Effectiveness of influenza and pneumococcal vaccination against hospitalisation for community-acquired pneumonia among persons $\geq 65$ years

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Submitted in total fulfilment of the requirements of the degree of Doctor of Philosophy

July 2007

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The University of Melbourne

Produced on archival quality paper
Abstract

Background

Although there are well-documented benefits from influenza vaccine and 23-valent pneumococcal polysaccharide vaccine (23vPPV) against invasive pneumococcal disease and laboratory confirmed influenza, their effectiveness against pneumonia remains controversial for community-based persons aged ≥65years. At the time of this research, within Australia, only the government of Victoria publicly funded these vaccines for elderly persons. With continued growth of the elderly population, the subsequent adoption of an Australia-wide program, and increasing uptake of similar programs in other countries, there is a need for data clarifying the impact of vaccination on pneumonia. This research estimates incremental vaccine effectiveness of 23vPPV over and above influenza vaccine against hospitalisation with community-acquired pneumonia (CAP) in the elderly.

The use of standardised ICD codes to retrospectively identify hospitalised cases of pneumonia is appealing to researchers because of time efficiencies compared with reviewing hospital records for clinical, radiological or laboratory evidence consistent with pneumonia, and in practice, few alternatives are available given the lack of an ideal diagnostic test or internationally agreed definition for pneumonia based on clinical symptoms and signs. Despite the widespread use of codes to identify hospitalised pneumonia cases, at the time of this research only two small studies (<150 subjects) from North America had examined the validity of this approach for all-cause pneumonia using ICD-9 codes (an earlier version of the codes). In order to examine the validity of using ICD-10-AM (Australian modification) codes to define the major outcome for measuring vaccine effectiveness for this research, and to contribute to a paucity of data internationally, an analysis of validity was undertaken.

Three further areas were examined for which there are currently very limited data. To assess program implementation and better inform approaches to program evaluation, missed opportunities for vaccination were assessed, and the validity of self-reported vaccination status as a measure of true status was examined. While self-reported vaccination status is frequently used in public health program evaluation, as well as in clinical research and clinical practice as a marker of true vaccination status, no large study had previously examined the validity of this practice in any setting or attempted to control estimates for potential confounders. Finally, to better inform management and prevention strategies, this study provides the most comprehensive data set to date examining the epidemiology of CAP for the elderly Australian population, and the first to evaluate underlying risk factors in this setting.
Methods

A case-cohort design was chosen as the best to answer the study question given widespread use of both vaccines and inability to conduct a randomised controlled trial. Patients aged ≥65 years discharged from April 2000 – March 2002 were selected from two large tertiary Australian hospitals. Cases had ICD-10-AM codes J10-J18 (encompassing pneumonia). Community-acquired pneumonia was restricted to those cases diagnosed before or within 48 hours of admission to hospital. The cohort sample was randomly selected from all discharged elderly persons, frequency matched to cases by month. Vaccination status was confirmed from provider records of vaccination dates. ICD-10 codes were validated against three comparators: medical record notation of pneumonia, chest radiograph (CXR) report and both. Provider-subject encounters were determined by hospital record review of admissions and self-report of doctor visits. Self-reported vaccination status was compared with provider records. Epidemiologic data were obtained by hospital record review. Logistic regression models adjusting for design factors and potential confounders were used to estimate risk ratios (RR) for determining vaccine effectiveness (VE) (VE=1-RR) and factors predicting hospitalisation with CAP or associated mortality.

Results

A total of 4772 patients were studied: 1952 cases and 2927 randomly selected cohort subjects (including 107 cases). Of 4039 (85%) subjects with provider-confirmed vaccination status, 71% had received influenza vaccine in the year prior to admission and 53% had received 23vPPV. Benefit against hospitalisation with CAP was not demonstrated in multivariate analysis for influenza vaccine compared with neither vaccine (RR 1.02, 95%CI 0.84-1.20) or for both vaccines compared with influenza vaccine (RR 0.98, 95%CI 0.81-1.18). Influenza vaccination was associated with a moderate reduction in CAP-related mortality (RR 0.72, 95%CI 0.51-1.01) and all-cause mortality (RR 0.77, 95%CI 0.58-1.03), although this just failed to reach statistical significance.

Using medical record notation of pneumonia as the comparator, this study was able to exclude estimates for sensitivity, specificity, PPV and NPV of ICD codes for pneumonia of less than 95%.

For subjects unvaccinated with influenza vaccine, 1110/1115 (99.6%) had visited either a doctor (99.4%, mean 11.2 visits) or the same hospital (52.0%, mean 1.5 visits). For those unvaccinated with 23vPPV (past five years), 1809/1813 (99.8%) had visited either a doctor (99.7%, mean 11.2 visits) or the same hospital (51.5%, mean 1.5 times) in the past year; 71% had been admitted to the same hospital in the past 5 years (mean 3.4 times). Two percent of all subjects had vaccination status recorded. No unvaccinated subject was vaccinated during their hospital admission, despite approximately 40% reporting acceptability of vaccination if offered.

Self-reported influenza vaccination status (previous year) had high sensitivity (98%), positive predictive value (PPV) (88%) and negative predictive value (NPV) (91%), but low specificity (56%)
compared with true vaccination status. Self-reported vaccination status for 23vPPV (previous 5 years) had a sensitivity of 84%, specificity of 77%, PPV of 85% and NPV of 76%.

1952 admissions with CAP represented 4% of all elderly admissions for the two hospitals. Mean length of stay was 9.0 days, intensive care admission occurred in 14% and 18% died within 30 days. Excluding CXR, 520/1864 (28%) had no investigations performed and 1755/1823 (96%) received antibiotics. The most frequently occurring symptoms or signs for 1863 subjects with notation of pneumonia were crackles (92%), dyspnoea (78%) and cough (74%). The strongest predictors of CAP were history of other respiratory disease (RR 2.42; 95%CI 2.10-2.77), previous pneumonia (RR 2.30; 95%CI 1.83-2.89) and aspiration (RR 2.19; 95%CI 1.20-3.99). ICU admission (RR 2.68; 95%CI 1.90-3.76), renal disease (RR 1.78; 95%CI 1.24-2.56) and increasing age (RR 3.05 in those ≥85 years) were the strongest predictors of mortality, while those vaccinated with influenza vaccine were protected (RR 0.55; 95%CI 0.40-0.76).

Conclusions

This thesis confirms that hospitalisation with CAP in the elderly is common, frequently fatal and a considerable burden to the Australian community. It did not find benefit from influenza vaccine or 23vPPV against hospitalisation with CAP in elderly inpatients. Current recommendations to vaccinate the elderly with influenza vaccine and 23vPPV should reduce emphasis on prevention of pneumonia, and sensitivity analyses for economic evaluations of these vaccines should include a benefit against pneumonia of zero. However, the current vaccination program should continue to be promoted based on existing evidence for prevention of other outcomes such as invasive pneumococcal disease and laboratory confirmed influenza, which have a high morbidity and mortality. Assessment of program implementation currently relies heavily on self-reported vaccination status, and this was found to be reasonably accurate as a measure of true vaccination status. However, self-report remains imperfect and a whole-of-life immunisation register would assist both vaccination program evaluation and implementation. Program implementation remains suboptimal as indicated by vaccination coverage levels. In particular, despite recommendations for vaccination being in place for some time, this research indicates that documentation of vaccination status and opportunistic vaccination for inpatients is negligible. Barriers to vaccination in the hospital setting require formal study in Australia. Finally, this thesis also confirms for researchers the validity of using ICD-10 codes to retrospectively identify cases of hospitalised CAP when compared with clinical notation of pneumonia, and their superiority to use of complexes of symptoms and signs, or radiology reports.
Declaration

This is to certify that

(i) the thesis comprises only my original work towards the PhD except where indicated in the
Preface,
(ii) due acknowledgement has been made in the text to all other material used,
(iii) the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and
appendices.
Preface

This thesis represents original work resulting from a case-cohort study on which I was the sole chief investigator. My contribution and that of my collaborators is outlined below:

As chief investigator of the study, I was responsible for

- substantial input to study conception and design
- writing the ethics and grant submissions, and all ongoing administrative matters related to these agencies
- staff recruitment, employment, administration, training and monitoring on a daily basis (research assistants, data entry persons)
- development of data collection forms
- review of all radiology reports for consensus interpretation
- monitoring of study progress on a daily basis
- chairing of the collaborator group meetings throughout the study period
- all statistical analyses including analysis planning and conduct, and interpretation of data presented in this report
- all writing in this report and subsequent preparation of manuscripts

My collaborators undertook the following roles:

- Ross Andrews had input to study conception and design. He designed the study database and contributed to monitoring study progress including data entry (approximately fortnightly).
- Don Campbell had input to study conception and design, monitoring of study progress (approximately monthly), assisted with staff administration and co-reviewed all radiology reports for consensus.
- Graham Byrnes had input particularly to statistical aspects of study design, conducted all random sampling, provided advice on statistical methods and analysis and subsequently acted as a PhD supervisor.
• Heath Kelly had input to study conception and design and reviewed data collection forms and submissions. He developed the microbiology data collection protocol and assisted with monitoring study progress (approximately monthly).

• Terry Nolan and Graham Brown reviewed final grant submissions. They subsequently became PhD supervisors.

Ross Andrews used a subset of data from this study as one of three data sources describing coverage for 23vPPV (but not influenza vaccine coverage) in a PhD thesis (one of six chapters). I have re-analysed all data in Chapter 5 and presented vaccination coverage data for both influenza vaccine and 23vPPV, to determine the primary outcome of vaccine effectiveness.

A small amount of material appearing in Chapter 5 related to cohort selection methods is adapted from a vaccination coverage paper co-written with Ross Andrews.

I originally commenced an M.D. based upon this project in 2002 (approval of candidature granted 11 Jan 02, University of Melbourne). Data collection was completed in March 2002. I converted to a Ph.D. in a part-time capacity on 1 Sep 2003.
Acknowledgments

I would like to thank my supervisors, Prof Terry Nolan (School of Population Health), Prof Graham Brown (Department of Medicine) and Dr Graham Byrnes (School of Population Health), for their insights and encouragement throughout the writing of this thesis.

I completed much of this thesis while based at the Clinical Epidemiology and Biostatistics Unit (CEBU) of the Royal Children’s Hospital. Staff from CEBU made coming to work enjoyable, and a number require special mention for their support. In particular, Prof John Carlin helped to protect my time and was always willing to provide suggestions and guidance; Ms Donna De Sair located many articles related to the background reading for this thesis, and Dr Obioha Ukoumunne enthusiastically advised on some Stata programming matters.

This study would not have been possible without those involved right from the conception phase: Assoc Prof Ross Andrews, Prof Donald Campbell and Assoc Prof Heath Kelly provided invaluable input through to project completion.

For fastidious data collection, patience and endless good cheer, I would like to thank Anne-Marie Woods, Carol Roberts, Joy Turner, and Caroline Watts who were excellent research assistants, very popular with the study participants and managed to make a lengthy and large-scale project enjoyable.

I am also grateful to data entry persons Thao Nguyen and Jason Zhu who did a scrupulous job entering and checking the study data, and to the Directors of Health Information Services at each hospital: Ms Lisette Bicknell and Ms Sarah Russell, who assisted with questions related to ICD coding and study subject selection.

The elderly participants of this study also deserve special acknowledgment for their willingness to contribute, as do the many general practitioners and practice managers who gave up their time to help make this project successful.

The study would not have been possible were it not for generous funding from the Department of Human Services Victoria and the National Health and Medical Research Council.

I would also like to thank Dr Siranda Torvaldsen for reading the thesis and providing helpful comments.

Finally, my husband Jonathan Carapetis deserves special thanks for his unwavering support throughout the undertaking of this doctorate, as do our children Evelyn and Stella who happily arrived during it and were so patient about letting me finish. They made it all so much more fun and provided a welcome perspective about the important things in life.
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<tr>
<td>23vPPV</td>
<td>23-valent pneumococcal polysaccharide vaccine</td>
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<td>ACIR</td>
<td>Australian Childhood Immunisation Register</td>
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<td>CAP</td>
<td>Community-acquired pneumonia</td>
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<td>CT</td>
<td>Computerised tomography</td>
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<td>CXR</td>
<td>Chest radiograph</td>
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<td>ICD-10-AM</td>
<td>International Statistical Classification of Diseases and Health Related Problems, 10th Revision, Australian Modification</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>ILI</td>
<td>Influenza-like illness</td>
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<td>IPD</td>
<td>Invasive pneumococcal disease</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
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<td>VE</td>
<td>Vaccine effectiveness</td>
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Thesis organisation and scope

The primary objective of this thesis was to estimate vaccine effectiveness for 23vPPV over and above influenza vaccine in terms of reducing hospitalisation with community-acquired pneumonia in older Victorians. Although use of ICD codes was the most practical and widely used method for ascertaining hospitalised cases of CAP by researchers at the time of this research, a review of the literature found that few studies had examined its validity. Since this approach was also used to underpin estimates for vaccine effectiveness for this thesis, it was important to examine its validity. In addition, as the largest study of CAP among elderly persons in Australia to date, this research provided the opportunity to contribute to very limited Australian data and inform future management and preventive strategies, by describing the epidemiology of CAP, including burden of disease, outcomes and risk factors. Furthermore, as the program to vaccinate elderly persons with influenza vaccine and 23vPPV was unique to Victoria at the time of undertaking the thesis, and few data existed evaluating its implementation, this thesis was also able to provide the most comprehensive data thus far on vaccination coverage and opportunistic vaccination by vaccine providers. In addition, since the validity of self-reported vaccination status as a marker of true vaccination status is important to both those evaluating vaccination programs and clinicians vaccinating individuals who frequently rely on self-report, this thesis was able to contribute the largest data set examining this question for the hospitalised elderly, the first from Australia, and the first to examine the impact of potential confounders on estimates for validity.

Chapter 1 describes the thesis objectives, detailed background information relevant to these based on existing published literature, and a summary of the thesis rationale. Where applicable, literature available at the time of undertaking the thesis is distinguished from that published subsequently. While focussing predominantly on presenting the evidence underpinning the rationale for undertaking the primary objective of estimating vaccine effectiveness and the key outcome chosen, this chapter also presents some background information related to secondary objectives that is further enhanced in the subsequent relevant chapters. A letter to the editor published in *Clinical Infectious Diseases* arose as a result of reviewing studies of vaccine effectiveness for 23vPPV.

Chapter 2 describes the methods and rationale for the case-cohort study upon which all subsequent chapters are based. As for chapter 1, the focus in on the primary objective, and additional information on methods is reported in the methods sections of individual subsequent chapters.

Chapter 3 presents a review of existing literature on the epidemiology of CAP and relevant data for the study population. In particular, it describes seasonality, burden of disease, outcomes and risk factors for CAP. The general overview of disease epidemiology is presented since this thesis crosses a number of disciplines including epidemiology, public health and clinical practice, and it was considered important to understand the relevance of CAP as a key outcome in this thesis. However, as the epidemiology of CAP is a secondary objective, the literature review comparing the results for
the study population with previous studies is not exhaustive. It is based primarily on recent summaries and key studies of CAP in elderly populations in addition to all known Australian studies. A manuscript summarising these data, from what is the largest and most comprehensive study of CAP in elderly Australians to date, has been submitted to the *International Journal of Epidemiology*.

Chapter 4 describes why ICD codes are frequently used as a tool by researchers to identify cases of pneumonia among hospitalised patients, and reviews available literature regarding the validity of using this approach. It explains why three comparators were developed in the absence of a reference standard for pneumonia, in order to examine the validity of using ICD-10 codes for retrospective ascertainment of pneumonia for the study population. Examination of validity was important since this approach is used to determine the primary objective of measuring vaccine effectiveness in this thesis. This is the largest study to date and the first from Australia to address this question and adds to a very limited international knowledge base. Results are substantially covered in a manuscript published in *Epidemiology in Infection*.

Chapter 5 addresses the primary objective of the thesis: to determine vaccine effectiveness of influenza vaccine and 23vPPV against hospitalisation with community-acquired pneumonia among persons aged ≥65 years. A brief overview of the background and methods presented in chapters 1 and 2 is included to provide immediate context. As the main outcome chapter of this thesis, results and their implications are discussed in some detail, as well as limitations and strengths of the study design and the potential for impact on study estimates. A manuscript arising from this work has been published in *Vaccine*. In addition, a manuscript on vaccination coverage has been published in *Communicable Diseases Intelligence*.

Chapter 6 discusses the limited available scientific literature on the validity of self-reported vaccination status for 23vPPV and influenza vaccine as an indicator of true vaccination status. At the time of commencing this thesis, only one small, non-Australian study had been published on this question, with five subsequent small studies published, all from outside Australia. This chapter presents estimates for sensitivity, specificity, positive and negative predictive values and kappa statistics for self report compared with the gold standard of dates recorded by vaccine providers (used in the assessment of VE). Adjustments for some potential confounders are made for the first time. Implications for vaccine providers and program evaluation are discussed. This work has been published in *Vaccine*. Using results from chapter 5 and 6 as a working example for the elderly population, an Editorial has also been written for the *Medical Journal of Australia* outlining the need for Australia to have a whole of life immunisation register.

Chapter 7 provides some of the first Australian data on missed opportunities for vaccination with influenza vaccine and 23vPPV among elderly inpatients, risk factors for being unvaccinated, the rate of recording inpatient vaccination status, and acceptability of vaccination with these vaccines among unvaccinated inpatients. It is the largest study to date in any setting to quantify missed opportunities for vaccination with 23vPPV and influenza vaccine among hospitalised elderly patients. Strategies
and challenges for improving vaccination coverage are discussed. This work has also been published in *Vaccine*.

Chapter 8 contains the concluding discussion for key outcomes of the thesis including limitations of study design, and a summary of implications for public health policy and research.

**Limitations**

Limitations of study design and results in this thesis are discussed in detail in individual chapters and summarised in chapter 8 according to each key outcome.
Publications related to this thesis

Peer-reviewed papers (journal impact factors provided where available, edition 2006)


Abstracts

Chapter 1 Objectives and Background

1.1 Overview

This chapter describes the objectives of the thesis and discusses existing literature underpinning the rationale for undertaking these objectives. In particular, it examines why it was important to undertake a study of VE for influenza vaccine and 23vPPV in the elderly, and why pneumonia was chosen as the principal outcome measure.

Throughout this thesis, “VE” is used to refer to vaccine effectiveness, as determined by a non-experimental design under field conditions. This differs from vaccine efficacy, which is the percentage reduction in disease incidence for vaccinated versus unvaccinated groups, as determined under “ideal” or experimental conditions, such as for a double-blind, randomised controlled trial (see also 1.4).

1.2 Thesis Objectives

1.2.1 Condensed background

Although influenza and 23vPPV vaccines have been shown to reduce laboratory-confirmed influenza and invasive disease due to Streptococcus pneumoniae (S.pneumoniae or pneumococcus) in persons aged ≥65 years,2-4 there is uncertainty regarding their effectiveness against pneumonia for elderly persons living in the community. During the period of this research, no southern hemisphere data were available for the effectiveness for either vaccine for any outcome. Victoria was the only Australian jurisdiction and one of very few worldwide to publicly fund both 23vPPV and influenza vaccine for persons aged ≥65 years. The aim of this program is to reduce pneumonia and other sequelae in the elderly due to Streptococcus pneumoniae and influenza viruses.5 The unique environment of relatively high vaccine coverage in Victoria provided an opportunity to estimate VE with implications for the ongoing support of the Victorian and more recently national program, and potentially, similar programs under consideration in other countries. It also provided an opportunity to assess program implementation in terms of vaccination coverage and rates of opportunistic vaccination for elderly inpatients.
1.2.2 Primary objective

To estimate benefit from 23vPPV over and above influenza vaccine in reducing hospitalisations for CAP in older Victorians.

1.2.3 Secondary objectives

To address specific questions related to CAP and vaccination program assessment for which currently available data are limited, by assessing for elderly Victorians inpatients:

a) The epidemiology of CAP, including burden of disease, outcomes and risk factors. This information is useful to direct management, target vaccination strategies and estimate program impact and will add to very limited Australian data.

b) The validity of using ICD-10-AM codes (International Statistical Classification of Diseases and Health Related Problems, 10th Revision, Australian Modification) as a tool for retrospectively identifying CAP. This will provide some of the first data in this field internationally using the largest dataset to date.

c) Vaccine coverage with 23vPPV and influenza vaccine following the introduction of a publicly funded program. The study will provide the most comprehensive data thus far informing the evaluation of the Victorian or national programs.

d) The validity of self-reported vaccination status for 23vPPV and influenza vaccines as an indicator of true vaccination status. This will be the largest dataset to date examining these outcomes, add to a limited international knowledge base and directly inform the evaluation process for current Australian vaccination programs.

e) Opportunistic vaccination rates for 23vPPV and influenza vaccine, and inform strategies for improvement through knowledge of missed opportunities and risk factors for non-vaccination. This will be the largest study to date to quantify missed opportunities for vaccination with 23vPPV and influenza vaccine among hospitalised elderly patients with and without pneumonia and contribute to limited Australian and international data.

1.3 *Streptococcus pneumoniae* and Influenza virus: burden of disease in the elderly

The bacterium *S. pneumoniae* causes substantial morbidity and mortality worldwide, particularly in the elderly in developed settings, and in children in developing settings. It is the single most common cause of CAP in adults, being responsible for approximately 25-50% of all pneumonia hospitalisations. Jokinen et al have estimated an annual incidence of *S. pneumoniae* pneumonia of
Chapter 1: Background

8/1000 for residents of Eastern Finland aged ≥60 years compared with 3.3/1000 for all residents aged ≥15 years.\textsuperscript{13} Pneumonia may or may not be associated with identification of \textit{S.pneumoniae} in the blood stream (septicaemia or bacteraemia). Studies using serological methods plus blood and sputum culture have identified \textit{S.pneumoniae} as the aetiological agent in 32-55% of CAP\textsuperscript{13-16} compared with lower aetiological fractions for studies using less rigorous diagnostic approaches.\textsuperscript{17} A recent study from New Zealand found 39% of hospitalised CAP is attributable to \textit{S.pneumoniae}.\textsuperscript{18} Australasian mortality rates for patients admitted to hospital with CAP are approximately 8-10%.\textsuperscript{18,19} In the United States of America (USA), CAP is responsible for 350 000\textsuperscript{20} to 620 000\textsuperscript{21} hospitalisations each year among persons aged ≥65 years, amongst whom the category of pneumonia and influenza is the fifth leading cause of death.\textsuperscript{22,23}

In addition, \textit{S.pneumoniae} causes a range of generally severe “invasive” pneumococcal diseases (IPD) defined by isolation of \textit{S.pneumoniae} from a normally sterile site such as blood (including in association with pneumonia in some cases) or cerebrospinal fluid.\textsuperscript{24} In developed country settings, case fatality rates for IPD among the elderly are estimated at 15-51%.\textsuperscript{8,24,25} In Australia, IPD rates have been shown to increase steadily above age 60, with rates as high as 100/100,000 population per year in those aged 85 years or more in New South Wales\textsuperscript{26} and higher in jurisdictions such as Central Australia for both indigenous and non-indigenous Australians aged ≥65 years.\textsuperscript{27,28} Most recent data from the National Notifiable Diseases Surveillance System in Australia indicate rates of IPD of 53.9/100,000 for persons aged ≥85 years.\textsuperscript{29} In Victoria, the annual incidence of pneumococcal pneumonia calculated from hospital separation data for those aged ≥65 years, is estimated at approximately 100 per 100 000 using the Victorian Inpatient Minimum Dataset.\textsuperscript{30}

Influenza viruses cause major annual epidemics of respiratory disease including pneumonia.\textsuperscript{31} It is estimated that approximately 10-15% of the world’s population contract influenza each year,\textsuperscript{32} and during major epidemics, the attack rate may be as high as 50%.\textsuperscript{33} The elderly carry a greater burden of disease, both in terms of incidence and severity.\textsuperscript{31,34,35} Few Australian data are available on the burden of influenza disease for persons aged ≥65 years. Recently, estimates for this population using multiple data sources for the population suggest an annual attack rate of approximately 4%, with hospitalisation rates for influenza and excess pneumonia of 392 per 100 000 persons per year, and mortality rates of 32/100 000.\textsuperscript{36} Excess pneumonia hospitalisations were calculated as the difference between all pneumonia hospitalisations in the months when influenza was circulating, and pneumonia admissions in other months. Given that other viruses responsible for influenza-like illness (ILI) such as respiratory syncytial virus, rhinovirus, enterovirus, coronavirus, adenovirus or parainfluenza virus may also have been circulating during the influenza season, this approach could overestimate disease due to influenza. Using only ICD-10-AM hospital admission codes J10 and J11 (influenza with pneumonia, with and without influenza virus identified) for the two year period July 1998-June 2000 (likely to provide a more conservative estimate for disease due to influenza disease), the National Centre for Immunisation Research and Surveillance most recently estimated
average annual age-specific rates for influenza in Australia. Persons aged 60 years or more comprised 29% of 8590 admissions; a rate of 45/100 000. The median length of stay for this age group (6 days) was twice that for all age groups. For the years 1998-2000 inclusive, of 258 deaths recorded as influenza on death certificates in Australia, 86% occurred in persons aged 60 years or more; a rate of 2.4/100 000 per annum.

1.4 Role of vaccines in disease prevention

Morbidity and mortality from influenza and *Streptococcus pneumoniae* are potentially at least partially preventable through vaccination. Ninety serotypes of *Streptococcus pneumoniae* have been identified on the basis of antigenic differences in their capsular polysaccharides. 23vPPV (containing 23 of the 90 serotypes) is generally available for use in adults. In Victoria, recent data suggest 90% of isolates from people aged two years or older have serotypes in the current 23-valent adult vaccine, and are therefore potentially preventable by vaccination. Most recent national IPD surveillance found a similar figure for Victoria of 94% (1441/1583 isolates). These figures underpin the rationale for vaccine use in the elderly and are consistent with the estimate by Robinson et al (86%) for potentially preventable cases of IPD among persons aged ≥65 years in the USA.

For influenza vaccine, periodic shifts and drifts in influenza virus lipid envelope antigens mean worldwide surveillance systems for circulating strains (usually type A and/or B) are necessary to inform annual vaccine composition. The process of matching circulating strains with vaccine strains is necessary to ensure vaccine effectiveness. Surveillance is coordinated by the World Health Organisation (WHO) and results in annual recommendations for vaccine content. In making its decision regarding vaccine content for Australia, the Australian Influenza Vaccine Committee considers international surveillance data from WHO, recent data from Australia, New Zealand, South Africa and Argentina on epidemiology and strain characterisation, and the recommendations of the WHO annual consultation on the composition of influenza vaccine for the Southern Hemisphere. There is generally a good match between circulating strains and vaccine strains.

The potential for influenza vaccine and 23vPPV programs to reduce diseases due to these organisms depends on a number of factors including vaccine effectiveness and successful program implementation. Vaccine effectiveness in turn depends on vaccine efficacy (the percentage reduction of disease incidence in a vaccinated group compared with an unvaccinated group under ideal conditions such as a double blind randomised controlled trial), plus other factors such as transportation, maintenance of the “cold chain” for vaccination storage and correct administration.
1.5 Vaccine effectiveness

1.5.1 Vaccine effectiveness for 23vPPV

The effectiveness of 23vPPV against pneumonia in the elderly remains contentious. Currently available data from clinical trials and non-experimental studies are discussed below.

1) Clinical trials of VE for pneumococcal polysaccharide vaccine in the elderly

All clinical trial data on the effectiveness of pneumococcal polysaccharide vaccines in older persons are from the northern hemisphere and overall, do not provide evidence of benefit against all-cause pneumonia. Those trials which have shown a benefit against pneumonia were conducted among institutionalised, predominantly non-elderly populations. In particular, two were conducted among army personnel and coal miners with high background rates of pneumonia, and are unlikely to be generalisable to the healthy elderly population. Recent meta-analyses conducted after the completion of this research (see below) excluded both these latter studies for methodological reasons. The army personnel study did not confirm pneumonia radiologically and there was inadequate concealment of randomisation. The coal miner study only reported interim results without explanation. Only two studies utilised 23vPPV.

The recent Cochrane meta-analysis of VE for pneumococcal vaccines in adults was unable to demonstrate significant benefit against all-cause pneumonia. VE was 23% (95%CI -2-42%) when data were combined from 14 clinical trials, dropping to 16% (95%CI -8-35%) with the exclusion of one trial from the 1940s (quality score zero on a scale of zero to five). Of the four other meta-analyses examining VE of pneumococcal vaccines against pneumonia, only one found effectiveness against pneumonia and this only included studies of young, healthy subjects (South African gold miners and New Guinean highlanders). A recent review of meta-analyses (prior to Dear et al) also concluded that vaccination was not effective against pneumonia in the elderly.

Recent criticism of prospective trials and meta-analyses has focussed on interpretation of results and methods used for determining VE for pneumococcal polysaccharide vaccine. Possible causes of inconclusive results included: unrepresentative populations, inadequate sample sizes (no study large enough to rule out false negatives) and inaccurate interpretation and inappropriate pooling of results in meta-analyses. These authors believe that lack of class I/II evidence (from systematic reviews and/or well-conducted randomised controlled trials) for VE against bacteraemia or pneumonia should not be a reason to restrict vaccination and that wide use of 23vPPV is justified based on proven VE against bacteraemia in non-experimental studies. It should be noted that at the time of article publication the authors worked for companies that manufacture vaccines. Recent evidence from non-experimental studies conducted since the completion of the study underpinning this thesis now adds weight to the contrary argument of no significant benefit against pneumonia.
2) Non-experimental studies of 23vPPV effectiveness against pneumonia in the elderly

Prior to 2002 the only non-experimental studies of 23vPPV including pneumonia as an outcome examined incremental effectiveness of 23vPPV above influenza vaccine, and were limited to high risk populations or reported interim data without adjustment for confounders. Only the study by Nichol et al was available prior to conducting this case-cohort study (2000-2002). Studies since 2002 have produced conflicting results.

Six non-experimental studies examining only VE for 23vPPV have been published since the completion of data collection for this study (March 2002) (Table 1.1). They have produced conflicting results. One matched case-control study found that vaccination reduced the risk of pneumonia (OR 0.28, p<0.001), death from pneumonia and all-cause mortality. However, Jackson et al’s retrospective cohort study found that vaccination was associated with increased hospitalisation for CAP verified by medical record review (hazard ratio 1.14; 95%CI 1.02-3.28), and a non-significant increase in hospitalisation with a discharge diagnosis code for pneumonia (HR 1.06; 95%CI 0.98-1.16). Ansaldi et al found no reduction in hospitalisation for pneumonia after vaccination of predominantly elderly (86%) Italians in univariate analysis, but did find a 38% increase in hospitalisation for pneumonia for unvaccinated subjects in multivariate analysis (7%, 76%). This study provides relatively weak evidence given its subjects provided their own historical control over a short period (mean 17 months post vaccination) (level III-2 evidence) and equal periods of time were considered for each subject in multivariate analysis. Similarly, in 2005 Vila-Córcoles et al published early data from a prospective cohort study and found no reduction in hospitalisations coded as pneumonia (HR 0.80; 95%CI 0.56-1.31). However, following completion of this four year study, the authors claimed a benefit against hospitalisation with CAP (RR 74%; 95%CI 59-92%). This study used unstable models for estimating VE in the presence of confounders, possibly due to a “healthy vaccinee” effect or influenza vaccination status. Given the uncertainty around the estimate and likelihood of confounding, the conclusions may be overstated.

Of four studies examining effectiveness against pneumococcal bacteraemia or IPD, three found in favour of significant benefit from the vaccine (Table 1.1). Most recently, Mushel et al compared vaccination rates in adult patients (mean age 64 years) with bacteraemic and non-bacteraemic pneumonia. The authors concluded that 23vPPV conferred a 54% protection rate against IPD, but did not protect against non-bacteraemic pneumonia, a result similar to the Cochrane meta-analysis by Dear et al. The fourth study by Benin et al among Navajo adults was powered to detect vaccine effectiveness of 59% with a lower 95% confidence limit of 33%. Rates of diabetes (41%) and alcoholism (43%) were high among the study population which may have predisposed to a greater susceptibility to pneumococcal disease or a poor vaccine response. In addition, predominant circulating serotypes in this population (1, 12F, 5, 4, 7F and 8) meant fewer vaccine serotypes compared with the general elderly population, and hence lower potential vaccine effectiveness. The study may therefore have been inadequately powered to detect an effect.
Table 1.1. Non-experimental studies of VE for 23vPPV among the elderly published after 2002.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study period</th>
<th>Study design</th>
<th>Age* (years)</th>
<th>Outcomes</th>
<th>Cases</th>
<th>Controls</th>
<th>VE (%) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagner, 2003</td>
<td>1996-8</td>
<td>Matched case-control</td>
<td>82</td>
<td>pneumonia death from pneumonia all-cause mortality</td>
<td>514</td>
<td>562</td>
<td>72 (p&lt;0.001) 67 (p&lt;0.001) 73 (p&lt;0.001)</td>
</tr>
<tr>
<td>Jackson, 2003</td>
<td>1998-2001</td>
<td>Retrospective cohort</td>
<td>75</td>
<td>hospitalisation for CAP non-hospitalised CAP any CAP pneumococcal bacteraemia</td>
<td>21052</td>
<td>26313</td>
<td>-14 (-28- -2) -4 (-13-4) -7 (-14-1) 44 (7-67)</td>
</tr>
<tr>
<td>Dominguez, 2005</td>
<td>2001-2</td>
<td>Matched case-control</td>
<td>76</td>
<td>IPD</td>
<td>149</td>
<td>447</td>
<td>70 (48-82)</td>
</tr>
<tr>
<td>Benin, 2003</td>
<td>1996-7</td>
<td>Matched case-control Indirect cohort</td>
<td>59</td>
<td>IPD - likely inadequate power</td>
<td>108</td>
<td>330</td>
<td>26 (-29-58) 35 (-33-69)</td>
</tr>
<tr>
<td>Ansaldi, 2005</td>
<td>1998-2002</td>
<td>Retrospective cohort (n=9170)</td>
<td>73</td>
<td>hospitalisation for pneumonia</td>
<td>n/a</td>
<td>n/a</td>
<td>38 (7-76)</td>
</tr>
<tr>
<td>Vila-Córcoles</td>
<td>2002</td>
<td>Prospective cohort (n=11241) Data from year 1</td>
<td>≥65</td>
<td>Hospitalisation for pneumonia any pneumonia death from pneumonia¹</td>
<td>n/a</td>
<td>n/a</td>
<td>20 (-28-50) 14 (-31-44) 72 (17-91)</td>
</tr>
<tr>
<td>Vila-Córcoles</td>
<td>2002-2005</td>
<td>Prospective cohort (n=11241) Complete data set</td>
<td>≥65</td>
<td>Hospitalisation for pneumonia any pneumonia death from pneumonia¹</td>
<td>n/a</td>
<td>n/a</td>
<td>26 (8-41) 21 (2-36) 39 (28-77)</td>
</tr>
<tr>
<td>Mushur, 2006</td>
<td>2001-2005</td>
<td>Case-control (n=300)</td>
<td>64</td>
<td>IPD Bacteraemic pneumonia Non-bacteraemic pneumonia Acute exacerbation chronic bronchitis</td>
<td>300+</td>
<td>n/a</td>
<td>54 (9-76) 49 (-2-75) -1 (-86-45) -39 (-236-42)</td>
</tr>
</tbody>
</table>

* Refers to the median age of total subjects where specified. Some studies only reported the mean age. One study did not provide mean or median age.61

¹ There were only 18 deaths due to pneumonia in the first year of the cohort study and 60 in the total study period; included outpatient and inpatient pneumonia within 30 days of diagnosis

‡ A total of 300 patients, all with S.pneumoniae isolated; subgroups were compared using a case-control analysis, with colonisation as the baseline group

§ One study not included here as 65% of study subjects had unknown vaccination status 66
Chapter 1: Background

Of note, Vila-Córcoles et al recently criticised methods of large non-experimental studies that often include non-pneumococcal pneumonia cases. They suggest that analysis of a primary outcome of CAP of unknown aetiology should occur, with a secondary variable being hospitalised CAP of non-pneumococcal origin. While it is probable that studies that do not exclude non-pneumococcal pneumonia cases potentially underestimate vaccine effectiveness, diagnosis of microbiologically proven pneumococcal pneumonia can be very difficult (see 1.6).

3) Studies examining combined effectiveness of 23vPPV plus influenza vaccine

Four published studies have examined the combined effectiveness of 23vPPV and influenza vaccine in persons aged ≥65 years. These have produced conflicting results. All were conducted in populations outside Australia and examined pneumonia as an outcome of interest.

Of the four published studies examining VE for 23vPPV plus influenza vaccine, two were non-experimental in nature. Nichol’s retrospective cohort study of high risk elderly subjects with chronic lung disease found that influenza vaccination had an additional effect against hospitalisations for pneumonia and influenza during two influenza seasons when receipt of both vaccines was compared to receiving neither vaccine (adjusted RR 0.28, 95%CI, 0.14-0.58; p<.001). There were high attack rates during the study period and the results from this study sample would have limited generalisability to the healthy elderly. Christenson et al’s large prospective cohort study of Stockholm County residents aged ≥65 years examined pneumonia (ICD-10: J12-J18, J69, A48.1) as one of several outcomes. Their early report of interim results six months into the three year study with no assessment of possible confounders found a highly significant benefit for those who had received either or both vaccines compared with those who had received neither. 23vPPV was also reported to have an additive benefit against CAP over and above influenza vaccine. For subjects receiving either or both vaccines versus no vaccine, the incidence (per 100 000 inhabitants per year) of hospital treatment was lower in the vaccinated than in the unvaccinated cohort for all diagnoses: 263 versus 484 (-46%; 95%CI 34-56) for influenza; 2199 versus 3097 (-29%; 95%CI 24-34) for pneumonia; 64 versus 100 (-36%; 95%CI 3-58) for pneumococcal pneumonia; and 20 versus 40 (-52%; 95%CI 1-77) for IPD. The total mortality was 57% (95%CI 55-60) lower in vaccinated compared with unvaccinated individuals (15.1 versus 34.7 deaths per 1000 inhabitants).

Since Christenson’s early report on VE for influenza vaccine and 23vPPV, Hedlund et al have published three subsequent reports from the same non-experimental study which provide further information. The most recent of these still presents interim data regarding hospitalisation and mortality due to influenza and pneumonia among the vaccinated versus unvaccinated cohorts (from the second year of the three year study). As with the previous report, there is no adjustment for potential confounders. The authors report an “additive effectiveness” of vaccination when both influenza vaccine and 23vPPV were given (versus no vaccinations), with a reduction of hospital
admissions for influenza (37%) and pneumonia (29%). For those who were admitted with influenza or pneumonia despite receiving both vaccines, hospital stay was considerably shorter, perhaps suggesting less severe disease resulting from partial immunity. However, review of the data indicate that for either vaccine alone versus no vaccination, confidence intervals crossed 1.0, indicative of a non-significant effect, for all outcomes studied.\textsuperscript{71} Mortality for pneumonia (but not influenza with or without pneumonia) was lower in those who received both vaccines compared with those who received none (OR 0.65, 95\%CI 0.54-0.78). There is a possibility the study may underestimate VE since vaccine recipients (compared with the non-vaccinated cohort) were older, more often institutionalised and therefore more susceptible to pneumococcal infection.

Apart from the two non-experimental studies described above, there are also two randomised controlled trials conducted in Finland examining combined effectiveness of influenza vaccine and 23vPPV.\textsuperscript{47,68} 23vPPV did not have additive benefit over and above influenza vaccine in the prevention of pneumonia among the elderly. A statistically significant protective effect found for a subgroup of elderly persons at high risk for contracting pneumonia who had received both vaccines compared to those who had influenza vaccine alone (VE 59\%, 95\%CI 6\%–82\%),\textsuperscript{68} was not replicated by Honkanen et al.\textsuperscript{47} Both studies relied on passive reporting, had a lower than expected rate of pneumonia and insufficient power to demonstrate protective effectiveness of 20\% or less for both vaccines above that of influenza vaccine alone.\textsuperscript{47}

Finally, two reviews published since completion of this study examining available evidence did not find in favour of benefit from 23vPPV.\textsuperscript{55,72} Lipsky in particular comments that there is no evidence from prospective studies indicating a reduction in bacteraemia in patients with pneumococcal pneumonia would result in less frequent or shorter hospitalisations, decreased mortality, or reduced medical expenses. Assendelft, from the Dutch Cochrane Centre concludes in response to increasing uptake of recommendations to use 23vPPV in the elderly that it is “as though international opinion had already been fully formed before published studies and systematic reviews became available in the last few years.”\textsuperscript{55}

In summary, there is considerable debate about VE for 23vPPV against pneumonia and there are no studies from the southern hemisphere examining VE of 23vPPV for any outcome. Clinical trial data do not provide evidence of benefit from 23vPPV against pneumonia, but there has been recent criticism of methods used based on use of unrepresentative populations and inadequate sample size planning. The most recent non-experimental studies conducted since completion of this study examining the outcome of pneumonia have produced conflicting results, and earlier studies examining incremental effectiveness over and above influenza vaccine have either used unrepresentative populations or failed to adjust for confounders and used interim data. It is appropriate to undertake a well-designed study in the southern hemisphere to address this uncertainty.
1.5.2 Influenza vaccine effectiveness

Overview

Although published data in the international literature generally favour benefit from influenza vaccine for persons aged ≥65 years against ILI and mortality within influenza seasons, controversy remains regarding effectiveness against pneumonia for elderly persons living in the community. Effectiveness against pneumonia is also unclear for those in long-term care facilities where environmental and vaccine viral strain match is poor or unknown. Most recently, criticism of observational studies showing benefit has suggested evidence of bias in estimates of effect in favour of vaccination due to preferential vaccination of healthy persons. There are no Australian and extremely limited southern hemisphere data examining VE for influenza vaccine. Currently available data are discussed below.

Available data

Five randomised placebo-controlled trials of influenza vaccine in the elderly examine efficacy. Only two have a low risk of bias, and one of these was published after the completion of the research project underpinning this thesis. Govaert et al found a 50% reduction in serologically confirmed influenza (RR 0.50, 95%CI 0.35-0.61) and clinical influenza (RR 0.53, 95%CI 0.39-0.73) during one influenza season in the Netherlands. Allsup et al found no reduction in general practitioner diagnosis of ILI for a one year period of low influenza activity. This study was reduced from the planned two year study to a one year study due to changes in national vaccination policy. Interpretation of these results should therefore be cautious. There were no cases of pneumonia or hospitalisation for respiratory illness, and due to the reduction in the study period, the study would have been underpowered to examine these outcomes. One further RCT assessed as having a medium risk of bias did not examine pneumonia as an outcome, however, it found efficacy in preventing laboratory-confirmed influenza in vaccinated versus unvaccinated individuals was 50% (95%CI -26- -80) for inactivated vaccine, 51% (95%CI -17- -19%) for live vaccine and 67% (95%CI 36-81) for recipients receiving both vaccines.

