocal vaccine claims validated with the following NAPPI codes
   755826=PNEUMOVAX VACCINE
   836699=IMOVAX PNEUMO 23
   715858=PREVENAR 13 PRE-FILL SYRINGE 28MCG/0.5ML

   Influenza vaccine claims validated with the following NAPPI codes
   711737=FLUARIX PREFILL SYRINGE 0.5ML
   732826=INFLUVAC 0.5ML
   813338=VAXIGRIP SINGLE DOSE 0.5ML PRE-FILL
   702733=X-FLU PREFILLED 0.5ML SYRINGE

3. Diabetes registration for the following codes:
   E10.0=TYPE 1 DIABETES MELLITUS WITH COMA
   E10.1=TYPE 1 DIABETES MELLITUS WITH KETOACIDOSIS
   E10.2=TYPE 1 DIABETES MELLITUS WITH RENAL COMPLICATIONS
   E10.3=TYPE 1 DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
   E10.4=TYPE 1 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
   E10.5=TYPE 1 DIABETES MELLITUS WITH PERIPHERAL CIRCULATORY COMPLICATIONS
   E10.6=TYPE 1 DIABETES MELLITUS WITH OTHER SPECIFIED COMPLICATIONS
   E10.7=TYPE 1 DIABETES MELLITUS WITH MULTIPLE COMPLICATIONS
   E10.8=TYPE 1 DIABETES MELLITUS WITH UNSPECIFIED COMPLICATIONS
   E10.9=TYPE 1 DIABETES MELLITUS WITHOUT COMPLICATIONS
   E11=TYPE 2 DIABETES MELLITUS
   E11.0=TYPE 2 DIABETES MELLITUS WITH COMA
   E11.1=TYPE 2 DIABETES MELLITUS WITH COMA
   E11.2=TYPE 2 DIABETES MELLITUS WITH RENAL COMPLICATIONS
   E11.3=TYPE 2 DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
   E11.4=TYPE 2 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
   E11.5=TYPE 2 DIABETES MELLITUS WITH PERIPHERAL CIRCULATORY
   E11.6=TYPE 2 DIABETES MELLITUS WITH OTHER SPECIFIED COMPLICATIONS
   E11.7=TYPE 2 DIABETES MELLITUS WITH MULTIPLE COMPLICATIONS
   E11.8=TYPE 2 DIABETES MELLITUS WITH UNSPECIFIED COMPLICATIONS
   E11.9=TYPE 2 DIABETES MELLITUS WITHOUT COMPLICATIONS
   E13=OTHER SPECIFIED DIABETES MELLITUS
   E13.0=OTHER SPECIFIED DIABETES MELLITUS WITH COMA
   E13.1=OTHER SPECIFIED DIABETES MELLITUS WITH KETOACIDOSIS
   E13.2=OTHER SPECIFIED DIABETES MELLITUS WITH RENAL COMPLICATIONS
   E13.3=OTHER SPECIFIED DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
   E13.4=OTHER SPECIFIED DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
   E13.5=OTHER SPECIFIED DIABETES MELLITUS WITH PERIPHERAL CIRCULATORY COMPLICATIONS
   E13.6=OTHER SPECIFIED DIABETES MELLITUS WITH OTHER SPECIFIED COMPLICATIONS
   E13.7=OTHER SPECIFIED DIABETES MELLITUS WITH MULTIPLE COMPLICATIONS
   E13.8=OTHER SPECIFIED DIABETES MELLITUS WITH UNSPECIFIED COMPLICATIONS
   E13.9=OTHER SPECIFIED DIABETES MELLITUS WITHOUT COMPLICATIONS
   O24.1=PRE-EXISTING TYPE 2 DIABETES MELLITUS
   O24.2=PRE-EXISTING MALNUTRITION-RELATED DIABETES MELLITUS
   O24.3=PRE-EXISTING DIABETES MELLITUS, UNSPECIFIED

O24.4=DIABETES MELLITUS ARISING IN PREGNANCY
O24.9=DIABETES MELLITUS IN PREGNANCY, UNSPECIFIED

4. COPD registration for the following codes:
   J43.0=MACLEOD'S SYNDROME
   J43.1=PANLOBULAR EMPHYSEMA
   J43.2=CENTRILOBULAR EMPHYSEMA
   J43.8=OTHER EMPHYSEMA
   J43.9=EMPHYSEMA, UNSPECIFIED
   J44=OTHER CHRONIC OBSTRUCTIVE PULMONARY DISEASE
   J44.0=CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ACUTE LOWER RESPIRATORY INFECTION
   J44.1=CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ACUTE EXACERBATION, UNSPECIFIED
   J44.8=OTHER SPECIFIED CHRONIC OBSTRUCTIVE PULMONARY DISEASE
   J44.9=CHRONIC OBSTRUCTIVE PULMONARY DISEASE, UNSPECIFIED

5. Asthma registration with the following codes:
   J45=ASTHMA
   J45.0=PREDOMINANTLY ALLERGIC ASTHMA
   J45.1=NONALLERGIC ASTHMA
   J45.8=MIXED ASTHMA
   J46=STATUS ASTHMATICUS

6. Ischaemic heart disease registration with the following codes:
   I20.0=UNSTABLE ANGINA
   I20.1=ANGINA PECTORIS WITH DOCUMENTED SPASM
   I20.8=OTHER FORMS OF ANGINA PECTORIS
   I20.9=ANGINA PECTORIS, UNSPECIFIED
   I25.0=ATHEROSCLEROTIC CARDIOVASCULAR DISEASE, SO DESCRIBED
   I25.1=ATHEROSCLEROTIC HEART DISEASE
   I25.2=OLD MYOCARDIAL INFARCTION
   I25.3=ANEURYSM OF HEART
   I25.4=CORONARY ARTERY ANEURYSM
   I25.5=CORONARY ARTERY ANEURYSM
   I25.6=SILENT MYOCARDIAL ISCHAEMIA
   I25.8=OTHER FORMS OF CHRONIC ISCHAEMIC HEART DISEASE
   I25.9=CHRONIC ISCHAEMIC HEART DISEASE, UNSPECIFIED