A recent meta-analysis of 15 studies of influenza vaccine effectiveness concluded that influenza vaccination reduced the risk of hospitalisation for pneumonia and influenza among persons aged ≥65 years by 33% (95%CI 27–38%) (based on cohort and case-control studies only). All included studies were conducted in the northern hemisphere. The meta-analysis excluded studies with denominators less than 30, and pooled estimates from studies of different design. The largest reduction was found in mortality following hospitalisation for pneumonia and influenza (95%CI 25-62). The smallest reduction was in outpatient visits for pneumonia and influenza (95%CI 6-26). Mortality from all causes was reduced by 50% (95%CI 45-56). This is higher than might be expected based upon the above estimates of vaccine effectiveness against laboratory-confirmed influenza from clinical trials. A more recent Australian evaluation estimated influenza vaccine
effectiveness of 0.58 (95% CI 0.26-0.77) for prevention of disease, and 0.33 (95% CI 0.27-0.38) for prevention of hospital admission for influenza and pneumonia. Since the meta-analysis by Vu et al, which included studies until 31 December 2000, a number of studies (occurring after the research for this thesis) have confirmed benefit from vaccination against these outcomes (Table 1.2; significant results indicating benefit shown in bold), including during influenza seasons of low activity.

However, there are exceptions to studies showing significant benefit from influenza vaccine (Table 1.2). In particular, the majority of recent studies have not shown a clear benefit from influenza vaccination against pneumonia. For example, Hara et al recently found a point estimate suggesting benefit against hospitalisation for influenza and pneumonia from influenza vaccine in a cohort study of elderly community-based persons in Japan, but with a wide confidence interval including no effect (one) (RR 0.37, 95% CI 0.09-1.47). Similarly, Voordouw et al, who conducted a large cohort study among community-based elderly in the Netherlands, found no significant benefit against pneumonia (HR 0.84, 95% CI 0.65-1.07), or lower respiratory tract infection (RR 0.96, 95% CI 0.82-1.11) (pneumonia, acute bronchitis and exacerbations of chronic bronchitis), including when restricted to the influenza epidemic period (HR 0.87, 95% CI 0.55-1.36 and HR 0.94, 95% CI 0.83-1.06 respectively) and when revaccination was accounted for (HR 0.89, 95% CI 0.67-1.18). In this study, benefit against pneumonia from influenza vaccine was associated with only one subset of study subjects: those who were revaccinated and had no comorbidity where pneumonia was examined only within influenza epidemic periods (HR 0.50, 95% CI 0.27-0.93), and those hospitalised with pneumonia (HR 0.29, 95% CI 0.10-0.96) based only three cases of pneumonia.
Table 1.2. Summary of studies of influenza vaccine effectiveness published after 2000 among persons aged ≥65 years, within influenza seasons.

<table>
<thead>
<tr>
<th>Study 1st author, year, study design</th>
<th>Adjusted for confounders</th>
<th>Influenza-like illness (RR, 95%CI)</th>
<th>Pneumonia (RR, 95%CI)</th>
<th>Hospitalisation (RR, 95%CI)</th>
<th>Death (RR, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voordouw, 200687 Prospective cohort</td>
<td>Yes³</td>
<td>-</td>
<td>0.84 (0.71-1.05)⁷</td>
<td>0.29 (0.10-0.96)⁷</td>
<td>-</td>
</tr>
<tr>
<td>Hara, 200682 Prospective cohort</td>
<td>Yes⁸</td>
<td>0.38 (0.17-0.85)</td>
<td>0.37 (0.09-1.47)</td>
<td>0.72 (0.46-1.13)</td>
<td>3.68 (0.75-18.12)</td>
</tr>
<tr>
<td>Ozasa, 200683 Retrospective cohort</td>
<td>Yes⁹</td>
<td>0.78 (0.40-1.52)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kobayashi, 200584 Prospective cohort</td>
<td>Yes⁵</td>
<td>1.06 (0.10-11.12)</td>
<td>0.28 (0.06-1.19)</td>
<td>0.2 (00-0.34)</td>
<td>-</td>
</tr>
<tr>
<td>Wang, 200589 Prospective non-experimental</td>
<td>Yes⁶</td>
<td>-</td>
<td>-</td>
<td>0.85 (0.76-0.96)³</td>
<td>0.71 (0.65-0.77)</td>
</tr>
<tr>
<td>Christenson, 200471 Prospective cohort⁹</td>
<td>No</td>
<td>0.74 (0.54-1.03)⁴</td>
<td>0.94 (0.86-1.02)⁹</td>
<td>-</td>
<td>0.70 (0.15-3.21)t 0.88 (0.69-1.11)t</td>
</tr>
<tr>
<td>Armstrong, 200490 Prospective cohort</td>
<td>Yes⁵</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.89 (0.90, 0.98)⁹</td>
</tr>
<tr>
<td>Puig-Barbera, 200481 Case-control</td>
<td>Yes⁵</td>
<td>-</td>
<td>-</td>
<td>0.52 (0.34,0.80)⁹</td>
<td>-</td>
</tr>
<tr>
<td>Mangtani, 200491 Historical cohort</td>
<td>Yes⁸</td>
<td>-</td>
<td>-</td>
<td>0.79 (0.74-0.83)³</td>
<td>0.88 (0.92-0.84)</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Retrospective/Prospective</td>
<td>Yes/No</td>
<td>95% CI Low</td>
<td>95% CI High</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------</td>
<td>---------------------------</td>
<td>--------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Voordouw, 2003</td>
<td>Retrospective</td>
<td>Yes8</td>
<td>0.48</td>
<td>0.26-0.91</td>
<td>0.77</td>
</tr>
<tr>
<td>Shapiro, 2003</td>
<td>Historical</td>
<td>Age only</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Herzog, 2003</td>
<td>Historical</td>
<td>Yes9</td>
<td>-</td>
<td>-</td>
<td>0.92</td>
</tr>
<tr>
<td>Nichol, 2003</td>
<td>Prospective</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>0.68</td>
</tr>
<tr>
<td>Landi, 2003</td>
<td>Prospective</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hak, 2002</td>
<td>Prospective</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>0.52</td>
</tr>
<tr>
<td>Saito, 2002</td>
<td>Prospective</td>
<td>Yes</td>
<td>1.42</td>
<td>0.86-2.33</td>
<td>0.95</td>
</tr>
<tr>
<td>Crocetti, 2001</td>
<td>Case-control</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>0.67</td>
</tr>
<tr>
<td>Christenson, 2001</td>
<td>Prospective</td>
<td>No</td>
<td>0.54</td>
<td>0.44-0.66</td>
<td>0.71</td>
</tr>
<tr>
<td>Monto, 2001</td>
<td>Prospective</td>
<td>Yes</td>
<td>0.65</td>
<td>0.51-0.85</td>
<td>0.45</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Prospective cohort</th>
<th>Yes/No</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis, 2001</td>
<td>Yes</td>
<td>1.0</td>
<td>(0.8-1.1)</td>
</tr>
<tr>
<td>Deguchi, 2000</td>
<td>No</td>
<td>0.40</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.33</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.31</td>
<td>(p&lt;0.001)</td>
</tr>
</tbody>
</table>

**Notes:**
- Adjusted for more than 15 potential confounders
- Adjusted for age, sex, propensity scores for underlying conditions and likelihood of exposure to influenza
- Adjusted for age, sex, institution, hypoalbuminaemia, activities of daily living, dementia and other underlying medical conditions; hazard ratios
- Adjusted for age, sex, frequency of hospitalisation, status of health check
- Adjusted for month, temperature, and number of days since 31 December; compares influenza exposure and mortality in vaccinated and unvaccinated cohorts
- Adjusted for heart disease, asthma, a Barthel Index score <60, being a smoker, having been administered 23vPPV, attending outpatient clinics; odds ratios
- Adjusted for risk, age, repeat prescription status
- Adjusted for respiratory disease, cardiac disease, hypertension diabetes, renal disease and vaccination history
- Adjusted for age, sex, race, pre-hospitalisation setting, the pneumonia severity index, and the presence of comorbid conditions; hazard ratios; VE not examined within influenza seasons
- Adjusted for age, gender, comorbidity, previous hospitalisation with pneumonia/influenza; single combined outcome of hospitalisation for pneumonia/influenza or death; 2 influenza seasons; see also Nordin et al 101
- Adjusted for age, sex, ADL score, CPS score, number of diseases, number of medications, depression, pressure ulcers
- Adjusted for chronic disease, education, type of heating, smoking habits (matched on age, sex, residence)
- Adjusted for age and gender only; RR for all respiratory illness (not ILI)
- Adjusted for age, gender, vaccination with 23vPPV, morbidity index, number of hospitalisations and doctor visits in the previous year
- Same study as Christenson, 2001, but interim data presented 1 year into the 3 year study, ORs presented, estimates are for those who have received influenza vaccine alone, estimates 1/2 are with/without influenza pneumonia
- Influenza, with or without pneumonia, coded by ICD-10 codes
- Proven influenza (serology or organism isolated)
- Hospitalisation due to influenza and pneumonia
- Hospitalisation for acute respiratory disease
- Deaths associated with hospitalisation for influenza and pneumonia respectively
- Ratio of exponentiated coefficients estimating impact of vaccination on tendency for mortality to increase during periods of high counts of circulating influenza
- Adjusted for age, gender, ADL, vaccination, cardiac, respiratory and cerebrovascular diseases; results for 2 separate influenza seasons
- Individuals vaccinated with influenza vaccine or 23vPPV alone or both were classified as “vaccinated” for the purpose of estimating VE; interim data only (1st 6 months of a 3 year study)
- Adjusted for age, sex, antibiotic use, GP visits, chronic respiratory tract disease, chronic cardiovascular disease, diabetes mellitus, hypertension, chronic renal insufficiency, malignancy, neurological/psychiatric disorders
- First result= for the full study period, 2nd study result for the influenza epidemic period
- Hospitalisation for pneumonia – based on only 3 cases
- One study not included here as more than 50% of subjects had unknown vaccination status 102
A recent, well-conducted Cochrane meta-analysis provides an excellent summary of influenza vaccine effectiveness in the elderly. This study indicates benefits of vaccination may differ in different elderly populations. Results were primarily reported from cohort and case-control studies due to the heterogeneity and quality issues among randomised controlled trials (see above). The study divided elderly persons into two groups: those living in long-term care facilities, and those living in the community. For the elderly in long-term care facilities, cohort studies found influenza vaccine effectiveness against ILI was 23% (95%CI 6-36) where there was good match between circulating and vaccine strains of influenza virus. Vaccination with vaccines well-matched to circulating strains was associated with prevention of pneumonia (VE 46%, 30-58), hospital admission for proven influenza and pneumonia (VE 60%, 16-64), deaths from influenza or pneumonia (VE 42%, 17-59) and all-cause mortality (VE 60%, 23-79). For the elderly living in the community, cohort studies found benefit from well-matched vaccines against hospital admission for influenza and pneumonia (VE 26%, 12-38), and all-cause mortality (VE 42%, 24-55). This was also the case when adjusted for confounders. Case-control studies also provide evidence of effectiveness against hospital admission for influenza and pneumonia.

However, in the same meta-analysis, there was no evidence of benefit from vaccination against proven influenza for elderly persons living in long-term care facilities regardless of the degree of matching of vaccine and circulating strains of influenza. There was also no evidence of benefit against any other outcome where viral strain match was poor or unknown (except all-cause mortality for which there were no studies found). For the elderly living in the community, benefit from vaccination was not shown against influenza, ILI or pneumonia.

In addition, it is possible that non-experimental studies may overestimate prevention of death from influenza among the elderly due to influenza vaccination. In a recent ecological study, Simonsen et al used cyclical regression modelling to generate seasonal estimates of national influenza-related mortality. The authors found increasing influenza-related mortality among the elderly population despite concurrent increases in influenza vaccination coverage. These estimates did allow for confounding due to ageing of the population, and circulating influenza strains with higher mortality rates. Simonsen proposed that selection biases among the control groups were responsible for overestimation of the protective effect against death. While measurement of mortality (a rare event) from non-experimental studies can be subject to confounding (for example if vaccinees are healthier than non-vaccinees, this may bias estimates of effectiveness upwards; conversely, sicker vaccinees could bias estimates downwards), potential biases such as these do appear to have been accounted for in many studies (Table 1.2). Furthermore, ecological studies themselves are an inherently weak study design in terms of proving causality. Nonetheless, this recent debate does make the question of influenza vaccine effectiveness among the elderly of interest.
In summary, controversy remains regarding effectiveness of influenza vaccine against pneumonia for those who live in the community and for those in long-term care facilities where environmental and vaccine viral strain match is poor or unknown. The controversy has increased since the research for this thesis was conducted, as a result of further studies questioning benefit. There remains an absolute paucity of data from the southern hemisphere on influenza vaccine effectiveness. As for 23vPPV, it is appropriate to undertake a well-designed study in the southern hemisphere to address this uncertainty for influenza vaccine.

1.6 Choice of outcome measure for estimating VE: CAP, as defined by ICD-10 codes

Many different disease outcome measurements have been used by researchers to determine VE against *S.pneumoniae*. A recent review of the methods used in clinical trials and meta-analyses of efficacy for 23vPPV summarises the six endpoints generally used across clinical trials: pneumococcal bacteraemia/IPD, pneumonia of all causes, pneumococcal pneumonia, lower respiratory tract infection, pneumonia-related death, and all-cause mortality. Outcome measures commonly used to determine influenza vaccine effectiveness include laboratory-confirmed influenza, death, and community consultation rates for ILI.

These varied approaches to measuring vaccine effectiveness highlight the difficulty of confirming that an illness is due to *S.pneumoniae* or influenza, and the choice that must be made between a highly specific but insensitive outcome measure such as pneumonia associated with pneumococcal bacteraemia or microbiologically proven influenza versus a sensitive, but non-specific surrogate outcome such as all-cause mortality or lower respiratory tract infection.

*S.pneumoniae* can be definitively diagnosed when cultured from blood, or another normally sterile site such as cerebrospinal, pleural or synovial fluid. However, definitive diagnostic tests, particularly those invasive tests most likely to identify *S.pneumoniae* are insensitive because only a small proportion of active or invasive disease has a laboratory-confirmed microbiological aetiology. This occurs for a number of reasons including failure to take a specimen, lack of sensitivity or specificity of available tests or, additionally in the case of pneumococcal disease, because antibiotics have been commenced. This is especially important in the context of pneumonia, the most frequent clinical presentation of *S.pneumoniae* and for which empiric antibiotic treatment is commenced in the majority of cases based on clinical grounds, and definitive tests are not frequently or routinely conducted.

Sputum culture is not a specific diagnostic test because identification in the upper respiratory tract can represent either simple colonisation or active disease. A positive sputum culture for *S.pneumoniae* does not distinguish between nasopharyngeal carriage and lower respiratory tract
infection.\textsuperscript{105} A sputum gram stain also misses the diagnosis of \textit{S. pneumoniae} in the majority of cases and reliability is dependent on production of a good specimen (often difficult in the elderly), the application of stringent criteria and laboratory staff well-trained in interpretation.\textsuperscript{105} Serologic tests may also not be reliable.\textsuperscript{110}

For influenza, there are still no widely available point of care diagnostic tests with sufficient sensitivity and specificity for routine use.\textsuperscript{111} Test validity varies with the setting (active surveillance versus clinical trial) and activity level of the influenza season (prevalence). Clinical diagnosis of influenza is difficult because of the similarity to other respiratory infections,\textsuperscript{111} hence the use of the term influenza-like illness (ILI) to describe the clinical syndrome that may be attributed to respiratory viruses other than influenza.\textsuperscript{112} In Victoria, laboratory testing of cases detected by active surveillance confirms approximately 40\% of ILI is due to influenza.\textsuperscript{113} Even with well-defined criteria, the accuracy of clinical diagnosis for influenza is no better than 63-75\%.\textsuperscript{111} The Australian clinical definition for ILI (cough, fever, fatigue) has an estimated sensitivity of 44-71\% and specificity of 47-80\% over two influenza seasons characterised by A H3N2 circulation in Victoria and Western Australia. The positive predictive value (PPV) is estimated as in the range of 25-60\% when compared against different diagnostic tests.\textsuperscript{114,115}

Polymerase chain reaction (PCR) assays are the most common diagnostic tests now used for the differential diagnosis of ILI in Victoria.\textsuperscript{112} Using virus isolation by culture or immunofluorescence as a gold standard, the sensitivity of PCR for influenza A and B among influenza surveillance cases for Victoria for 2002-2003 was 85.7\% (95\%CI 57.2-98.2) and 86.7\% (95\%CI 59.5-98.3) respectively. The corresponding specificities were 98.4\% (95\%CI 96.4-99.5) and 98.4\% (95\%CI 96.4-99.5).\textsuperscript{116} Other diagnostic tests for influenza test for influenza antibodies or antigens, such as immunofluorescence or convalescent serology, but are not frequently carried out for practical reasons.\textsuperscript{115}

In their review of endpoints for VE of 23vPPV, Fedson et al suggested that only pneumococcal bacteraemia/IPD (unambiguous and the most specific measure of vaccine effectiveness) and pneumonia of all causes (seen also as reliable in terms of confirmation by chest radiograph and clinical course) are acceptable endpoints for vaccine effectiveness based on sensitivity and specificity tradeoffs.\textsuperscript{56} Non-specific outcomes like all-cause mortality are likely to be caused by non-pneumococcal illnesses that cannot be prevented by the vaccine and would therefore underestimate vaccine effectiveness. By contrast, most trials have attempted to include pneumococcal pneumonia as an outcome, but as discussed above, there are difficulties in making an organism-specific diagnosis. Since most cases of pneumococcal pneumonia are not associated with proven pneumococcal bacteraemia,\textsuperscript{22} it makes sense to use all-cause pneumonia as an outcome.

All-cause pneumonia is also a highly relevant outcome in terms of burden of disease. Vila-Córcoles et al recently found an incidence rate of CAP of 10.4/1000 per year in the elderly.\textsuperscript{61} In the USA,
Chapter 1: Background

CAP is the fifth leading cause of death in persons aged ≥65 years, and is responsible for approximately 60,000 deaths annually.22 Approximately 20% of people with CAP require hospitalisation,117-119 although a recent large prospective study from Spain found 81% of elderly persons with CAP (8.5/1000 per year) were hospitalised.61 Fedson et al also suggests that since 30-50% of pneumonia is thought to be due to S.pneumoniae, provided a study has sufficient numbers of cases, it should be possible to demonstrate benefit from 23vPPV against all-cause pneumonia. The use of all-cause pneumonia as an outcome also accounts for the potential issue of “replacement pneumonia” where other organisms “step in” to cause pneumonia where S.pneumoniae has been prevented.56

Hospitalisation for CAP is a particularly relevant outcome measure for measuring VE for influenza vaccine and 23vPPV from a public health sector or program point of view. This is because persons hospitalised with pneumonia comprise the greatest burden of disease due to pneumonia occurring in community-based individuals (in terms of severity and health care costs) at whom prevention by vaccination is largely targeted. The mortality rate of all hospitalised patients with CAP ranges from 7-18%,19,61,117 but of the 10-35% admitted to an intensive care unit, mortality ranges from 20-50%.118,120 Basing estimates of VE upon prevention of hospital admission with pneumonia is likely to result in an underestimate compared with use of a more specific outcome such as IPD. However, such an estimate would represent a greater proportion of disease preventable by vaccination compared with IPD, and use of pneumonia as an outcome for estimating VE is likely to be more valid compared with previous studies with very low IPD rates.42-49,121,122 Only one previous clinical trial examining IPD as an outcome had more than seven cases among their control groups.48 Furthermore, it is appropriate to exclude nosocomial (or hospital-acquired) pneumonia (as opposed to CAP) as it is less often due to S.pneumoniae and influenza and more often attributable to “unusual” organisms endemic in the hospital environment, frequently related to mechanical ventilation or other invasive procedures.123

Diagnosis of CAP using clinical criteria is imprecise. There is no internationally agreed upon definition for pneumonia based on clinical symptoms and signs. No one sign or symptom, nor combination of these clearly differentiates pneumonia from other respiratory illnesses.119,124 A small study of clinical diagnostic validity for pneumonia found a sensitivity of 47-69%, specificity of 58-75% and PPV of 53-61% for certain combinations of symptoms and signs versus radiological diagnosis.125 Among the elderly, clinical presentation is also less distinct than for younger patients.126 There are also challenges with defining CAP radiologically (see 4.3.2).

The lack of a clear clinical definition is a key reason why internationally recognised ICD codes for hospitalised persons are frequently used as surrogate measures to identify pneumococcal and influenza-related disease outcomes in clinical research, and in particular for pneumonia-related illnesses.2,57,58,61 The process of coding occurs when a trained medical “coder” examines the separation diagnosis in hospital records and allocate specific ICD-10 codes which best fit the
information provided in the hospital record, according to coding guidelines. Use of ICD-10 codes by researchers to retrospectively identify persons hospitalised with pneumonia in studies of vaccine effectiveness is also time efficient compared with reviewing hospital records for clinical, microbiological and radiological evidence consistent with the diagnosis. However, very few studies have examined the validity of this approach.

Marrie et al found a PPV for ICD-9-CM codes for pneumonia of 57% in a small prospective study of adult patients hospitalised with pneumonia (sensitivity 69%). Guevara et al examined the validity of individual codes only for the specific subcategory of pneumococcal pneumonia against various clinical definitions. This study is therefore not directly relevant to the broader outcome of pneumonia. However, they found considerable variability in validity depending on the clinical definition used as the comparator. With removal of the broadest of the six diagnostic coding groups, ranges for a combination of codes indicative of pneumococcal pneumonia were: sensitivity: 55-85%, specificity 96-97%, PPV 72-95% and negative predictive value (NPV) 93-95%. Similarly, Whittle et al found good agreement between ICD9-CM coded cases of CAP (principal diagnostic position) and review of clinical notes: sensitivity 84%, specificity 86%, PPV 92%, kappa 68%. These limited data suggest ICD codes may be used as a valid tool for ascertainment of persons with hospitalisation for pneumonia, but further examination is prudent given the paucity of available data and lack of any data from outside North America.

In using CAP as an endpoint for measuring VE, knowledge of risk factors for CAP is important, since unequal distribution among vaccinated and unvaccinated study subjects could either over- or under-estimate measures of vaccine effectiveness. Known risk factors for CAP include smoking tobacco, alcoholism, asthma, diabetes, immunosuppression, malignancy, asplenia, chronic respiratory or cardiac or renal disease, institutionalisation, and increasing age.

In summary, hospitalisation for CAP is an important and appropriate measure of potential benefit from vaccination against influenza and S. pneumoniae. It is particularly relevant in terms of vaccination programs targeting the greatest burden of disease attributable to pneumonia. Identification of such cases using ICD-10 codes is time efficient and practical, but the validity of using codes to retrospectively identify patients with CAP requires further assessment.

1.7 Validity of self-reported vaccination status

1.7.1 Overview

Self-reported vaccination status is used frequently in clinical practice to inform decisions about whether to vaccinate individuals, and is also used by researchers and assessors of public health programs as a measure of true vaccination status for both 23vPPV and influenza vaccine. From an Australian context, there are limited data evaluating the implementation of the Victorian and/or
national programs prior to and during the period of the research for this thesis, and these surveys have also relied on self-report to determine vaccine coverage via computer-assisted telephone interview.\textsuperscript{135-137} In practice, there are few alternatives given the lack of a register for adult vaccinations in most countries, including Australia. However, very few studies have evaluated the validity of this practice. No large study has examined the validity of self-reported vaccination status for these vaccines in any setting. Robust data on the validity of self-reported vaccination status would assist decision-making regarding choice of an appropriate method of evaluating population-level programs for these vaccines, as well as interpretation of existing survey data.

\textbf{1.7.2 23vPPV}

Only two small studies of the validity of self-reported 23vPPV status were published at the time of undertaking the research for this thesis.\textsuperscript{138,139} In total, few studies have examined this question and all have had relatively small sample sizes (Table 1.3).\textsuperscript{138-144} One of these studies has only been published as a conference proceeding.\textsuperscript{139} Results from these studies suggest moderately good sensitivity and specificity for self-report as a true indicator of vaccination status (Table 1.3). A detailed summary of the three papers published to 2003 (all from the USA)\textsuperscript{138-140} has been previously reported.\textsuperscript{142} Based on these small studies, self-report of vaccination with 23vPPV is reported to have moderate internal validity (sensitivity 65-87\%, specificity 46-90\%), with subjects both underestimating (Mac Donald 74\% versus 79\%, Long 58\% versus 48\%)\textsuperscript{138,139} and overestimating (Zimmerman 71\% versus 52\%)\textsuperscript{140} their vaccination coverage when compared with the gold standard of documentation of vaccination in medical records. Estimates in these three studies could have been affected in either direction by potential biases including poor response rates (as low as 59\%)\textsuperscript{140}, respondent bias\textsuperscript{138} and selection bias.\textsuperscript{139} More recently, Andrews reported estimates based on Australian data from 278 randomly selected elderly telephone interview respondents in Victoria.\textsuperscript{142,143} This study showed lower reliability for reported vaccination status for the previous year (74\% sensitivity, 88\% specificity, an overestimate compared with medical records) compared with recall for the previous five years (81\% sensitivity, 90\% specificity, an underestimate compared with medical records). Since this report, one further study from the USA found consistent results, with a sensitivity of 75\% and specificity of 83\% among random-digit dialled elderly survey recipients in four counties.\textsuperscript{141} Most recently, a study by Mangtani et al with a low population coverage for 23vPPV found self-reported coverage underestimated true coverage by 4\% (23\% versus 27\%).\textsuperscript{144}
Table 1.3. Summary of published studies examining the validity of self-reported vaccination status for 23vPPV.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>135-820</td>
<td>64-97</td>
<td>46-92</td>
<td>40-93</td>
<td>60-97</td>
</tr>
<tr>
<td>Long, 1999139</td>
<td>285</td>
<td>65</td>
<td>74</td>
<td>78</td>
<td>61</td>
</tr>
<tr>
<td>Mac Donald, 1999138</td>
<td>432</td>
<td>87-97</td>
<td>53-76</td>
<td>54-93</td>
<td>60-97</td>
</tr>
<tr>
<td>Zimmerman, 2003140</td>
<td>820</td>
<td>85</td>
<td>46</td>
<td>63</td>
<td>74</td>
</tr>
<tr>
<td>Shenson, 2005141</td>
<td>135</td>
<td>75</td>
<td>83</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>Andrews, 2005143 recall at 1y</td>
<td>278</td>
<td>74</td>
<td>88</td>
<td>40</td>
<td>97</td>
</tr>
<tr>
<td>Andrews, 2005143 recall at 5y</td>
<td>278</td>
<td>81</td>
<td>90</td>
<td>92</td>
<td>77</td>
</tr>
<tr>
<td>Mangtani, 2007144</td>
<td>326</td>
<td>64</td>
<td>92</td>
<td>74</td>
<td>88</td>
</tr>
</tbody>
</table>

1.7.3 Influenza vaccine

Data showing evidence of the validity of self-reported vaccination status for influenza vaccine are also limited (range 278-819 subjects)\textsuperscript{138,140,143-145} but suggest very high sensitivity and moderate specificity. Not surprisingly, the validity of self-reported influenza vaccine, an annual vaccine, has generally been shown to be higher than that for 23vPPV.\textsuperscript{138,140,143,144} Three North American studies report a sensitivity of 92-100%, and specificity of 38-96%.\textsuperscript{138,140,145} The studies by Zimmerman et al and Mac Donald et al have potential selection and respondent bias as discussed above. The study by Hutchison et al was conducted in a community-based group family practice in an affluent middle class urban area and its generalisability may also be limited.\textsuperscript{145} A recent Victorian telephone survey found estimates consistent with these findings, reporting a sensitivity of 96-99% and specificity of 67-77%.\textsuperscript{143} A study from Ireland with an 81% response rate found 144/293 (49%) participants reported being vaccinated against influenza.\textsuperscript{146} Only 64/293 (22%) had their vaccination status confirmed from medical records, and all but two of these had reported their vaccination status correctly. However, interpretation of these results is difficult due to potential selection bias resulting from inability to confirm vaccination status for 78% of the study sample.\textsuperscript{146} Most recently, a small study by Mangtani et al found similar results to Andrews in a population with relatively low
All the above studies have found over-estimation of true vaccination coverage (range 1-29%, average 11%), although the highest estimate is from the study by Zimmerman et al, for which considerable potential for response bias has been noted.

This thesis describes the first study from Australia to examine the validity of self-reported vaccination status as a marker of true vaccination status for influenza vaccine and 23vPPV in the hospitalised elderly. It is also the largest study to examine this question for both vaccines in any setting, the first to adjust estimates for potential confounders, and has direct relevance to the ongoing assessment of current influenza and S.pneumoniae vaccination programs for Victorians aged ≥65 years.

1.8 Policy for influenza vaccine and 23vPPV

In Australia, the National Health and Medical Research Council recommends that all persons aged ≥65 years receive annual influenza and five yearly 23vPPV. While influenza vaccine and 23vPPV are currently funded for all Australians in this age group through the Immunise Australia program (influenza vaccine since 1998, 23vPPV since 2005), at the time of this research Victoria was the only State or Territory that provided 23vPPV free in addition to influenza vaccine to persons in this age group. The Victorian 23vPPV program commenced in February 1998. At the time of undertaking this research, I was unable to find any report of similarly publicly funded programs for 23vPPV in other countries, although a number of countries had just begun to recommend its routine use for the elderly (for example the USA, Canada, Sweden, Belgium, Norway, Denmark, Finland and Germany). More recently, the province of British Columbia, Canada and Scotland provided free 23vPPV in this age group and Catalonia, Spain has introduced both free 23vPPV and influenza vaccine.

Policy for vaccination with 23vPPV in the elderly remains controversial, with much debate currently about the evidence upon which recommendations to vaccinate have been based (see 1.5). Perhaps in response to this, the emphasis of recommendations has shifted from prevention of pneumonia to what is known to be prevented: IPD.

Influenza vaccination is currently recommended for persons aged ≥65 years in many countries including the United Kingdom, the USA and Europe. The World Health Assembly has also made recommendations for Member States. A recent review reported that in 2000, 40 of 51 developed or rapidly developing countries recommended vaccination for all individuals aged 60-65 or older, but that none fully-implemented this.

Government policy to recommend and/or fund 23vPPV and influenza vaccine in the elderly can have considerable impact on vaccination coverage. For example, Fedson reports dramatic increases in 23vPPV coverage among developed countries from the 1990s when new registrations and/or
national recommendations were put in place – including in Iceland (1991), the United Kingdom (1994), Sweden (1995), and Norway, Belgium and Ontario, Canada (1996). Before the 1990s, very little 23vPPV was used. In the USA, among persons aged ≥65 years, at least part of the increased coverage for influenza vaccination from 33% in 1989 to 66% in 1999 was attributed to the initiation of Medicare reimbursement for influenza vaccination in 1993. Stone also makes a case for explicit targets by contrasting the USA, which has an explicit target stated for vaccine uptake among the elderly of 60% and achieved 45% coverage, and the United Kingdom, where there is no stated target and coverage among recommended high risk groups (not the elderly) is only 4%.

In summary, despite the uncertainty related to 23vPPV effectiveness against pneumonia in the elderly, recommendations to vaccinate this population have been increasingly adopted by industrialised countries. Similar policy for influenza vaccine is in widespread use internationally. Local policy to fund both 23vPPV and influenza vaccine in Victoria provides a unique environment of high vaccination coverage, particularly for 23vPPV (with coverage approaching 60%). This environment enables examination of coverage in relation to policy, as well as the broader community impact from disease prevention. Such information obviously has implications for local as well as national and international policy and economic assessment of associated health benefits.

1.9 Missed opportunities for vaccination

In evaluating the impact of jurisdictional or national immunisation policy, it is prudent to examine missed opportunities for vaccination. Since hospitalised persons are at greater risk of subsequent disease due to influenza and S.pneumoniae, knowledge of their risk factors for an incomplete vaccination status and their rate of opportunistic vaccination in hospital can also inform the process of improving policy implementation.

Although it is likely that in Australia, as in the USA, elderly persons with an incomplete vaccination status for 23vPPV and influenza vaccine experience numerous missed opportunities to be vaccinated, and hospital staff do not often document vaccination status or order vaccinations, there is currently a paucity of data for the Australian elderly population. No study has evaluated missed opportunities for vaccination in the elderly as its primary focus, and no Australian data were found on the rate of recording inpatient influenza or 23vPPV vaccination status or acceptability of vaccination with these vaccines among unvaccinated inpatients. This study is the largest to date in any setting to quantify missed opportunities for vaccination with 23vPPV and influenza vaccine among hospitalised elderly patients with and without pneumonia.
1.10 Thesis rationale and Summary

The primary hypothesis of this thesis is to determine whether vaccination with 23vPPV for older Victorians provides additional benefit over and above influenza vaccination in preventing hospitalisation for CAP.

Controversy remains regarding benefit from 23vPPV against pneumonia in the elderly. More recently there has also been criticism of methods utilised in trials for determining vaccine effectiveness, and by meta-analyses when pooling results. There has also been criticism regarding lack of control for potential confounders when making estimates of vaccine effectiveness in non-experimental studies.

Although studies of influenza vaccine generally show benefit against influenza-like illness, hospitalisation and death, controversy remains regarding the outcome of pneumonia for those who live in the community, and for those in long-term care facilities where environmental and vaccine viral strain match is poor or unknown.

There are no southern hemisphere data available for the effectiveness of 23vPPV against pneumonia, alone or in combination with influenza vaccine, and extremely limited southern hemisphere data for influenza vaccine.

Evidence supports the use of hospitalisation for CAP as an appropriate outcome measure for measuring vaccine effectiveness for both influenza vaccine and 23vPPV in the elderly. The use of ICD-10 codes to identify cases of hospitalisation with CAP is consistent with earlier studies, practical and arguably valid when compared with retrospectively establishing a clinical diagnosis, but further assessment is prudent given the ongoing use of ICD codes by researchers to identify hospitalised patients with pneumonia, the paucity of available data, and the potential for differences in estimates from settings outside North America.

Despite the uncertainty related to effectiveness of both influenza vaccine and 23vPPV against pneumonia in the elderly, recommendations to vaccinate this population have been increasingly adopted by industrialised countries and some continue to place emphasis on prevention of pneumonia. Such policies clearly have important implications for vaccination coverage and associated health care costs, and require evaluation.

Victoria provides a unique environment in which both influenza vaccine and 23vPPV are recommended and funded for persons aged ≥65 years and there is a high population coverage. It therefore becomes feasible to examine the effectiveness of both vaccines at a broader population level.
Monitoring the effectiveness of vaccination programs is also an integral component of good public health practice and helps to best direct limited resources. In this case, demonstration of vaccine effectiveness (or otherwise) could have major implications for public health policy and associated health care costs, particularly with regard to the provision of the publicly funded 23vPPV for persons aged ≥65 years in Victoria and Australia, and potentially for similar programs internationally. Additionally, evaluation of program impact in terms of vaccine coverage, missed opportunities to vaccinate, and identification of risk factors for hospitalisation with CAP can assist the development of targeted vaccination strategies. At the time of conducting this study, data evaluating the implementation of the Victorian program were limited. In particular, the use of self-reported vaccination status as a valid assessment tool needs further evaluation. No large study has examined the validity of self-reported vaccination status in any setting or attempted to control estimates for potential confounders.

This thesis therefore aims to test the hypothesis that Victorians aged ≥65 years vaccinated against influenza and *Streptococcus pneumoniae* are protected against hospitalisation for CAP. It uses ICD-10 coded cases of hospitalised pneumonia as the clinical endpoint for assessing vaccine effectiveness, and by using dates of admission and diagnosis, limits evaluation to community-acquired cases. It provides the first southern hemisphere data on VE for either vaccine against this outcome, and high quality data that can inform the current international debate on the appropriateness of 23vPPV and influenza vaccination programs for the prevention of pneumonia in the elderly.

Secondary objectives and their contribution to the current state of knowledge are outlined in detail in 1.2.3.

Detailed methods for undertaking the study are presented in the following chapter.
Chapter 2 Methods

2.1 Overview

This chapter describes the methods used for the case-cohort study proposed in Chapter 1 and upon which all subsequent chapters in this thesis are based. The study aims to estimate VE of 23vPPV over and above influenza vaccine in terms of reducing hospitalisation for CAP in elderly Victorians. The rationale for why particular methods were chosen is presented here, or in Chapter 1 where appropriate.

Additional detail is reported in the methods sections of individual chapters, in particular for those other than chapter 5 (addressing the key outcome of VE).

2.2 Study design

2.2.1 Choice of case-cohort design

A case-cohort study was chosen as the best non-experimental design to estimate VE (described below). Although a randomised controlled trial (experimental) design would best control for both known and unknown confounders, since subjects are randomly allocated to the exposure of vaccination, this study design was not feasible because the vaccines in question were in widespread use with a funded population program in place for the elderly. Non-experimental study designs other than the case-cohort design were also considered. A prospective cohort study of subjects with known vaccination (exposure) status followed prospectively for the outcome of hospitalisation with CAP would have been a strong design in terms of providing a logical temporal sequence from exposure to outcome and a high likelihood of good quality data unaffected by recall bias. However, it would have been prohibitive in terms of the time and resources required to follow a large number of elderly subjects for the outcomes of interest, with potential for considerable loss to follow-up.

In addition, there are no national or jurisdictional administrative databases of immunisation status for adults in Australia, and since such databases typically contain few fields beyond demographic descriptors, this would have also reduced the ability to control for potential confounders in estimating VE, as has occurred with some previous studies.

In choosing a case-cohort design to answer the study question, the limitations of retrospective data collection were recognised as well as the potential for selection bias in defining the cohort (discussed in detail below). In addition, as for all non-experimental studies, the likelihood of being vaccinated is never truly random compared with a randomised controlled trial, and depends upon personal factors that affect the decision to be vaccinated, as well as the targeting strategies used by individual
vaccine providers. However, advantages of this design over a controlled trial are that it involves relatively fewer participants, the necessary information can be obtained within a short time, and the results are based on actual field conditions.

In particular, the case-cohort design was preferred over a case-control study. Case-cohort studies are an accepted method for evaluating VE and are essentially a variant of the case-control study where the comparison group is selected to represent the entire population (the cohort), and is a random sample (independent of case characteristics) of all persons in the population from which the cases are drawn, rather than only those who are unaffected (controls). Hence some cases may also be sampled in the cohort. This design has advantages over a case-control study because of the random sampling of cohort subjects, and the ability to make external comparisons. Cohort selection is also rapid because subjects are selected independently of case characteristics and can begin immediately. In general, the rare disease assumption is also unnecessary in case-cohort studies.

The decision to use the case-cohort approach to measure incidence depends on how it is thought the vaccine works. Whereas a case-control approach assumes that all vaccinees have their risk of disease reduced by the same amount, the case-cohort approach generally assumes that a certain proportion have complete immunity while others remain susceptible.

Compared with a case-control study where incidence is measured as the average instantaneous incidence rate or incidence density rate (number of cases divided by person-time at risk), a case-cohort study measures incidence as the probability of developing the disease during the study period (number of cases divided by the initial population at risk). The comparison group for a case-cohort study is therefore a sample of the total initial population from which the cases came (as opposed to a sample of persons who had not yet developed the disease at the time the case was diagnosed). In this case-cohort study, a modified approach was used by undertaking incidence density sampling within individual months of the study (see 2.5.1).

### 2.2.2 Measurement of VE

In a case-cohort study, unlike a case-control study, the RR for vaccination status is directly estimated from the ratio of incidence proportions without the need to obtain information on every cohort member. VE can be calculated using the formula $VE = 1 - RR$, where RR is the risk ratio of becoming a case with respect to vaccination status, or the ratio of incidence in the vaccinated population divided by the incidence in the unvaccinated population.

To account for the seasonality of influenza (see 2.10.1), VE for influenza vaccine was estimated within the influenza seasons of the study period, avoiding violation of the proportional hazard assumption implicit in estimating incidence density rate odds ratios.
2.2.3 Choice of hospitalised subjects

Criticism of previous non-experimental studies examining VE for influenza vaccine and 23vPPV has focused on the problems of selection bias (in particular use of high risk or non-representative study samples), lack of adjustment for confounders and the use of interim data (described in Chapter 1).

The ability to select a representative sample to enable generalisation of the study results to as broad a population as possible was an important consideration for this study. Ideally, a randomly selected community-based sample of elderly persons would have been utilised to enable generalisability of results to the wider community of elderly persons. However, a hospitalised cohort was chosen for important practical reasons.

The ability to examine the role of comorbidities was considered essential in terms of these being potential confounders for both vaccination status and the outcome of pneumonia. Use of a hospitalised cohort enabled examination of hospital records for comorbidities, blinded to whether subjects were cases or not. The community-based alternative would have required obtaining details of comorbidities from subjects’ primary providers(s). It was felt that the likely level of cooperation from primary providers, from whom accurate data on the key exposure measure of vaccination status was also required, was likely to be dramatically and negatively affected if excessive amounts of information were requested. Provider reporting on comorbidities might also be biased by knowledge of case or cohort status. While it was possible that hospitalised subjects were potentially more likely to suffer from comorbidities than community-based subjects, there was sufficient uncertainty regarding how this would affect vaccination status for the choice of hospital-based subjects to be justified. I was unable to find direct comparisons of vaccination rates for hospitalised and non-hospitalised patients. However, it is known that despite recommendations to the contrary in many countries, hospital staff are not successful in improving inpatient vaccination coverage. Similarly, the presence of comorbidity is not clearly related to vaccination status. For example, some studies have found that subjects with cardiovascular disease, diabetes, depression and cognitive impairment are less likely to be vaccinated or have vaccination coverage that is no different to the wider population. Others have found that the extent of comorbidity is directly related to likelihood of vaccination. Use of a hospitalised cohort also enabled selection of cases based upon internationally recognised and standardised descriptors: ICD-10-AM codes (see 2.4).

Hospitalised study samples are commonly utilised in medical research and their general advantages and disadvantages are well known. Advantages include easy identification of both cases and comparator subjects, potentially increased likelihood of recall of antecedent events or exposures (reduction of recall bias), likely exposure to the same intangible selection factors that influence cases to come to the particular hospital, and higher levels of cooperation compared with “healthy” individuals. The major disadvantage is that hospitalised subjects may not be representative of the same exposures experienced by the population from which cases were derived. This is discussed
further in Chapter 5. This case-cohort study of hospitalised subjects was therefore designed such that its results, at worst, could be generalisable only to a hospitalised population, with a likely higher degree of accuracy for the key exposure variable of vaccination and for essential comorbidity data compared with alternative designs.

Adjustment for confounders in this study is discussed in 2.10.

2.3 Study period

The time period of interest was 1 April 2000 and 31 March 2002.

2.4 Selection of cases

The presence of CAP defined cases for the purpose of determining VE (see 1.5 for rationale). All cases of pneumonia were identified from monthly discharge lists (indicating completed admissions) of persons aged ≥65 years from two large, adult teaching hospitals in Melbourne, Australia: the Royal Melbourne Hospital (RMH) and Western Hospital (WH). A case was defined by the recording of ICD-10-AM codes J10-J18 (pneumonia including those cases due to influenza) in any of the 14 diagnostic code positions6 (Appendix 1).

Use of codes J10-J18 is consistent with previous studies in the international literature examining hospitalisation for pneumonia due to influenza and Streptococcus pneumoniae (see Background for further detail).57,58,60,61,102 The rationale for use of ICD-10 codes has been outlined previously (see 1.6) and relates to the lack of a clear clinical definition for pneumonia (a particular problem in the elderly), the availability of internationally standardised codes to facilitate case identification, and efficiency. Validation of ICD-10 coding as a diagnostic tool for identifying patients hospitalised with pneumonia is examined in Chapter 4.

Nosocomially acquired pneumonia cases were subsequently excluded, defined as pneumonia diagnosed more than 48 hours after admission to hospital.123,180 If an individual subject appeared on the hospital discharge list more than once in any given month, one episode was selected at random, and the others excluded. Likewise, for month-to-month repeat admissions with pneumonia for an individual, the first selected admission was retained, and subsequent episodes excluded. This was important because of the possibility of participation in the study affecting the exposure of vaccination status for subsequent presentations (the Hawthorne effect)181 and to improve comparability of subjects. A similar approach was utilised for cohort selection.

As per a case-cohort design, cases were also eligible for selection in the cohort.
Subjects were excluded from monthly discharge lists if not resident in Victoria or if admitted for short-stay procedures such as dialysis and chemotherapy (ICD-10-AM codes Z49.1, Z49.2 and Z51.1) (see 2.5.3).

2.5 Selection of the cohort sample

2.5.1 Monthly sampling

Subjects for the cohort sample were randomly selected from the monthly cohort of all persons $\geq 65$ years discharged from the two hospitals for the time period of interest, frequency matched to cases.

In using a case-cohort design, vaccinated and unvaccinated populations must ideally be sufficiently alike in all relevant characteristics other than vaccination to allow a reasonable conclusion that vaccination effectiveness (determined under field conditions) approximates vaccine efficacy (determined under “ideal” or experimental conditions). To improve the comparability of cases and the cohort, sampling within defined time periods (approximating incidence density sampling) was particularly important because of the seasonal nature of the outcome of interest. Figure 2.1 shows a seasonal pattern for pneumonia hospitalisations, with peaks during winter months. Sampling by month was chosen for the study because a) there is a clear seasonal pattern by month; b) while pneumonia can recur, the period of one month is reasonable clinically in terms of recovery from one episode and the possibility of another episode; and c) at the conclusion of each month of the study period, a list of persons aged $\geq 65$ years discharged from each hospital was available from the medical records department of each hospital. This list became available following coding by medical records staff, usually occurring within 10 days of the completion of each month.
Based on data available before commencement of the study for the three financial years 1996-1999, it was estimated that admissions from the two hospitals of interest would represent approximately 11% of the total hospitalised population aged ≥65 years in Victoria, or 13% of all hospitalisations for pneumonia for this age group (personal communication JS Ewan, Victorian Inpatient Medical Database, Department of Human Services Victoria, 15 May 04).

### 2.5.2 Over-sampling

Over-sampling was conducted to allow for subsequent exclusion of repeat admissions among the cohort, with the aim of avoiding over-representation due to an increased probability of selection for certain individuals. In addition, in a case-cohort study, it is important to allow for those cohort subjects that are also selected as cases (because all cases are included in the study), if the same statistical power and efficiency are to be achieved (these are determined by the number of distinct cases and non-cases).\(^{172,174}\) The “cohort” sample was therefore formed by randomly selecting a total of 1.2 times the number of cases from the entire monthly discharge list at each hospital using a random number generator. This allowed for approximately 5% of the cohort also being cases, and 15% of the cohort being repeat admissions.

### 2.5.3 Exclusions

As for cases, within each month, a subject could be selected only once. This was achieved by first reducing the monthly list by selecting at random one completed hospital admission per subject (if they had been discharged more than once in a calendar month) to give each subject an equal
probability of selection. At the end of the study, repeat admissions for the same subject from month to month were managed by retaining the first selected admission, and excluding subsequent admissions.

The cohort for comparison in a case-cohort study must ideally represent the source population from which cases are derived, and represent persons who if a case, would have been identified and included.\textsuperscript{170} To improve the comparability of the study population with the general population of elderly persons in Victoria and to ensure access to the Victorian vaccination program, subjects were also excluded if non-residents of Australia or if an interstate visitor (where Victoria was not the usual state or jurisdiction for medical treatment). To maximise the representativeness of selected admissions in terms of potential for admission with CAP, subjects were also excluded if admitted for a consecutive admission between RMH and WH with the same diagnosis, or for short-stay procedures such as dialysis and chemotherapy (ICD-10-AM codes Z49.1, Z49.2 and Z51.1). These latter exclusions based on ICD-10 codes were conducted on the complete monthly list.

### 2.5.4 Adjustment for frequency of admission

Since those who were admitted to hospital more frequently over the two-year study period were more likely to be selected, adjustment was made for potential selection bias by using a weight equal to the inverse of the total number of admissions for each subject over the duration of the study period.

### 2.5.5 Blinding

As for a case-control study, in a case-cohort study, the subjects in the cohort for comparison must ideally be selected independently of the exposure of vaccination status.\textsuperscript{179} Cohort subjects were randomly selected from complete hospital discharge lists before any information on vaccination status had been sought.

### 2.5.6 Matching

Matching can introduce selection bias, and is particularly problematic if it occurs on a factor that is correlated with the exposure of vaccination, resulting in bias of the effect towards the null hypothesis.\textsuperscript{172} It can also potentially harm statistical efficiency if it occurs on a variable associated with exposure but not disease.\textsuperscript{182} As there was no a priori reason to expect dramatically different age profiles between cases and the cohort, matching was not performed except by month of discharge through monthly sampling (see 2.5.2 and 2.10).
2.6 Exposure of interest: Vaccination status

2.6.1 Definition of vaccination status

Vaccination status was classified as “confirmed” if a complete vaccination date (day, month and year) was provided from a hospital, general practitioner, other vaccine provider, or nursing home record within a specified period (14-365 days prior to hospital admission for influenza vaccine, and 14-1825 days (5 years) prior for 23vPPV); “unconfirmed” if the vaccine was reported as given but no vaccination date or a partial date (for example, month and year only) was provided, “unvaccinated” if the vaccine was reported as not given (and there was no evidence to the contrary) and “unknown” if none of the above. As with previous studies, 14 days was chosen as the period required to establish vaccine-induced immunity.\textsuperscript{183} In order to minimise potential misclassification bias, only “confirmed” dates were used as evidence of vaccination in analyses.

Although not used to define vaccination status for the purpose of the main analysis estimating VE, evidence of prior vaccination was also sought from hospital records (including medication charts, outpatient pharmacy prescriptions or appointment notes) and from subjects (self-report) (Appendix 2) or their next of kin (Appendix 3) in the event of a subject having been deceased at the time of scheduled interview. These data were used for secondary objectives of the thesis, including the validity of self-reported vaccination status, and estimations of in-hospital opportunistic vaccination.

2.6.2 Blinding

It was essential to ascertain vaccination status in an unbiased fashion, in an effort to best approximate the ideal conditions of a randomised, controlled trial.\textsuperscript{170} Vaccine provider interviews were therefore conducted blinded to the case or cohort status of subjects. ICD-10 codes and case-cohort status were not known to research assistants collecting data, and were not integrated with the database until after data collection for the study was complete. Data quality should therefore be similar in relation to exposures (vaccination) and other characteristics for both cases and the cohort subjects. Although staff may however have formed their own opinion as to whether subjects had pneumonia during the review of hospital records, it is unlikely that exposure data could have been greatly affected by this since data collection from vaccine providers (vaccination status) and subjects was conducted at different times and not necessarily by the same person, and did not seek information about pneumonia.

2.7 Summary of methods for secondary objectives

Additional information on methods related to secondary objectives (see 1.2.3) is reported in the methods sections of individual chapters.
2.7.1 Epidemiology of hospitalisation with CAP

Objective: To describe for elderly Victorian inpatients the epidemiology of CAP including burden of disease, outcomes and risk factors.

Trained research assistants used a pre-tested data collection form to review hospital records to ascertain the presence of CAP based on notation by the clinical team responsible for the patient (Appendix 4). If present, they sought documentation of some additional epidemiological features including symptoms and signs commonly associated with pneumonia, and reviewed laboratory and drug records as well as radiology reports (detailed below). The burden of disease attributable to hospitalisation with CAP was measured primarily in terms of length of hospital stay and/or intensive care unit admission, mortality and place of discharge.

Risk factors for CAP were identified before study commencement via review of the published medical literature and based upon biological plausibility, and later examined in multivariate analysis for all study subjects. Factors collected from record review included age, gender, place of residence, English as a first language, marital status, previous hospitalisations, previous provider visits or hospitalisation for pneumonia, smoking habits, excessive alcohol intake, presence of diabetes, cardiovascular disease, immunosuppression, other respiratory disease, renal disease, rheumatological disease, liver disease, cerebrovascular disease and history of aspiration (Appendix 4). Similar factors were studied as potential predictors for mortality associated with hospitalisation with CAP, in addition to intensive care unit management and extent of consolidation on CXR. Secondary objectives and their methods are described in detail in Chapter 3.

2.7.2 Validation of ICD-10 coding for pneumonia

Objective: To assess the validity of using ICD-10-AM codes to retrospectively identify CAP among elderly Victorian inpatients.

Sensitivity analyses were conducted comparing cases of pneumonia identified by ICD-10 codes J10-J18 in hospitalised patients against three reference standards: clinical notation of pneumonia, CXR reports consistent with pneumonia, and a combination of both. Radiologist reports of CXRs undertaken as part of routine management of eligible subjects were reviewed by trained research assistants using pre-specified criteria. Sensitivity, specificity, PPV and NPV were estimated along with percentage agreement (with kappa statistics) for ICD-10 codes compared with the three reference standards. For those subjects with notation of pneumonia documented, records were reviewed for clinical signs and symptoms commonly associated with pneumonia, including fever $\geq 37.5^\circ$C, shortness of breath, cough, sputum production, crackles (crepitations), pleuritic chest pain and documented aspiration.


### 2.7.3 Vaccination coverage

**Objective:** To estimate vaccine coverage with 23vPPV and influenza vaccine for elderly Victorian inpatients following the introduction of a publicly funded program.

Based on obtaining complete dates of vaccination reported by vaccine providers, estimates were made for annual influenza vaccine coverage, 23vPPV coverage within the previous five years and cumulative 23vPPV coverage over the study period for the cohort. Estimates were adjusted for selection probability to examine any effect from increased likelihood of selection due to repeat admission. Factors predicting an incomplete vaccination status were examined using multivariate analysis. Those included in the model were based upon biologically plausibility and literature review.

### 2.7.4 Validity of self-reported vaccination status

**Objective:** To assess for elderly Victorian inpatients the validity of self reported vaccination status for 23vPPV and influenza vaccines as an indicator of true vaccination status.

The validity of self-reported vaccination status for the cohort was examined by comparing self-report against the gold standard of complete dates of vaccination provided by vaccine providers. The effects of various factors on the ability to accurately report vaccination status were examined. These included age, gender, case status, discharge location, comorbidities, correct vaccination status with one vaccine, number of hospitalisations, number of vaccine provider visits and years since vaccination (for 23vPPV).

### 2.7.5 Opportunistic vaccination

**Objective:** To assess opportunistic vaccination rates for 23vPPV and influenza vaccine among elderly Victorian inpatients, and inform strategies for improvement through knowledge of missed opportunities and risk factors for non-vaccination.

The total number of provider-subject encounters prior to hospitalisation was determined from hospital record review (number of hospitalisations for the hospital of the selected (Appendix 4) and self-report of doctor visits among those consenting to completing a questionnaire (Appendix 2). Encounters were measured over the year prior to hospitalisation (23vPPV and influenza vaccine), during the four years prior to this (23vPPV), and during periods of “peak influenza vaccination” (influenza vaccine) (see 7.4.3). Comparisons between vaccinated and unvaccinated subjects were made. Factors predicting unvaccinated status prior to admission were examined. Secondary analyses were conducted including only subjects completing interviews themselves (for self-reported provider visits) and comparing hospitalised subjects with and without CAP. The rate of in-hospital opportunistic vaccination was estimated for unvaccinated subjects alive at discharge and not
discharged to a hospital setting. Recording of vaccination status by hospital staff and self-reported acceptability of vaccination (had it been offered) was examined for unvaccinated subjects who completed interviews themselves (Appendix 2).

2.8 Data sources and quality assurance

Data were sourced from subject hospital records, and telephone interviews with subjects (or their next of kin if deceased), and their vaccine providers. All data collection was conducted blinded to the case status of subjects.

2.8.1 Hospital records

Subject hospital records were reviewed by trained research personnel using a standardised form (Appendix 4) with an accompanying detailed instruction manual, for a range of information including demographics, confirmation of pneumonia, vaccination status, comorbidities, admission outcomes and vaccine provider details. Pilot data from previous studies of chronic obstructive pulmonary disease at RMH indicated that 85-95% of hospital records would contain comments on the data fields of interest (personal communication Prof Donald Campbell, February 2000). For patients with pneumonia noted as a diagnosis by medical staff in the hospital record, research personnel collected further data. Electronic laboratory records were reviewed for details of investigations performed, and drug charts, referral and discharge letters for use of antimicrobials.

2.8.2 Subject interviews and consent

An introductory letter was mailed to subjects (or their next of kin if deceased) explaining the nature of the study and advising that they would be contacted by telephone. A maximum of five calls were made to contact selected subjects unless an answering machine message was able to be left, in which case a maximum of three further calls were made. If the subject was not successfully contacted using this process, “no response” was recorded in the database. For those subjects able to be contacted, verbal consent was sought to participate in a questionnaire and/or to contact their medical practitioner(s) or other nominated vaccine providers for details of vaccination status (Appendix 2). Subject interviews were administered by trained personnel using a pre-piloted questionnaire (Appendix 2) with an accompanying instruction manual, to confirm demographic data, self-reported vaccination status, vaccine provider contact details, visits to a doctor in the past year and if unvaccinated, willingness to receive either vaccine if it had been offered.

Subjects were advised they were under no obligation to participate and that all information provided would be strictly confidential. If deceased, a modified letter was sent to the subject’s next of kin no earlier than four weeks after the recorded date of death (Appendix 3). It was important to attempt to include information from deceased cases, since they may have died from the outcome of interest.
For non-English speakers or frail elderly, alternative arrangements were made to conduct interviews with a trained telephone interpreter or a nominated family member. With the exception of deceased subjects, the aim was to conduct interviews within four weeks of establishing eligibility for study participation.

### 2.8.3 Vaccine provider interviews

A covering letter and questionnaire (Appendix 5) was faxed or mailed to all known vaccine providers advising that the subject or next of kin had consented to the provision of information on vaccination status for 23vPPV and influenza vaccine. Where requested, written confirmation of this consent was provided. The questionnaire sought to confirm a record of influenza vaccine within the year prior to admission or 23vPPV within the five years prior to admission and, if so, to specify the vaccination date (day/month/year). Details could be returned by facsimile or within the reply-paid envelope provided. Vaccine providers who had not responded within seven days were offered the opportunity to answer the two questions by telephone. Where long delays were experienced in receiving these data, study staff offered to visit the practice to assist in their collection.

### 2.8.4 Quality Assurance

All aspects of the study were piloted in full for one month before commencement of the study proper. This enabled refinement of study protocols, training procedures and data collection forms.

I worked with research assistant and data entry staff on a daily basis for the purpose of general training, trouble shooting and monitoring of data collection, but also undertook weekly formal meetings. I also chaired the collaborator group meetings which occurred weekly for the first three months, then fortnightly for three months, then monthly for the duration of the study. This group was used as an additional forum to identify and resolve issues related to the study such as design, data collection and data entry. Data were formally reviewed fortnightly for quality assurance purposes in relation to data entry and consistency of collection in line with study protocols. I also intermittently monitored subject interviews for consistency of delivery as per the training manual.

Record review, subject interviews and vaccine provider interviews were conducted blinded to the case or cohort status of subjects. Codes were not made available to research assistants responsible for data collection; nor were they integrated with the general database until after completion of the study. The quality of data extraction for exposure (vaccination) and other characteristics was therefore not expected to differ between cases and the cohort subjects.
2.9 Sample size considerations

Approximately 5% of all admissions to hospital in persons aged ≥65 years are due to pneumonia (Table 2.1). Over the three years prior to the study commencement, there were 4,717 admissions for pneumonia at RMH and WH among persons aged ≥65 years.

Table 2.1. Pneumonia hospitalisations among persons aged ≥65 years, RMH and WH by year, 1 July 1996 – 30 June 1999. (Source Victorian Inpatient Minimum Dataset)*

<table>
<thead>
<tr>
<th>Year</th>
<th>RMH</th>
<th>WH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>1996/1997</td>
<td>673 (4)</td>
<td>778 (6)</td>
<td>1451 (5)</td>
</tr>
<tr>
<td>1997/1998</td>
<td>865 (4)</td>
<td>1055 (7)</td>
<td>1920 (6)</td>
</tr>
<tr>
<td>1998/1999</td>
<td>680 (3)</td>
<td>666 (5)</td>
<td>1346 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>2218 (4)</td>
<td>2499 (6)</td>
<td>4717 (5)</td>
</tr>
</tbody>
</table>

* Pneumonia hospitalisation data (including influenza) (ICD-9-CM Code 480-487, equivalent to ICD-10-AM codes J10-J18) in any diagnostic field position (1-14).
† Pneumonia hospitalisations as a percentage of total hospitalisations for the specified time period.

Figure 2.1 (above) shows on average there were 131 hospitalisations with pneumonia per month for persons in this age group admitted to the two hospitals, with a peak of 259 in July 1997 and a nadir of 75 in February 1999.

Based on these data, an estimate of 1300 patients hospitalised with pneumonia at the two hospitals in one year was conservative. Assuming 85% (1105) would be CAP, 90% (995) of these records could be located and 70% of subjects (696) consented to participate and had vaccination data available, approximately 700 cases would be available for the study.

Based on RMH data from 1998, it was expected that most of those who received 23vPPV would also receive influenza vaccine. These data suggested that 30% of all hospital inpatients aged ≥65 years had influenza vaccine alone, 35% had both influenza vaccine and 23vPPV, and 5% had 23vPPV alone. Assuming these levels of vaccine coverage, a case-cohort study with 1200 cases and 1200 randomly selected cohort subjects would have 80% power to detect simultaneously (using a Bonferroni-corrected Type I error rate of 0.025) a VE of 30% for influenza vaccine (RR 0.70) and an incremental VE for the combined vaccines of 25% (RR 0.75), corresponding to a total VE for both vaccines of 48% (RR 0.52 or 0.70 x 0.75).
2.10  **Statistical methods**

2.10.1  **Pre-specified analyses**

In examining the primary hypothesis for the study, to determine whether 23vPPV provides additional benefit over and above influenza vaccination in preventing hospitalisation for CAP in elderly Victorians, pre-specified analyses were undertaken to estimate RRs with 95% confidence intervals (CI) for:

a) the effect of influenza vaccine (alone or in combination with 23vPPV) versus neither vaccine and

b) the incremental effect of 23vPPV by comparing influenza vaccine plus 23vPPV to influenza vaccine alone.

Vaccine effectiveness was calculated using the formula 1-RR.

Influenza vaccination effectiveness was also examined during the two influenza seasons of the study period, defined according to active Sentinel Influenza Surveillance reports for Victoria.\(^31,113,187\)

During the study years, these were defined as 14 July 2000 to 28 Oct 2000, and 6 May 2001 to 7 Oct 2001. In addition, where the effects of both vaccines were examined together, the entire study period was included in the analysis.

In addition, to examine any potential effect on vaccination status from repeat admissions with CAP, the pre-specified analyses were conducted firstly by including only first admissions with CAP (the standard approach for all analyses), and secondly, by including all hospitalisations with CAP.

To examine any potential effect upon estimates for VE due to those with unknown vaccination status, sensitivity analyses were performed reassigning these to a) vaccinated and b) unvaccinated status.

Finally, to examine any effect due to waning of immunity inferred by influenza vaccine, positive influenza vaccination status was restricted to those receiving vaccine between 14 days and six months prior to admission.

2.10.2  **Exploratory analyses**

The following exploratory analyses were subsequently conducted using logistic regression to examine the effects of:

a) 23vPPV (alone or with influenza vaccine) versus neither vaccine,

b) both vaccines versus neither vaccine,

c) influenza vaccine (alone or with 23vPPV) versus no influenza vaccine,
Chapter 2: Methods

d) 23vPPV (alone or with influenza vaccine) versus no 23vPPV,
e) 23vPPV alone versus no 23vPPV,
f) an interaction term (compared with a step-wise approach), to explore potential supra-additive effects of vaccination with influenza vaccine plus 23vPPV
g) years since vaccination with 23vPPV,
h) vaccination with either vaccine on deaths in hospital associated with pneumonia or all-cause mortality using final models from the pre-specified analyses and the exploratory analysis examining 23vPPV alone, and
i) an interaction term, to explore potential supra-additive effects of age on VE using final models from the pre-specified analyses.

In the case of separate analyses for influenza vaccine and 23vPPV, a Bonferroni correction was made,\textsuperscript{188} (each null to be rejected at 2.5%) to maintain an overall 5\% type 1 error rate.

2.10.3 Adjustment for covariates

In a case-cohort study, adjustment for covariates can be made using logistic regression. Corrections were made to the variance estimates to allow for monthly recruitment and hospital of recruitment by including month and hospital of recruitment as independent variables in all regression analyses. Although adjusting for the effect of month by month recruitment imposes a degree of matching which could lead to biased variance and parameter estimates,\textsuperscript{172} because there were relatively few (24) large matched groups each with 100 or more subjects, the bias in parameter estimates is therefore inconsequential. Adjustment was also made for selection probability in the cohort using weighting (see 2.5.4).

Variables representing potential confounders (and/or predictors of hospitalisation with CAP) considered for inclusion in the model were based upon literature review and biological plausibility, and were identified prior to study commencement.\textsuperscript{147,184} These included age, gender, residence, English as a first language, marital status, previous hospitalisations, previous provider visits or hospitalisation for pneumonia, smoking habits, alcohol consumption, presence of diabetes, cardiovascular disease, immunosuppression, other respiratory disease (including asthma, chronic obstructive airways disease), renal disease, rheumatological disease, liver disease, cerebrovascular disease and history of aspiration (Appendix 4).

To determine which variables should be included in logistic regression statements estimating VE, the association between each factor and hospitalisation with CAP was examined using individual logistic statements without vaccination status and adjusted for hospital of discharge, month of
sampling, and selection probability (see Cohort Selection, above). Vaccination status was not included so as to examine the impact on CAP from the variable of interest alone. Covariates with p-values <0.20 were retained for multivariate analysis with the exception of four variables with >15% missing data. Their impact was examined by addition only to the final models.

Backward stepwise logistic regression was used to estimate the RRs of the vaccinated versus unvaccinated populations to determine VE (1-RR) against hospitalisation with CAP, adjusted for hospital of discharge, month of sampling, and selection probability. Step-wise elimination of variables was determined by removing the variable with the largest Wald p-value larger than 0.2. The impact of adding or removing independent variables from the model was assessed by examining the stability of the coefficients of all other variables in the model. Because of weighting adjustments in regression statements, examination of log likelihood ratios was not possible. The final model was determined when all remaining variables had a p-value <0.20. This inclusive approach was taken rather than stopping the model when all remaining “prognostic” variables were <0.05 as the interest was in including potential confounders rather than in the prediction of hospitalisation with CAP. Stata version 9.1 was used.

2.11 Summary of management of design limitations

The following approaches were used to minimise bias and confounding:

2.11.1 Selection bias

- random selection of the cohort subjects: to improve cohort representativeness
- frequency sampling by month: to address issues of seasonality of hospitalisation with CAP and improved representativeness of cohort subjects
- weighting: to adjust for over-representation by those who were admitted to hospital more frequently
- exclusion of non-Victorian residents: to ensure opportunity for exposure to the funded vaccination program
- exclusion of those likely to be unrepresentative of potential CAP admissions: to maximise the representativeness of selected subjects in terms of potential for admission with CAP
- minimal matching by month of hospital discharge only
• over-sampling was also conducted to allow for over-representation by frequently admitted subjects, and for cohort subjects also selected as cases

2.11.2 Measurement bias

• Conducting record reviews, subject interviews and vaccine provider interviews blinded to the case or cohort status of subjects: to ensure similar quality of data extraction for exposure (vaccination) and other characteristics between cases and cohort subjects

• Rigorous interviewer training and monitoring, use of a data collection manual and monitoring of data quality: to ensure consistent and accurate data collection

• Piloting of all aspects of the study for one month before commencement of the study proper: to enable refinement of study protocols and data collection forms, and to ensure consistent, accurate data collection.

2.11.3 Confounding

• Multivariate analysis was conducted using logistic regression to adjust for suspected confounders based upon biological plausibility and literature review.

2.11.4 Interim analyses

• The reporting of results based only on analyses of interim data has been a weakness of some previous publications from non-experimental studies.\textsuperscript{58,71} No interim analyses were conducted for this study.

2.12 Ethics approval

The study was approved by the Human Research Ethics Committee, Melbourne Health (ref 2000.022).
Chapter 3 Epidemiology of community-acquired pneumonia presenting to hospital in persons aged ≥65 years

3.1 Overview

Current Australian data for CAP are limited to four studies, each with less than 200 subjects,\textsuperscript{19,120,185,191} with none focusing on the elderly or examining risk factors for disease or related mortality. Data are therefore lacking for many aspects of basic epidemiology for CAP in elderly Australians. The burden of disease attributable to CAP will continue to increase as the Australian population ages, and is important to document in order to direct preventive strategies and management, and minimise impact. After reviewing existing literature on CAP in the elderly, this chapter presents data from the thesis which comprise the largest and most comprehensive study of CAP in elderly Australians to date. It focuses primarily on describing general epidemiology including seasonality, burden of disease, mortality and risk factors.

3.2 Objectives

Primary objectives are to describe for hospitalised elderly Victorians the epidemiology of CAP, and discuss in relation to published data; including seasonality, burden of disease, outcomes including mortality, risk factors for CAP versus non-CAP, and risk factors for mortality in those with CAP.

Secondary objectives, given limitations of available data (detailed in 3.4.1 and 3.4.2), are to describe common symptoms and signs associated with CAP, investigation types performed and use of antimicrobial agents.

3.3 Background

3.3.1 Disease overview and burden

Community-acquired pneumonia is pneumonia contracted by individuals outside the hospital or within 48h of admission.\textsuperscript{180} It is one of the leading causes of morbidity and mortality in persons aged ≥65 years,\textsuperscript{192} with incidence and mortality rates increasing with advancing age.\textsuperscript{131} Disease incidence peaks in winter and spring\textsuperscript{193}, especially for cases due to \textit{S.pneumoniae}.\textsuperscript{20} In Victoria, approximately 400 people aged ≥65 years die each year from influenza and pneumonia\textsuperscript{194} while
thousands more are hospitalised (Figure 2.1). Limited data from South Australia suggest CAP occurs in approximately 2/1000 adults per year. Limited data from South Australia suggest CAP occurs in approximately 2/1000 adults per year. Among elderly populations, an incidence of 10.4/1000 per year has been reported from Spain, and in Finland, Jokinen et al estimated age-specific incidences of 15/1000 among 60-74 year olds, increasing to 34/1000 for those aged ≥75 years.

Limited data on hospitalisation associated with CAP show variability by setting. Vila-Corcoles et al estimated the proportion of elderly persons with CAP requiring admission to hospital as 81% (8.5/1000 elderly persons per year), while in the USA, an incidence rate for hospitalised CAP of 18.3/1000 population ≥65 years has been reported. Lower figures have been reported in other settings: Marston et al reported a rate of 1/1000 elderly persons per year for two Ohio counties and Bochud et al found 13% of all-age outpatient pneumonia cases required admission. In South Australia, CAP was the cause of two percent of all adult overnight hospital admissions. Hospitalisations comprise the greatest burden of disease due to pneumonia in terms of severity and health care costs.

ICU admission has been reported as occurring in 2-3% of elderly persons admitted with CAP, although a more recent, large prospective cohort study also from the USA found 22% of the cohort of 623718 admissions for CAP in elderly persons required ICU management. This latter study found that a complex course (ICU admission or mechanical ventilation) was more likely for younger patients (27% in 65-69 year olds versus 15% in those aged ≥90 years; p<0.001), males (24% versus 21%, p<0.001) and those with underlying disease (comorbidity index 1.26 versus 1.05; p<0.001).

The mean length of hospital stay in the elderly admitted with CAP is reported as between 7.6 and 21 days (range 4-69 days) for survivors. Elderly patients with CAP are likely to be hospitalised for longer than younger patients (7.8 days compared with 5.8 days). In the USA it has been reported that those admitted to ICU have a mean length of stay of 11.3 days. Slower resolution has been shown to be associated with severe illness, alcoholism, chronic obstructive airways disease, bacteraemia and multiple comorbidities. Of note, a prospective cohort study from Spain studying 101 persons aged ≥65 years hospitalised with pneumonia found no significant difference in length of stay compared to age, gender and date-matched controls admitted with a diagnosis other than pneumonia (10.8+/−11.6 days versus 9.1+/−13.3 days).

### 3.3.2 Investigation

Although various guidelines have been developed for investigation and management of CAP, empiric treatment is generally commenced in the absence of aetiological information and clinicians generally use their own judgement regarding the relative importance of undertaking investigations to obtain a specific diagnosis. Frequently used tests include blood cultures, sputum gram stain and culture, and thoracentesis if pleural fluid is present, with less routine investigations including urinary
antigen assays for \textit{L.pneumophila} and \textit{S.pneumoniae}, acid fast stain for mycobacteria, PCR testing of a range of specimens for particular pathogens (increasingly available), serological tests, transthoracic needle aspiration, bronchoscopy and biopsy.\textsuperscript{108} 

In the absence of a clear clinical definition for pneumonia or an ideal diagnostic test for microbiological diagnosis,\textsuperscript{180} CXR is useful to confirm the diagnosis of pneumonia and its severity. CXR is particularly relevant to establishing a diagnosis in elderly patients with a respiratory presentation, since co-pathology such as malignancy is more common, and associated pathology such as effusion important to recognise. Other radiological investigations such as chest computerised tomography (CT) are less routine.

### 3.3.3 Causative organisms

Even after extensive investigation, a causative agent is not found in about 50\% of cases of CAP.\textsuperscript{192} This figure varies in different settings. Two studies from the USA of all-age inpatients found a causative organism in 25\% and up to 81\% (17\% definite, 20\% probable, 44\% possible) respectively.\textsuperscript{20,200} A high quality prospective cohort study of active investigation of all outpatient and inpatient pneumonia cases \(\geq 15\) years for four municipalities in Finland found a causative organism in 183/345 (53\%) cases.\textsuperscript{13} Venkatesan et al found a causative organism for 43\% of 73 elderly inpatients in the UK\textsuperscript{198} while in Spain, Riquelme et al conducted extensive testing and established a diagnosis in 53/101 inpatients (42\%).\textsuperscript{199} Two Australian studies have identified specific aetiologic agents in 46\%\textsuperscript{120} and 77\%\textsuperscript{19} of all-age adult pneumonia inpatients (n=96 and 200 respectively). The study by Wilson et al included only severe CAP requiring ICU admission.\textsuperscript{120} A further small study from north-east Australia by Thompson et al also found that of 115/182 (63\%) persons with pneumonia who had blood cultures taken, 14\% had positive results, and 50\% of the 62/182 (34\%) who had sputum cultures taken were positive.\textsuperscript{191} 

Causative organisms for CAP vary in different settings and with severity of illness, although in general, \textit{S.pneumoniae} is the most likely cause, particularly in the elderly. In Australia, Lim et al reported the most common organisms identified among 106 adult inpatients with CAP as \textit{S.pneumoniae} (42\%), viruses (18\%), \textit{H.influenzae} (9\%), Enterobacteriaceae (8\%) and \textit{M.pneumoniae} (8\%).\textsuperscript{19} Similarly, Wilson et al reported \textit{S.pneumoniae} as the most common cause (42\%) of 96 cases of severe CAP followed by influenza A,\textsuperscript{120} and Thompson reported \textit{S.pneumoniae} and \textit{H.influenzae} to be the most common causes.\textsuperscript{191} Outside Australia, a large cohort of all-age adults in two Ohio (USA) counties hospitalised with CAP found the most commonly identified causative organisms were \textit{M.pneumoniae}, \textit{S.pneumoniae}, \textit{H.influenzae} and \textit{C.pneumoniae}.\textsuperscript{20} The study by Jokinen et al (described above) found the most common organisms among 345 cases to be \textit{S.pneumoniae}, followed by \textit{M.catarrhalis}, \textit{C.pneumoniae}, \textit{M.pneumoniae} and viruses,\textsuperscript{13} while Riquelme et al (described above) reported \textit{S.pneumoniae}, \textit{C.pneumoniae}, \textit{C.burnetti}, \textit{L.pneumoniae} and \textit{M.pneumoniae} as the most commonly identified agents. \textit{S.pneumoniae} was significantly more
frequent among patients aged ≥60 years (48%) compared with those aged <60 years (35%).¹³ A recent review of studies from 2003-2004 of CAP in the very old also confirmed the predominance of *S. pneumoniae* in the elderly.²⁰¹

### 3.3.4 Antimicrobial management

Many guidelines exist for management of CAP with antimicrobial agents. Some are risk factor driven and most are empiric and frequently include routine therapy for atypical pathogens.¹⁹² Duration of therapy with antibiotics is traditionally 7-10 days.¹⁹² Riquelme et al reported a mean of 2.3 antibiotics were used to treat 101 cases of pneumonia identified prospectively in Spain.¹⁹⁹ These were most commonly a combination of a second or third generation cephalosporin and macrolides (74), clindamycin in 15, a combination of second or third generation cephalosporins plus macrolides plus aminoglycosides in 14, penicillin in three, and macrolides alone in two subjects. In Australia, Lim et al reported that the most frequently used antibiotics among 106 adult inpatients with CAP were amoxicillin (39%) and erythromycin (29%).¹⁹

### 3.3.5 Clinical symptoms and signs

No one sign or symptom, nor combination of these has ever been shown to clearly differentiate pneumonia from other respiratory illnesses (see 4.3.2 for further detail).¹¹⁹ However, a number of studies have attempted to describe the most common symptoms and signs associated with pneumonia. Metlay et al has described the most common respiratory symptoms occurring in patients ≥18 years with pneumonia; defined as acute onset of one or more of a broad array of symptoms suggestive of acute illness plus radiographic evidence of pneumonia within 24 hours of presentation. These were cough (82%), dyspnoea (69%), sputum production (65%) and pleuritic chest pain (32%).²⁰² In addition, this group described fatigue (330/583, 57%) and fever as the most common non-respiratory symptoms, and tachypnoea as the most common sign (388/583, 66%). A recent prospective study from New Zealand studied patients hospitalised with CAP (mean age 58 years) defined as an acute illness with new radiographic pulmonary opacity due to pneumonia. This study found the three most common symptoms were cough (88%), sputum production (64%) and chest pain (57%); and abnormal chest findings (81%) (most often crackles), fever (53%) and tachypnoea (52%) were among the most common signs.¹⁸ All commonly used surveillance definitions of influenza include cough and fever,¹¹²,¹¹⁵ although fatigue is also included in the Australian Sentinel Practice Research Network (ASPREN) surveillance system for ILI.¹¹⁴

Defining pneumonia in the elderly based on clinical signs and symptoms is further complicated by the fact that there is evidence for a less distinct clinical presentation with advancing age.¹²⁶ One large, prospective study of 1812 patients with pneumonia which adjusted for specified confounders found that those aged 65-74 years and ≥75 years reported a mean of 2.9 and 3.3 fewer symptoms respectively than those aged 18-44 years (of a possible 18 symptoms and signs).²⁰² An earlier study
by Marrie et al found that 26% of subjects aged ≥65 years had fever, compared with 56% of those aged<65 years.203

### 3.3.6 Risk factors for hospitalisation with CAP

Knowledge of risk factors for CAP is useful to target preventive strategies including vaccination. There are currently no published Australian data on risk factors for CAP in the elderly. While Thompson et al described comorbidities for inpatients with CAP (most commonly alcoholism, chronic lung disease, diabetes mellitus and immunosuppression) this 10 year old study of 181 cases of all-age adult inpatient CAP was unable to assess risk for CAP due to these factors in the absence of a comparison group.191 Similarly, Wilson et al described comorbidity for 96 adults admitted to ICU with CAP (most commonly chronic obstructive pulmonary disease, ischaemic heart disease, diabetes mellitus and immunosuppression) but again could not estimate risk for CAP associated with these factors.120 Patterns of comorbidity are similar to a large, well-conducted prospective cohort study from the USA that found underlying disease in more than two thirds of 600 000 cases of hospitalised CAP in the elderly; most commonly congestive heart failure, chronic pulmonary disease, and diabetes mellitus.21

Studies from outside Australia have established commonly occurring risk factors. Koivula et al studied all 4175 inhabitants aged ≥60 years in one township in Finland. Independent risk factors in multivariate analysis for the 274 episodes of CAP were alcoholism (RR 9.0; 95%CI 5.1-16.2), asthma (RR 4.2; 95%CI 3.3-5.4), immunosuppression (RR 3.1; 95%CI 1.9-5.1), lung disease (RR 3.0; 95%CI 2.3-3.9), heart disease (RR 1.9; 95%CI 1.7-2.3), institutionalisation (RR 1.8; 95%CI 1.4-2.4), and greater age (RR 1.5; 95%CI 1.3-1.7 for ≥70 years versus 60-69 years) (this group was unable to assess smoking, however did assess renal disease and malignancy).204 Kaplan et al conducted a large prospective cohort study and reported a five fold increase in incidence with age from 8.4/1000 in those aged 65-69 years to 48/1000 in those aged 90 years or older.21 In addition, Riquelme et al conducted a case-control study in Spain for 101 inpatients aged ≥65 years, and age, sex and date matched controls and found independent risk factors for CAP were clinical suspicion of large volume aspiration (OR 10.8; 95%CI 1.7-66.8), and low serum albumin (OR 9.4; 95%CI 3.4-25.5) (non-significant factors included alcohol intake, smoking, mental state, nutritional status, dental problems, previous hospitalisation, swallowing disorders, quality of life, being bedridden and comorbidity).199 Of note, patients with immunosuppression or recent admission were excluded, as were cases with non-infectious pneumonia, and confidence intervals for the point estimates were wide.
3.3.7 Mortality and discharge location

Death associated with hospitalisation for CAP

Australian data on mortality associated with hospitalisation with CAP in the elderly are limited to three small studies but are consistent, with rates of 10-12% reported. Lim et al found a mortality rate of 10% among 106 adult inpatients (mean age 60 years) admitted with CAP (exclusions included patients with immunosuppression, pneumonia secondary to lung cancer, pulmonary infarction, cerebrovascular accident or coma). Lim et al studied 77 adult inpatients aged >55 years with CAP and an *S.pneumoniae* isolate and found a mortality rate of 12% (exclusions included lung disease requiring previous hospitalisation in the last five years, end-stage renal failure and immunosuppression). A study of consecutive pneumonia inpatients aged >10 years in north-eastern Australia reported an 11% mortality rate among 87 non-Aboriginal patients with CAP and 17% among 90 Aboriginal patients.

Studies from outside Australia of inpatients with CAP have generally reported mortality rates consistent with those from Australia. Kaplan et al estimated in-hospital mortality for elderly inpatients with CAP at 11% versus 5.5% for controls without pneumonia. Another large study from the USA using a prospective cohort design estimated an overall mortality rate for all-age adults with CAP of 9% compared with 12.5% among those >65 years. Similarly, Conte et al reported mortality rates of 9% (derivation cohort of 1000 randomly sampled cases from four states) and 12% (validation cohort of 1356 sampled randomly from a national database) for elderly inpatients with CAP ≥65 years. In the USA these rates mean that CAP is the fifth leading cause of death in persons aged ≥65 years, and is responsible for approximately 60,000 deaths annually. In the UK, a higher rate of mortality was found by Venkatesan et al who reported 24 deaths among 73 (33%) elderly persons hospitalised with CAP. Similarly, Riquelme et al reported 26 deaths among 101 (26%) elderly Spaniards admitted with CAP.

Not surprisingly, ambulatory patients have been shown to have a lower mortality rate (Bochud reported 2/107 (1.2%) cases) than those admitted to ICU (20-50%). An Australian study of 96 patients with CAP requiring ICU admission reported a mortality rate of 32%.

In examining mortality, it is important to use an appropriate time frame. Kaplan et al reported one year mortality adjusted for age for those discharged alive was 34% versus 25% for controls hospitalised without pneumonia. Differences were not explained by underlying disease and the standardised mortality ratio (standardised against the general population) was 2.7 for hospitalisation with CAP and 1.9 for hospitalisation for non-pneumonia. Importantly, however, Mortensen et al conducted a large study of 2287 inpatients and outpatients in the USA and Canada with clinical and radiographic evidence of pneumonia and found 208 (9%) deaths within 90 days of presentation. Only 110 (53%) of these deaths were attributed to pneumonia by a review panel (pneumonia considered the underlying or immediate cause of death or played a major role in the cause of death).
Pneumonia-related deaths were 7.7 times more likely to occur within 30 days of initial presentation compared with pneumonia-unrelated deaths, with 45% occurring within two weeks and 76% occurring within 30 days. The authors therefore advocated shorter follow-up when measuring mortality rates (30 days), because deaths are more likely to be pneumonia-related.

Mortensen et al also reported that the most frequent immediate causes of pneumonia-related deaths were respiratory failure (50%), pneumonia (6%), multisystem organ failure (6%) and sepsis (6%); while the most frequent underlying causes of death were neurological conditions (22%), pneumonia (18%) and cerebrovascular accident (13%).

**Risk Factors for increased mortality**

Three well-conducted studies from the USA describe risk factors for mortality among adults hospitalised with CAP. Mortensen et al used regression models to describe factors independently associated with pneumonia-related death and that were not associated with non-pneumonia-related deaths. These were hypothermia (RR 1.9; 95%CI 1.0-3.5), altered mental status (RR 2.3; 95%CI 1.5-3.4), elevated serum urea nitrogen level (RR 2.4; 95%CI 1.6-3.7), chronic liver disease (RR 3.8; 95%CI 1.2-12.7), leukopenia (3.0; 95%CI 1.1-8.0) and hypoxaemia (2.0; 95%CI 1.3-3.0). In addition, increasing age (per 10 years: RR 1.6; 95%CI 1.4-1.9) and evidence of aspiration (RR 3.1; 95%CI 1.9-5.0) were common to both groups. Male gender just failed to reach statistical significance (RR 1.5; 95%CI 0.99-2.2). Kaplan et al examined risk factors for in-hospital mortality adjusted for baseline characteristics. Congestive cardiac failure, malignancy, myocardial infarction, renal and liver disease were the most important predictors (OR range 1.5-2.3). In addition, men were at greater risk (OR 1.15; 95%CI 1.13-1.17) as were nursing home residents (OR 1.5; 95%CI 1.4-1.6) and those of greater age (OR 1.75; 95%CI 1.7-1.8 for those ≥90 years versus 65-69 baseline group). Those with a complex course and any organ dysfunction were also more likely to die. Finally, Conte et al reported five independent predictors of mortality: age≥85 years (OR 1.8; 95%CI 1.1-3.1), comorbid disease (4.1; 95%CI 2.1-8.1); impaired motor response (OR 2.3; 95%CI 1.4-3.7); vital sign abnormality (OR 3.4; 95%CI 2.1-5.4); and creatinine level ≥1.4mg/dL (OR 2.5; 95%CI 1.5-4.2).

In Spain, Riquelme examined some different factors using multivariate analysis and found the following were important predictors of mortality (although confidence intervals were wide): being bedridden (RR 10.7; 95%CI 1.1-104.5), prior swallowing disorders (RR 7.9; 95%CI 0.9-67.6), presence of pyrexia >37°C (RR 10.5; 95%CI 2.1-51.9), more than three affected lobes (RR 2.3; 95%CI 1.0-5.2) and higher respiratory frequency on admission >30/min (RR 5.3; 95%CI 1.1-24.8).

Limited Australian data have found predictors of mortality to be increasing age and chronic respiratory and/or cardiovascular disease. In this study of 106 adults >60 years there were 11 deaths. Gender and smoking were not predictive of mortality. In a separate study of 96 patients
with severe CAP admitted to an ICU, age was reported as the strongest predictor of mortality based on multivariate analysis (6.4% per year of age), as well as antibiotic administration prior to admission, delay in hospital administration of antibiotics of more than four hours, and presence of multilobar or bilateral consolidation on chest x-ray.\textsuperscript{120}

**Other discharge locations**

Few data exist for location of discharge for elderly inpatients with CAP. A study by Conte et al of 2356 elderly inpatients utilised two samples: a derivation cohort of 1000 subjects randomly sampled from four states of the USA, and a validation cohort of 1356 taken from a national sample from the USA.\textsuperscript{197} The majority of patients were discharged to their own home (Table 3.1).

Table 3.1. Discharge location for elderly inpatients with CAP, Conte et al.\textsuperscript{197}

<table>
<thead>
<tr>
<th>Discharge location</th>
<th>Four state sample derivation set (n=1000) (%)</th>
<th>National sample validation set (n=1356) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>66</td>
<td>61</td>
</tr>
<tr>
<td>Non-institutional setting</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Skilled nursing facility</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>Acute care hospital</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Chronic hospital</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

* Table reproduced in part from Conte et al.\textsuperscript{197}

3.4 Methods

3.4.1 Study subjects

The study sampling frame was all hospitalisations for persons aged $\geq 65$ years from the two Melbourne hospitals of interest (RMH and WH) from 1 April 2000 to 31 March 2002, representing approximately 11% of all hospitalisations for Victorians aged $\geq 65$ years, and 13% of all hospitalisations for pneumonia for this age group. All first presentation cases of CAP were included for analysis. Subjects with ICD-10-AM codes J10-J18 (pneumonia including those due to influenza)
in any of the 14 diagnostic code positions were considered to have pneumonia. Patients with nosocomial pneumonia, defined as pneumonia diagnosed more than 48 hours after admission to hospital, were excluded.

First presentations were chosen since they were independent events compared with repeat admissions for the same individual. Subjects were excluded if admitted from one hospital to the other with the same diagnosis, if admitted for short stay procedures such as dialysis and chemotherapy (based on ICD codes), if they were not residents of Victoria and subsequently, if their hospital records were not available for review.

For seasonality, burden of disease and mortality, ICD-10 coded pneumonia cases were compared with ICD-10-coded non-pneumonia subjects. Where risk factor analysis for CAP versus non-CAP was conducted, as per a case-cohort design, the entire cohort was the comparison group. For secondary objectives (CAP associated symptoms and signs, investigations and antimicrobial use), data were available only for subjects with notation of pneumonia in hospital records. For inclusion in these analyses, subjects were required to also have ICD-codes consistent with pneumonia.

3.4.2 Data collection

Demographic data and data on outcomes, comorbidities and other risk factors for CAP were obtained by hospital record review by research assistants blinded to the case status of study subjects. The entire hospital medical record was reviewed for information within the time period of the selected admission, including day-to-day records and discharge summaries.

Factors included for examination as predictors of hospitalisation with CAP were based upon literature review and biological plausibility. These included age, gender, place of residence, speaking English as a first language, marital status, previous hospitalisations, previous provider visits or hospitalisation for pneumonia, smoking habits, excessive alcohol intake, presence of diabetes, cardiovascular disease, immunosuppression, other (non-pneumonia) respiratory disease, renal disease, rheumatological disease, liver disease, cerebrovascular disease and history of aspiration (Appendix 2). Presence of comorbidity was defined as having at least one of the following: excessive alcohol intake, current tobacco smoking, past history of pneumonia, aspiration, other respiratory disease, cerebrovascular disease, diabetes, immunosuppression, ischaemic heart disease, liver disease, renal disease or rheumatological disease. Additional factors examined as potential predictors of mortality associated with admission for CAP included ICU admission, and extent of consolidation on CXR (lobar, bilateral or other).

All radiology reports for CXRs undertaken as part of routine management were reviewed by two trained research assistants using pre-specified criteria (Table 3.2). For patients with more than one CXR during their selected admission, only the first abnormal report was reviewed, and the reviewers were blinded to other reports. When reports could not be confidently interpreted, two of the
investigators made the final assessment. High inter-operator agreement was first established between myself (a paediatrician) and Prof Donald Campbell (an adult respiratory physician) on a sample of pilot subjects. We independently reviewed CXR reports for consecutive groups of 20 pilot subjects and compared interpretation for agreement. No further groups were examined and review of study reports did not commence until a kappa statistic\(^ {207} \) indicating >95% concurrence was achieved. Consensus was obtained on subsequent “in dispute” reports after independent review and before data entry.

Table 3.2. Criteria for defining pneumonia based on review of CXR reports.

<table>
<thead>
<tr>
<th>Pneumonia category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar pneumonia</td>
<td>Any opacity confined to a lobar anatomical distribution</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>Opacity distributed beyond a single lobe in conjunction with terms that are similar to or include the words “patchy” and/or “airspace”</td>
</tr>
<tr>
<td>Other pneumonia</td>
<td>Opacity consistent with pneumonia not previously classified</td>
</tr>
<tr>
<td>Not pneumonia</td>
<td>None of the above</td>
</tr>
</tbody>
</table>

To examine secondary objectives, additional data were sought for: 1) investigations performed, obtained by review of electronic laboratory records; 2) use of antimicrobial agents, obtained from drug charts, referral and discharge letters; and 3) symptoms and signs commonly associated with pneumonia, determined by hospital record review (Appendix 4). These data were not considered a primary focus of this chapter since they could only be collected retrospectively and investigations in particular were unlikely to have been conducted systematically. Symptoms and signs sought were based on those most commonly described by earlier studies (see 3.3.5).\(^ {18,202} \) These were documentation of cough, sputum production, pleuritic chest pain, fever \( \geq 37.5^\circ \text{C} \), shortness of breath, crackles (crepitations), and aspiration. These factors were noted as present, absent or not recorded.

### 3.4.3 Statistical methods

Logistic regression was used to estimate the RRs for factors predicting CAP, or associated mortality. Factors were first assessed individually in logistic statements adjusting for hospital of discharge, month of sampling, and selection probability (see 2.5.4). Covariates with p-values <0.20 were retained for multivariate analysis with the exception of variables with >15% missing data (added to final models only). Backward stepwise logistic regression was used to estimate the RRs adjusted for hospital of discharge, month of sampling, and selection probability (using down weighting as previously described). Step-wise elimination of variables was determined by removing the variable
with the largest p-value greater than 0.05. The impact of adding or removing independent variables from the model was assessed by examining the stability of the coefficients of all other variables in the model. The final model was determined when all remaining variables had a p-value <0.05. Stata version 9.1 was used. It is relevant to note that chapter 5 (vaccine effectiveness) includes many of the same factors in multivariate models in order to improve the validity of estimates for the primary study outcome, whereas in this chapter, these factors are analysed purely in relation to prediction of CAP.

3.5 Results

3.5.1 Study subjects

After exclusions, there were 1952 first presentation cases of CAP using ICD codes for pneumonia, and 2927 first presentation cohort subjects were selected for comparison, including 107 who were also selected as cases. There were therefore 4772 eligible study subjects in total (Figure 3.1). Chapter 5, as the key outcomes chapter of this thesis, provides greater detail of exclusions in Figures 5.1 and 5.3. Only 12 subjects (5 cases of CAP and 7 cohort subjects) were excluded due to inability to review their medical record.

Figure 3.1. Eligible 1st presentation cases of CAP and cohort subjects.
3.5.2 Basic epidemiology and disease burden

1952 first presentations of CAP represented 1952/49 692 (3.9%) total admissions in persons aged ≥65 years for the study period in the two hospitals (denominator excludes repeat presentations in the same month for the same person, and those admitted for dialysis and chemotherapy).

The mean number of admissions with CAP was 81/month (median 81, range 50-125). Admissions with CAP peaked in winter (588/1952, 30%) and spring (490/1952, 25%) (Figure 3.2 and Table 3.3). By season, the proportions of CAP admissions were the same as for total admissions (Table 3.3).

Figure 3.2. Seasonality of 1st admissions with CAP, Apr 2000 – Mar 2002.

Table 3.3. Seasonality of all 1st admissions and 1st admissions with CAP, Apr 2000 - Mar 2002 (study subjects only).

<table>
<thead>
<tr>
<th>Season</th>
<th>Definition</th>
<th>All 1st admissions (%) n=4772</th>
<th>1st CAP admissions (%) n=1952</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summer</td>
<td>Dec Jan Feb</td>
<td>1050 (22%)</td>
<td>413 (21%)</td>
</tr>
<tr>
<td>Autumn</td>
<td>Mar Apr May</td>
<td>1110 (23%)</td>
<td>459 (23%)</td>
</tr>
<tr>
<td>Winter</td>
<td>Jun Jul Aug</td>
<td>1401 (29%)</td>
<td>588 (30%)</td>
</tr>
<tr>
<td>Spring</td>
<td>Sep Oct Nov</td>
<td>1209 (25%)</td>
<td>490 (25%)</td>
</tr>
</tbody>
</table>
Characteristics of subjects with CAP are shown in Table 3.4. Their mean (and median) age was 78 years and 1126/1952 (58%) were male. At least one comorbid condition was present in 1833/1870 (98%). The mean number of comorbid conditions was 2.5 (median 2, range 0-8).

Table 3.4. Characteristics of 1952‡ persons with 1st admissions for CAP.

<table>
<thead>
<tr>
<th>Variable*</th>
<th>% †</th>
<th>Variable*</th>
<th>% †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>78.4</td>
<td>Rheumatological disease</td>
<td>15.7</td>
</tr>
<tr>
<td>Male gender</td>
<td>57.7</td>
<td>Liver disease</td>
<td>2.6</td>
</tr>
<tr>
<td>Live in own home</td>
<td>80.6</td>
<td>Cerebrovascular disease</td>
<td>21.0</td>
</tr>
<tr>
<td>First language English</td>
<td>70.4</td>
<td>Aspiration</td>
<td>2.2</td>
</tr>
<tr>
<td>Mean hospitalisations past 1 year</td>
<td>1.2</td>
<td>Previous pneumonia (any)</td>
<td>22.2</td>
</tr>
<tr>
<td>Mean hospitalisations past 2-5 years</td>
<td>2.1</td>
<td>Pneumonia past year</td>
<td>8.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26.5</td>
<td>Pneumonia past 2-5 years</td>
<td>12.9</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>46.6</td>
<td>Excessive alcohol intake‡</td>
<td>20.1</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>27.0</td>
<td>Current smoker‡</td>
<td>8.5</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>47.9</td>
<td>Current/Ex-smoker‡</td>
<td>65.7</td>
</tr>
<tr>
<td>Renal disease</td>
<td>13.3</td>
<td>Death during hospitalisation</td>
<td>16</td>
</tr>
</tbody>
</table>

* See Appendix 4 or Table 3.7 for detailed description of variables
† Percentage, unless labelled as a mean
‡ Variables with missing data from medical record review (n subjects): previous hospitalisations: 4 (0.2%), alcohol: 1027 (53%), smoking: 550 (28%), deaths during hospitalisation: 6 (0.3%); all other variables had no missing data

The median length of stay was 6.0 days (mean 9 days, range 0-100 days). This was significantly longer than for subjects admitted without CAP (mean 5.3 days, median 2: difference in means 4 days; p<0.001). For subjects admitted with CAP, those who were older (>79 years) had a similar median length of hospital stay compared with younger subjects (65-79 years) (6 days each group; p=0.37). Similarly, gender had no significant impact on median length of stay (6 days each group; p=0.31). However, presence of more than two comorbid conditions was associated with a longer median duration of hospitalisation (difference 1 day; p=0.001).

Intensive care admission occurred more often in subjects admitted with CAP (278/1951, 14.2%), compared with subjects admitted with non-CAP (291/2820, 10.3%) (difference 3.9%; 95%CI 2.0-8.6). Those admitted to ICU with CAP had a median length of stay of 10 days (mean 15.2 days,
range 0-67). This was significantly longer compared with those admitted with CAP but not admitted to an ICU (5 days: difference 5 days; p<0.001). Younger patients (65-79 years) were much more likely to be admitted for intensive care than older patients (≥80 years) (19.1%, 95%CI 16.7-21.4% versus 8.0%, 95%CI 6.2-9.8%; p<0.001). Neither gender nor presence of two or more comorbidities were associated with ICU admission.

3.5.3 Investigation

A CXR was performed for 1800/1861 (97%) of subjects with clinical notation and ICD codes for CAP. Of these, 1736 (96%) had radiology reports available for review, and 1731 (96%) had a result recorded regarding type of pneumonia or otherwise. Bronchopneumonia was present in 617 (35.6%), lobar pneumonia in 610 (35.2%), other pneumonia in seven (0.4%) and 497 (28.7%) were not thought to have pneumonia based on CXR. A more detailed analysis of CXR reports is presented in Chapter 4. The most common laboratory investigations performed were on blood, sputum and urine (Table 3.5). Excluding CXR, of the categories of investigations listed in Table 3.5, subjects hospitalised with CAP had a mean of 1.2 performed (range 0-6, median 1). None were performed in 520/1864 (28%) subjects. While 1344/1864 (72%) subjects had one or more of these categories of investigation performed, only 641/1864 (34%) had two or more performed.

Table 3.5. Investigations performed or specimen types taken for 1864 subjects with clinical notation and ICD codes for pneumonia.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Performed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR</td>
<td>1800/1861 (96.6)</td>
</tr>
<tr>
<td>CT scan</td>
<td>64/1863 (3.4)</td>
</tr>
<tr>
<td>Blood*</td>
<td>1018/1863 (54.6)</td>
</tr>
<tr>
<td>Sputum</td>
<td>713/1864 (38.2)</td>
</tr>
<tr>
<td>Urine†</td>
<td>310/1864 (16.6)</td>
</tr>
<tr>
<td>Nasopharyngeal aspirate</td>
<td>28/1864 (1.5)</td>
</tr>
<tr>
<td>Nose or throat swab</td>
<td>14/1864 (0.8)</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>8/1864 (0.4)</td>
</tr>
<tr>
<td>Other‡</td>
<td>152/1864 (8.2)</td>
</tr>
</tbody>
</table>

*Includes culture, PCR, immunofluorescence
†Includes urinary antigen
‡Includes tracheal aspirate, bronchial washings, pleural fluid, lung biopsy, wound swabs
3.5.4 Causative organisms

Given the retrospective nature of data collection and the limited number of investigations performed using a non-systematic approach, describing causative organisms for CAP could not be a primary focus of this study, and it is not appropriate to present or interpret data in any detail. However, the most commonly identified pathogens were: influenza A or B (41/1854 subjects, 2.2%), followed by *Staphylococcus aureus* (17/1854, 0.9%) and *S.pneumoniae* (11/1854, 0.6%).

3.5.5 Antimicrobial management

1823/1854 (98%) of eligible subjects had data available on use of antibiotics during admission, and of these 1755 (96%) were noted to have received antibiotics. The most commonly prescribed antibiotics were: roxithromycin (380, 21%), ceftriaxone (363, 20%), amoxycillin/clavulanate (264, 14%), benzyl penicillin G (170, 9%), erythromycin (114, 6%) and amoxycillin (70, 4%). Only 1060/1854 (57%) of eligible subjects had data available on preadmission use of antibiotics, and of these, 147 (14%) were noted to have received them.

3.5.6 Clinical symptoms and signs

Of the 1952 subjects with first presentations coded as CAP and records available for review, 1863/1952 (95%) had clinical notation of pneumonia. These subjects had a mean of 4.0 (median 4) of the seven symptoms and signs of interest (Figure 3.3).

Figure 3.3. Number of symptoms and signs* extracted from medical records for 1863 subjects with clinical notation of pneumonia and ICD codes for pneumonia.

* Documented evidence was sought for cough, sputum production, pleuritic chest pain, fever ≥37.5°C, shortness of breath, crackles and evidence of aspiration.
Three or fewer symptoms and signs were present in 627/1863 (34%) subjects and only four (0.2%) had all seven. Some factors were recorded poorly (no notation, either positive or negative), but those most frequently recorded as present or absent, and that were present most often were crackles, shortness of breath, cough, fever $\geq 37.5^\circ C$ and sputum production (Table 3.6). 522/1863 (28%) subjects had all five of these most commonly occurring factors.

Table 3.6. Frequency of symptoms and signs extracted from medical records for 1863 subjects with clinical notation of pneumonia and ICD codes for pneumonia.

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Present n (%)</th>
<th>Absent n (%)</th>
<th>Not recorded n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crackles</td>
<td>1724 (92.5)</td>
<td>119 (6.4)</td>
<td>20 (1.1)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1447 (77.7)</td>
<td>346 (18.6)</td>
<td>70 (3.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>1392 (74.7)</td>
<td>337 (18.1)</td>
<td>134 (7.2)</td>
</tr>
<tr>
<td>Fever $\geq 37.5^\circ C$</td>
<td>1224 (65.7)</td>
<td>638 (33.8)</td>
<td>9 (0.5)</td>
</tr>
<tr>
<td>Sputum production</td>
<td>1038 (55.7)</td>
<td>614 (33.0)</td>
<td>211 (11.3)</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>468 (25.1)</td>
<td>780 (41.9)</td>
<td>615 (33.0)</td>
</tr>
<tr>
<td>Evidence of aspiration</td>
<td>92 (4.9)</td>
<td>397 (21.3)</td>
<td>1374 (73.8)</td>
</tr>
</tbody>
</table>

3.5.7 Risk factors for hospitalisation with CAP

3.5.7.1 Determining prognostic variables for inclusion in multivariate analyses

Twenty nine variables were examined in univariate analysis to examine their association with CAP. Five were excluded. Three variables had a p-value $>0.20$ (marital status, influenza vaccination status and 23vPPV status) and two variables were excluded due to colinearity (numbers of previous episodes of pneumonia in the past year and past 2-5 years). A further four variables had considerable amounts of missing data (17-45% of observations in the initial multivariate model) and were excluded as appropriate adjustments could not be made for such large data deficits, while excluding data for individuals where these were missing would increase the risk of bias. These “excluded variables” related to smoking habits, alcohol intake and vaccine provider visit variables. However, separate analyses were subsequently conducted to explore the effect of these variables on the subset of subjects for whom data were available. This was achieved by adding the variables separately to the final multivariate model after completing the backward stepwise process. The final 20 variables for inclusion in the model, plus the four “excluded” variables are shown in Table 3.7.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Description†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td>65-69, 70-74, 75-79, 80-84, 85+</td>
</tr>
<tr>
<td>Male gender</td>
<td>Male versus female</td>
</tr>
<tr>
<td>Live in own home</td>
<td>private residence versus group setting (nursing home, retirement village, hostel, lodge etc)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>past history (yes, no)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>angina, myocardial infarction, coronary artery bypass grafting (yes, no)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>AIDS, cancer (excluding basal cell and squamous cell carcinoma), chronic steroid Rx, HIV infection before development of AIDS, organ transplantation, dys gammaglobulinaemia, sickle cell disease, asplenia (functional or anatomical), nephrotic syndrome (yes, no)</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>Bronchitis, asthma, emphysema, other chronic obstructive airways disease (not pneumonia) (yes, no)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Particularly renal failure requiring dialysis. Note renal transplant included under immunosuppression (yes, no)</td>
</tr>
<tr>
<td>Rheumatological disease</td>
<td>Rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, multiple connective tissue disease (yes, no)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Chronic infection (hepatitis), cirrhosis, liver failure (yes, no)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Stroke, transient ischaemic attacks (yes, no)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>History (yes, no)</td>
</tr>
<tr>
<td>First language English</td>
<td>Primary language spoken (English, other)</td>
</tr>
<tr>
<td>Prior hospitalisations past 1 year</td>
<td>Number of hospitalisations in the past 12 months</td>
</tr>
<tr>
<td>Prior hospitalisations past 2-5 years</td>
<td>Number of hospitalisations in the past 2-5 years</td>
</tr>
</tbody>
</table>
### Multivariable analysis

The final multivariate model contained 12 predictors of CAP (Table 3.8). In addition, when the four “excluded” variables were separately added to the final model, two (excessive alcohol intake and visits to a doctor in the past year) were also predictors of CAP.

The following factors were independent predictors of admission with CAP: male gender, living in one’s own home, a history of diabetes, immunosuppression, respiratory disease, renal disease, aspiration, previous pneumonia or excessive alcohol intake (Table 3.8). Risk of admission with CAP also increased progressively with increasing age over 75 years (Table 3.9) and increasing numbers of doctor visits in the past year. Subjects with a history of pneumonia in the previous year, those who spoke a language other than English as their first language, and those with a history of rheumatological disease had a reduced risk of hospitalisation with CAP.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia ever</td>
<td>Past history (yes, no)</td>
</tr>
<tr>
<td>Pneumonia past 1 year</td>
<td>History of pneumonia in the past 12 months (yes, no)</td>
</tr>
<tr>
<td>Pneumonia past 2-5 years</td>
<td>History of pneumonia in the past 2-5 years (yes, no)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>More than 2 comorbid conditions versus ≤ 2 comorbid conditions†</td>
</tr>
<tr>
<td>Years since 23vPPV</td>
<td>≥3 years since 23vPPV versus ≤ 2 years</td>
</tr>
<tr>
<td>Alcohol intake*</td>
<td>History of excess alcohol intake (yes, no) : medical record documentation including “alcoholism”, “alcohol abuse”, “EtOH abuse” or alcohol consumption described as in excess of 4 standard drinks/day for men and 2 standard drinks/day for women</td>
</tr>
<tr>
<td>Smoking habit*</td>
<td>History of smoking (never, ex-smoker, current smoker) (subject report)</td>
</tr>
<tr>
<td>Dr visits past 1 year*</td>
<td>Number of doctor visits in the past year (categorical, subject report)</td>
</tr>
<tr>
<td>Dr visits past 2-5 years*</td>
<td>Doctor visits in the past 2-5 years inclusive (yes, no) (subject report)</td>
</tr>
</tbody>
</table>

* “Excluded” variable added only to final model following backward stepwise process, due to missing data
† See appendices 2 and 4 for greater detail
‡ Comorbidity defined in 3.4.2
Table 3.8. Predictors of CAP, final multivariate model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age group (5y categories)</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.34 (1.18-1.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Living in own home</td>
<td>1.41 (1.17-1.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.22 (1.05-1.42)</td>
<td>0.01</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>1.35 (1.16-1.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>2.41 (2.10-2.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.57 (1.26-1.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rheumatological disease</td>
<td>0.82 (0.69-0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Aspiration</td>
<td>2.19 (1.20-3.99)</td>
<td>0.01</td>
</tr>
<tr>
<td>First language English</td>
<td>0.80 (0.69-0.93)</td>
<td>0.003</td>
</tr>
<tr>
<td>Pneumonia ever</td>
<td>2.30 (1.83-2.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia past 1 year</td>
<td>0.66 (0.46-0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>Excess alcohol intake*</td>
<td>1.34 (1.03-1.74)</td>
<td>0.03</td>
</tr>
<tr>
<td>Increasing doctor visits past 1 year*</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*“Excluded” variable added only to final model following backward stepwise process

Table 3.9. Age group as a risk factor for hospitalisation with CAP, final multivariate model.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference group 65-69 years</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>70-74</td>
<td>1.07 (0.87, 1.30)</td>
<td>0.53</td>
</tr>
<tr>
<td>75-79</td>
<td>1.46 (1.19, 1.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>80-84</td>
<td>2.01 (1.62, 2.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥85</td>
<td>2.17 (1.74, 2.70)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
3.5.8 Mortality and discharge location

3.5.8.1 Discharge location

Subjects with CAP were most often discharged to their own home (65%) followed by discharge to other hospitals (9%), a nursing home (5%) or hostel accommodation (2%) (Table 3.10). Prior to admission, 1569/1948 (81%) subjects admitted with CAP lived in their own home, 202 (10%) in a nursing home and 121 (6%) in a hostel. Of those admitted from their own home, 1131/1563 (72%) returned there (14% died in hospital, 13% required alternative living arrangements). Subjects admitted with CAP were more likely to be discharged to a nursing home or the same hospital, but less likely to be discharged to their own home and more likely to die compared with subjects without CAP. Deaths are discussed in detail below.

Table 3.10. Discharge location for eligible study subjects.

<table>
<thead>
<tr>
<th></th>
<th>All subjects (%) n=4749</th>
<th>CAP only (%) n=1946</th>
<th>Non-CAP n= 2803 (%)</th>
<th>Difference (%) (95%CI) (CAP versus non-CAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>3578 (75.3)</td>
<td>1273 (65.4)</td>
<td>2305 (82.2)</td>
<td>-16.8 (-19.4- -14.3)</td>
</tr>
<tr>
<td>Hostel</td>
<td>74 (1.6)</td>
<td>31 (1.6)</td>
<td>43 (1.5)</td>
<td>0.05 (-0.6-0.7)</td>
</tr>
<tr>
<td>Nursing home</td>
<td>188 (4.0)</td>
<td>106 (5.5)</td>
<td>82 (2.9)</td>
<td>2.5 (1.3-3.7)</td>
</tr>
<tr>
<td>Other hospital</td>
<td>411 (8.7)</td>
<td>185 (9.5)</td>
<td>226 (8.1)</td>
<td>1.4 (-0.2-3.1)</td>
</tr>
<tr>
<td>Same hospital</td>
<td>51 (1.1)</td>
<td>33 (1.7)</td>
<td>18 (0.6)</td>
<td>1.1 (0.4-1.7)</td>
</tr>
<tr>
<td>Died in hospital</td>
<td>447 (9.4)</td>
<td>318 (16.3)</td>
<td>129 (4.6)</td>
<td>11.7 (10.0-13.6)</td>
</tr>
</tbody>
</table>

3.5.8.2 Mortality

For the 1952 subjects admitted with CAP, the majority of deaths occurred within 30 days of admission: 16.3% died in hospital, 17.9% died within 30 days of admission, and 26.0% by the time of interview with next of kin (Table 3.11). Subjects with CAP had a significantly higher in-hospital mortality rate (difference 11.7%; 95%CI 10.0-13.6) and 30 day mortality rate (difference 17.5%; 95%CI 10.5-24.4) compared with those with non-CAP. Those with CAP who died in hospital also had a more rapid demise (9.8 days after admission versus 12.6 days, difference -2.8 days; 95%CI -5.5- -0.1) compared with those with non-CAP (Table 3.11).

For those admitted to ICU, mortality was significantly higher than the general hospital admission mortality rate (104/566, 18.4% versus 447/4749, 9.4%), due to the significantly higher mortality
among CAP inpatients admitted to ICU (26% versus 11% for non-CAP; difference 15.6%, 95%CI 9.3-21.9). Of note, 68/277 (24%) of those with CAP admitted to ICU were aged >79 years: 21 (31%) died in hospital and 28 (41%) by the time of next of kin interview. This was not significantly higher than for younger patients aged 65-79 years (difference -6.0%; 95%CI -18.4-6.4% and -12.1%; 95%CI -25.3-1.2% respectively). Older patients with CAP and more than two comorbid conditions were not significantly more likely to be admitted to ICU than those with fewer comorbid conditions (8.7% versus 7.8%; 95%CI -0.9; 95%CI -4.6-2.9%).

Table 3.11. Mortality for eligible study subjects.

<table>
<thead>
<tr>
<th></th>
<th>All study subjects (%)</th>
<th>CAP only (%)</th>
<th>Non-CAP only (%)</th>
<th>Difference (%) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality*</td>
<td>813/4772 (17.0)</td>
<td>507/1952 (26.0)</td>
<td>306/2820 (10.9)</td>
<td>15.1 (12.9-17.4)</td>
</tr>
<tr>
<td>Mortality within 30d of admission*</td>
<td>507/4772 (10.6)</td>
<td>350/1952 (17.9)</td>
<td>157/2820 (5.6)</td>
<td>12.3 (10.4-14.3)</td>
</tr>
<tr>
<td>Proportion of deaths within 30d of admission*</td>
<td>507/806 (62.9)</td>
<td>350/504 (69.4)</td>
<td>157/302 (52.0)</td>
<td>17.5 (10.5-24.4)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>447/4749 (9.4)</td>
<td>318/1946 (16.3)</td>
<td>129/2803 (4.6)</td>
<td>11.7 (10.0-13.6)</td>
</tr>
<tr>
<td>In-hospital mortality within 30d of admission</td>
<td>414/4772 (8.7)</td>
<td>299/1952 (15.3)</td>
<td>115/2820 (4.1)</td>
<td>11.2 (9.5-13.0)</td>
</tr>
<tr>
<td>Days until death (for deaths in hospital)</td>
<td>10.6 (median 6)</td>
<td>9.8 (median 6)</td>
<td>12.6 (median 7)</td>
<td>-2.8 (-5.5--0.1)</td>
</tr>
<tr>
<td>ICU-related mortality† (for deaths in hospital)</td>
<td>104/566 (18.4)</td>
<td>73/277 (26.3)</td>
<td>31/289 (10.7)</td>
<td>15.6 (9.3-21.9)</td>
</tr>
</tbody>
</table>

* Includes deaths up until the time of interview with next of kin
† Mortality among hospitalised subjects admitted to an ICU
3.5.8.3 Risk factors for in-hospital mortality associated with admission with CAP

Determining prognostic variables for inclusion in multivariate analyses

Thirty three variables were examined in univariate analysis to examine their association with CAP. Nineteen were excluded as their p-value was >0.20 (marital status, 23vPPV status, gender, excess alcohol intake, history of diabetes or rheumatological disease or liver disease or ischaemic heart disease, comorbidity (2 variables: dichotomous and continuous), English as a first language, the number of admissions in the past year or 2-5 years, pneumonia in the past year (2 variables: dichotomous and continuous), number of admissions for pneumonia in the past 2-5 years, doctor visits in the past 2-5 years, and years since vaccination with 23vPPV (2 variables: dichotomous and continuous). A further three variables had considerable amounts of missing data (19-31% of observations in the initial multivariate model) and were excluded as appropriate adjustments could not be made for such large data deficits. These “excluded variables” related to smoking habits, influenza vaccination status and the number of vaccine provider visits in the past year. Separate analyses were subsequently conducted to explore the effect of these variables on the subset of subjects for whom data were available. This was done by adding the variables separately to the final multivariate model after the backward stepwise process was completed. The final 11 variables for inclusion in the model, plus the three “excluded” variables are shown in Table 3.12.
Table 3.12. Variables for inclusion in backward stepwise logistic regression models (p<0.20).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td>65-69, 70-74, 75-79, 80-84, 85+</td>
</tr>
<tr>
<td>Live in own home</td>
<td>private residence versus group setting (nursing home, retirement village, hostel, lodge etc)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>AIDS, cancer (excluding basal cell carcinoma and squamous cell carcinoma), chronic steroid Rx, HIV infection before development of AIDS, organ transplantation, dysgammaglobulinaemia, sickle cell disease, asplenia (functional or anatomical), nephrotic syndrome (yes, no)</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>Bronchitis, asthma, emphysema, other chronic obstructive airways disease (not pneumonia) (yes, no)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Particularly renal failure requiring dialysis. Note renal transplant included under immunosuppression (yes, no)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Stroke, transient ischaemic attacks (yes, no)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>History (yes, no)</td>
</tr>
<tr>
<td>Pneumonia ever</td>
<td>Past history (yes, no)</td>
</tr>
<tr>
<td>Pneumonia past 2-5 years</td>
<td>History of pneumonia in the past 2-5 years (yes, no)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Admitted to ICU during hospitalisation</td>
</tr>
<tr>
<td>CXR appearance</td>
<td>0=not pneumonia, 1=lobar pneumonia, 2=bronchopneumonia (multiple lobes affected)</td>
</tr>
<tr>
<td>Smoking habit*</td>
<td>History of smoking (0=never, 1=ex-smoker, 2=current smoker; subject report)</td>
</tr>
<tr>
<td>Dr visits past 1 year*</td>
<td>Number of doctor visits in the past year (categorical, subject report)</td>
</tr>
<tr>
<td></td>
<td>(0-4, 5-9, 10-14, 15-19, 20+)</td>
</tr>
<tr>
<td>Influenza vaccination status*</td>
<td>Vaccinated or not (date confirmed from provider records)</td>
</tr>
</tbody>
</table>

* “Excluded” variable added only to final model following backward stepwise process, due to missing data
† See appendices 2 and 4 for greater detail

**Multivariable analysis**

The final multivariate model contained 9 factors predictive of mortality for subjects admitted with CAP (Table 3.12), including two of the three “excluded” variables added to the final model (influenza vaccination status and smoking history). The following factors were independent predictors of mortality: ICU admission, renal disease, living in one’s own home and history of
immunosuppression (Table 3.13), increasing age (particularly over 79 years) (Table 3.14), multilobe involvement on CXR (multilobar RR 3.0, 95%CI 2.1-4.3 versus RR 1.4, 95%CI 0.97-2.1 for lobar pneumonia against the referent category of “not pneumonia”) and smoking. Smokers were at increased risk of death compared with the referent category of “never smoked”, with current smokers at greater risk than ex-smokers (RR 4.2, 95%CI 2.4-7.6 versus RR 1.5, 95%CI 1.1-2.2). A reduction in risk of death was associated with influenza vaccination in the year prior to admission (RR 0.55; 95%CI 0.40-0.76) and a history of other respiratory disease (RR 0.78; 95%CI 0.56-0.93).

Table 3.13. Predictors of mortality for subjects admitted with CAP, final multivariate model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>2.68 (1.90-3.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.78 (1.24-2.56)</td>
<td>0.002</td>
</tr>
<tr>
<td>Living in own home</td>
<td>1.68 (1.21-2.35)</td>
<td>0.002</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>1.58 (1.16-2.14)</td>
<td>0.003</td>
</tr>
<tr>
<td>Increasing age group (5y categories)</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CXR appearance</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking habit*</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Influenza vaccination*</td>
<td>0.55 (0.40-0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>0.78 (0.56-0.93)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

* “Excluded” variable added only to final model following backward stepwise process, due to missing data

Table 3.14. Risk of mortality for subjects admitted with CAP in relation to age group, final multivariate model.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>n (%)</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69 (referent)</td>
<td>286 (14.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>70-74</td>
<td>375 (19.2)</td>
<td>1.65 (0.97-2.80)</td>
<td>0.06</td>
</tr>
<tr>
<td>75-79</td>
<td>442 (22.6)</td>
<td>1.59 (0.96-2.64)</td>
<td>0.07</td>
</tr>
<tr>
<td>80-84</td>
<td>398 (20.4)</td>
<td>2.10 (1.25-3.50)</td>
<td>p=0.005</td>
</tr>
<tr>
<td>85+</td>
<td>451 (23.1)</td>
<td>3.05 (1.85-5.03)</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
3.6 Discussion

3.6.1 Key outcomes

Basic epidemiology and disease burden

This study, the largest to date in Australia examining CAP in the elderly, confirms the considerable burden of disease attributable to CAP among the hospitalised elderly population, and a seasonal pattern similar to that reported from other countries,\textsuperscript{20,193} with admissions peaking in winter and spring. Hospitalisations with CAP represented approximately 4% of total admissions in persons aged $\geq 65$ years for the two hospitals included in the study. This is consistent with the only other Australian estimate, made in all-age adults, of two percent of all overnight hospital admissions,\textsuperscript{195} given the higher admission rate for CAP expected in older persons. Those admitted with CAP required hospitalisation for a mean of nine days, consistent with previous international studies.\textsuperscript{21,192,199} This was on average four days longer than those admitted with a non-CAP diagnosis. By contrast, Riquelme et al reported no difference between duration of stay for CAP and non-CAP admissions.\textsuperscript{199} Data from this thesis also show that those with more than two comorbidities had a median duration of hospitalisation of one extra day, gender and older age had no significant impact on length of stay.

Admission to an ICU occurred for 14% of all CAP admissions, consistent with the range of 2-22% provided by two studies from the USA.\textsuperscript{21,197} ICU admission occurred significantly more often than for patients admitted with a non-CAP diagnosis (difference 4%). Median length of stay for those hospitalised with CAP and admitted to an ICU was 10 days, similar to the mean of 11 days reported from the USA.\textsuperscript{21} Younger patients (< 80 years) were much more likely to be admitted to an ICU than older patients (19% versus 8%), consistent with the results of Kaplan et al (15% for those <90 years versus 27%).\textsuperscript{21} However, unlike Kaplan et al, data from this thesis did not show any difference related to gender or number of comorbidities.

Almost all (98%) elderly persons admitted with CAP had at least one comorbid condition present (mean 2.5), the most common of which were respiratory disease other than pneumonia, ischaemic heart disease, immunosuppression and diabetes. These comorbid factors are the same as previously described as the most common in adults admitted with CAP in Australian studies by Thompson et al and Wilson et al.\textsuperscript{120,191}

Risk factors for hospitalisation with CAP

This study has produced the first Australian data on risk factors for CAP in the elderly. Such information is useful if knowledge of risk factors can assist health providers in making an earlier diagnosis or commencing earlier treatment, and potentially result in a better outcome. The three
factors most strongly predictive of CAP versus non-CAP for elderly inpatients were other respiratory
disease, history of any previous pneumonia or aspiration, in addition to male gender, living in one’s
own home, history of diabetes, immunosuppression, renal disease or excessive alcohol intake,
increasing age over 75 years and numbers of doctor visits in the past year. These factors may be a
marker for some other unmeasured factor predisposing to hospitalisation with CAP. Koivula et al
reported similar findings from their large cohort study from Finland for the risk factors of age,
immunosuppression, other lung disease and alcohol intake.\textsuperscript{204} This group differed in their results for
renal disease (not predictive of CAP), heart disease and institutionalisation (increased risk of CAP).
It is feasible that local differences in setting and epidemiology could explain the different findings.
Inpatients with a history of pneumonia in the previous year were under-represented in the CAP
group. This could be because of increased contact with medical personnel, or greater awareness of
early symptoms and signs of pneumonia resulting in seeking earlier medical care. It is difficult to
explain why speaking a language other than English as a first language, or history of
rheumatological disease were negatively correlated with CAP.

\textbf{Discharge location and mortality}

Data from this study indicate that although two thirds of those admitted with CAP return to their
own homes, (consistent with Conte et al: 61-65\%)\textsuperscript{197} they are less likely to do so than those admitted
with a non-CAP diagnosis, and more likely to be admitted to a nursing home or die than those
admitted with a non-CAP diagnosis.

Most deaths associated with hospitalisation for CAP occurred within 30 days of admission, as
previously shown by Mortensen et al in North America.\textsuperscript{206} The 11% 30 day mortality rate in this
study is very similar to the 10-12% reported by previous small Australian studies in non-Aboriginal
populations\textsuperscript{9,185,191} as well as international studies.\textsuperscript{20,197,205} It was not surprising that death was
much more likely for CAP patients than those admitted with other diagnoses, nor that those with
CAP requiring admission to ICU had an even higher mortality rate.\textsuperscript{118,120}

Factors predictive of mortality among elderly persons hospitalised with CAP concur with earlier
studies, including: a history of renal disease,\textsuperscript{205} increasing age,\textsuperscript{19,120,197,206} multi-lobe involvement on
CXR,\textsuperscript{120,199} admission to an ICU\textsuperscript{21} and immunosuppression.\textsuperscript{205} This study also confirms the
considerable risk reduction for mortality associated with antecedent influenza vaccination\textsuperscript{32} and
increased risk with smoking, including for ex-smokers.

It is important to note that although those aged >80 years were less likely to be admitted to ICU,
those that were did not die significantly more often than younger patients admitted to ICU. While
suggesting aggressive management in the very old is appropriate, these findings are also consistent
with a selection bias in favour of admission to ICU for those very old patients who are less severely
ill. While no significant differences in comorbidity were found for older patients admitted versus
not admitted to ICU, differences in clinical severity were not assessed. A future prospective study of clinical features in these two groups could address this question.

Unlike previous studies however, data from this thesis also suggest a reduction in risk of death associated with other respiratory disease. Increased contact with respiratory specialists and/or greater awareness of symptoms or signs of pneumonia might result in seeking earlier medical care. Similarly, health provider knowledge of the presence of another respiratory condition might prompt earlier intervention. In addition, this thesis provides evidence of greater risk of mortality among those living in their own home (perhaps due to isolation). No association was found with liver disease (compared with Kaplan et al)\textsuperscript{205} aspiration (compared with Mortensen et al)\textsuperscript{206} or ischaemic heart disease (compared with Kaplan et al)\textsuperscript{205}. These disparities may be due to differences in the study populations or treatment approaches.

**Clinical signs and symptoms**

The most common symptoms and signs noted for elderly persons admitted with CAP were dyspnoea (78%), cough (75%), fever (66%), sputum production (56%) and pleuritic chest pain (25%), similar to those described in previous studies from the USA and New Zealand.\textsuperscript{18,202} Of note, two thirds of subjects had three or fewer symptoms and signs present, in keeping with the less distinct clinical presentation described for older patients.\textsuperscript{126}

**Investigations and antimicrobial management**

Almost all patients (97%) with clinical notation and ICD codes for CAP had a CXR performed. Approximately 30% had reports inconsistent with pneumonia on review, suggesting this remains an imperfect approach for retrospective identification of elderly inpatients with pneumonia. This is discussed in greater detail in Chapter 4.

Although not designed to examine investigations, causative organisms or antimicrobial agent use in any detail, some general observations can be made from this study. Over one quarter of elderly persons admitted with CAP had no laboratory investigations performed, and of those who did, most had only one type (for example, a blood test), indicating that an empiric approach to management is frequently used and many patients will not have a causative organism identified. Almost all (96%) patients admitted with CAP received antibiotics during admission; most commonly roxithromycin, ceftriaxone or amoxycillin/clavulanate, which were prescribed in 55% of cases. The antibiotics most commonly prescribed are generally consistent with national antibiotic guidelines for the study period.\textsuperscript{208} They differ from those of Lim et al who studied 106 adult inpatients with CAP and found amoxycillin and erythromycin were the most frequently prescribed.\textsuperscript{19} These differences may be explained by differences in available antibiotics, guidelines, setting or epidemiology of disease at that time.
There were too few investigations identifying a causative organism to make any meaningful interpretation of those found. However, the most commonly identified organisms were influenza viruses, *S. aureus* and *S. pneumoniae*, consistent with previous studies in other settings.120,201

### 3.6.2 Study limitations and strengths

This study was designed to examine vaccine effectiveness of 23vPPV and influenza vaccine against hospitalisation with CAP rather than the epidemiology of CAP. In examining persons admitted with CAP, data were obtained retrospectively by hospital record review. While some variables were well documented (basic epidemiology, burden of disease, risk factors and outcomes), others captured the non-uniform practices of staff investigating and managing such cases. In addition, these latter fields were only collected on persons with notation of pneumonia in their hospital record, thus preventing any comparisons with non-CAP admissions.

Cases of pneumonia described in this chapter were defined using ICD-10 codes, and in addition, for secondary objectives, subjects were required to have a CXR consistent with pneumonia. It is possible that some subjects did not have CAP and that their inclusion could have affected estimates. However, the following chapter addresses this potential limitation in detail and shows that ICD-10 codes are a valid tool for retrospective identification of hospitalised cases of CAP.

The study population is likely to have been representative of hospitalised elderly persons in Victoria, as outlined in chapter 2. In particular, selection bias was minimised by random selection of the cohort, frequency sampling by month, and exclusion of non-Victorian residents. In addition the two study hospitals represented approximately 13% of all hospitalisations for pneumonia for this age group for the years immediately prior to the study (see 2.5.1). Measurement bias was reduced by blinding those collecting data to ICD-coded case status, rigorous training and monitoring, and piloting the study before commencement of data collection for analysis.

### 3.6.3 Conclusions

This study of CAP provides the largest and most comprehensive epidemiological data set for elderly Australians thus far, including the first on risk factors for CAP and associated mortality in elderly inpatients. It confirms that hospitalisation for CAP in the elderly is common, frequently fatal and responsible for a considerable burden to the community that will increase with the growth of the elderly population.

Investigation of hospitalised CAP in the elderly remains ad hoc and the approach to management generally empiric. The study highlights the disparity in ICU admission rates between older and younger elderly patients and raises the question of whether their similar ICU survival rates reflect preferential admission of older patients likely to have a good prognosis. Influenza vaccination should continue to be promoted in this age group as it is associated with reduced mortality associated
with CAP. Further evidence is also produced to advocate smoking cessation. For health practitioners, characteristics present at admission can predict likelihood of CAP and risk of mortality. Greater awareness of risk factors such as aspiration and alcoholism could potentially lead to implementation of preventive strategies and improved outcomes. With one in six receiving intensive care management, early identification and treatment of elderly persons admitted with CAP remains a priority.
Chapter 4 Validity of ICD-10-AM coding for identification of pneumonia

4.1 Overview

Although ICD codes are the most frequently used and convenient method for researchers to retrospectively identify cases of hospitalised pneumonia, there is a paucity of data regarding the validity of this approach, and the potential for differences in settings from outside North America where previous studies have been conducted. Since ICD codes were used to determine the principal outcome measure for this thesis, it was important to examine the validity of this method. This study is the largest to date to examine the validity of using ICD codes to retrospectively identify cases of pneumonia among hospitalised patients, and the first to examine ICD-10-AM codes specifically.

4.2 Objectives

To examine the validity of using ICD-10-AM codes to identify patients hospitalised with pneumonia in terms of sensitivity, specificity, PPV, NPV and kappa statistics.

4.3 Background

4.3.1 Examining Validity

In evaluating the accuracy of ICD-10 codes to correctly identify cases and non-cases of pneumonia for determination of vaccine effectiveness in this study, codes should ideally have a high internal validity (accuracy of measurement). A high sensitivity (patients without the designated codes should not have pneumonia) plus high specificity (patients with the designated codes should have pneumonia) is therefore desirable. In order to measure these, it is necessary to define a comparator for the diagnosis of pneumonia.

Where a true comparator is not available to accurately measure validity (criterion validity), other forms of validity can be considered. It may be possible to explore associations with expected outcomes (predictive validity) or other expected correlates (construct validity). In addition, face validity is a subjective judgement that the measurement is reasonable and is generally a prerequisite for any measure under consideration. Similarly, consensual validity exists where a group of experts agree that the measure is valid. Content validity also reflects whether the measurement adequately incorporates all or most of the aspects of the outcome of interest. In order for a measurement to be valid, repeatability or measurement stability must also be present. This can be examined in terms
Chapter 4: Validity of ICD-10 coding

of percentage agreement and the kappa statistic for discrete variables which gives the percentage agreement adjusted for chance agreement.209

4.3.2 Difficulties in diagnosing pneumonia

As outlined in Chapter 1, all-cause pneumonia is an important clinical endpoint for determining vaccine effectiveness for 23vPPV and influenza vaccine (see 1.6). However, clinical criteria alone are imprecise for identifying cases of pneumonia since the absence of symptoms does not exclude the diagnosis, and presence of symptoms can be non-specific.180 There remains no internationally agreed definition for pneumonia based on clinical symptoms and signs.

Although researchers have described the most commonly occurring symptoms and signs associated with pneumonia in adults and the elderly (cough, dyspnoea, sputum production, fatigue, pleuritic chest pain, fever, abnormal chest findings and tachypnoea),18,202,203 no one sign or symptom, nor combination of these has ever been shown to clearly differentiate pneumonia from other respiratory illnesses.119 One small study of validity of clinical diagnosis for pneumonia found sensitivity of 47-69%, specificity of 58-75% and PPV of 53-61% for certain combinations of symptoms and signs compared with a comparator of radiological diagnosis.125 Defining pneumonia in the elderly based on clinical signs and symptoms is further complicated by the fact that there is evidence for a less distinct clinical presentation with advancing age (see 3.3.5 for further detail).126

In the absence of a clear clinical definition or an ideal diagnostic test for pneumonia,180 CXR is useful and considered by some to be the reference standard for diagnosis of CAP.180 However, it is important to recognise that CXR also has limitations for the diagnosis of pneumonia. One study of 282 patients with pneumonia confirmed by a radiologist found that the agreement rate by a further two radiologists was 79%.210 Standardisation of CXR interpretation is yet to be conducted for adult patients, and even in paediatrics, the standardisation of CXR reading has not been correlated with clinical disease and is only valid for prospective studies following special training of CXR reviewers.211

4.3.3 Use of ICD-10 codes to identify hospitalised pneumonia

Given the difficulty in identifying cases of all-cause pneumonia using a clinical definition, the use of ICD-10-AM codes6 was explored as an alternative method, necessary for subsequent estimation of vaccine effectiveness. ICD codes have been used previously as surrogate measures to identify pneumococcal and influenza-related disease among hospitalised subjects in studies of VE for 23vPPV and influenza vaccine.2,57,58,61,66,102 Use of ICD codes is likely to be at least as valid as the use of a clinical or radiological definition based upon knowledge of sensitivity, specificity and PPV from the medical literature (see 4.3.2).125
The process of coding occurs when a trained medical "coder" examines the discharge diagnoses in hospital records noted by the medical team responsible for the patient, and allocates specific ICD-10 codes which best fit the information provided. Well documented national guidelines are utilised. In Victoria, all coders have a three year university degree to become Health Information Managers (Bachelor of Health Information Management) including annual units on nosology (use of ICD codes according to national guidelines).

Use of standardised ICD codes to identify retrospectively cases of pneumonia among hospitalised patients is appealing to researchers primarily because of time efficiencies. The alternative of reviewing hospital records for clinical, radiological and occasionally microbiological evidence consistent with the diagnosis of pneumonia, is time consuming and resource intensive. In addition, access to hospital records provides the opportunity to examine other subject variables such as comorbidities, thus providing a rich dataset with potential to control for confounding variables.

Despite the practical advantages and continued use of ICD codes by researchers to identify cases of pneumonia, at the time of this research only three studies had examined the validity of this approach, and these were all from outside Australia. Firstly, Marrie et al examined ICD-9-CM codes 011.6, 021.2, 136.3, 480-487, 506 and 507 in a small prospective study of 105 adult patients hospitalised with pneumonia. Codes 480-487 correspond to ICD-10-AM codes J10-J18 used in this thesis (see 2.4). Codes were compared with clinical pneumonia diagnosed within 48 hours of admission to hospital by medical resident staff, plus a new opacity on CXR consistent with pneumonia confirmed by the researchers. The study found a sensitivity of 69% and PPV of 57% for these ICD codes as a group. Secondly, Guevara et al examined the validity of individual ICD-9-CM codes for the specific subcategory of pneumococcal pneumonia against various clinical definitions. Their study is therefore not directly relevant to the broader outcome of all-cause pneumonia. It is important to note however, that validity was found to vary considerably depending on the definition used as the comparator. Inclusion criteria for the analysis of CAP requiring hospitalisation included age ≥18 years, CXR taken within 48 hours of admission revealing a new density consistent with pneumonia in a patient with any one of the following: fever, abnormal white blood cell count, hypothermia or productive cough. Patients were classified as having definite, probable, possible or no pneumococcal pneumonia based on different levels of isolation of S. pneumoniae. With removal of the narrowest of the six diagnostic coding groups (one code only, for pneumococcal sepsis: 38.20), ranges for a combination of codes indicative of pneumococcal pneumonia were sensitivity: 55-85% and NPV: 93-95%. With removal of the broadest of the six diagnostic coding groups (all six evaluated codes: 38.20, 481.00, 38.00, 482.30, 518.81, 486.00), the range for specificity and PPV was 96-100% and 72-95% respectively.

In 1997, Whittle et al also published a small study of agreement of 144 ICD-9-CM classified cases of CAP compared with retrospective review of clinical and radiological records. This study defined CAP using ICD-9 codes 480-487 plus 13 other codes that might capture pneumonia based
on an earlier study.\textsuperscript{213} Confirmation of CAP by clinical review required symptoms compatible with pneumonia within 24 hours of admission and a report consistent with pneumonia from a CXR performed within 48 hours of admission. This study found that where the diagnostic code for CAP was in the principal diagnosis position, compared with the reference standard, codes had a sensitivity of 84%, specificity of 86%, PPV of 92% and kappa of 0.68.

Data from these three studies suggest ICD-10 codes can be used as a valid tool for ascertainment of persons hospitalised with pneumonia, but further examination would be prudent given the small number of studies conducted.

Since the research for this thesis was conducted, a further recent study confirmed estimates for validity in the same range as those from the studies by Marrie et al and Guevara et al.\textsuperscript{214} Aronsky et al compared ICD-9 codes 480-483 plus 485-487 with a rigorous reference standard requiring all of the following: symptoms and a CXR report compatible with pneumonia, an ICD-9 code for or discharge diagnosis of pneumonia, at least a 1% probability of pneumonia calculated by a decision support system,\textsuperscript{215} notation of “pneumonia” in the medical notes and a consensus vote of pneumonia as the diagnosis by three independent physicians. Estimates for validity were: sensitivity 55% (95%CI 48-61), specificity 99% (95%CI 99-99), PPV 84% (95%CI 77-90) and NPV 96% (95%CI 95-97). The lower sensitivity may have been at least partially due to the exclusion of code 484 representing “pneumonia in infectious diseases classified elsewhere”.

The choice of ICD-10 AM codes J10-J18 to identify cases hospitalised with pneumonia in this thesis is consistent with previous studies in the international literature examining VE of influenza vaccine and 23vPPV against pneumonia.\textsuperscript{57,58,60,61,66} Descriptors for these codes are shown in Table 4.6. Most researchers have examined hospitalisation for pneumonia using ICD-9 codes 480-487, exactly equivalent to ICD-10 AM codes J10-J18.\textsuperscript{57,60,61,66} A recent study by Christenson et al used ICD-10 codes J12-J18, J69 and A48.1.\textsuperscript{58} Codes J10 and J11 were not included by Christensen et al but were important to include in the study informing this thesis as they refer to influenza with pneumonia (virus identified and not identified respectively), a key study outcome. As for other researchers, codes J69 (pneumonitis) and A48.1 (Legionnaire’s disease) were excluded from this thesis. J69 encompasses only pneumonitis of non-infectious aetiology (due to food and vomit, oils and essences, and other solids and liquids) and does not include pneumonia Although Legionelllosis can cause pneumonia, this should be captured by codes J10-J18 (for example: J15.8: other bacterial pneumonia).

4.4 Methods

This section presents additional detail relevant to the examination of the validity of ICD-10 codes for the identification of cases of pneumonia. Greater detail for the methods of the overall study are contained in Chapter 2.
4.4.1 Study subjects

First presentation cases and cohort subjects were eligible for the study. All first presentation cases of pneumonia were identified from monthly hospital discharge lists using ICD-10 codes J10-J18 (pneumonia including those cases due to influenza). A case of pneumonia was identified if one or more of these codes appeared in any of the 14 diagnostic code positions for each completed hospital admission. Cohort subjects were sampled monthly as per section 2.4, frequency matched to cases. Codes were allocated by eight coders at each hospital, each with a qualification of Bachelor of Health Information Management, independently of this study and using national standards. To determine the extent of any effect of repeat admission for pneumonia on coding practices, analyses were repeated with inclusion of all pneumonia cases. ICD-10 coded pneumonia cases were compared with ICD-10-non-pneumonia coded subjects for these analyses whether such cases were selected in the case or cohort group.

Examination of the validity of codes for subgroups of microbiologically proven pneumococcal pneumonia (J13) or pneumonia associated with proven influenza (J10 and J11) was not conducted due to small numbers in these subgroups (S. pneumoniae pneumonia was coded in only 11 first presentation pneumonia cases, and there were none coded as influenza pneumonia).

4.4.2 Development of comparators for pneumonia ICD-10 codes

Given the difficulty of defining a reference standard for the diagnosis of pneumonia, three comparators were developed for the purpose of examining the validity of ICD-10 coded cases using retrospective chart review: 1) A clinical comparator: medical record notation of “pneumonia”, 2) CXR report consistent with pneumonia, and 3) both, since interpretation of both clinical and radiological findings is generally used in clinical practice to make a definitive diagnosis of pneumonia.

4.4.2.1 Clinical comparator

Consideration was given to developing a clinical comparator for pneumonia based on the most frequent symptoms and signs suggested by Metlay et al and Neill et al (cough, sputum, pleuritic chest pain, fever, shortness of breath and crackles, plus the documentation of evidence of aspiration) (see 3.3.5). However, this approach was not taken given the apparent poor validity of individual signs and symptoms or combinations of these for the diagnosis of pneumonia, the time associated with reviewing hospital records for a potentially long list of clinical features on a large number of subjects, and the likelihood of missing data on retrospective record review. Instead, hospital records for the selected admission were reviewed for notation of “pneumonia” as a diagnosis considered likely by the hospital clinical team under whose care the subject was admitted. This notation was considered more likely to be consistent with a diagnosis of pneumonia given it would be based on all
Chapter 4: Validity of ICD-10 coding

information available to the hospital clinical team at the time of discharge. As a comparator, it was therefore subjectively reasonable as well as incorporating different components used for diagnosing pneumonia on clinical grounds. It therefore had both face and content validity. The entire hospital medical record was reviewed for information within the time period of the selected admission, including day-to-day records and discharge summaries. Record review occurred without knowledge of ICD-10 codes for individuals. For those subjects with notation of pneumonia in hospital records, the documentation of cough, sputum production, pleuritic chest pain, fever ≥37.5°C, shortness of breath, crackles (crepitations), and aspiration was examined (Appendix 4). For data entry purposes, these factors were noted as definitely present, definitely absent or not recorded. This was done to further confirm the likelihood of pneumonia and to enable examination of the relevance of these factors in probable pneumonia cases.

4.4.2.2 Radiological comparator

As outlined above, it was appropriate in terms of face and construct validity to include a comparator based on CXR results in sensitivity analyses of the validity of ICD-10 codes for pneumonia. The radiological comparator was based on review of radiologist reports for all study subjects with CXRs undertaken as part of routine management. For patients with more than one CXR during their selected admission, the first abnormal report was reviewed blinded to other reports. Trained research assistants used pre-specified criteria to interpret radiologist reports (Table 3.2). Details of establishing inter-operator agreement are discussed in 3.4.2. For the main analysis, outcomes were categorised as “consistent with pneumonia” (lobar pneumonia, bronchopneumonia or other pneumonia) or not.

4.4.2.3 Both

This comparator required the presence of clinical notation of pneumonia plus a CXR report consistent with pneumonia. Since in practise, interpretation of both clinical and radiological findings is used to make a definitive diagnosis, inclusion of a comparator incorporating both these aspects is appropriate in terms of face, content and construct validity. This approach is consistent with that used by previous researchers, including Marrie et al who examined the validity of ICD-9 codes (see 4.3.3),¹²⁸ and a recent prospective cohort study in the elderly where confirmation of ICD-9 coded cases of CAP required review of clinical notes and the presence of “infiltrate on CXR”."⁶¹

4.4.3 Statistical methods

The validity of ICD-10 codes for identification of cases of pneumonia in hospitalised subjects was examined by comparing codes J10-J18 as a group versus the three comparators. Sensitivity, specificity, PPV and NPV were calculated using Stata version 9.1.¹⁹⁰ In addition, because of the absence of a true reference standard, raw data are presented with percentage agreement between
ICD-10 codes and the comparators, and kappa statistics (agreement adjusted for chance agreement). The effect on coding validity of hospital of admission and season was examined using stratification. The influenza season, defined by influenza surveillance independently of this study, was used as a proxy for a period of increased pneumonia activity. Adjustment for frequency of admission using weighting (as described in 2.5.4) was not undertaken since this was not relevant to the validity of the coding process (admissions being seen as independent episodes). Analyses were repeated with inclusion of all pneumonia cases. ICD-10 coded pneumonia cases were compared with ICD-10-coded non-pneumonia subjects for these analyses, regardless of whether such cases were selected in the case or cohort group.

4.5 Results

4.5.1 Study subjects

There were 2319 first presentation cases coded as pneumonia and 2912 first presentation cohort subjects, including 130 who were also selected as cases, giving a total of 5101 eligible study subjects (Figures 4.1 and 4.2). The mean age of eligible subjects was 77 years and 2740 (54%) were male. CXRs were conducted for 3 464/5101 (68%) eligible subjects, 96% of cases and 47% of cohort subjects) and of these 3349 (97%) (97% of cases and 97% of cohort subjects) had radiology reports available for review.

Figure 4.1 Flow chart of eligible first presentation cases, based on ICD-10 codes J10-J18.
4.5.2 Validity

Using medical record notation of pneumonia as the comparator

Clinical notation of pneumonia (or otherwise) was able to be determined for all but three of 5101 eligible subjects (99.9%). Of these, 2281 (45%) had pneumonia documented as the likely diagnosis by hospital clinical staff. This represented 2230/2318 (96%) ICD-10-coded cases and 51/2780 (2%) ICD-10-coded non-cases. 128/179 (72%) pneumonia notations among cohort subjects were cases as defined by ICD-10 codes. There was a very high level of agreement between ICD-10 coded cases or non-cases and clinical notation (Table 4.1), with a kappa statistic of 0.95. Compared with clinical notation as the comparator, ICD-10 codes J10-J18 were found to have a sensitivity of 98%, specificity of 97%, PPV of 96% and NPV of 98% for identification of pneumonia (Table 4.1). Stratification by season and hospital of selection indicated these factors did not play an important role, with small differences between strata in real terms (range 0.1-5.5%) (Table 4.2).
Table 4.1. Validity of ICD-10 coding versus three comparators.

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Cases (%) (J10-J18)</th>
<th>Non-cases (%) (other codes)</th>
<th>% agreement</th>
<th>kappa</th>
<th>Sensitivity (%) (95%CI)</th>
<th>Specificity (%) (95%CI)</th>
<th>PPV (%) (95%CI)</th>
<th>NPV (%) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR report (n=3345)</td>
<td>1538/2154 (71)</td>
<td>1005/1191 (84)</td>
<td>76</td>
<td>0.52</td>
<td>89.2 (87.7-90.6)</td>
<td>62.0 (59.6-64.4)</td>
<td>71.4</td>
<td>84.4</td>
</tr>
<tr>
<td>Notation of pneumonia (n=5098)</td>
<td>2230/2318 (96)</td>
<td>2729/2780 (98)</td>
<td>97</td>
<td>0.95</td>
<td>97.8 (97.1-98.3)</td>
<td>96.9 (96.2-97.5)</td>
<td>96.2</td>
<td>98.2</td>
</tr>
<tr>
<td>Both (n=3343)</td>
<td>1509/2153 (70)</td>
<td>34/1190 (0.3)</td>
<td>80</td>
<td>0.60</td>
<td>97.8 (96.9-98.5)</td>
<td>64.2 (62.0-66.4)</td>
<td>68.1</td>
<td>97.1</td>
</tr>
</tbody>
</table>
Table 4.2. Validity of ICD-10 coding versus 3 comparators (%): stratification by hospital of admission and influenza season.

<table>
<thead>
<tr>
<th>Comparator (n subjects)</th>
<th>sensitivity</th>
<th>Difference (95%CI)</th>
<th>specificity</th>
<th>Difference (95%CI)</th>
<th>PPV</th>
<th>Difference (95%CI)</th>
<th>NPV</th>
<th>Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR report</td>
<td>89.2</td>
<td>62.0</td>
<td>71.4</td>
<td>84.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital 1 (1522)</td>
<td>88.1</td>
<td>61.0</td>
<td>72.8</td>
<td>81.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital 2 (1823)</td>
<td>90.2</td>
<td>-2.1 (-5.0-0.8)</td>
<td>62.8</td>
<td>-1.8 (-6.6-3.0)</td>
<td>70.2</td>
<td>2.6 (-1.3-6.4)</td>
<td>86.8</td>
<td>-5.5 (-9.8- -1.3)*</td>
</tr>
<tr>
<td>Influenza season (1291)</td>
<td>88.2</td>
<td>61.9</td>
<td>70.8</td>
<td>83.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not influenza season (2054)</td>
<td>89.8</td>
<td>-1.6 (-4.7-1.4)</td>
<td>62.1</td>
<td>-0.1 (-5.0-4.7)</td>
<td>71.8</td>
<td>-1.9 (-4.8-3.0)</td>
<td>85.1</td>
<td>-1.7 (-6.0-2.5)</td>
</tr>
<tr>
<td>Notation of pneumonia</td>
<td>97.8</td>
<td>96.9</td>
<td>96.2</td>
<td>98.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital 1 (2430)</td>
<td>97.2</td>
<td>96.4</td>
<td>95.5</td>
<td>97.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital 2 (2678)</td>
<td>98.3</td>
<td>-1.0 (-2.3-0.1)</td>
<td>97.3</td>
<td>-1.0 (-2.3-0.3)</td>
<td>96.8</td>
<td>-1.3 (-2.9-0.2)</td>
<td>98.6</td>
<td>-0.8 (-1.8-0.2)</td>
</tr>
<tr>
<td>Influenza season (1964)</td>
<td>97.6</td>
<td>97.5</td>
<td>97.0</td>
<td>98.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not influenza season (3144)</td>
<td>97.9</td>
<td>-0.2 (-1.5, 1.0)</td>
<td>96.5</td>
<td>1.0 (-0.2-2.3)</td>
<td>95.7</td>
<td>1.2 (-0.3-2.8)</td>
<td>98.2</td>
<td>-0.2 (-1.2-0.8)</td>
</tr>
<tr>
<td>Both</td>
<td>97.8</td>
<td>64.2</td>
<td>68.1</td>
<td>97.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital 1 (1617)</td>
<td>97.5</td>
<td>63.6</td>
<td>71.1</td>
<td>96.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital 2 (1857)</td>
<td>98.0</td>
<td>-0.5 (-2.0-1.0)</td>
<td>64.7</td>
<td>-10.0 (-5.5-3.4)</td>
<td>69.2</td>
<td>-0.6 (-2.0-1.0)</td>
<td>97.6</td>
<td>-1.1 (-3.0-0.9)</td>
</tr>
<tr>
<td>Influenza season</td>
<td>97.6</td>
<td>64.7</td>
<td>70.0</td>
<td>97.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not influenza season</td>
<td>97.9</td>
<td>-0.3 (-1.8-1.2)</td>
<td>63.9</td>
<td>-0.2 (-2.2-1.7)</td>
<td>70.2</td>
<td>-0.2 (-1.8-1.3)</td>
<td>97.2</td>
<td>0.8 (-3.7-5.3)</td>
</tr>
</tbody>
</table>
Among the 2281 subjects with pneumonia documented in their records as a likely diagnosis, an average of 3.9 (median 4) of the seven symptoms and signs of interest were present. Three or more symptoms and signs were present in 1911/2281 (84%) of these subjects. Factors most frequently recorded as present or absent and that were present most often were crackles (92%), shortness of breath (74%), cough (71%), fever $\geq 37.5^\circ$C (66%) and sputum production (54%) (Table 4.3).

Table 4.3. Frequency of symptoms and signs extracted from medical records for subjects with pneumonia documented as a likely diagnosis (n=2281).

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Present n (%)</th>
<th>Absent n (%)</th>
<th>Not recorded n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crackles</td>
<td>2110 (92.5)</td>
<td>138 (6.0)</td>
<td>33 (1.5)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1680 (73.6)</td>
<td>496 (21.7)</td>
<td>105 (4.6)</td>
</tr>
<tr>
<td>Cough</td>
<td>1623 (71.1)</td>
<td>437 (19.2)</td>
<td>221 (9.7)</td>
</tr>
<tr>
<td>Fever $\geq 37.5^\circ$C</td>
<td>1508 (66.1)</td>
<td>764 (33.5)</td>
<td>9 (0.4)</td>
</tr>
<tr>
<td>Sputum production</td>
<td>1229 (53.9)</td>
<td>757 (33.2)</td>
<td>295 (12.9)</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>508 (22.3)</td>
<td>915 (40.1)</td>
<td>858 (37.6)</td>
</tr>
<tr>
<td>Evidence of aspiration</td>
<td>154 (6.7)</td>
<td>469 (20.6)</td>
<td>1658 (72.7)</td>
</tr>
</tbody>
</table>

Using CXR as the comparator

Of 5101 eligible subjects, 3464 (68%) had a CXR conducted, representing 2239/2329 (96%) subjects with ICD codes for pneumonia and 1374/2927 (47%) subjects not coded as having pneumonia. 87 (1.7%) subjects had no CXR performed and an ICD-coded diagnosis of pneumonia. 3345 (97%) subjects with a CXR had radiology reports available for review. 1724/3345 (52%) subjects with CXR reports had some form of pneumonia based on expert review (Table 4.4). This represented 1538/2154 (71%) ICD-10-coded cases and 186/1191 (16%) ICD-10-coded non-cases with a report.
Table 4.4.  Review of radiology reports for 3345 subjects with CXR reports.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopneumonia</td>
<td>860</td>
<td>24.8</td>
</tr>
<tr>
<td>Lobar pneumonia</td>
<td>856</td>
<td>24.7</td>
</tr>
<tr>
<td>Other pneumonia</td>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>Not pneumonia</td>
<td>1621</td>
<td>46.8</td>
</tr>
<tr>
<td>Investigator unsure</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>Missing report</td>
<td>115</td>
<td>3.3</td>
</tr>
</tbody>
</table>

A good level of agreement was present between case status according to ICD-10 codes and CXR reports (kappa 0.52) (Table 4.1). Compared with CXR report as the comparator, ICD-10 coding was found to have a sensitivity of 89%, specificity of 62%, PPV of 71% and NPV of 84% for identification of cases of pneumonia (Table 4.1). No difference in estimates was found when stratifying by season, and only one difference in strata-specific estimates for NPV when stratifying by hospital suggesting a true difference (-5.5; -9.8 -1.3) (Table 4.2).

**Using CXR plus medical record notation of pneumonia as the comparator**

The level of agreement between ICD-10 coding of case status and a combination of notation of pneumonia plus CXR report was similar to that of CXR report alone (kappa 0.60) (Table 4.1). Using this combination of indicators as a comparator, ICD-10 coding had validity within the range provided by the previous two comparators, except for PPV which was lower (Tables 4.1 and 4.2). Stratification indicated no effect of season or hospital of admission on estimates (Table 4.2).

**Repeat analyses including all cases of pneumonia**

Estimates for validity changed very little when all cases of pneumonia were included rather than just first presentations with pneumonia (Table 4.5).
Table 4.5. Validity of ICD-10 coding versus three comparators; all cases of pneumonia included.

<table>
<thead>
<tr>
<th>Comparator (%)</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>PPV (95%CI)</th>
<th>NPV (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notation of pneumonia (n=5378)</td>
<td>98.0 (97.4-98.5)</td>
<td>96.6 (95.9-97.3)</td>
<td>96.3 (95.5-97.0)</td>
<td>98.2 (97.6-98.6)</td>
</tr>
<tr>
<td>CXR report (n=3604)</td>
<td>90.3 (88.9-91.6)</td>
<td>59.7 (57.3-62.0)</td>
<td>71.9 (70.0-73.6)</td>
<td>84.4 (82.2-86.4)</td>
</tr>
<tr>
<td>Both (n=3602)</td>
<td>98.1 (97.3-98.6)</td>
<td>61.9 (59.6-64.1)</td>
<td>70.6 (68.7-72.4)</td>
<td>97.1 (96.0-98.0)</td>
</tr>
</tbody>
</table>

4.5.3 ICD-10 codes and diagnostic positions used for pneumonia

The most common ICD-10 codes used and the diagnostic positions (1-14; for example, the primary diagnosis should appear in the 1st of the possible 14 diagnostic positions) in which they occurred during the study period for the 2319 eligible first presentation cases of pneumonia are shown in Table 4.6. Eight subjects (0.3%) had two codes for pneumonia assigned. By far the most common ICD-10 code used for cases of pneumonia was J18.9 (pneumonia, unspecified) which comprised 91.5% (2122/2319) of all first cases of pneumonia. The next most common codes were J18.0 (bronchopneumonia, unspecified): 1.6% (37/2319) and J15.1 (pneumonia due to Pseudomonas): 1.4% (32/2319). Of first presentation cases of pneumonia with codes J10-J18 listed, codes for pneumonia occurred most frequently in diagnostic position 1 (51%). 82% of cases were documented in the first four positions (Figure 4.3).

Figure 4.3. Utilisation of diagnostic coding positions for first presentation cases of pneumonia.
### Table 4.6. ICD-10 codes used to describe pneumonia by diagnostic code position (1-14).

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Rank</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>J10.0</td>
<td>Influenza with pneumonia, influenza virus identified</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>J11.0</td>
<td>Influenza with pneumonia, virus not identified</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>J11.1</td>
<td>Influenza with other respiratory manifestations, virus not identified</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.0</td>
</tr>
<tr>
<td>J12.9</td>
<td>Viral pneumonia, unspecified</td>
<td>14</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>J13</td>
<td>Pneumonia due to <em>Streptococcus pneumoniae</em></td>
<td>7</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>J14</td>
<td>Pneumonia due to <em>Haemophilus influenzae</em></td>
<td>5</td>
<td>10</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>J15.0</td>
<td>Pneumonia due to <em>Klebsiella pneumoniae</em></td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>J15.1</td>
<td>Pneumonia due to <em>Pseudomonas</em></td>
<td>3</td>
<td>9</td>
<td>12</td>
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<td>2</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>32</td>
<td>32.0</td>
<td></td>
</tr>
<tr>
<td>J15.2</td>
<td>Pneumonia due to staphylococcus</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>29</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>J15.3</td>
<td>Pneumonia due to streptococcus, group B</td>
<td>8</td>
<td>10</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10.4</td>
<td></td>
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<tr>
<td>J15.4</td>
<td>Pneumonia due to other streptococci</td>
<td>10</td>
<td>3</td>
<td>2</td>
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<td>0</td>
<td>1</td>
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<td>0</td>
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<td>1</td>
<td>0</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>J15.5</td>
<td>Pneumonia due to <em>Escherichia coli</em></td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<td>2</td>
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</tr>
<tr>
<td>J15.6</td>
<td>Pneumonia due to other aerobic Gram-negative bacteria</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>J15.7</td>
<td>Pneumonia due to <em>Mycoplasma pneumoniae</em></td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>J15.8</td>
<td>Other bacterial pneumonia</td>
<td>12</td>
<td>1</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>J15.9</td>
<td>Bacterial pneumonia, unspecified</td>
<td>14</td>
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<tr>
<td>J16.8</td>
<td>Pneumonia due to other specified infectious organisms</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>J17.0</td>
<td>Pneumonia in bacterial diseases classified elsewhere</td>
<td>9</td>
<td>5</td>
<td>1</td>
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<td>2</td>
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<td>0</td>
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<td>J17.2</td>
<td>Pneumonia in mycoses</td>
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<td>0</td>
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<tr>
<td>J17.3</td>
<td>Pneumonia in parasitic diseases</td>
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</tr>
<tr>
<td>J17.8</td>
<td>Pneumonia in diseases classified elsewhere</td>
<td>13</td>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Bronchopneumonia, unspecified</td>
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<td>1</td>
<td>37</td>
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<td></td>
</tr>
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<td>J18.1</td>
<td>Lobar pneumonia, unspecified</td>
<td>6</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>J18.8</td>
<td>Other pneumonia, organisms unspecified</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td></td>
</tr>
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<td>J18.9</td>
<td>Pneumonia, unspecified</td>
<td>1</td>
<td>1096</td>
<td>387</td>
<td>165</td>
<td>105</td>
<td>83</td>
<td>74</td>
<td>60</td>
<td>43</td>
<td>29</td>
<td>18</td>
<td>27</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>2122</td>
<td>91.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
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<td></td>
<td>1182</td>
<td>432</td>
<td>183</td>
<td>114</td>
<td>95</td>
<td>81</td>
<td>65</td>
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<td>12</td>
<td>10</td>
<td>2327</td>
<td>-</td>
</tr>
<tr>
<td><strong>%</strong></td>
<td></td>
<td></td>
<td>50.8</td>
<td>18.6</td>
<td>7.9</td>
<td>4.9</td>
<td>4.1</td>
<td>3.5</td>
<td>2.8</td>
<td>2.0</td>
<td>1.4</td>
<td>1.0</td>
<td>1.3</td>
<td>0.9</td>
<td>0.5</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.6 Discussion

4.6.1 Validity

These data confirm the place of ICD-10 coding (as performed by expert hospital coders) as a valid tool for the retrospective identification of persons discharged from hospital with a diagnosis of pneumonia.

Using medical record notation of pneumonia as the comparator, this study was able to exclude estimates for sensitivity, specificity, PPV and NPV of less than 95% (range of 95% CIs 95.4-98.6). The kappa statistic of 0.95 indicated excellent levels of agreement after adjustment for chance agreement. This is reassuring, as intuitively this comparator implies synthesis of all clinical and diagnostic information available to the medical team caring for the patient and has both face and content validity. Given that coding staff are trained to translate hospital record notations into codes in a way that captures as much information as possible, rather than by searching for individual symptoms and signs, these data confirm that the coding process is being performed at a high standard in the two hospitals studied. They are also important for researchers of hospitalised subjects, since use of ICD-10 codes to retrospectively identify pneumonia patients is quick, simple and efficient compared with expert interpretation of radiology reports or identification of clinical signs and symptoms consistent with pneumonia.

This study found somewhat higher levels of internal validity for ICD-10 coding as a tool for identifying persons discharged from hospital with pneumonia than previous studies conducted outside Australia. Although none of the studies was exactly comparable in design, it is possible that the differences in results could be partly explained by differences in design or setting (for example, coding practices or training). In Victoria, for instance, a high level of training is required for clinical coders, there is linking of hospital funding to codes, and annual audits of coding accuracy are conducted by independent and/or government agencies. In general, results from earlier studies were nonetheless favourable towards use of ICD codes as a tool for identifying cases of pneumonia (see 4.3.3).

Searching for individual symptoms and signs has particular difficulties due to uncertainty about which are the most important to include, as well as the problem of missing data with retrospective chart review. Although this study did not examine individual signs and symptoms consistent with pneumonia for all participants, previous studies suggest that symptom complexes are likely to be inferior to ICD-10 codes as a tool for researchers to retrospectively identify cases of pneumonia, given data suggesting relatively low validity of clinically-based definitions of pneumonia (see 4.3.2). Based on review of hospital records, for subjects with notation of pneumonia as a likely diagnosis, a median of four of the seven symptoms and signs of interest were present.
It may not be surprising that using radiology reports as a reference standard to define pneumonia retrospectively did not result in close agreement with ICD-10 codes. Firstly, non-specific language was often used. Words such as “opacity” were frequently used to describe the appearance of a CXR rather than reporting a definitive diagnosis, and may indicate pathology other than pneumonia. Radiology reports are therefore open to a degree of interpretation and may not be an ideal comparator. Even with the high level of inter-rater consensus achieved, the criteria used for interpretation may also be open to criticism, given the lack of agreement on a definition for pneumonia. This study did not review CXRs themselves. While it is possible that radiologist review of CXRs (rather than of their associated reports) may be of greater diagnostic value, limited data suggest this is also imperfect (see 4.3.2). A standardised approach to the interpretation of adult CXRs is not yet available, however, future development may improve the usefulness of radiology reports as a comparator for future studies. Although a standardised approach to interpretation of paediatric CXRs has been developed, this has not yet been correlated with clinical disease and is only valid for prospective studies following specific training of reviewers.211

4.6.2 ICD-10 codes and diagnostic positions used for pneumonia

Code J18.9 for “unspecified pneumonia” comprised over 91% of all hospital admissions for pneumonia. Therefore while ICD-10 codes are both sensitive and specific for the identification of cases of pneumonia, they are unlikely to be helpful, at least in this setting, for the identification of subcategories of pneumonia. This may be due to low rates of microbiological testing as shown in chapter 3, or poor sensitivity and specificity of laboratory tests. For others conducting research using this method of case ascertainment, it might be reasonable to examine only the first eight diagnostic coding positions, which capture 95% of all cases of pneumonia.

4.6.3 Study limitations and strengths

A key limitation in this area of research is the lack of a reference standard for diagnosis of pneumonia against which to compare ICD-10 coding. Analyses were conducted using three comparators suggested by review of the literature, but estimates of validity should still be interpreted with caution. However, this study was large enough to exclude a sensitivity, specificity, NPV and PPV for ICD-10 codes for pneumonia of less than 95% when compared with medical record notation for pneumonia and kappa statistics for agreement were very high. Kappa statistics for agreement confirmed very high levels of agreement in keeping with these estimates. There were few missing data for any comparator, with 97% of radiology reports available for eligible subjects, and notation of pneumonia or otherwise able to be determined for all but three of 5101 subjects (<0.1%). The study population is likely to have been representative of hospitalised elderly persons in Victoria (as outlined in 2.3.2 and 3.6.2). Estimates made including all cases of pneumonia were virtually identical to those made using only first presentation cases of pneumonia, suggesting that repeat
presentations were not coded differently and their exclusion from the primary analyses was unlikely to have biased the outcome measures.

4.6.4 Conclusions

ICD-10 codes are a valid method for retrospective ascertainment of patients hospitalised with pneumonia and likely to be better than use of complexes of symptoms and signs, or interpretation of radiology reports. Use of ICD-10 codes is therefore an appropriate method for case ascertainment of pneumonia in the estimation of vaccine effectiveness where pneumonia is the outcome of interest.
Chapter 5 Effectiveness of influenza vaccine and 23vPPV against hospital admission for CAP in persons aged ≥65 years

5.1 Overview

In order to address ongoing controversy, this chapter estimates VE for influenza vaccine and 23vPPV against hospitalisation with CAP among elderly persons in Victoria, and provides the first data from the southern hemisphere regarding this question. In particular, it aims to determine whether 23vPPV has additional benefit over and above influenza vaccine alone. A summary of the background and methods presented in chapters 1 and 2 is included here to provide immediate context. Detailed data and discussion on vaccination coverage and risk factors for hospitalisation with CAP are presented elsewhere (see Chapters 7 and 3 respectively). Chapter 1 provides a detailed rationale for the use of the case-cohort study design and of all-cause pneumonia as an appropriate clinical end point for the assessment of VE.

5.2 Background

Despite well-documented benefits from 23vPPV and influenza vaccine against IPD and laboratory confirmed influenza, their effectiveness against pneumonia remains controversial for community-based elderly ≥65 years.

Overall, clinical trial data do not provide evidence of benefit from pneumococcal polysaccharide vaccines against pneumonia, and those few showing benefit used non-representative populations and/or potentially over-estimated VE (see 1.5.1). A recent Cochrane review (conducted after this study) of VE for polysaccharide vaccine in adults was unable to demonstrate significant benefit against pneumonia. VE was 23% (95%CI -2-42%) when data were combined from 14 clinical trials, dropping to 16% (95%CI -8-35%) after exclusion of one low quality trial (see 1.5.1). Of non-experimental studies of 23vPPV examining pneumonia as an outcome, only one was published at the time of undertaking this study. Prior to 2002 (and the completion of this research), non-experimental studies examined incremental effectiveness over and above influenza vaccine, and were limited to high risk populations or only reported interim data without adjustment for confounders. These data are unlikely to be generalisable to the healthy elderly. Studies since 2002
have produced conflicting results, with not all studies showing benefit. A recent study using patients with *S. pneumoniae* colonisation as a comparator group also found lack of benefit against non-bacteraemic pneumococcal pneumonia.

Although the Advisory Committee on Immunization Practices in the USA reports that influenza vaccine is between 30 and 70% effective in preventing hospitalisation with pneumonia and influenza in the elderly (excluding those living in long-term care facilities where environmental and vaccine viral strain match is poor or unknown), a degree of controversy still remains regarding the effectiveness of influenza vaccine against pneumonia for those who live in the community. While two recent prospective cohort studies suggest effectiveness against pneumonia (Christenson: RR 0.54; 95%CI 0.44-0.66 unadjusted for confounders, Monto: RR 0.65; 95%CI 0.51-0.85 for nursing home residents), others have found benefit that has not reached statistical significance. Hara et al reported moderate but non-significant benefit against hospitalisation for influenza and pneumonia in a cohort study of elderly community-based persons in Japan (OR 0.37, 95%CI 0.09-1.47). Voordouw et al conducted a cohort study among community-based elderly in the Netherlands and found a non-significant smaller benefit against pneumonia among the community-based elderly (HR 0.84, 95%CI 0.65-1.07), including when restricted to the influenza epidemic period (HR 0.87, 95%CI 0.55-1.36) and when revaccination was accounted for (HR 0.89, 95%CI 0.67-1.18). Although benefit was reported against pneumonia in those who were hospitalised (HR 0.29, 95%CI 0.10-0.96), this was based on the occurrence of only three cases of pneumonia. Simonsen et al reported no decline in mortality due to influenza and pneumonia in the elderly despite 30 years of increasing vaccination coverage. Recent criticism of observational studies showing benefit cites biased estimates of effect in favour of vaccination due to preferential vaccination of healthy subjects.

At the time of this research, no southern hemisphere data were available for the effectiveness of either 23vPPV or influenza vaccine against pneumonia (or any other outcome), and none of the above studies examining VE for influenza vaccine were available.

Despite uncertainty related to VE of 23vPPV and influenza vaccine against pneumonia in the elderly, recommendations to vaccinate this population have been increasingly adopted by industrialised countries. Debate has escalated in recent times as to their appropriateness, and perhaps as a response to this, their justification has shifted to prevention of IPD from prevention of pneumonia (less so for influenza). Such policies have important implications for ongoing health care costs, and require evaluation.

During this research, Victoria was the only Australian jurisdiction to publicly fund both vaccines in this age group. This unique setting of relatively high vaccine coverage enabled testing of the hypothesis that Victorians aged ≥65 years vaccinated against influenza and *Streptococcus pneumoniae* are protected against hospitalisation for CAP, and in particular to examine whether
Chapter 5: VE against CAP in the elderly

23vPPV provides additional benefit for prevention of hospitalisation with CAP over and above influenza vaccine.

5.3 Methods

Chapter 2 comprehensively discusses the methods for the case-cohort study. This section represents an overview.

Using a case-cohort design, subjects were randomly selected from the monthly discharge lists (indicating completed admissions) of all persons aged ≥65 years discharged from two large teaching hospitals in Melbourne, Victoria, for the period 1 April 2000 to 31 March 2002. Subjects with pneumonia diagnosis codes including those encompassing influenza (ICD-10 AM codes J10-J18) were selected as cases. Cases were also eligible for selection in the cohort. If a subject appeared on the hospital discharge list more than once in any given month, one episode was selected at random, and the rest excluded. For month-to-month repeat admissions for pneumonia for an individual, the first selected admission was retained and subsequent episodes excluded. Subjects were also excluded from monthly discharge lists if not resident in Victoria or if admitted for short-stay procedures such as dialysis and chemotherapy (ICD-10-AM codes Z49.1, Z49.2 and Z51.1).

The cohort sample was randomly selected from all monthly hospital discharges in persons aged ≥65 years, frequency matched to cases. Over-sampling was conducted to allow for subsequent exclusion of repeat admissions among the cohort, as well as those subjects also selected as cases. A total of 1.2 times the number of cases was randomly selected from all monthly hospital discharges to form the cohort. A cohort subject could also be selected only once each month and admissions selected for the same subject in subsequent months were excluded. Since subjects who were admitted to hospital more frequently over the two-year study period were more likely to be selected, adjustment was made for potential selection bias by using a weight equal to the inverse of the total number of admissions for each subject over the duration of the study period.

Vaccination status was determined by receipt of a complete vaccination date (day, month, year) from a vaccine provider within 14-365 days prior to hospital admission for influenza vaccine or 14-1825 days (5 years) prior for 23vPPV.

CAP was defined as pneumonia diagnosed before or within 48 hours of admission.

Logistic regression was used to estimate the risk ratios for VE against hospitalisation with CAP, adjusting for hospital of discharge, month of sampling, and selection probability. Potential confounders were included in the models and eliminated using the backward stepwise process.

Pre-specified analyses were undertaken to estimate risk ratios (RRs) with 95% confidence intervals for a) the effect of influenza vaccine (alone or in combination with 23vPPV) versus neither vaccine,
and b) the incremental effect of 23vPPV by comparing influenza vaccine plus 23vPPV to influenza vaccine alone. Further detail can be found in 2.10.1.

Influenza vaccination effectiveness was examined during the two influenza seasons of the study period, defined according to active Sentinel Influenza Surveillance reports for Victoria. In addition, where the effects of both vaccines were examined together, the entire study period was included in the analysis.

Sensitivity analyses were also conducted for the pre-specified analyses to examine effects due to:

a) repeat admission for CAP on the exposure of vaccination status, by including all CAP admissions.

b) subjects for whom vaccination status was unknown, by reassigning those with unknown vaccination status to a) vaccinated status and b) unvaccinated status.

c) waning of immunity inferred by influenza vaccine, by restricting positive influenza vaccination status to those receiving vaccine between 14 days and six months prior to admission.

Subsequent exploratory analyses examined the effect of:

a) 23vPPV (alone or with influenza vaccine) versus neither vaccine,
b) both vaccines versus neither vaccine,
c) influenza vaccine (alone or with 23vPPV) versus no influenza vaccine,
d) 23vPPV (alone or with influenza vaccine) versus no 23vPPV,
e) 23vPPV alone versus no 23vPPV,
f) an interaction term (compared with a step-wise approach) to explore potential supra-additive effects of vaccination with influenza vaccine plus 23vPPV,
g) years since vaccination with 23vPPV,
h) vaccination with either vaccine on deaths during hospitalisation associated with pneumonia or all-cause mortality using final models from the pre-specified analyses and the exploratory analysis examining 23vPPV alone, and
i) an interaction term exploring potential supra-additive effects of age on VE using final models from the pre-specified analyses.

5.4 Results

5.4.1 Description of eligible cases

There were 2670 cases of pneumonia during the study period, of which 161 were also selected in the cohort (Figure 5.1). 2244/2670 (84%) pneumonia cases were community-acquired. Two cases were excluded as duplicate entries, a further 51 were ineligible and 5 had lost hospital records (Table 5.1),
leaving 2186 eligible cases of hospitalisation with CAP. Of these, 1952/2186 (89%) were first time CAP admissions used for further analysis.

Table 5.1. Summary of ineligible cases of pneumonia after data cleaning.

<table>
<thead>
<tr>
<th>Reason for ineligibility</th>
<th>cases</th>
<th>cohort 1st admits</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstate visitor</td>
<td>12</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Dialysis, chemotherapy admissions</td>
<td>20</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>Overseas visitor</td>
<td>10</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Less than 65 years of age</td>
<td>5</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Hospital record lost</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Treatment at other hospital for same episode of pneumonia</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Record of admission not found</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>78</td>
<td>134</td>
</tr>
</tbody>
</table>

Figure 5.1: Flow chart for cases of participation rate and availability of vaccination data.

Selected cases 2670

CAP cases 2244 (84%)

Excluded 2 duplicates, 51 ineligible

5 lost records

Eligible CAP cases 2186 (97%)

Eligible 1st CAP cases 1952 (89%)

Consent to contact provider 1686

Vaccine provider uncontactable 6

Vaccine provider declined 42

Lost record 4

Response from provider 1634 (97%)

23vPPV vaccine status 1606 (98%)

Influenza vaccine status 1582 (97%)
5.4.2 Description of eligible cohort subjects

Of the 83,280 hospital admissions occurring for persons aged ≥65 years for the two year study period, 27,372 (33%) were excluded as day admissions for dialysis or chemotherapy, and 6,216 (7%) because they were repeat admissions for the same person within the same month, leaving a total of 49,692 admissions. A random sample of 3204 (6%) admissions was selected for the cohort, representing 1.2 times the number of initially identified cases. The proportion of subjects selected from the hospital discharge list each month ranged from 5.2% to 8.4%, with peaks over winter months corresponding to the increase in the number of cases selected (Figure 5.2).

Figure 5.2. Proportion of hospitalised cohort selected from monthly discharge lists.

Of the 3204 randomly selected cohort admissions, 200 (6%) were subsequently excluded because they were repeat admissions for previously selected subjects and 77 (2%) for other reasons (26 non-Victorian residents, 24 aged < 65 years, 20 admissions for dialysis or chemotherapy, and 7 lost records), leaving 2,927 eligible cohort subjects (Figure 5.3). Of these, 107 (4%) were also selected as first presentation cases of CAP.
Figure 5.3. Flow chart for selected cohort subjects of participation rate and availability of vaccination data.

5.4.3 Baseline characteristics

The mean age of study subjects was 77 years (median 76 years) and 2552/4772 (53.5%) were male. Cases were slightly older and a greater proportion were male compared with cohort subjects (Table 5.2). The two groups differed for a number of baseline characteristics (Table 5.2). Exceptions were: mean number of hospitalisations in the past 2-5 years, a history of rheumatological disease, liver disease or cerebrovascular disease, and smoking habits.
Table 5.2. Baseline characteristics for 1st admission cases of CAP and cohort subjects. *

<table>
<thead>
<tr>
<th>Variable (%)*</th>
<th>CAP cases n=1952 (95%CI)</th>
<th>Cohort subjects n=2927 (95%CI)</th>
<th>Difference (cases-cohort) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>78.4 (78.0-78.7)</td>
<td>76.1 (75.8-76.4)</td>
<td>2.3 (1.9-2.7)</td>
</tr>
<tr>
<td>Male gender</td>
<td>57.7 (55.5-59.9)</td>
<td>50.9 (49.1-52.7)</td>
<td>6.7 (3.9-9.6)</td>
</tr>
<tr>
<td>Live in own home</td>
<td>19.5 (17.7-21.2)</td>
<td>12.5 (11.3-13.7)</td>
<td>6.9 (4.8-9.1)</td>
</tr>
<tr>
<td>First language English</td>
<td>70.4 (68.4-72.5)</td>
<td>73.1 (71.5-74.7)</td>
<td>-2.6 (-0.5--5.2)</td>
</tr>
<tr>
<td>Mean hospitalisations past 1 year</td>
<td>1.2 (1.1-1.3)</td>
<td>1.4 (1.3-1.5)</td>
<td>-0.2 (-0.3-0.0)</td>
</tr>
<tr>
<td>Mean hospitalisations past 2-5 years</td>
<td>2.1 (2.0-2.3)</td>
<td>2.0 (1.8-2.1)</td>
<td>0.1 (0.1-0.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26.5 (22.6-26.4)</td>
<td>24.9 (23.3-26.4)</td>
<td>1.7 (0.8-4.2)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>46.6 (44.8-48.4)</td>
<td>53.0 (50.8-55.2)</td>
<td>-6.4 (-9.3--3.5)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>27.0 (25.0-28.9)</td>
<td>23.9 (22.3-25.4)</td>
<td>2.9 (0.4-5.4)</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>47.9 (45.7-50.1)</td>
<td>27.8 (26.2-29.4)</td>
<td>20.1 (17.3-22.8)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>13.3 (11.8-14.8)</td>
<td>8.8 (7.7-9.8)</td>
<td>4.5 (2.7-6.4)</td>
</tr>
<tr>
<td>Rheumatological disease</td>
<td>15.7 (14.1-17.3)</td>
<td>17.0 (15.6-18.3)</td>
<td>-1.3 (-3.4--0.9)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>2.6 (1.9-3.3)</td>
<td>2.0 (1.5-2.5)</td>
<td>0.6 (0.3-1.4)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>21.0 (18.4-21.3)</td>
<td>19.9 (19.1-22.7)</td>
<td>1.1 (0.3-1.2)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>2.2 (1.6-2.9)</td>
<td>1.0 (0.6-1.3)</td>
<td>1.3 (0.5-2.0)</td>
</tr>
<tr>
<td>Previous pneumonia</td>
<td>22.2 (20.4-24.1)</td>
<td>11.4 (10.3-12.6)</td>
<td>10.8 (8.6-13.0)</td>
</tr>
<tr>
<td>Pneumonia past year</td>
<td>8.2 (7.0-9.5)</td>
<td>5.2 (4.4-6.0)</td>
<td>3.0 (1.6-4.5)</td>
</tr>
<tr>
<td>Pneumonia past 2-5 years</td>
<td>12.9 (11.4-14.4)</td>
<td>5.4 (4.6-6.3)</td>
<td>7.5 (5.8-9.2)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>20.1 (17.5-22.7)</td>
<td>14.0 (12.3-15.7)</td>
<td>6.1 (3.0-9.2)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>8.5 (7.0-9.9)</td>
<td>8.3 (7.1-9.4)</td>
<td>0.2 (-0.2-1.6)</td>
</tr>
<tr>
<td>Current/Ex-smoker</td>
<td>65.7 (63.2-68.2)</td>
<td>58.3 (56.3-60.4)</td>
<td>7.4 (4.1-10.6)</td>
</tr>
<tr>
<td>Death during hospitalisation</td>
<td>16.3 (14.7-18.0)</td>
<td>5.0 (4.2-5.8)</td>
<td>11.4 (9.5-13.2)</td>
</tr>
</tbody>
</table>

* See Table 3.7 or Appendix 4 for detailed description of variables
† Percentage, unless labelled as a mean
5.4.4 Consent to participate and information from next of kin

Overall, 3534/4772 (74%) selected subjects consented to participate in the questionnaire and 4166/4772 (87%) agreed for contact to be made with their nominated vaccine providers to request information on vaccination status. Participation in the questionnaire was slightly higher among eligible cohort subjects compared with cases (Table 5.3, Figures 5.1 and 5.3). The number of selected subjects for whom information was provided by next of kin differed significantly between eligible cases and cohort subjects (Table 5.3).

Table 5.3. Consent and information from next of kin among 1st admission CAP cases and cohort subjects.

<table>
<thead>
<tr>
<th>Consent to</th>
<th>CAP cases n=1952 (%) (95%CI)</th>
<th>Cohort subjects n=2927 (%) (95%CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undertake questionnaire</td>
<td>1407 (72.1%) (70.1-74.1)</td>
<td>2203 (75.3%) (73.7-76.8)</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Allow contact with vaccine providers</td>
<td>1686 (86.4%) (84.9-87.9)</td>
<td>2573 (87.9%) (86.7-89.1)</td>
<td>p = 0.12</td>
</tr>
<tr>
<td>Information from next of kin†</td>
<td>507 (26.0%) (24.0-27.9)</td>
<td>334 (11.4%) (10.3-12.6)</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

* Adjusted by removing cases with CAP from the total number of eligible cohort subjects
† Deaths at time of questionnaire administration (includes deaths during hospital admission)

Consent to participate in questionnaires and vaccination coverage for 23vPPV did not differ between those subjects who participated in person versus those who had information provided by their next of kin (p=0.13 and p=0.82 respectively). However, availability of vaccination status data from providers and influenza vaccine coverage was lower among the group who had information provided by next of kin compared with those who did not (vaccine data: 79.9% versus 85.5% p=0.01; influenza vaccine: 66.4% versus 71.6% p=0.01).

5.4.5 Completeness of vaccination data from vaccine providers

The majority of vaccine providers were willing to provide information on vaccination status (Figures 5.1 and 5.3 above). Of the 4166 selected subjects who provided consent to contact vaccine providers, contact could not be made with 19 (0.4%) providers, and providers declined to provide information for 119 (2.9%) subjects. Information on vaccination status was therefore available from vaccine providers for 4039/4166 (97.0%) subjects providing consent. This represented 4039/4772
(84.6%) total selected subjects. This proportion did not differ significantly between eligible cohort subjects and cases (p=0.36).

After exclusions due to incomplete vaccination dates and subjects unable to be confirmed as known to the nominated vaccine provider, a definite medical record of influenza vaccination status was obtained for 3902/4772 (81.8%) subjects (or 93.7% of those who provided consent). For 23vPPV status the proportion was 3964/4772 (82.1%) (or 95.2% of those who provided consent). There was no difference in these proportions between eligible cohort subjects and cases (influenza vaccine: p=0.31; 23vPPV: p=0.25).

There was no difference in age and sex distribution between those eligible subjects for from whom vaccination status was ascertained and those for whom it was not (data not shown).

### 5.4.6 Vaccination coverage

#### 5.4.6.1 Weighted estimates for the cohort

Weighted coverage estimates (adjusted for selection probability) among the study subjects were 71% (95%CI 69-72) for influenza vaccine within the year prior to admission, 53% (95%CI 52-55) for 23vPPV within five years prior to admission and 47% (95%CI 45-49) for both vaccines (Table 5.4). Of note, 24% had received only influenza vaccine, and 8% had received 23vPPV only. Estimates for cohort subjects and cases of hospitalisation with CAP are shown in Table 5.4.

<table>
<thead>
<tr>
<th></th>
<th>All subjects n=4772</th>
<th>Cohort subjects n=2927</th>
<th>CAP cases n=1952</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data available (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n Influenza vaccine</td>
<td>3902 (82%)</td>
<td>2408 (82%)</td>
<td>1582 (82%)</td>
</tr>
<tr>
<td>n 23vPPV</td>
<td>3964 (83%)</td>
<td>2448 (84%)</td>
<td>1606 (82%)</td>
</tr>
<tr>
<td>n Both</td>
<td>3851 (81%)</td>
<td>2380 (81%)</td>
<td>1557 (80%)</td>
</tr>
<tr>
<td>Vaccine coverage % (95%CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>70.9 (69.4-72.4)</td>
<td>70.8 (68.8-72.8)</td>
<td>70.7 (68.4-73.0)</td>
</tr>
<tr>
<td>(n=3902)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23vPPV</td>
<td>53.5 (51.9-55.2)</td>
<td>52.6 (50.4-54.7)</td>
<td>54.4 (51.9-56.9)</td>
</tr>
<tr>
<td>(n=3964)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>47.1 (45.4-48.8)</td>
<td>46.6 (44.4-48.8)</td>
<td>47.3 (44.8-49.9)</td>
</tr>
<tr>
<td>(n=3851)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 5.4.6.2 Unweighted estimates

Unweighted vaccination coverage estimates (unadjusted for selection probability) were virtually identical to weighted estimates, implying that vaccination coverage estimates were not biased by increased chance of selection due to repeat admission (Table 5.5).

**Table 5.5. Unweighted influenza and 23vPPV coverage.**

<table>
<thead>
<tr>
<th>Vaccine coverage (%) (95%CI)</th>
<th>All subjects n=4772</th>
<th>CAP cases n=1952</th>
<th>Cohort subjects n=2927</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine (n=3902)</td>
<td>70.8 (69.3-72.2)</td>
<td>70.7 (68.4-73.0)</td>
<td>70.7 (68.6-72.5)</td>
</tr>
<tr>
<td>23vPPV (n=3964)</td>
<td>53.3 (51.7-54.8)</td>
<td>54.4 (51.9-56.9)</td>
<td>52.4 (50.4-54.4)</td>
</tr>
<tr>
<td>Both (n=3851)</td>
<td>46.9 (45.3-48.5)</td>
<td>47.3 (44.8-49.9)</td>
<td>46.4 (44.4-48.4)</td>
</tr>
</tbody>
</table>

### 5.4.6.3 Weighted estimates by study year

Vaccination coverage increased during the study period from the first to the second year (Table 5.6).

**Table 5.6. Weighted influenza and 23vPPV coverage by study year.**

<table>
<thead>
<tr>
<th>Vaccine coverage (%) (95%CI)</th>
<th>Year 1 (Apr 2000-Mar 2001)</th>
<th>Year 2 (Apr 2001-Mar 2002)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (n=3902)</td>
<td>69.0 (66.9-71.1)</td>
<td>73.1 (70.9-75.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>23vPPV (n=3964)</td>
<td>51.5 (49.3-53.7)</td>
<td>55.8 (53.4-58.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Both (n=3851)</td>
<td>45.2 (43.0-47.5)</td>
<td>49.3 (46.8-51.7)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
5.4.7 Vaccine effectiveness

5.4.7.1 Univariate analyses (adjusted for design variables only)

Pre-specified analyses

Logistic regression did not demonstrate benefit from influenza vaccination against hospitalisation with CAP compared with neither vaccine (RR 1.06; 95%CI 0.90-1.25), including when VE was estimated only within the two influenza seasons (RR 1.12; 95%CI 0.86-1.46). Similarly, there was no demonstrable benefit from 23vPPV over and above influenza vaccine alone (RR 1.03; 95%CI 0.87-1.22), including when restricted to the influenza seasons (RR 1.00; 95%CI 0.80-1.33).

Exploratory analyses

Evidence of benefit against hospitalisation with CAP was also not demonstrated for any of the exploratory analyses (Table 5.7), including when estimates were restricted to influenza seasons only (data not shown).

Table 5.7. Univariate exploratory analyses using logistic regression.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>RR (95%CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23vPPV versus neither vaccine</td>
<td>1.10 (0.93-1.30)</td>
</tr>
<tr>
<td>Influenza vaccine + 23vPPV versus neither vaccine</td>
<td>1.08 (0.91-1.29)</td>
</tr>
<tr>
<td>Influenza vaccine versus no influenza vaccine</td>
<td>0.99 (0.86-1.15)</td>
</tr>
<tr>
<td>23vPPV (any) versus no 23vPPV</td>
<td>1.08 (0.94-1.23)</td>
</tr>
<tr>
<td>23vPPV alone versus no 23vPPV</td>
<td>1.30 (0.98-1.74)</td>
</tr>
</tbody>
</table>

Examination of an interaction term of the variables “any influenza vaccine versus no influenza vaccine” and “any 23vPPV versus no 23vPPV” produced an anomalous result. No benefit against hospitalisation with CAP was found for influenza vaccine or both vaccines together, but there was a suggestion of benefit for 23vPPV (Table 5.8). By using a logarithmic scale, it appeared that 23vPPV might be beneficial, but that the use of influenza vaccine and 23vPPV together was detrimental. Examination of 23vPPV alone did not indicate benefit (RR 1.40, 95%CI 1.02, 1.91), however, the number of subjects included in this final analysis was only 1130 (of whom only 231 had 23vPPV alone). It is therefore likely that these results are anomalous given the small number of subjects who had only received 23vPPV.
Table 5.8. Exploratory analysis using an interaction term for “influenza vaccine versus no influenza vaccine” and “23vPPV versus no 23vPPV”.

<table>
<thead>
<tr>
<th></th>
<th>RR (95%CI)</th>
<th>p-value</th>
<th>log RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine versus no flu vaccine</td>
<td>1.03 (0.85-1.26)</td>
<td>0.74</td>
<td>0.09 (-0.22-0.41)</td>
</tr>
<tr>
<td>23vPPV versus no 23vPPV</td>
<td>1.28 (0.97-1.70)</td>
<td>0.08</td>
<td>0.55 (0.02-1.08)</td>
</tr>
<tr>
<td>Interaction term</td>
<td>0.81 (0.58-1.12)</td>
<td>0.19</td>
<td>-0.52 (-1.11-0.07)</td>
</tr>
</tbody>
</table>

In addition, the effectiveness of 23vPPV over time was examined in terms of years lapsed since vaccination. The number of years since 23vPPV (for those who had received it) was predictive of admission with CAP (p=0.01). Of note after five years, vaccinated subjects were at greater risk than unvaccinated subjects (Table 5.9). A test for trend indicated that the RR for admission with CAP increased by 1.05 (or VE decreased by 5%) for each year further from the year of vaccination (RR 1.05; 95%CI 1.02-1.10).

Table 5.9. Risk of admission with CAP by number of years since receiving 23vPPV.

<table>
<thead>
<tr>
<th>Years since vaccination</th>
<th>n</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>413</td>
<td>0.91 (0.73-1.15)</td>
<td>0.44</td>
</tr>
<tr>
<td>2</td>
<td>412</td>
<td>1.02 (0.81-1.28)</td>
<td>0.84</td>
</tr>
<tr>
<td>3</td>
<td>586</td>
<td>0.99 (0.81-1.21)</td>
<td>0.93</td>
</tr>
<tr>
<td>4</td>
<td>510</td>
<td>1.24 (1.01-1.53)</td>
<td>0.04</td>
</tr>
<tr>
<td>5</td>
<td>189</td>
<td>1.26 (1.19-2.24)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Examination of an interaction term of the variables “age group” and the vaccine variables found no potential additive effect (on the logistic scale) of age on VE for either influenza vaccine or 23vPPV (Table 5.10).
Table 5.10. Univariate estimates for an interaction term of age with vaccination variables for the pre-specified analyses.

<table>
<thead>
<tr>
<th>Stratum-specific RR (95%CI)</th>
<th>Overall p-value for interaction</th>
<th>Stratum-specific log RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group x Influenza vaccine versus no flu vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference group 65-69 yrs</td>
<td>0.89 (0.61-1.29)</td>
<td>0.70</td>
</tr>
<tr>
<td>70-74</td>
<td>1.07 (0.73-1.56)</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>1.07 (0.76-1.51)</td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>1.06 (0.72-1.57)</td>
<td></td>
</tr>
<tr>
<td>≥85</td>
<td>1.24 (0.85-1.83)</td>
<td></td>
</tr>
<tr>
<td>Age group x Both vaccines versus influenza vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reference group 65-69 yrs</td>
<td>1.18 (0.77-1.83)</td>
<td>0.11</td>
</tr>
<tr>
<td>70-74</td>
<td>1.55 (1.07-2.25)</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>0.70 (0.48-1.02)</td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>0.93 (0.61-1.42)</td>
<td></td>
</tr>
<tr>
<td>≥85</td>
<td>1.00 (0.68-1.49)</td>
<td></td>
</tr>
</tbody>
</table>

There were a very small number of cases of CAP associated with laboratory proven *S.pneumoniae*. These comprised 33/4472 (0.7%) eligible cases and cohort subjects. 23vPPV (versus neither vaccine) was also not shown to be effective against this subgroup of pneumonia cases (RR 0.96, 95%CI 0.39-2.37), although the numbers were too small for these results to be meaningfully interpreted.

5.4.7.2 Determining prognostic variables for inclusion in multivariate analyses

Twenty five variables were examined in univariate analysis in order to examine their association with the primary outcome of CAP (for further details see 2.10.3). Seven were excluded. One variable had a p-value >0.20 (marital status) and two variables describing numbers of previous episodes of pneumonia were excluded due to colinearity. Three other variables describing occurrence of previous pneumonia were however retained for the initial multivariate model. A further four variables had considerable amounts of missing data (17-47% of observations in the initial multivariate model) and were excluded from initial models (inclusive of all other variables of interest) as appropriate adjustments could not be made for such large data deficits. These “excluded variables” related to smoking habits, alcohol intake and vaccine provider visit variables (Table 3.7). However, separate analyses were subsequently conducted to explore the effect of these variables on
the subset of subjects for whom data were available. This was achieved by adding the variables separately to the final multivariate model after the backward stepwise process was completed. The final 18 variables for inclusion in the model, plus the four “excluded” variables are the same as for Table 3.5 with the exception of the variables for comorbidity and years since vaccination with 23vPPV.

### 5.4.7.3 Backward stepwise logistic regression

In addition to adjustment for design variables (as in univariate analysis above), backward stepwise logistic regression was conducted with adjustment for potential confounders.

#### Pre-specified analyses: Influenza vaccine versus neither vaccine

The final logistic regression model following the backward stepwise procedure demonstrated similar estimates to univariate analyses, with no evidence of a reduction in hospitalisation with CAP for influenza vaccine (alone or in combination with 23vPPV) versus neither vaccine (RR 1.02; 95%CI 0.84-1.20). This estimate was similar to the univariate model adjusted only for design factors (RR 1.06; 95%CI 0.90-1.25).

This multivariate final model contained 13 potential confounders. A positive association with admission for CAP was found for the following factors: male gender, living in one’s own home, a history of diabetes, ischaemic heart disease, immunosuppression, respiratory disease, renal disease, aspiration or previous pneumonia (Table 5.11), and increasing age over 70 years. Factors with a negative association with admission for CAP were a history of pneumonia in the previous year and speaking a first language other than English.

The model was further scrutinised by separately adding each of the four “excluded” variables (significant in univariate analyses but initially excluded due to loss of considerable data). Two were significant (vaccine provider visits in the past year and alcohol intake) and their addition to the model resulted in changes in the RR of the vaccine variable by >=10%, suggesting confounding.

Restriction to the influenza season made little difference to the estimate (RR 1.11, 95%CI 0.83-1.48). Similarly, there was very little change to the estimate when all cases admitted with CAP were examined compared with only first hospital presentations (RR 0.98, 95%CI 0.80-1.20), suggesting that there was unlikely to have been an effect upon vaccination status attributable to previous admission with pneumonia. Sensitivity analyses also did not demonstrate benefit against hospitalisation with CAP. These included reassigning all subjects with unknown vaccination status to vaccinated (RR 1.02, 95%CI 0.86-1.20) and unvaccinated (RR 0.96, 95%CI 0.84, 95%CI 0.84-1.09) status, and restricting positive influenza vaccination status only to those who had received vaccine in the six months prior to hospital admission (RR 1.06, 95%CI 0.84-1.37), including when further restricted to influenza seasons (RR 1.14, 95%CI 0.79-1.63).
Table 5.11. Statistically significant covariates (p<0.20) for the final logistic regression models of the two primary analyses predicting VE against hospitalisation with CAP.

| Final models predicting hospitalisation with CAP for: | Any influenza vaccine versus neither vaccine | | Both vaccines versus influenza vaccine alone | |
|---|---|---|---|
| **Variables** | **Relative risk (95%CI)** | **p-value** | **Relative risk (95%CI)** | **p-value** |
| Male | 1.47 (1.26-1.70) | <0.001 | 1.45 (1.22-1.73) | <0.001 |
| Diabetes | 1.30 (1.09-1.55) | 0.004 | 1.25 (1.02-1.53) | 0.03 |
| Ischaemic heart disease | 1.21 (1.04-1.42) | 0.01 | 1.25 (1.04-1.49) | 0.02 |
| Immunosuppression | 1.47 (1.23-1.76) | <0.001 | 1.42 (1.15-1.75) | 0.001 |
| Other respiratory disease | 2.51 (2.14-2.94) | <0.001 | 2.57 (2.14-3.09) | <0.001 |
| Renal disease | 1.57 (1.22-2.02) | <0.001 | 1.37 (1.02-1.84) | 0.03 |
| Cerebrovascular disease | - | - | 0.83 (0.67-1.05) | 0.12 |
| Aspiration | 3.10 (1.47-6.58) | 0.003 | 2.53 (1.03-6.22) | 0.04 |
| Language | 0.80 (0.67-0.94) | 0.01 | 0.86 (0.71-1.05) | 0.14 |
| Previous Pneumonia | 2.23 (1.72-2.90) | <0.001 | 2.28 (1.69-3.08) | <0.001 |
| Pneumonia in past year | 0.66 (0.43-0.99) | 0.05 | 0.67 (0.41-1.07) | 0.09 |
| Hospitalisation past year | - | 0.07 | - | - |
| Age group | - | <0.001 | - | <0.001 |
| Doctor visits past year* | - | <0.001 | - | <0.001 |
| Doctor visits past 2-5 years* | - | - | - | 0.07 |
| Excessive alcohol intake* | 1.31 (0.95-1.80) | 0.10 | - | - |

* “Excluded” variable added only to final model following backward stepwise process due to missing data (see 5.4.7.2)
Adjustment of the final model for death during hospitalisation did not result in any substantial change to the estimate of RR (1.9% change), suggesting it was not a confounder. Point estimates suggested moderate benefit associated with influenza vaccination against deaths from hospitalisation with CAP (RR 0.72, 95%CI 0.51-1.01) and all-cause mortality (RR 0.77, 95%CI 0.58-1.03), however these just failed to reach statistical significance. Estimates were similar, but with wider confidence intervals when restricted to the two influenza seasons of the study (RR 0.71, 95%CI 0.40-1.28 and RR 0.81, 95%CI 0.51-1.31 respectively).

**Pre-specified analyses: Both vaccines versus influenza vaccine alone**

The final logistic regression model also indicated no evidence of incremental benefit from 23vPPV over and above influenza vaccine (RR 0.98, 95%CI 0.81-1.18). As for influenza vaccine, this estimate was similar to that from univariate analysis adjusted only for design variables (RR 1.03; 95%CI 0.87-1.22).

This model contained 14 factors associated with CAP: the same 13 variables and in the same direction of effect as the first pre-specified analysis, in addition to the variable “history of cerebrovascular disease” (Table 5.11). Separate addition of each of the four “excluded” variables (see 5.4.7.2) resulted in two variables predictive of hospitalisation with CAP that were not confounders (numbers of doctor visits in the past year and doctor visits in the past 2-5 years).

Restriction to the influenza season (RR 1.06, 95%CI 0.76-1.48) and inclusion of all cases of hospitalisation with CAP (compared with only first presentations) (RR 0.97, 95%CI 0.79-1.19) made little difference to the estimate. Sensitivity analyses assigning all subjects with unknown vaccination status to vaccinated (RR 1.01, 95%CI 0.86-1.19) and unvaccinated (RR 0.96, 95%CI 0.84-1.10) status also found no evidence of benefit. Similarly, adjustment of the final model for death during hospitalisation did not result in any substantial change (0.6%), suggesting it was not a confounder. There was a non-significant increase in deaths associated with hospitalisation with CAP from 23vPPV over and above influenza vaccine (RR 1.29, 95%CI 0.86-1.94) and all-cause mortality (RR 1.24, 95%CI 0.90-1.71). Similar estimates were provided when restricted to the influenza season (RR 1.41, 95%CI 0.72-2.74 and RR 1.11, 95%CI 0.67-1.84 respectively) and when deaths occurring between discharge and the time of interview were included (data not shown). There was no evidence of benefit where the effect of any 23vPPV was examined against no 23vPPV (see exploratory analyses).

**Exploratory analyses**

At completion of the backward stepwise process, VE (1-RR) against CAP among hospitalised subjects was not shown for any of the exploratory analyses of vaccination exposure, (Table 5.12) including with restriction of the final models to the two influenza seasons of the study period (data not shown). The models were very stable, with similar results both to each other (Table 5.12 and 5.13) and to univariate estimates adjusted only for design variables (Table 5.7).
Table 5.12. RR of hospitalisation with CAP under different exploratory models of vaccine exposure.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Relative risk (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>23vPPV (any) versus neither</td>
<td>0.99 (0.82-1.19)</td>
<td>0.93</td>
</tr>
<tr>
<td>Both vaccines versus neither</td>
<td>0.97 (0.80-1.18)</td>
<td>0.76</td>
</tr>
<tr>
<td>Influenza vaccine (any) versus no influenza vaccine</td>
<td>0.98 (0.84-1.15)</td>
<td>0.84</td>
</tr>
<tr>
<td>23vPPV (any) versus no 23vPPV vaccine</td>
<td>1.01 (0.87-1.16)</td>
<td>0.95</td>
</tr>
<tr>
<td>23vPPV alone versus no 23vPPV</td>
<td>1.10 (0.92-1.49)</td>
<td>0.50</td>
</tr>
<tr>
<td>Years since 23vPPV vaccination</td>
<td>-</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Statistically significant variables remaining under the final models are shown in Table 5.13. Results for each variable were highly consistent across different analyses. Variables that were not predictive of hospitalisation with CAP or considered potential confounders under any model of vaccination exposure were: liver disease, cerebrovascular disease, pneumonia in the past two to five years, and number of hospitalisations in the past two to five years.
Table 5.13. Variables in final multivariate models as potential confounders/prognostic variables for hospitalisation with CAP given vaccination exposure.

<table>
<thead>
<tr>
<th>Final models predicting hospitalisation with CAP for:</th>
<th>23vPPV(any) versus neither vaccine</th>
<th>Both versus neither vaccine</th>
<th>Influenza vaccine (any) versus no influenza vaccine</th>
<th>23vPPV (any) versus no 23vPPV</th>
<th>Years since 23vPPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
</tr>
<tr>
<td>Male</td>
<td>1.31 (1.11-1.46); 0.002</td>
<td>1.39 (1.16-1.65); &lt;0.001</td>
<td>1.40 (1.21-1.62); &lt;0.001</td>
<td>1.40 (1.21-1.62); &lt;0.001</td>
<td>1.41 (1.21-1.72); &lt;0.001</td>
</tr>
<tr>
<td>Residence</td>
<td>1.36 (1.05-1.77); 0.02</td>
<td>1.27 (0.97-1.68); 0.09</td>
<td>1.58 (1.29-1.95); &lt;0.001</td>
<td>1.59 (1.29-1.96); &lt;0.001</td>
<td>1.51 (1.22-1.86); &lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.40 (1.14-1.72); 0.001</td>
<td>1.38 (1.13-1.69); 0.001</td>
<td>1.28 (1.08-1.51); 0.005</td>
<td>1.28 (1.08-1.51); 0.005</td>
<td>1.27 (1.07-1.50); 0.005</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1.20 (1.00-1.44); 0.05</td>
<td>-</td>
<td>1.20 (1.03-1.39); 0.02</td>
<td>1.20 (1.03-1.39); 0.02</td>
<td>1.16 (1.01-1.35); 0.04</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>1.60 (1.29-1.98); &lt;0.001</td>
<td>1.49 (1.21-1.83); &lt;0.001</td>
<td>1.44 (1.21-1.72); &lt;0.001</td>
<td>1.44 (1.21-1.72); &lt;0.001</td>
<td>1.40 (1.18-1.66); &lt;0.001</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>2.69 (2.24-3.24); &lt;0.001</td>
<td>2.69 (2.24-3.22); &lt;0.001</td>
<td>2.45 (2.11-2.85); &lt;0.001</td>
<td>2.45 (2.10-2.86); &lt;0.001</td>
<td>2.39 (2.05-2.79); &lt;0.001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.65 (1.24-2.12); 0.001</td>
<td>1.65 (1.24-2.20); 0.001</td>
<td>1.55 (1.22-1.98); &lt;0.001</td>
<td>1.56 (1.22-1.98); &lt;0.001</td>
<td>1.532 (1.21-1.94); &lt;0.001</td>
</tr>
<tr>
<td>Rheumatological disease</td>
<td>0.85 (0.68-1.06); 0.15</td>
<td>-</td>
<td>0.86 (0.70-1.05); 0.13</td>
<td>0.86 (0.70-1.05); 0.13</td>
<td>-</td>
</tr>
<tr>
<td>Aspiration</td>
<td>2.22 (0.91-5.54); 0.08</td>
<td>2.39 (0.94-6.06); 0.07</td>
<td>3.01 (1.45-6.25); 0.003</td>
<td>3.00 (1.45-6.24); 0.003</td>
<td>2.59 (1.25-5.38); 0.01</td>
</tr>
<tr>
<td>English 1st language</td>
<td>0.74 (0.61-0.89); 0.002</td>
<td>0.76 (0.62-0.94); 0.01</td>
<td>0.78 (0.66-0.91); 0.002</td>
<td>0.78 (0.66-0.91); 0.002</td>
<td>0.78 (0.66-0.92); 0.002</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.95 (1.55-2.46); &lt;0.001</td>
<td>2.29 (1.70-3.10); &lt;0.001</td>
<td>1.91 (1.56-2.35); &lt;0.001</td>
<td>2.16 (1.69-2.76); &lt;0.001</td>
<td>1.83 (1.49-2.24); &lt;0.001</td>
</tr>
<tr>
<td>Pneumonia in the past 1yr</td>
<td>-</td>
<td>0.68 (0.43-1.08); 0.10</td>
<td>-</td>
<td>0.73 (0.49-1.07); 0.11</td>
<td>p=0.08</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Age group</th>
<th>p &lt;0.001</th>
<th>p &lt;0.001</th>
<th>p &lt;0.001</th>
<th>p &lt;0.001</th>
<th>p &lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisations past 1yr</td>
<td>p=0.09</td>
<td>p=0.10</td>
<td>p=0.04</td>
<td>p=0.06</td>
<td>p=0.08</td>
</tr>
<tr>
<td>Alcohol*</td>
<td>1.49 (1.05-2.12); 0.02†</td>
<td>-</td>
<td>1.42 (1.05-1.92); 0.02</td>
<td>1.42 (1.05-1.93); 0.02</td>
<td>1.44 (1.06-1.96); 0.02†</td>
</tr>
<tr>
<td>Dr visits past 1 yr*</td>
<td>p=0.002</td>
<td>p=0.002</td>
<td>P &lt;0.001</td>
<td>p &lt;0.001</td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td>Dr visits past 2-5 yrs*</td>
<td>-</td>
<td>-</td>
<td>p=0.10</td>
<td>-</td>
<td>p=0.15</td>
</tr>
<tr>
<td>Smoking habit*</td>
<td>-</td>
<td>-</td>
<td>p=0.16</td>
<td>p=0.16</td>
<td>p=0.18</td>
</tr>
</tbody>
</table>

* Variables added to final model only (see 2.4.7.2); model stable (RR of vaccine exposure) with addition of variable unless marked otherwise
† With addition of “excluded” variable, RR for vaccine variable/variable strata changed by >=10% suggesting confounding
Unlike estimates from univariate analysis, use of an interaction term for both 23vPPV and influenza vaccine exposure did not suggest benefit against hospitalisation with CAP (Table 5.14) and this did not change when the final model was examined within influenza seasons only (data not shown).

Table 5.14. RR of hospitalisation with CAP under an interaction term of vaccine exposure.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>23vPPV(any) versus no 23vPPV</td>
<td>1.09 (0.81-1.47)</td>
<td>0.58</td>
</tr>
<tr>
<td>Influenza vaccine (any) versus no influenza vaccine</td>
<td>1.02 (0.82-1.25)</td>
<td>0.71</td>
</tr>
<tr>
<td>Interaction term*</td>
<td>0.91 (0.64-1.28)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

* Interaction term of (any influenza vaccine versus no influenza vaccine) x (any 23vPPV versus no 23vPPV)

Also, unlike univariate analysis, the number of years since 23vPPV was not predictive of hospitalisation with CAP (p=0.47), and no individual stratum was predictive (Table 5.15). There was also no trend of decreasing VE with increasing years since vaccination with 23vPPV (RR 0.98/year; 95%CI 0.94-1.02).

Table 5.15. Risk of hospitalisation with CAP by number of years since receiving 23vPPV.

<table>
<thead>
<tr>
<th>Years since vaccination</th>
<th>n</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>413</td>
<td>0.92 (0.72-1.18)</td>
<td>0.53</td>
</tr>
<tr>
<td>2</td>
<td>412</td>
<td>1.03 (0.81-1.31)</td>
<td>0.81</td>
</tr>
<tr>
<td>3</td>
<td>586</td>
<td>0.90 (0.73-1.12)</td>
<td>0.35</td>
</tr>
<tr>
<td>4</td>
<td>510</td>
<td>1.09 (0.87-1.38)</td>
<td>0.44</td>
</tr>
<tr>
<td>5</td>
<td>189</td>
<td>1.26 (0.90-1.77)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

To explore any benefit attributable to 23vPPV alone against death during hospitalisation or all-cause mortality, an exploratory analysis was conducted. This did not demonstrate significant benefit for either outcome (all-cause mortality: RR 0.92; 95%CI 0.71-1.20; death associated with hospitalisation with CAP: RR 0.92; 95%CI 0.66-1.28). When restricted to the influenza season there was a non-significant increase in these outcomes (RR 1.41, 95%CI 0.72-2.74 and RR 1.11, 95%CI 0.67-1.84 respectively), and when deaths occurring between hospital discharge and the time of interview were included (data not shown).
As for univariate analysis, adjusting only for design variables, examination of an interaction term of “age group” and the vaccine variables found no potential additive effect (on the logarithmic scale) of age on VE for either influenza vaccine or 23vPPV (Table 5.16).

Table 5.16. Multivariate estimates for an interaction term of age with vaccination variables for the pre-specified analyses.

<table>
<thead>
<tr>
<th>Stratum-specific RR (95%CI)</th>
<th>Overall p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group x Influenza vaccine versus no flu vaccine</strong></td>
<td></td>
</tr>
<tr>
<td>reference group 65-69 yrs</td>
<td>0.78 (0.51-1.19)</td>
</tr>
<tr>
<td>70-74</td>
<td>1.01 (0.67-1.53)</td>
</tr>
<tr>
<td>75-79</td>
<td>0.95 (0.65-1.40)</td>
</tr>
<tr>
<td>80-84</td>
<td>1.08 (0.69-1.68)</td>
</tr>
<tr>
<td>≥85</td>
<td>1.32 (0.88-1.99)</td>
</tr>
<tr>
<td><strong>Age group x Both vaccines versus influenza vaccine</strong></td>
<td></td>
</tr>
<tr>
<td>reference group 65-69 yrs</td>
<td>1.00 (0.60-1.67)</td>
</tr>
<tr>
<td>70-74</td>
<td>1.34 (0.88-2.04)</td>
</tr>
<tr>
<td>75-79</td>
<td>0.66 (0.43-1.00)</td>
</tr>
<tr>
<td>80-84</td>
<td>0.94 (0.57-1.55)</td>
</tr>
<tr>
<td>≥85</td>
<td>1.11 (0.72-1.71)</td>
</tr>
</tbody>
</table>

Examination of the incremental effectiveness of 23vPPV against cases of laboratory proven pneumococcal disease resulted in a model with few observations (n=766). Of the 60% of subjects who had some form of laboratory test to identify a causative infectious agent, only 33 had proven *S.pneumoniae*, and 26 of these occurred among first presentation cases of hospitalisation with CAP. The estimate for RR was not significant (RR 0.85; 95%CI 0.26-2.81).

**5.5 Discussion**

**5.5.1 Vaccine effectiveness against hospitalisation with CAP**

While both 23vPPV and influenza vaccine have proven benefit against other outcomes, during a period of typical disease rates due to *S.pneumoniae* and influenza, there was no demonstrable benefit to study subjects from either vaccine for the prevention of hospitalisation with CAP based on ICD-
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10 coding. However, the possibility of small protective effects of less than 19% and 16% respectively cannot be excluded (the lower bounds of the 95% CIs). Results were consistent across adjusted and unadjusted, pre-specified and exploratory analyses, including when examined only within the two influenza seasons of the study and when sensitivity analyses were conducted reassigning those with unknown vaccination status. Logistic regression models were stable. There was no demonstrable benefit when analyses were restricted to those receiving influenza vaccination within six months of admission, or for 23vPPV against hospitalisation with CAP over and above influenza vaccine when examined by individual year since vaccination. Although the study was not designed to examine the outcome of death, exploratory analyses suggested moderate benefit from influenza vaccine and a small benefit from 23vPPV against deaths associated with hospitalisation with CAP and all-cause mortality, however these results were not statistically significant.

5.5.1.1 Comparison with available data

VE for 23vPPV

This study did not demonstrate benefit from 23vPPV against hospitalisation with CAP (incremental benefit over influenza vaccine: RR 0.98, 95%CI 0.81-1.18). This finding is consistent with clinical trials, including those examining the combined effectiveness of influenza plus 23vPPV.47,68 It is also similar to the conclusions drawn from a recent evaluation of systematic reviews of RCTs (Table 5.17),55 a Cochrane meta-analysis (VE 16%; 95%CI -8-35%) and a recent large cohort study which found no reduction in risk of hospitalisation with a discharge diagnosis code for pneumonia (Jackson et al: HR 1.06; 95%CI 0.98-1.16).23 It should be noted however that these two clinical trials relied on passive reporting and had insufficient power to demonstrate protective effectiveness of 20% or less.47,68 There has also been criticism of meta-analyses for pooling non-representative populations and having an inadequate sample size to rule out false negative results.56

Table 5.17. Systematic reviews examining VE of 23vPPV against all-cause pneumonia (adapted from Assendelft, Dutch Cochrane Centre).55

<table>
<thead>
<tr>
<th>Systematic review (reference)</th>
<th>Included studies (n)</th>
<th>Population</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine, 199452</td>
<td>8</td>
<td>5 low risk, 3 high risk populations (mostly non-elderly)</td>
<td>OR 0.90 (0.77-1.04)</td>
</tr>
<tr>
<td>Moore, 200053</td>
<td>5</td>
<td>Elderly or high risk</td>
<td>RR 1.08 (0.92-1.27)</td>
</tr>
<tr>
<td>Watson, 200251</td>
<td>2</td>
<td>Elderly, Industrialised setting</td>
<td>RR 1.15 (0.95-1.40)</td>
</tr>
</tbody>
</table>
The findings of a number of non-experimental studies in favour of VE against CAP for 23vPPV should also be interpreted with caution. Two examining the incremental effectiveness against CAP of 23vPPV over and above influenza vaccine found a VE of 43% (16-72%) against hospitalisation for pneumonia and influenza and 29% (24-34%) against pneumonia respectively. However, Christenson et al reported interim data only and did not adjust for confounders, while Nichol et al used a high-risk study population with chronic lung disease. Of three other recent non-experimental studies examining 23vPPV alone, Ansaldi et al utilised subjects who acted as their own historical controls over only a mean of 17 months, thus providing only weak evidence of VE. Estimates from this thesis are only marginally inconsistent with those of Vila-Córcoles et al (VE 2%, 95%CI -18-19% versus 26%, 95%CI 8-41%, ratio of RR 1.24, 95%CI 1.02-1.49). However, this study used unstable models for estimating VE, with point estimates varying from harm to benefit after adjustment for various factors, possibly due to a “healthy vaccinee” effect or influenza vaccination status. Wagner et al found a reduction in the risk of pneumonia (OR 0.28, p<0.001) using a case-control design.

Although the study was not designed to examine mortality, exploratory analyses found a small but non-significant reduction in deaths associated with hospitalisation with CAP due to 23vPPV (VE 8%; 95%CI -28-34%), and a non-significant increase when examined only within influenza seasons and when deaths occurring between discharge and the time of interview were included. This finding is in contrast to Vila-Córcoles et al (VE 59%; 95%CI 38-77%), although results are not directly comparable given the inclusion by Vila-Córcoles et al of deaths associated with both outpatient and hospitalised pneumonia occurring within 30 days of diagnosis. Very recently, Fisman et al also found a reduction in death attributable to 23vPPV among adults ≥18 years attending 100 hospitals in the USA with CAP. The adjusted odds ratio of 0.5 (95%CI 0.43-0.59) was determined for just 35% of 68,289 subjects admitted with CAP who had known vaccination status. Although not designed to examine the group aged ≥65 years the authors reported a similar effect (OR 0.29, 95%CI 0.25-0.50). Sensitivity analyses allocating the 65% of all subjects aged ≥18 years with unknown vaccination status to different vaccination categories (vaccinated, unvaccinated, random allocation based on proportions for subjects with known vaccination status) confirmed protection against mortality. However, the results should be interpreted with caution given the large proportion of subjects with unknown vaccination status and potential for bias. Sensitivity analyses would need to be performed by the authors allocating all those who died and who had unknown vaccination status to “vaccinated” status, and those who did not die and had unknown vaccination status to “unvaccinated” status, in order to determine the full potential effect of bias on the point estimate.

**Influenza VE**

Results from this study showing no evidence of benefit from influenza vaccine against hospitalisation for CAP in the elderly (RR 1.02 95%CI 0.84-1.20) are consistent with a recent high quality systematic review by Rivetti et al. This review focussed on non-experimental studies and
Chapter 5: VE against CAP in the elderly

reported a non-significant reduction in pneumonia for community-dwelling elderly persons (versus those based in nursing homes or institutions) (RR 0.88; 95%CI 0.64-1.20). Voordouw et al conducted a population-based cohort study among community-based elderly in the Netherlands and also found no significant reduction in pneumonia among community-based elderly subjects (HR 0.84; 95%CI 0.65-1.07),86,87 Most recently, Hara et al conducted a population-based cohort study of 4787 community-dwelling elderly and did not find significant benefit against hospitalisation for pneumonia and influenza (OR 1.37; 95%CI 0.09-1.47).82 As outlined in Chapter 1, there are no RCTS of low bias examining influenza VE against pneumonia (see 1.5.2).

Contrary to the results of this thesis, some recent non-experimental studies suggest effectiveness, including those by Wang et al (RR 0.85; 95%CI 0.76-0.96),89 Puig-Barbera et al (OR 0.52, 95%CI 0.34-0.80)81 and Crocetti et al (OR 0.67; 95%CI 0.48-0.95).97 However, it is possible that these studies suffered from selection bias, resulting in over-estimates of VE.78,104 Two of the above studies81,97 were included in the systematic review discussed above that found no significant reduction overall in pneumonia for the community-based elderly.32

Although not designed to examine the outcome of deaths among those hospitalised with influenza and pneumonia, exploratory analyses from this thesis suggest a moderate benefit from influenza vaccine (VE 28%, 95%CI -1%-51%), although this just failed to reach statistical significance, including when restricted to influenza seasons and when deaths occurring between discharge and the time of interview were included. However, given the wide confidence intervals, it is possible that inadequate sample size may have been responsible for the inability to find a significant benefit. In general, previous researchers have found moderate benefit against this outcome, including Vu et al, (VE 47%, 95%CI 25-62%)80, Jefferson et al (VE 42%, 95%CI 17-59%; well-matched vaccines only)78 and Voordouw et al (elderly with comorbidity only: RR, 0.67; 95%CI, 0.48-0.94).86 However, different conclusions could be drawn from two recent studies. Hara et al did not find a significant reduction in death (OR 3.68; 95%CI 0.75-18.12), however, this may have been due to an inadequate sample size.82 Christenson et al reported point estimates indicating a moderate reduction in death for those with influenza pneumonia (OR 0.70; 95%CI 0.15-3.21), and those with influenza but not pneumonia (OR 0.88; 95%CI 0.69-1.11),71 however these did not reach statistical significance. Very recently, Spaude et al found a reduction in all-cause mortality for adults ≥18 years (OR 0.61; 95%CI 0.43-0.87) attributable to influenza vaccination.102 However, vaccination status was unknown for 53% of subjects, and sensitivity analyses allocating all those in the unknown group to “vaccinated” status resulted in changes in the estimates that just failed to reach statistical significance (OR 0.78; 95%CI 0.60-1.00). As for Fisman et al above,86 sensitivity analyses would need to be performed by the authors allocating all those who died and had unknown vaccination status to “vaccinated” status, and those who did not die and had unknown vaccination status to “unvaccinated” status, in order to determine the full potential effect of bias on the point estimate.
5.5.2 Possible explanations for lack of VE against hospitalisation with CAP

Real effect

This case-cohort study presents high quality data (see 2.11), adjusted for known confounders and based on a population which, at worst, is representative of the hospitalised elderly population in Victoria, against whom the vaccine is in large part targeted. These strengths in study design may indicate a real finding of a lack of benefit from 23vPPV and influenza vaccine against hospitalisation for CAP for this population. This is biologically plausible, since elderly patients more often fail to generate an adequate immunological response. Some elderly individuals have been shown to fail to respond to particular capsular polysaccharides contained in 23vPPV, and as a five-yearly vaccine, waning immunity may also play a role, as suggested by the finding of reducing VE with increasing years since vaccination. Similarly, a reduced antibody response for individual strains contained in influenza vaccines, and generally lower cell-mediated and antibody responses to influenza vaccine have been shown in the elderly population. A recent quantitative review of antibody response to influenza vaccination in the elderly concluded that the considerably lower response in the elderly suggested a corresponding clinical efficacy of 17-53% in comparison with corresponding estimates for young adults of 70-90%.

Low aetiological fraction of hospitalised CAP due to influenza or S. pneumoniae

Alternatively, if there had been little pneumonia in the study population attributable to either influenza viruses or S. pneumoniae, an effect against hospitalisation for CAP could not have been expected. However, limited Australian estimates for the proportion of CAP attributable to S. pneumoniae (42% and 30%), and similar figures from New Zealand (39%) are within the range quoted from other countries where studies of VE have been conducted (25-50%). Surveillance data indicate invasive disease due to S. pneumoniae was stable during the study period in Victoria. Similarly, influenza activity for Victoria during the study period was reported within the range for “normal seasonal activity”: 2.5-15 influenza-like illness cases/1000 patients/week. It remains possible, however, that in a setting of very high endemic rates of influenza or S. pneumoniae, a greater impact from vaccination could have been detected.

Poor vaccine and circulating strain match

It is possible that even if the same aetiological fraction of cases of hospitalisation with CAP were attributable to influenza and S. pneumoniae, that poor match between circulating and vaccine strains could reduce the potential impact of either vaccine on related disease. However, influenza strain match was good in Victoria during the study period, with the only exception being the circulation of B/Hong Kong/330/2001-like virus during 2002 (Table 5.18). Similarly, vaccine and circulating
serotype match for \textit{S.pneumoniae} has been very stable over the past 10 years and is estimated at 91-94\% for 23vPPV for those aged $\geq$65 years in Victoria.$^{28,30}$

Table 5.18. Influenza virus circulating strains, Victoria and vaccine composition, Australia, 2000-2002.$^{113}$

<table>
<thead>
<tr>
<th>Year</th>
<th>Predominant circulating strains</th>
<th>Vaccine composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>A/Moscow/10/99 (H3N2)-like virus</td>
<td>A/NewCaledonia/20/99(H1N1)-like virus A/Moscow/10/99(H3N2)-like virus B/Beijing/184/93-like virus</td>
</tr>
<tr>
<td>2001</td>
<td>A/New Caledonia/20/99 (H1N1) -like virus</td>
<td>A/New Caledonia/20/99(H1N1)-like virus A/Moscow/10/99(H3N2)-like virus B/Sichuan/379/99-like virus</td>
</tr>
<tr>
<td>2002</td>
<td>A/Moscow/10/99 (H3N2)-like virus B/Hong Kong/330/2001-like virus</td>
<td>A/New Caledonia/20/99(H1N1)-like virus A/Moscow/10/99(H3N2)-like virus B/Sichuan/379/99-like virus</td>
</tr>
</tbody>
</table>

\subsection*{5.5.3 Study limitations}

Although known potential confounders were adjusted for in multivariate analyses, this approach is less optimal than a randomised design because uncontrolled confounding can still occur, and adjustment may mean removing the linear contribution of imperfectly measured variables.$^{226,227}$ However, as explained in Chapter 2, a randomised design was not feasible given the vaccines of interest were funded at a population-level for the elderly and were in widespread use. Similar estimates for all analyses for both univariate (adjusted for design variables) and multivariate models adjusting for known confounders suggest that confounding is unlikely to have played a major role.

Although differences in some baseline characteristics occurred between cases and cohort subjects (Table 5.2) these factors were adjusted for in regression models. Differences between eligible cases and cohort subjects (Table 5.2) were probably not large in real terms (for example small differences between case and cohort subjects for: speaking English as a first language, hospitalisations in the past year, history of immunosuppression, aspiration or pneumonia in the past year), and many of those noted are described in the medical literature. For example, it is well known that persons with pneumonia are more likely to be male, have experienced a previous episode of pneumonia and to have a history of other respiratory disease.$^{17,126}$ Similarly, ischaemic heart disease, excessive alcohol consumption, aspiration and immunosuppression are known to occur more frequently in persons with pneumonia.$^{61,126}$
If selection of vaccination was confounded with patient factors (for example self-selection factors, clinical factors such as those above, or physician preferences) that were also related to the outcome of hospitalisation with CAP, then confounding by indication could occur.\textsuperscript{228} However, unlike a recent cohort study finding evidence of a bias attributable to preferential vaccination of healthy subjects, resulting in over-estimation of benefit attributable to influenza vaccine,\textsuperscript{73} no such benefit was found. This suggests that either the bias was not present, it was opposed by another unspecified bias, or vaccination is potentially harmful. The choice of hospitalised subjects as controls and the use of multivariate analysis to adjust for patient factors may have minimised bias by improving the likelihood of the populations under comparison having a similar prognosis. Jackson et al also proposed that the difference between estimates for VE within and outside the influenza season would be the true estimate of VE (assuming that vaccination has no incidental benefits outside the influenza season). However, again, no demonstrable benefit was shown within or outside the influenza season, and data from this thesis do not provide evidence of any bias by indication and are consistent with vaccination providing neither benefit nor harm.

Use of hospitalised patients could distort the estimate of effect if hospitalisation with CAP and vaccination status were over- or under-represented in the study population due to patient or hospital factors (Berkson bias). For example, if vaccinated subjects with CAP were more likely to be admitted to hospital than unvaccinated subjects with CAP, this could result in higher vaccination coverage for study cases relative to the overall cohort, and subsequently lower the estimate for VE. However, when cases are chosen from hospitalised patients, the estimate is generally falsely lowered (and therefore VE elevated) where the control group is also chosen from hospitalised patients who do not have the target disease.\textsuperscript{229} Based on data from a 1999/2000 survey of community-based elderly persons in Victoria who had their vaccination status confirmed by vaccine providers, vaccination coverage was similar (or slightly higher) in the community sample than that experienced by the hospitalised cases analysed in this thesis (23vPPV: 57.9\% versus 54.4\%, influenza vaccine 77.7\% versus 70.7\% respectively).\textsuperscript{142,143} These data also show no evidence of persons frequently admitted to hospital having higher vaccination rates as demonstrated by virtually identical weighted and unweighted coverage estimates. As previously described in 2.2.3, it is also unclear whether vaccination status is more or less likely to be associated with factors such as comorbidities that are related to hospitalisation. Estimates including repeat hospitalisations with CAP were similar to those using only first presentations.

It was expected that subjects hospitalised with CAP were more likely to have died than those in the cohort.\textsuperscript{63} Although this meant that more subjects in the CAP group had information provided by next of kin, there was no significant difference in the rate of consent to participate in questionnaires or in 23vPPV coverage. However, the rate of determination of vaccination status (from providers) and influenza vaccination coverage was 5\% lower among the group who had information provided by next of kin. Had there been more individuals without influenza vaccination in the CAP group, this could have overestimated influenza VE. Since the opposite result was found, this disparity
between groups does not explain the findings in this thesis. Addition of death during hospitalisation as a variable to the final primary analyses showed that this was not a confounder, since the estimates for VE did not change.

As VE was calculated only for those subjects for whom vaccination status was confirmed by the gold standard of obtaining a complete date of vaccination from a vaccine provider, consideration was given to adjusting this estimate by including the excluded group for whom only self-reported vaccination status was available. Exclusion of this group could bias estimates for VE if vaccination coverage was substantially different from the verified group between cases and the cohort subjects. A recent report by Andrews dealt with this issue by applying the sensitivity and specificity of self-report of the verified group to the unverified group; arguably a better approach that assuming self-report among this group was correct (likely to be an overestimate). An adjusted estimate including this wider study population would potentially enable greater generalisability to the wider population of Victorians aged ≥65 years. Fortunately, in this study, only 71 subjects self-reported vaccination status without giving consent for vaccine provider verification, of which only 27 (0.6% of all subjects) were cases of pneumonia as defined by ICD-10 codes. This small number of subjects could not have substantively biased the estimate for VE.

The choice of a study sample frame of hospitalised elderly persons does mean that the study subjects may not be representative of the wider population of elderly persons in the community, even though they are drawn from this population. If at worst, the study population is only representative of hospitalised elderly persons, this remains an appropriate reference population since the funded population program of giving influenza vaccine and 23vPPV to the elderly in Australia is largely focussed on preventing severe disease due to these organisms that would be expected to require hospitalisation in the majority of cases. The benefits of accurate data collection for key outcomes and exposures from hospitalised cohort subjects in this study are very likely to have outweighed any potential disadvantage from reduced generalisability of results (see 2.2.3).

### 5.5.4 Study strengths

This study has a number of strengths compared with some other non-experimental studies. It was conducted under field conditions, which has relevance to a vaccination program that is already funded within the community. The study was large and at the very least able to exclude a VE against hospitalisation with CAP of greater than 19% for 23vPPV (over and above influenza vaccine) and 16% for influenza vaccine alone with 95% confidence. There were many more cases and cohort subjects available to the study than assumed by the conservative sample size estimate (cases: 1952 versus 1200 and cohort subjects: 2484 versus 1200). Data were relatively complete, with high participation rates by subjects (87%) and vaccine providers (83%) and high data extraction rates from hospital records (98%). The assumption for the proportion of cases coded as pneumonia having CAP was also accurate (85% versus 84%). Coverage estimates were higher than estimated,
particularly for 23vPPV, (53% versus 40%) and this would also have improved the ability to find an
effect.

A number of steps were taken to minimise bias as outlined in chapter 2 (see 2.11). Selection bias
was minimised by random selection of cohort subjects, frequency sampling by month with over-
sampling to allow for over-representation by frequently admitted subjects, use of weighting to adjust
for these subjects, exclusions of non-Victorian residents and some limited subgroups unlikely to be
representative of potential admissions with CAP, and minimal matching. If matching had been more
extensive, it might have occurred on a factor correlated with vaccination status, resulting in bias of
the effect size towards the null hypothesis. Measurement bias was reduced by blinding those
collecting data to case status (see 2.6.2), rigorous training and monitoring, and piloting the study
before commencement of data collection for analysis.

In addition, multivariate analysis adjusted for a large number of known confounders and is likely to
have been effective given there were only small amounts of missing data. Estimates were derived
from stable models and were consistent, with relatively narrow CIs across adjusted and unadjusted,
and pre-specified and exploratory analyses. No interim analyses were conducted.

5.5.5 Implications

This study was unable to demonstrate benefit to individuals from either 23vPPV or influenza vaccine
against hospitalisations coded as CAP despite excellent participation rates and adequate power.
Although not designed to examine mortality as an outcome and the estimates from exploratory
analyses were imprecise, a moderate benefit from influenza vaccine, and a small benefit from
23vPPV were suggested. The study was also not designed to assess the more specific outcomes of
confirmed influenza or IPD, which have a high mortality rate and remain important to prevent, and
against which vaccination has proven benefits. However, this study suggests the current program of
funding these vaccines for the elderly population in Australia is having no discernable impact on
hospital admission for CAP. These findings provide evidence to support the current trend to reduce
emphasis on prevention of pneumonia in policy for use of both influenza vaccine and 23vPPV in the
elderly. Economic assessments of these vaccines should include a benefit against pneumonia in
sensitivity analyses that includes zero.
Chapter 6: Validity of self-reported vaccination status

6.1 Overview

At the time of undertaking this thesis, there was only one small published study from outside Australia examining the validity of self-reported 23vPPV and influenza vaccination status as an indicator of true vaccination status. Such information is important for those evaluating vaccination programs, as well as clinicians vaccinating individuals, who generally rely on self-report. This is the largest study to date examining this question for the hospitalised elderly, and the first to examine the impact of a number of potential confounders on estimates for validity.

6.2 Objective

To examine the validity of self-reported vaccination status for 23vPPV and influenza vaccine as an indicator of true vaccination status among persons aged ≥65 years.

6.3 Background

This section represents an overview. Additional background information is detailed in Chapter 1 (see 1.7).

Since self-reported vaccination status is frequently used in public health program evaluation, clinical research and clinical practice as a marker of true vaccination status, and there are few practical alternatives where there is no register of adult vaccinations (as in Australia), it is important to quantify the validity of this practice.

There are six studies published in the international literature and one conference proceeding examining the validity of self-reported 23vPPV and/or influenza vaccination status. These studies were based on relatively small numbers of subjects (mean 379, range 135-820) (Table 6.5), have data limitations, conflicting results and only one was available at the time of designing this research project. Of the seven studies, five were conducted in North America, and most recently, one in the United Kingdom. The other small study from Australia has direct relevance to the funded Victorian (and now national) program of 23vPPV and influenza vaccine in the elderly. This was based on a subset of Victorian households selected by random digit dialling. Estimates
from the earlier studies were likely to have been affected by bias due to poor response rates, response bias or selection bias (see 1.7 for greater detail). The latest three studies were very small (n=135-354). Five of these earlier studies also examined the validity of self-reported influenza vaccination status. Only one other study has since been published on validity of self-reported influenza vaccination status and it suffered from substantial potential selection bias (see 1.7). No study has adjusted estimates for potential confounders with the exceptions of Zimmerman et al who restricted analyses to examine effects due to age and vaccination within physicians’ offices, and Mac Donald et al, who examined time since vaccination with 23vPPV.

Given the small sample sizes of recently published studies and for some, potential biases that could affect estimates for validity, further exploration of the validity of self-reported 23vPPV and influenza vaccination status as an evaluation tool is warranted. Such information can directly inform the evaluation process for the current Australian program for 23vPPV and influenza vaccine in elderly persons, as well as similar programs in other countries and clinicians vaccinating individuals.

6.4 Methods

6.4.1 Subject selection

All first selected cohort subjects were included for the primary analysis (selected as per Chapter 5). A step-wise approach was then taken to enable analysis of first selected cases plus cohort subjects as the study population (see 6.4.4 below).

6.4.2 Consent to self-report and validate vaccination status

Participating subjects were those who consented to completing a brief telephone questionnaire “about vaccinations against pneumonia in people 65 years or older” (Appendix 2). An explanatory statement about each vaccine was provided before asking whether they had been vaccinated in the year prior to hospitalisation (influenza vaccine or 23vPPV). In addition, for 23vPPV, if the subject indicated they had not been vaccinated in the year prior to hospitalisation, they were asked if they had ever received 23vPPV, and if so, whether this had occurred during the five years prior to admission. Contact details of vaccine providers nominated by participants as having probably administered the vaccines were requested of subjects. A modified questionnaire was administered to next of kin in the event of the subject being deceased at the time of interview (Appendix 3).

Subjects who responded “don’t know” to vaccination status questions were managed in the analysis in two ways. Firstly, those who were uncertain were excluded from the denominator. Secondly, a “don’t know” response was assumed to be the same as being unvaccinated (a “no” response”). This additional approach was taken because in a clinical or public health setting of risk assessment, it is standard practice to assume that persons responding “don’t know” are unvaccinated and therefore
require vaccination, since the risk of inadvertent revaccination (generally minor local side effects) would be considered less than the risk of remaining unvaccinated and potentially susceptible to strains of *S. pneumoniae* or influenza not present in either 23vPPV or influenza vaccine.\(^{147}\)

Regardless of consent to complete the questionnaire, subjects or their next of kin were also asked to provide consent to contact the selected subject’s vaccine providers to confirm details of vaccination with 23vPPV and influenza vaccine.

### 6.4.3 Gold standard for vaccination status

In order to estimate the internal validity of self-reported vaccination status as a predictor of true vaccination status, it is necessary to define a gold standard comparator for vaccination status. As consistent with previous studies, the gold standard against which self-reported vaccination status was compared was vaccination status confirmed from medical records. In this study, however, unlike most previous studies, a complete date of vaccination from a vaccine provider (including nursing home staff and other potential vaccine providers) was required for inclusion of a subject in the analysis as vaccinated, rather than just notation of vaccination with a “yes” or a partial date (see 2.6.1). In addition, all vaccine providers nominated by subjects completing questionnaires (or their next of kin) were contacted for confirmation of vaccination status (see 2.6 or Appendix 5).

### 6.4.4 Statistical analysis

Estimates with 95% confidence intervals were made for sensitivity, specificity, PPV and NPV for self-reported vaccination status using vaccine provider records as the gold standard. Stata 9.1 was used.\(^ {190}\) Percentage agreement and kappa statistics (percentage agreement adjusted for chance agreement) are also reported.

Primary analyses were conducted for the cohort including only those subjects whose completed questionnaires themselves (as opposed to relatives, household members, staff members, next of kin). Two approaches were taken with regard to “don’t know” responses with regard to vaccination status: 1) exclusion and 2) assume unvaccinated status (for the reasons outlined above).

Secondary analyses were conducted where all selected subjects with data on vaccination status from the subject or next of kin questionnaire were included (regardless of who completed the questionnaire). The effect of repeat admission on self-reported vaccination status was also examined by repeating primary analyses with the inclusion of all cohort subjects (compared with first presentations only).

Exploratory analyses were then conducted as above using first selected cases of CAP as the study population. Assuming no significant differences were found in validity estimates between the case and cohort groups, the plan was to then conduct all further analyses using both cases and cohort
subjects as the study population. The aim of this approach was to increase the available sample size as well as to enable examination of the impact of case status on the adjusted estimates for validity of self-reported vaccination status for 23vPPV and influenza vaccine.

To adjust for unequal probabilities of recruitment due to multiple admissions, and for clustering due to the month-by-month selection process, sensitivity, specificity, PPV and NPV were estimated from a weighted logistic regression model including month of discharge as a factor and either self-reported vaccination, or the vaccination gold-standard as the outcome. Weighting was included for primary analyses only, for influenza vaccine in the previous year and 23vPPV in the previous 5 years. Estimates for sensitivity, specificity, PPV and NPV were first made indirectly using logistic regression to calculate the log odds of the relevant outcome, restricting the outcome to the appropriate denominator for the statistic in question and then converting this to a proportion using the equation “proportion = exp(log odds)/ (1 + exp(log odds))”. For sensitivity, the outcome was whether or not subjects reported they were vaccinated (0= no; 1= yes) with the analysis restricted only to those who were truly vaccinated according to confirmed provider dates. For specificity, the outcome was whether or not the subjects reported they were unvaccinated (0= no; 1= yes) with the analysis restricted only to those who truly were unvaccinated according to providers. For PPV, the outcome was whether or not the subject truly was vaccinated (0= unvaccinated; 1= vaccinated) with the analysis restricted to those who self-reported being vaccinated. For NPV, the outcome was whether or not the subject truly was unvaccinated (0= vaccinated; 1= unvaccinated) with the analysis restricted to those who self-reported being unvaccinated. Proportions were calculated for each category of the variables of interest (shown in Tables 6.3 and 6.4).

The impact of the following factors on estimates for validity was examined: age, gender, case status (pneumonia or not), comorbidity (defined as one or more of: excessive alcohol intake, current tobacco smoker, past history of pneumonia, aspiration, other respiratory disease, cerebrovascular disease, diabetes, immunosuppression, ischaemic heart disease, liver disease, renal disease or rheumatological disease), previous hospitalisations, previous vaccine provider visits, years since vaccination (for 23vPPV) and correctly nominated vaccination status for influenza vaccine (in the case of 23vPPV self-report) or 23vPPV (in the case of influenza vaccine self-report). These factors were selected based on biological plausibility and review of published literature on the validity of self-reported vaccination status. As adjusted analyses utilised information on self-report provided only by subjects in person, and where subjects responding “don’t know” for self-reported vaccination status were excluded, the impact of death (information provided by next of kin) and discharge location were unable to be examined.

Although to guarantee an unbiased estimate of sensitivity, specificity, PPV and NPV it would have been ideal to have had a random sample of all provider records independent of self-report, this was not possible in practice. It was therefore an assumption of the study that consent was independent of provider record vaccination status for those who self-reported that they had been vaccinated and
unvaccinated, thus underpinning unbiased estimates for PPV and NPV respectively. This is plausible if errors in self-report are random (for example the result of mistaken memory versus deliberate misinformation). Since estimates for sensitivity and specificity might be subject to bias if rates of consent to vaccine provider confirmation of vaccination status in the vaccinated and unvaccinated groups (based on self-report) are different, the association between consent and self-reported vaccination status was examined.

6.5 Results

6.5.1 Description of eligible subjects and data availability

More selected subjects consented to their vaccine providers providing information on vaccination status (2573/3002, 86%) compared with personally undertaking a questionnaire including self-reported vaccination status (2203/3002, 73%) (Figure 6.1). Overall, 1568/2203 (71%) of those consenting provided a certain response (“yes” or “no”) for their 23vPPV status for the preceding five years and 2053/2203 (93%) for influenza vaccination status for the previous year. Providers responded to requests for information on vaccination status for 2478/2573 (96%) consenting participants. Definitive vaccination status (a complete date of vaccination or definite non-vaccination) was available for 2440/2573 (95%) consenting participants for 23vPPV and 2400/2573 (93%) for influenza vaccine. In total, 1884 subjects contributed information on both self-report and the gold standard for influenza vaccine, and 1450 for 23vPPV.

Figure 6.1. Flow chart for data availability, 1st presentation cohort subjects.
6.5.2 Comparison of consenting and non-consenting subjects

6.5.2.1 Consent to self-report

The group consenting to self-report vaccination status contained significantly more men, had higher vaccination coverage according to provider records for both influenza vaccine and 23vPPV and a slightly lower proportion with comorbidity compared with the group who did not consent to self-report (Table 6.1). They were also slightly younger, although the mean difference of 1.4 years is not large in real terms.

Table 6.1. Comparison of consenting and non-consenting 1st presentation cohort subjects

<table>
<thead>
<tr>
<th>Consent to determine vaccination status</th>
<th>Yes (95%CI)</th>
<th>No (95%CI)</th>
<th>Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report</td>
<td>n=2203</td>
<td>n=799</td>
<td></td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>75.8 (75.1-76.1)</td>
<td>77.2 (76.6-77.8)</td>
<td>1.4 (0.8- -2.0)*</td>
</tr>
<tr>
<td>Males (%)</td>
<td>52.8 (50.1-55.9)</td>
<td>45.3 (41.9-48.8)</td>
<td>-7.5 (-11.6- -3.5) *</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td>92.8 (91.7-94.0)</td>
<td>95.6 (94.1-97.2)</td>
<td>2.8 (0.9-4.7)</td>
</tr>
<tr>
<td>Influenza vaccine coverage (%)</td>
<td>72.44 (70.5-74.4)</td>
<td>61.5 (56.6-66.3)</td>
<td>-10.9 (-16.2- -5.7)*</td>
</tr>
<tr>
<td>23vPPV coverage (%)</td>
<td>55.1 (52.9-57.2)</td>
<td>38.6 (33.8-43.3)</td>
<td>-16.5 (-21.7- -11.3)*</td>
</tr>
</tbody>
</table>

Provider disclosure

| Mean age (yrs)                         | 76.1 (75.8-76.4) | 76.4 (75.6-77.2) | 0.2 (-0.5-1.0) |
| Males (%)                              | 51.1 (49.2-53.0) | 49.2 (44.4-53.9) | -1.9 (-0.7-0.3) |
| Comorbidity (%)                        | 93.4 (92.4-94.4) | 94.5 (92.0-97.0) | 1.1 (-1.5-3.8) |

*Statistically significant difference (p<0.05)

6.5.2.2 Consent to contact vaccine providers

Those who consented to vaccine provider confirmation of vaccination status did not differ significantly from those who did not consent with regard to age, gender or presence of comorbidity (Table 6.1). Subjects who self-reported being vaccinated were more likely to consent to contact with their vaccine providers than those self-reporting to be unvaccinated (Table 6.2).
Table 6.2. Rates of consent to contact vaccine providers in vaccinated and unvaccinated groups (based on self-report).

<table>
<thead>
<tr>
<th>Consent to determine vaccination status</th>
<th>Yes (95%CI) n=1728</th>
<th>No (95%CI) n=328</th>
<th>Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported influenza vaccine coverage</td>
<td>98.9 (98.4-99.4)</td>
<td>91.9 (88.8-94.7)</td>
<td>7.1 (4.1-10.1)</td>
</tr>
<tr>
<td>Self-reported 23vPPV coverage</td>
<td>99.0 (98.3-99.6)</td>
<td>95.4 (93.8-97.0)</td>
<td>3.6 (1.9-5.3)</td>
</tr>
</tbody>
</table>

6.5.3 Proportion of interviews completed by selected subjects

Of those participants for whom consent was available to undertake a questionnaire including self-reported vaccination status, 1382/2203 (63%) completed questionnaires themselves, while the remainder were completed by relatives (800, 36%) or household members, staff members (from, for example, nursing homes) and others such as interpreter staff. Almost one third (234/821, 29%) of these non-subject interviewees were nominated next of kin (that is, subjects were deceased at the time of interview) and 284/592 (48%) of the remaining non-deceased subjects requested a relative act as an interpreter.

Consent to participate in questionnaires did not differ significantly between those subjects who participated in person and those who had information provided by next of kin (difference 5.1%, 95%CI 0.0-10.3). However, confirmation of vaccination status by providers was higher among subjects who participated in person compared with deceased subjects (difference 5.0%; 95%CI 0.4-9.6). Vaccination coverage did not differ between these two groups for 23vPPV (difference -1.2%; 95%CI -7.6-5.1) or influenza vaccine (difference 2.9%; 95%CI -3.1-8.9).

6.5.4 Validity of self-reported vaccination status: unadjusted estimates

6.5.4.1 Influenza vaccination

There was good agreement (kappa 0.62) between self-reported influenza vaccination status and provider-confirmed vaccination status (Table 6.3). However, while sensitivity (99%), PPV (88%) and NPV (93%) were high, specificity was low (57%) (Table 6.3). Estimates changed little with inclusion of repeat admissions and all subjects contributing self-reported vaccination data, and when subjects responding “don’t know” were assumed to be unvaccinated (Table 6.3).
### Chapter 6: Validity of self-reported vaccination status

#### Table 6.3. Validity of self-reported vaccination status versus the gold standard of vaccine provider confirmed vaccination status (unadjusted estimates).

<table>
<thead>
<tr>
<th>Study population</th>
<th>Self-reported status (%)</th>
<th>Gold standard (%)</th>
<th>Kappa</th>
<th>Sensitivity (%) (95%CI)</th>
<th>Specificity (%) (95%CI)</th>
<th>PPV (%) (95%CI)</th>
<th>NPV (%) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed influenza vaccination</strong></td>
<td><strong>Cohort</strong></td>
<td>1051/1238 85%</td>
<td>933/1238 75%</td>
<td>0.64</td>
<td>921/933 98.6 (97.6-99.3)</td>
<td>174/305 57.0 (51.3-62.7)</td>
<td>920/1051 87.5 (85.4-89.5)</td>
</tr>
<tr>
<td></td>
<td><strong>Cases</strong></td>
<td>460/525 88%</td>
<td>418/525 80%</td>
<td>0.59</td>
<td>409/418 97.8 (96.0-99.0)</td>
<td>56/107 52.3 (42.5-62.1)</td>
<td>409/460 88.9 (85.7-91.6)</td>
</tr>
<tr>
<td></td>
<td><strong>Cases+cohort</strong></td>
<td>1489/1737 86%</td>
<td>1331/1737 76%</td>
<td>0.62</td>
<td>1309/1331 98.3 (97.5-99.0)</td>
<td>226/406 55.7 (50.7-60.6)</td>
<td>1309/1489 87.9 (86.1-89.5)</td>
</tr>
<tr>
<td><strong>All responses</strong></td>
<td><strong>Cohort</strong></td>
<td>1598/1884 85%</td>
<td>1388/1884 74%</td>
<td>0.56</td>
<td>1354/1388 97.6 (96.6-98.3)</td>
<td>252/496 50.8 (46.3-55.3)</td>
<td>1354/1598 84.7 (82.9-86.5)</td>
</tr>
<tr>
<td></td>
<td><strong>Cases</strong></td>
<td>998/1156 86%</td>
<td>861/1156 74%</td>
<td>0.49</td>
<td>835/861 97.0 (95.6-98.0)</td>
<td>132/295 44.7 (39.0-50.6)</td>
<td>835/998 83.7 (81.2-85.9)</td>
</tr>
<tr>
<td></td>
<td><strong>Cases+cohort</strong></td>
<td>2543/2980 85%</td>
<td>2204/2980 74%</td>
<td>0.53</td>
<td>2144/2204 97.3 (96.5-97.9)</td>
<td>377/776 48.6 (45.0-52.2)</td>
<td>2144/2543 84.3 (82.8-85.7)</td>
</tr>
<tr>
<td><strong>Don’t know= unvaccinated</strong></td>
<td><strong>Cohort</strong></td>
<td>1051/1265 83%</td>
<td>949/1265 75%</td>
<td>0.62</td>
<td>920/949 96.9 (95.6-97.9)</td>
<td>185/316 58.5 (52.9-64.0)</td>
<td>920/1051 87.5 (85.4-89.5)</td>
</tr>
<tr>
<td></td>
<td><strong>Cases</strong></td>
<td>460/538 86%</td>
<td>426/538 79%</td>
<td>0.57</td>
<td>409/426 96.0 (93.7-97.7)</td>
<td>61/112 54.5 (44.8-63.9)</td>
<td>409/460 88.9 (85.7-91.6)</td>
</tr>
<tr>
<td></td>
<td><strong>Cases+cohort</strong></td>
<td>1489/1774 84%</td>
<td>1353/1774 76%</td>
<td>0.61</td>
<td>1309/1353 96.7 (95.7-97.6)</td>
<td>241/421 57.2 (52.4-62.0)</td>
<td>1309/1489 87.9 (86.1-89.5)</td>
</tr>
</tbody>
</table>
## Chapter 6: Validity of self-reported vaccination status

### All presentations§
<table>
<thead>
<tr>
<th>Cohort</th>
<th>1115/1316</th>
<th>986/1316</th>
<th>0.64</th>
<th>973/986</th>
<th>98.7 (97.8-99.3)</th>
<th>188/330</th>
<th>57.0 (51.4-62.4)</th>
<th>973/1115</th>
<th>87.3 (85.2-89.2)</th>
<th>188/201</th>
<th>93.5 (89.2-96.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>510/576</td>
<td>460/576</td>
<td>0.56</td>
<td>451/460</td>
<td>98.0 (96.3-99.1)</td>
<td>57/116</td>
<td>49.1 (39.7-58.6)</td>
<td>451/510</td>
<td>88.4 (85.3-91.1)</td>
<td>241/263</td>
<td>86.4 (75.7-93.6)</td>
</tr>
<tr>
<td>Cases+cohort</td>
<td>1599/1862</td>
<td>1423/1862</td>
<td>0.62</td>
<td>1401/1423</td>
<td>98.5 (97.7-99.0)</td>
<td>241/439</td>
<td>54.9 (50.1-59.6)</td>
<td>1401/1599</td>
<td>87.6 (85.9-89.2)</td>
<td>241/263</td>
<td>91.6 (87.6-94.7)</td>
</tr>
</tbody>
</table>

### Confirmed 23vPPV (past 5 yrs)§
<table>
<thead>
<tr>
<th>Cohort</th>
<th>632/1072</th>
<th>637/1072</th>
<th>0.65</th>
<th>544/637</th>
<th>85.4 (82.4-88.1)</th>
<th>347/435</th>
<th>79.8 (75.7-83.4)</th>
<th>544/632</th>
<th>86.1 (83.1-88.7)</th>
<th>347/440</th>
<th>78.9 (74.7-82.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>302/456</td>
<td>303/456</td>
<td>0.60</td>
<td>262/303</td>
<td>86.5 (82.1-90.1)</td>
<td>113/153</td>
<td>73.9 (66.1-80.6)</td>
<td>262/302</td>
<td>86.8 (82.4-90.4)</td>
<td>113/154</td>
<td>73.4 (65.7-80.2)</td>
</tr>
<tr>
<td>Cases+cohort</td>
<td>919/1504</td>
<td>925/1504</td>
<td>0.64</td>
<td>794/925</td>
<td>85.8 (83.4-88.0)</td>
<td>454/579</td>
<td>78.4 (74.8-81.7)</td>
<td>794/919</td>
<td>86.4 (84.0-88.5)</td>
<td>454/585</td>
<td>77.6 (74.0-80.9)</td>
</tr>
</tbody>
</table>

### All responses‡
<table>
<thead>
<tr>
<th>Cohort</th>
<th>843/1450</th>
<th>865/1450</th>
<th>0.62</th>
<th>721/865</th>
<th>83.4 (80.7-85.8)</th>
<th>463/585</th>
<th>79.1 (75.6-82.4)</th>
<th>721/843</th>
<th>85.5 (83.0-87.8)</th>
<th>463/607</th>
<th>76.3 (72.7-79.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>528/822</td>
<td>518/822</td>
<td>0.58</td>
<td>443/518</td>
<td>85.8 (82.2-88.4)</td>
<td>219/304</td>
<td>72.0 (66.6-77.0)</td>
<td>443/528</td>
<td>83.9 (80.5-86.9)</td>
<td>219/294</td>
<td>74.5 (69.1-79.4)</td>
</tr>
<tr>
<td>Cases+cohort</td>
<td>1342/2228</td>
<td>1355/2228</td>
<td>0.61</td>
<td>1141/1355</td>
<td>84.2 (82.2-86.1)</td>
<td>672/873</td>
<td>77.0 (74.0-79.7)</td>
<td>1141/1342</td>
<td>85.0 (83.0-86.9)</td>
<td>672/886</td>
<td>75.8 (72.9-78.6)</td>
</tr>
</tbody>
</table>

### Don’t know= unvaccinated‡
<table>
<thead>
<tr>
<th>Cohort</th>
<th>632/1288</th>
<th>736/1288</th>
<th>0.57</th>
<th>544/736</th>
<th>73.9 (70.6-77.1)</th>
<th>464/552</th>
<th>84.1 (80.7-87.0)</th>
<th>544/632</th>
<th>86.1 (83.1-88.7)</th>
<th>464/656</th>
<th>70.7 (67.1-74.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>302/541</td>
<td>356/541</td>
<td>0.49</td>
<td>262/356</td>
<td>73.6 (68.7-78.1)</td>
<td>145/185</td>
<td>78.4 (71.7-84.1)</td>
<td>262/302</td>
<td>86.8 (82.4-90.4)</td>
<td>145/239</td>
<td>60.7 (52.3-66.9)</td>
</tr>
<tr>
<td></td>
<td>Cases+cohort</td>
<td>1074/1798</td>
<td>60%</td>
<td>794/1074</td>
<td>73.9 (71.2-76.5)</td>
<td>599/724</td>
<td>82.7 (79.8-85.4)</td>
<td>794/919</td>
<td>86.4 (84.0-88.5)</td>
<td>599/879</td>
<td>68.1 (65.0-71.2)</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>---------</td>
<td>-----------------</td>
<td>---------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>All presentations‡</strong></td>
<td>Cohort</td>
<td>671/1143</td>
<td>59%</td>
<td>663/1143</td>
<td>58%</td>
<td>370/460</td>
<td>80.4 (76.5-84.0)</td>
<td>581/671</td>
<td>86.6 (83.8-89.1)</td>
<td>370/472</td>
<td>78.4 (74.4-82.0)</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>334/492</td>
<td>68%</td>
<td>334/492</td>
<td>68%</td>
<td>291/334</td>
<td>72.8 (65.1-79.6)</td>
<td>291/334</td>
<td>72.8 (65.1-79.6)</td>
<td>291/334</td>
<td>72.8 (65.1-79.6)</td>
</tr>
<tr>
<td></td>
<td>Cases+cohort</td>
<td>986/1607</td>
<td>61%</td>
<td>998/1607</td>
<td>62%</td>
<td>856/998</td>
<td>85.8 (83.4-87.9)</td>
<td>856/986</td>
<td>86.8 (84.5-88.9)</td>
<td>479/621</td>
<td>77.1 (73.6-80.4)</td>
</tr>
<tr>
<td><strong>Confirmed 23vPPV</strong></td>
<td>(past 1 yr)*</td>
<td>Cohort</td>
<td>229/631</td>
<td>36%</td>
<td>130/631</td>
<td>21%</td>
<td>85/130</td>
<td>65.4 (56.5-73.5)</td>
<td>357/501</td>
<td>71.3 (67.1-75.2)</td>
<td>85/229</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>103/300</td>
<td>34%</td>
<td>52/300</td>
<td>17%</td>
<td>28/52</td>
<td>53.8 (39.5-67.8)</td>
<td>173/248</td>
<td>69.8 (63.6-75.4)</td>
<td>28/103</td>
<td>18.9 (13.8-26.8)</td>
</tr>
<tr>
<td></td>
<td>Cases+cohort</td>
<td>325/916</td>
<td>35%</td>
<td>179/916</td>
<td>20%</td>
<td>112/174</td>
<td>62.6 (55.0-69.7)</td>
<td>524/737</td>
<td>71.1 (67.7-74.3)</td>
<td>112/325</td>
<td>34.5 (29.3-39.9)</td>
</tr>
<tr>
<td><strong>All responses‡</strong></td>
<td>Cohort</td>
<td>314/868</td>
<td>36%</td>
<td>177/868</td>
<td>20%</td>
<td>116/177</td>
<td>65.5 (58.0-72.5)</td>
<td>493/691</td>
<td>71.3 (67.8-74.7)</td>
<td>116/314</td>
<td>36.9 (31.6-42.5)</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>178/515</td>
<td>35%</td>
<td>95/515</td>
<td>18%</td>
<td>54/95</td>
<td>56.8 (46.3-67.0)</td>
<td>296/420</td>
<td>70.5 (65.9-74.8)</td>
<td>54/178</td>
<td>30.3 (23.7-37.7)</td>
</tr>
<tr>
<td></td>
<td>Cases+cohort</td>
<td>480/1357</td>
<td>35%</td>
<td>269/1357</td>
<td>20%</td>
<td>169/269</td>
<td>62.8 (56.7-68.6)</td>
<td>777/1088</td>
<td>71.4 (68.6-74.1)</td>
<td>169/480</td>
<td>35.2 (30.9-39.7)</td>
</tr>
<tr>
<td><strong>Don’t know=</strong></td>
<td>unvaccinated‡</td>
<td>Cohort</td>
<td>229/736</td>
<td>31%</td>
<td>145/736</td>
<td>20%</td>
<td>85/145</td>
<td>58.6 (50.2-66.7)</td>
<td>447/591</td>
<td>75.6 (72.0-79.0)</td>
<td>85/229</td>
</tr>
</tbody>
</table>

Chapter 6: Validity of self-reported vaccination status
### Chapter 6: Validity of self-reported vaccination status

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Cases+cohort</th>
<th>Cohort</th>
<th>Cases+cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>103/357</td>
<td>60/357</td>
<td>0.17</td>
<td>28/60</td>
</tr>
<tr>
<td></td>
<td>29%</td>
<td>17%</td>
<td></td>
<td>46.7 (33.7-60.0)</td>
</tr>
<tr>
<td></td>
<td>60/357</td>
<td>202/1075</td>
<td>0.25</td>
<td>112/202</td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td>19%</td>
<td></td>
<td>55.4 (48.3-62.4)</td>
</tr>
<tr>
<td></td>
<td>0.17</td>
<td>0.25</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>28/60</td>
<td>112/202</td>
<td>660/873</td>
<td>112/325</td>
</tr>
<tr>
<td></td>
<td>46.7 (33.7-60.0)</td>
<td>55.4 (48.3-62.4)</td>
<td>75.6 (72.6-78.4)</td>
<td>34.5 (29.3-39.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>222/297</td>
<td>660/873</td>
<td>112/325</td>
<td>660/750</td>
</tr>
<tr>
<td></td>
<td>74.7 (69.4-79.6)</td>
<td>75.6 (72.6-78.4)</td>
<td>34.5 (29.3-39.9)</td>
<td>88 (85.5-90.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>222/103</td>
<td>112/325</td>
<td>660/873</td>
<td>660/750</td>
</tr>
<tr>
<td></td>
<td>27.2 (18.9-36.8)</td>
<td>34.5 (29.3-39.9)</td>
<td>34.5 (29.3-39.9)</td>
<td>88 (85.5-90.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>222/254</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>87.4 (82.7-91.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Exclusions:
- * Exclusions: responses from non-subjects (eg relatives), repeat presentations, “don’t know” responses
- † Exclusions: repeat presentations, “don’t know” responses, (all subject responses included)
- ‡ Exclusions: responses not from subjects, repeat presentations, (“don’t know” assumed unvaccinated)
- § Exclusions: responses not from subjects, responses not from subjects, (all presentations included)
6.5.4.2 23vPPV

There was also good agreement (kappa 0.65) between self-reported 23vPPV vaccination status for the past five years and the gold standard (Table 6.3). Sensitivity (85%), specificity (80%), PPV (86%) and NPV (79%) were all moderately high (Table 6.3). As for self-reported influenza vaccination status, estimates changed little with inclusion of repeat admissions or all subjects contributing self-reported vaccination data, and when subjects responding “don’t know” were assumed to be unvaccinated (Table 6.3).

Of note, agreement was poor (kappa 0.29) between self-report for the previous year and the gold standard. Poor PPV (approximately 37%) was the main source of disagreement, while sensitivity (63%), specificity (71%) and NPV (89%) were fair.

6.5.4.3 Cohort versus cases and use of a combined study population

Estimates of validity for the cases were very similar to those for the cohort, with no statistically significant differences, and kappa statistics differing by less than 0.1 in all instances (Table 6.3). All estimates were therefore repeated with a new study population including all first selected cases of CAP plus first selected cohort subjects (Figure 6.2), producing similar results (Table 6.3). This study population was used for all further analyses described below.

Figure 6.2. Flow chart for data availability, 1st presentation cohort subjects plus CAP cases.
6.5.5 Adjusted estimates of validity

In general, estimates adjusted for the factors of interest (Table 6.4) and selection probability varied little from the unadjusted estimates. The exceptions for self-reported influenza vaccine were admission to hospital in the previous 12 months (lower specificity, PPV and NPV), or the previous 2-5 years (lower specificity and NPV), and frequent provider visits (lower specificity) (Table 6.4). In addition, incorrect nomination of 23vPPV status was associated with lower specificity and NPV, however, the number of observations was very small for this subgroup. Only incorrect nomination of influenza vaccination status impacted on validity of self-reported 23vPPV (lower PPV) (Table 6.4).
Table 6.4. Validity of self-report versus confirmed influenza vaccine and 23vPPV status, adjusted for potential confounders and weighted for selection probability.

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Confirmed influenza vaccination</th>
<th>Confirmed 23vPPV past 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95%CI)</td>
<td>Specificity (95%CI)</td>
</tr>
<tr>
<td>Unadjusted estimates</td>
<td>98.3% (97.5-99.0)</td>
<td>55.7% (50.7-60.6)</td>
</tr>
<tr>
<td>Male</td>
<td>98.3 (97.0-99.0)</td>
<td>53.9 (47.0-60.7)</td>
</tr>
<tr>
<td>Female</td>
<td>98.6 (97.2-99.3)</td>
<td>52.6 (44.9-60.2)</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>98.5 (97.2-99.2)</td>
<td>55.2 (48.4-61.8)</td>
</tr>
<tr>
<td>Age &gt;=75</td>
<td>98.4 (97.0-99.1)</td>
<td>50.8 (42.9-58.7)</td>
</tr>
<tr>
<td>Case (1st presentation)</td>
<td>97.9 (95.9-98.9)</td>
<td>52.3 (42.9-61.6)</td>
</tr>
<tr>
<td>Cohort (1st presentation)</td>
<td>98.7 (97.7-99.3)</td>
<td>55.3 (49.1-61.4)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>98.6 (97.8-99.2)</td>
<td>50.2 (44.6-55.8)</td>
</tr>
<tr>
<td>No comorbidity</td>
<td>97.2 (89.5-99.3)</td>
<td>75.6 (55.2-88.6)</td>
</tr>
<tr>
<td></td>
<td>Admitted last 1 year</td>
<td>Not admitted last 1y</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>97.7 (96.0-98.7)</td>
<td>99.0 (97.8-99.5)</td>
</tr>
<tr>
<td></td>
<td>44.3 (36.9-51.9)</td>
<td>60.6 (52.9-67.2)</td>
</tr>
<tr>
<td></td>
<td>84.5 (81.3-87.2)</td>
<td>90.1* (87.8-92.0)</td>
</tr>
<tr>
<td></td>
<td>86.1 (77.3-91.9)</td>
<td>94.1* (88.2-97.2)</td>
</tr>
<tr>
<td></td>
<td>86.8 (82.9-90.0)</td>
<td>85.4 (82.0-88.3)</td>
</tr>
<tr>
<td></td>
<td>77.1 (71.0-82.3)</td>
<td>77.6 (72.5-81.9)</td>
</tr>
<tr>
<td></td>
<td>86.9 (83.0-90.0)</td>
<td>86.2 (82.8-89.0)</td>
</tr>
<tr>
<td></td>
<td>77.0 (70.8-82.3)</td>
<td>76.4 (71.4-80.9)</td>
</tr>
</tbody>
</table>

* Statistically significant difference  ‡ 42 observations only § 13 observations only  ‖ 98 observations
Chapter 6: Validity of self-reported vaccination status

6.6 Discussion

6.6.1 Comparison with published data

6.6.1.1 Influenza vaccine

Estimates from this study of the validity of self-reported influenza vaccination status were consistent with the range provided by earlier smaller studies (Table 6.5). Estimates remained consistent when the study population was no longer restricted to those providing vaccination status data in person, first admissions, and when “don’t know” responses were taken as indicative of being unvaccinated (the most rigorous approach for estimating true coverage). Self-reported influenza vaccination status was highly sensitive but only moderately specific. Only about half those who were truly unvaccinated indicated correctly that they were unvaccinated, whereas almost all truly vaccinated patients correctly identified that they were vaccinated. PPV and NPV were high, indicating that asking subjects their vaccination status was generally likely to produce a correct response. However, self-report over-estimated true vaccination coverage by approximately 10%, assuming ascertainment of coverage from providers was complete. While all nominated providers were contacted for details of vaccination status and a definitive response was obtained for 96% of consenting subjects, it is possible that subjects may have been vaccinated through some other means. Other studies have consistently shown over-estimation of true vaccination coverage (range 1-29%, average 11%) (Table 6.5), although the highest estimate is from the study by Zimmerman et al, for which considerable potential for response bias has been noted previously, see 1.7).

Age, gender, case status (pneumonia or not) and comorbidity did not significantly affect estimates for validity of self-reported influenza vaccination status. Incorrect identification of 23vPPV status was associated with lower specificity and NPV, however, there were so few subjects in this group as to make these results of questionable value. Of these factors, only age has been previously examined in the published literature and this single study also found no evidence of impact from age on estimates of validity. Data from this thesis indicate that admission to hospital in the previous year was associated with lower specificity, PPV and NPV, and admission in the previous 2-5 years with lower specificity and NPV. Similarly, frequent provider visits in the previous year resulted in lower specificity (Table 6.5). Thus, subject factors seem to have little influence on validity of self-report, while contact with medical personnel or institutions reduces validity. Why additional contact with medical personnel or institutions could negatively influence accuracy of subject recall of vaccination status is uncertain. It is possible that contact with multiple medical personnel over a relatively short period may result in a degree of confusion regarding vaccination status, or alternatively, that being unwell reduces the ability to accurately recall vaccinations, particularly if received when unwell. No comparable data are available for the impact of any of these factors on estimates of the validity of self-reported influenza vaccination status.
Table 6.5. Summary of published studies examining validity of self-reported influenza vaccination status against a gold standard representing true coverage: comparison with thesis results.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>kappa</th>
<th>True coverage (%)</th>
<th>Self-reported coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>278-819</td>
<td>92-100</td>
<td>38-96</td>
<td>62-94</td>
<td>89-100</td>
<td>0.36-0.88</td>
<td>29-78</td>
<td>30-81</td>
</tr>
<tr>
<td>Hutchison, 1989¹⁴⁵</td>
<td>535</td>
<td>92</td>
<td>96</td>
<td>91</td>
<td>97</td>
<td>0.88</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Mac Donald, 1999¹³⁸</td>
<td>432</td>
<td>100</td>
<td>79</td>
<td>82</td>
<td>100</td>
<td>0.79</td>
<td>64</td>
<td>71</td>
</tr>
<tr>
<td>Zimmerman, 2003¹⁴⁰</td>
<td>819</td>
<td>98</td>
<td>38</td>
<td>62</td>
<td>94</td>
<td>0.36</td>
<td>51</td>
<td>80</td>
</tr>
<tr>
<td>Andrews, 2005¹⁴³</td>
<td>278</td>
<td>97</td>
<td>77</td>
<td>94</td>
<td>89</td>
<td>0.78</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td>Mangtani, 2007¹⁴⁴</td>
<td>354</td>
<td>95</td>
<td>90</td>
<td>93</td>
<td>93</td>
<td>0.85</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>Skull, 2007</td>
<td>1737</td>
<td>98</td>
<td>56</td>
<td>88</td>
<td>91</td>
<td>0.62</td>
<td>76</td>
<td>86</td>
</tr>
<tr>
<td>Skull, 2007 range across analyses</td>
<td>1737-2980</td>
<td>97-98</td>
<td>47-57</td>
<td>84-88</td>
<td>85-92</td>
<td>0.53-0.62</td>
<td>76</td>
<td>86</td>
</tr>
</tbody>
</table>

*Based on medical record review
6.6.1.2  23vPPV

The validity of self-reported 23vPPV vaccination status was high where subjects were asked to recall vaccination for the previous five year period. As for self-reported influenza vaccination, estimates were consistent with the range provided by previously published smaller studies,\textsuperscript{138-141,143} and similar across secondary analyses with a lower level of population restriction (Table 6.6). Self-report overestimated true vaccination coverage according to the gold standard by only 1%. Previous studies have differed in their conclusions regarding over- or under-estimation of vaccination coverage from self-report. Such estimates will vary according to the true coverage in the population, and Table 6.6 shows that studies by Zimmerman et al, Shenson et al and Mangtani et al had lower population coverage. While Zimmerman et al (note issues with response bias mentioned previously) and Mac Donald et al found over-estimation by 19% and 10% respectively, Long et al, Andrews and Mangtani et al found underestimation of vaccination coverage by 10%, 7% and 4% respectively (Table 6.6).\textsuperscript{138-140,143} Only two of the factors adjusted for in logistic regression impacted significantly on estimates for validity of self-reported 23vPPV vaccination status. Incorrect nomination of influenza vaccination status was associated with a lower PPV for self-reported 23vPPV status (Table 6.4). These findings have face validity, in that it is feasible that those who have incorrectly self-reported their influenza vaccination status might be more likely to also be incorrect regarding their 23vPPV status. Time since vaccination has been previously examined by Mac Donald et al\textsuperscript{138} who found improved NPV but no change in other validity estimates.

By contrast, there was poor agreement between self-report and the gold standard where subjects were asked to recall whether they had been vaccinated in the past one year only. Here, the issue was not that subjects were unvaccinated, but rather that they could not recall exactly when they had received their vaccination – that is, it was more than one year ago. Poorer recall of receiving 23vPPV in the past one year compared with five years has previously been shown by Andrews.\textsuperscript{143} In general, self-reported vaccination status for 23vPPV in the last year tended to overestimate true vaccination coverage defined by the gold standard by approximately 6%. This is consistent with the findings of the smaller study by Andrews.\textsuperscript{143}

Not surprisingly, estimates for validity of self-report were lower for 23vPPV, a vaccine given every five years, compared with influenza vaccine, given annually. This has been shown in previous smaller studies.\textsuperscript{138,143,144}
Table 6.6. Summary of published studies examining validity of self-reported vaccination status for 23vPPV against a gold standard representing true coverage: comparison with thesis results.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>kappa</th>
<th>True coverage (%)*</th>
<th>Self-reported coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>135-820</td>
<td>64-97</td>
<td>46-92</td>
<td>40-93</td>
<td>60-97</td>
<td>0.31-0.69</td>
<td>27-65</td>
<td>23-71</td>
</tr>
<tr>
<td>Long, 1999</td>
<td>285</td>
<td>65</td>
<td>74</td>
<td>78</td>
<td>61</td>
<td>0.38</td>
<td>58</td>
<td>48</td>
</tr>
<tr>
<td>Mac Donald, 1999</td>
<td>432</td>
<td>87-97</td>
<td>53-76</td>
<td>54-93</td>
<td>60-97</td>
<td>0.42-0.57</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Zimmerman, 2003</td>
<td>820</td>
<td>85</td>
<td>46</td>
<td>63</td>
<td>74</td>
<td>0.31</td>
<td>52</td>
<td>71</td>
</tr>
<tr>
<td>Shenson, 2005</td>
<td>135</td>
<td>75</td>
<td>83</td>
<td>75</td>
<td>82</td>
<td>-</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>Andrews, 2005 (recall at 1y)</td>
<td>278</td>
<td>74</td>
<td>88</td>
<td>40</td>
<td>97</td>
<td>0.45</td>
<td>58</td>
<td>51</td>
</tr>
<tr>
<td>Andrews, 2005 (recall at 5y)</td>
<td>278</td>
<td>81</td>
<td>90</td>
<td>92</td>
<td>77</td>
<td>0.69</td>
<td>58</td>
<td>51</td>
</tr>
<tr>
<td>Mangtani, 2007</td>
<td>326</td>
<td>64</td>
<td>92</td>
<td>74</td>
<td>88</td>
<td>0.59</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Skull, 2007 (past 5 yrs)</td>
<td>1504</td>
<td>86</td>
<td>78</td>
<td>86</td>
<td>77</td>
<td><strong>0.64</strong></td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>Skull, 2007 range across analyses (past 5yrs)</td>
<td>1504-2228</td>
<td>74-86</td>
<td>77-83</td>
<td>85-87</td>
<td>68-78</td>
<td>0.55-0.64</td>
<td>60</td>
<td>61</td>
</tr>
</tbody>
</table>

*Based on medical record review
6.6.2 Study limitations

Only 72% of selected study subjects consented to undertake a questionnaire to provide data on self-reported vaccination status. Those who consented to self-report were slightly younger (mean 1.3 years), were significantly more likely to be male, less likely to have comorbidity and more likely to be vaccinated with both influenza vaccine and 23vPPV (confirmed by provider records) than those who did not consent to self-report. These differences may have affected estimates of validity. While 85% of selected study subjects consented to contact with their vaccine providers to confirm vaccination status, there were no significant differences between the groups who did and did not give consent to contact providers with respect to age, gender or comorbidity. Although this lack of difference between the two groups might suggest response rate bias could not have had a major impact on validity estimates, unmeasured factors may remain unaccounted for.

Although primary analyses restricted the study population to only those subjects who completed questionnaires themselves, inclusion in exploratory analyses of all participating selected subjects with data on self-reported vaccination status information produced similar results. Although restriction to the truly self-reporting group was intuitively more likely to produce accurate estimates of validity, the results suggest that the accuracy of these exploratory analyses was in fact was affected very little by inclusion of data provided by others. Similarly, primary analyses restricting the study population to first presentations or that reclassified “don’t know” responses to unvaccinated status produced similar estimates, again suggesting these factors had little influence.

Potential bias in estimates of sensitivity and specificity could have occurred if lack of consent to contact providers was associated with true vaccination status (defined by the gold standard) given self-reported status, since consent to confirm vaccination status with providers was associated with self-reported vaccination status. This is unknown since those who did not provide consent for vaccine provider contact could not have their true vaccination status confirmed. Such a bias could occur if those who did not provide consent for vaccine provider contact (15% of subjects) did so on the basis of their self-reported vaccination status differing systematically from their true vaccination status. This effect was reported by Andrews, where those who did not provide consent to validate their vaccination status had lower self-reported coverage.143 Given the small numbers of persons in the non-consenting group, it is likely that should such a bias have occurred, it would not have greatly affected the estimates for sensitivity and specificity. Although as previously discussed, it is assumed that consent was independent of provider record vaccination status, it is possible that estimates for PPV and NPV could have been biased if errors in self-report were non-random.

Issues of generalisability have been discussed previously (see 5.5.3). At worst, the estimates from this analysis are generalisable to the hospitalised elderly population of Victoria.
6.6.3 Study strengths

This is the largest study to date to examine the validity of self-reported vaccination status for 23vPPV and influenza vaccine. The high response rate, study sample size, conservative definition for definite vaccination, determination of the gold standard for true vaccination coverage by provision of complete dates of vaccination from multiple vaccine providers’ records and ability to restrict analysis to subjects potentially providing the most accurate information (self-report by subject only, exclusion of “don’t know” responses) resulted in high quality estimates with reasonably narrow confidence intervals. The large sample size also meant that estimates could be adjusted for a number of potential confounders. This enabled examination of the impact of these factors on estimates for validity for the first time. In addition, analyses from this thesis adjusted for selection probability using weighting. These strengths of study design mean that the results are likely to be the most informative in the literature to date.

6.6.4 Implications for vaccine providers and program evaluation

For vaccine providers who must vaccinate based on the self-reported vaccination status of the patient in front of them, asking subjects their influenza vaccination status is generally likely to produce a correct response (PPV 88%) in this setting. Self-reported 23vPPV status is similarly accurate for the previous five year period (PPV 86%) but is likely to be reduced in those instances where self-reported influenza vaccination status is known to be incorrect (PPV 69%).

For policy makers assessing the impact of state or national programs, self-reported influenza vaccination coverage among the hospitalised elderly over-estimates vaccination coverage determined from provider records by about 10% (86% versus 76%), while 23vPPV coverage is not dramatically under- or over-estimated (61% versus 60%) (Table 6.3). Although sensitivity of self-reported influenza vaccination status was high (98%), specificity was poor (56%) and this was associated with a further reduction among those with frequent provider or hospital visits. For 23vPPV, sensitivity was also high (86%) and specificity moderately high (78%). In general, this approach to measuring vaccination coverage remains imperfect. Expansion of the Australian Childhood Immunisation Register to a whole-of-life register including adult vaccinations remains a feasible goal and evidence to support such a change is provided by this thesis. Of note, an announcement was made in the May 2006 Budget by the Australian Government Department of Health and Ageing announcing this as the subject of a future scoping study.230
Chapter 7 Missed opportunities to vaccinate elderly inpatients with 23vPPV and influenza vaccine

7.1 Overview

This case-cohort study was also designed to evaluate and provide some of the first Australian data on missed opportunities for vaccination with influenza vaccine and 23vPPV among elderly inpatients, risk factors for being unvaccinated, the rate of recording inpatient vaccination status, and acceptability of vaccination with these vaccines among unvaccinated inpatients. It is the largest study to date in any setting to quantify missed opportunities for vaccination with 23vPPV and influenza vaccine among hospitalised elderly patients.

7.2 Objectives

7.2.1 Primary objective

To describe missed opportunities to vaccinate elderly hospitalised persons with 23vPPV and influenza vaccine.

7.2.2 Secondary objectives

To describe for hospitalised elderly persons:

1. Vaccination coverage for 23vPPV and influenza vaccine prior to admission.

2. Provider-subject encounters (hospitalisations and doctor visits) during a defined period prior to admission for vaccinated and unvaccinated subjects.

3. Risk factors associated with being unvaccinated prior to admission.

4. The opportunistic vaccination rate during hospitalisation.

5. Risk factors for missed opportunities to vaccinate in hospital.

6. Recording of vaccination status by hospital staff.

7. Acceptability of vaccination among those reporting to be unvaccinated.
7.3 Background

The considerable burden of disease due to influenza and *S. pneumoniae* among persons ≥65 years has been described previously (see 1.3). Aside from any uncertainty concerning benefit against hospitalisation for pneumonia from vaccination with influenza vaccine or 23vPPV, there is evidence of benefit against invasive pneumococcal disease and laboratory confirmed influenza in persons aged ≥65 years.\(^2\)\(^3\) National recommendations are to vaccinate all persons aged ≥65 years with annual influenza vaccine and five yearly 23vPPV.\(^1\)\(^4\)\(^7\) Every contact with a vaccine provider should be seen as an opportunity to update vaccinations. Hospitalisation in particular should prompt review of vaccination status since hospitalised persons are at increased risk of subsequent disease.\(^1\)\(^6\)\(^4\),\(^2\)\(^3\)\(^1\)\(^2\)\(^7\)\(^2\)\(^3\)\(^2\)\(^3\) The American Advisory Committee on Immunization advises vaccination prior to discharge from hospital for both 23vPPV and influenza vaccine through the use of standing orders.\(^2\)\(^3\)\(^3\)

Assessment of missed opportunities for vaccination and risk factors for an incomplete vaccination status for hospitalised patients can inform the evaluation of policy implementation for the funded 23vPPV and influenza vaccination program in the elderly population in Australia, as well as future implementation strategies. Although data are currently lacking for Australian inpatients, it is likely that as in the USA,\(^1\)\(^6\)\(^5\)-\(^1\)\(^6\)\(^7\) elderly persons with an incomplete vaccination status for 23vPPV and influenza vaccine experience numerous missed opportunities to be vaccinated, and that hospital staff do not often document vaccination status or order vaccinations. Of note, previous studies of hospitalised patients have not examined the general elderly population as they include only subjects with IPD, pneumonia or “high risk” conditions (for example, myocardial infarction and stroke), and some include subjects younger than 65 years of age.

Very few Australian studies have addressed missed opportunities for influenza vaccine or 23vPPV in the elderly population (hospitalised or otherwise). Only one study by Padiglione et al was available at the time of commencing this thesis,\(^1\)\(^8\)\(^5\) and no Australian study to date has had a primary focus of examining missed opportunities for vaccination. In a study of 82 inpatients aged ≥55 years with CAP, Padiglione et al reported that 59 (77%) had been hospitalised within the previous five years. Only 7% had ever received 23vPPV and 53 (69%) had received influenza vaccine.\(^1\)\(^8\)\(^5\)

Two very recently published studies have provided the first, albeit limited insight into individual attitudes towards influenza vaccination among the elderly in Australia,\(^1\)\(^3\)\(^5\),\(^2\)\(^3\)\(^4\) and one of these examined acceptability of vaccination among the unvaccinated population.\(^1\)\(^3\)\(^5\)

No Australian data were found on the rate of recording inpatient vaccination status.
7.4 Methods

7.4.1 Subject selection

First presentation cases and cohort subjects with hospital records for review were eligible for primary analyses (as per chapter 5). This approach enabled examination of the impact of case status on various estimates.

7.4.2 Vaccination status

Vaccination status was confirmed for study subjects by receipt of a complete vaccination date (day, month, year) from a vaccine provider within 14-365 days prior to hospital admission for influenza vaccine or 14-1825 days (5 years) prior for 23vPPV (see 2.6). Estimates of vaccination coverage for influenza vaccine and 23vPPV were adjusted for selection probability (see 2.7.3).

7.4.3 Provider-subject encounters prior to hospitalisation

The total number of provider-subject encounters was determined from hospital record review (number of hospitalisations for the hospital of the selected admission: Appendix 4) and self-report of doctor visits among those consenting to completing a questionnaire (Appendix 2). For self-reported provider visits, subjects were asked only to recall visits to a doctor rather than other potential vaccine providers to reduce confusion or the risk of introducing recall bias. This therefore represents a minimum estimate of visits to vaccine providers. For the year prior to admission subjects were asked to estimate the number of doctor visits in categories (zero, 1-4, 5-9, 10-14, 15-19, 20 or more, don’t know/can’t remember). To give a minimum estimate of doctor visits in the year prior to admission, subjects were allocated the number forming the lower bound of the category they nominated (as above). For example, if they nominated 10-14 visits in the past year, they were allocated 10 visits. For the 2-5 years prior to admission (not including the year immediately prior to admission), subjects were asked only if they had visited a doctor at any time, and not to estimate the number of events. This was again to reduce the risk of recall bias.

Estimates were determined for three defined periods:
1) 1 year prior to admission for influenza vaccine and 23vPPV,
2) 2-5 years prior to admission for 23vPPV, and
3) periods of “peak influenza vaccination” for influenza vaccine.\textsuperscript{235}

Periods of “peak influenza vaccination” were defined in two ways 1) autumn plus winter (March-August inclusive) and 2) autumn only (March-May) (equivalent to the approach of previous researchers).\textsuperscript{166,167,235}
Numbers of encounters were compared for vaccinated and unvaccinated subjects. Missed opportunities to vaccinate are provided by the number of subject-provider encounters among unvaccinated subjects.

The following secondary analyses were conducted:

a) Inclusion of only subjects completing interviews themselves (for self-reported vaccine provider visits). Any subject who died either during admission or between the time of discharge and the time of interview were excluded.

b) Comparison of subjects with and without CAP at the selected admission.

### 7.4.4 Risk factors for being unvaccinated prior to admission

Analyses were restricted to those subjects who had vaccination status confirmed by their nominated vaccine provider. Potential risk factors for being unvaccinated were explored using a similar method to that outlined in 2.10.3. Factors under consideration for multivariate models were first examined in individual logistic statements adjusted for hospital of discharge, month of sampling, and selection probability. These included age, gender, residence, English as a first language, marital status, previous hospitalisations, previous provider visits or hospitalisations, previous pneumonia, smoking habits, excessive alcohol intake, presence of diabetes, cardiovascular disease, immunosuppression, obstructive respiratory disease, renal disease, rheumatological disease, liver disease, cerebrovascular disease and history of aspiration (Appendix 4). Presence of any comorbid condition (see 6.4.4 for definition) was also examined. Case status at admission was not examined because this was not strictly related to the period prior to admission.

Covariates with p-values <0.20 in univariate analysis were considered as potential factors associated with being unvaccinated prior to admission and were evaluated in multivariate analysis. Backward stepwise logistic regression statements adjusted for hospital of discharge, month of sampling, and selection probability were used to estimate the RR of being unvaccinated associated with each factor. Step-wise elimination of variables in multivariate analysis was determined by removing the variable with the largest Wald p-value. The impact of adding or removing independent variables from the model was assessed by examining the stability of the coefficients of all other variables in the model. The final model was determined when all remaining variables had a p-value <0.05.

### 7.4.5 Opportunistic vaccination rate during hospitalisation

Analyses were restricted to those subjects who were confirmed as being unvaccinated prior to admission, who were alive at discharge, not discharged to a hospital, and whose records were able to be reviewed. Subjects were not excluded based on having specific medical conditions or
circumstances including admission to intensive care during admission, taking the approach that if subjects were well enough to be discharged from hospital, then they were sufficiently well to be vaccinated (given the very few contraindications for either vaccine). For influenza vaccine, analyses were restricted to those admissions occurring during the period of peak influenza vaccination activity (see 7.4.3), whereas all selected admissions were eligible for inclusion in analyses of 23vPPV opportunistic vaccination.

All relevant parts of hospital records were reviewed for evidence of vaccination during the selected admission including medication charts, admission notes and discharge summaries.

Secondary analyses were conducted comparing subjects with and without CAP for the selected admission.

### 7.4.6 Recording of vaccination status by hospital staff

Hospital records were reviewed for all eligible participants for documentation of influenza vaccination status (past 12 months) and 23vPPV status (past 5 years) (Appendix 4). Where available, the date and site of the vaccination was also noted (hospital, general practitioner or other provider).

### 7.4.7 Acceptability of vaccination among those reporting to be unvaccinated

Self-reported acceptability of vaccination (had it been offered) was examined for subjects reporting to be unvaccinated (Appendix 2). Subjects who reported being unvaccinated in telephone interviews were asked if they were offered 23vPPV or influenza vaccination in the year before admission to hospital. If not, they were asked to comment on whether they would have accepted it if it had been offered. Only subjects completing interviews themselves were included in the analysis.

### 7.4.8 Statistical analysis

Data analyses were performed as outlined above using Stata version 9.1.\(^1\)

### 7.5 Results

#### 7.5.1 Subject numbers and demographics

4772/4887 (97\%) subjects had medical records available for review and were included in analysis. There were 1952 first presentation cases coded as CAP and 2927 first presentation cohort subjects, including 107 who were also selected as cases (see Figures 5.1 and 5.3 for flow charts). The mean
age of eligible subjects was 77 years and 2552/4772 (54%) were male. At least one comorbid condition was present in 4273/4483 (95%) subjects, 1334/4772 (28%) had a first language other than English, 722/4739 (15%) lived in their own home and 447/4749 (9%) died during admission.

7.5.2 Consent to contact vaccine providers

Rates of consent and obtaining vaccination data have been described previously (see 5.4.5). Briefly, 4166/4772 (87%) first presentation subjects gave consent for confirmation of vaccination status with their vaccine provider(s), and information on vaccination status was subsequently provided for 4039/4166 (97%). After exclusions due to incomplete vaccination dates and subjects unable to be confirmed as known to the nominated vaccine provider, a definite medical record of influenza vaccination status was obtained for 3902/4772 (82%) subjects (or 94% of those who provided consent). For 23vPPV status the proportion was 3964/4772 (82%) (or 95% of those who provided consent).

7.5.3 Vaccination status

Weighted coverage estimates (adjusted for selection probability) among the study subjects were 71% (95%CI 69-72) for influenza vaccine within the year prior to admission, 53% (95%CI 52-55) for 23vPPV within five years prior to admission and 47% (95%CI 45-49) for both vaccines (see 5.4.6).

7.5.4 Provider-subject encounters prior to hospitalisation

7.5.4.1 Data availability

Of 4772 selected subjects with medical records available (and therefore data on numbers of hospitalisations), 3534 (74%) provided consent to undertake the questionnaire. Therefore 1238 (26%) subjects had no information on numbers of doctor visits prior to hospitalisation during the time periods of interest and were excluded from calculations of doctor visits. The subgroup of persons consenting to undertaking the questionnaire did not differ from the whole study group with respect to gender, presence of at least one comorbid condition, English as a first language and mortality (Table 7.1). Although they were on average younger, this was by a small amount in real terms (<5 months) (Table 7.1). However, significantly fewer subjects consenting to undertake questionnaires lived in their own homes.

When those excluded from calculations of doctor visits were compared with those who were included, the former group were more likely to be older, to have a comorbid condition, much more likely to live in their own homes, and less likely to be male (Table 7.1).
### Table 7.1 Comparison of demographic data for selected subjects, with comparisons of subgroups providing consent/no consent for questionnaires.

<table>
<thead>
<tr>
<th></th>
<th>Medical records available (count of hospitalisations) (%) n=4772</th>
<th>Subgroup of subjects consenting to questionnaire (count of doctor visits) (%) n=3534</th>
<th>Difference 1† (95%CIs)</th>
<th>Subjects not consenting to questionnaire (%) n=1238</th>
<th>Difference 2§ (95%CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>77.0</td>
<td>76.6</td>
<td>0.4 (0.1-0.7)*</td>
<td>78.0</td>
<td>-1.4 (-1.9- -0.9)*</td>
</tr>
<tr>
<td>Male gender</td>
<td>2552 (54)</td>
<td>1948 (55)</td>
<td>-1.6 (-3.7-0.6)</td>
<td>604 (49)</td>
<td>6.3 (3.1- 9.6)*</td>
</tr>
<tr>
<td>Comorbidity†</td>
<td>4273 (95)</td>
<td>3155 (95)</td>
<td>0.6 (-0.3-1.6)</td>
<td>1118 (97)</td>
<td>2.4 (1.2-3.7)*</td>
</tr>
<tr>
<td>First language English</td>
<td>3438 (72)</td>
<td>2576 (73)</td>
<td>-0.8 (-2.8-1.1)</td>
<td>862 (70)</td>
<td>-3.3 (-6.2- -3.1)</td>
</tr>
<tr>
<td>Live in own home</td>
<td>722/4739 (15)</td>
<td>336/3510 (10)</td>
<td>5.7 (4.3-7.1)*</td>
<td>386/1229 (31)</td>
<td>21.8 (19.1-24.6)*</td>
</tr>
<tr>
<td>Died in hospital</td>
<td>447 (9)</td>
<td>334 (9)</td>
<td>-0.1 (-1.4-1.2)</td>
<td>228 (18)</td>
<td>-0.3 (-2.2-1.6)</td>
</tr>
</tbody>
</table>

* Statistically significant difference
† One or more of: excessive alcohol intake, current tobacco smoker, past history of pneumonia, aspiration, other respiratory disease, cerebrovascular disease, diabetes, immunosuppression, ischaemic heart disease, liver disease, renal disease or rheumatological disease (see Table 3.7)
‡ Difference between the eligible subjects in columns 1 (subjects with medical records available) and 2 (subjects consenting to questionnaire)
§ Difference between the eligible subjects in columns 2 (subjects consenting to questionnaire) and 4 (excluded subjects not consenting to questionnaire)
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7.5.4.2 Provider-subject encounters: numbers and sites for vaccinated and unvaccinated subjects

During the year prior to the selected admission, subjects had a mean of 1.3 hospitalisations and 2317/4765 (49%) subjects had been hospitalised at least once (once: 21%, twice: 12%, three times: 7%). An average of 2.0 additional admissions occurred during the 2-5 years prior to admission, with 2524/4758 (53%) hospitalised at least once (once: 17%, twice: 11%, three times: 7%) (Table 7.2). Over the five years prior to admission 3307/4756 (70%) had been admitted at least once.

The median category of self-reported doctor visits for the past one year was 10-14 visits (29%). Excluding the 128 subjects unable to recall doctor visits in the past year, only 14/3406 (0.4%) had experienced no visits and 3044/3406 (89%) had experienced five or more visits. The average minimum estimate for doctor visits in the past one year was 11.7 (median 10 visits).

Of 3501 subjects, 98% reported at least one visit to a doctor in the 2-5 years prior to admission. These estimates were not significantly different when restricted to those subjects providing self-reported data in person, and those who were alive at discharge (Table 7.2). Subjects with CAP for the selected admission had similar estimates to those without CAP with the exception of hospitalisations in the preceding one year, which were fewer in subjects hospitalised with CAP (Table 7.2).

Over the year prior to admission, 4691/4702 (99.8%) subjects had experienced at least one encounter with the hospital of admission or a doctor. For subjects unvaccinated against influenza, this figure was 1110/1115 (99.6%): 843/848 (99.4%) had visited a doctor (mean minimum estimate 11.2 visits) and 592/1139 (52.0%) had been admitted to the same hospital (mean 1.5 times). For those unvaccinated in the past five years with 23vPPV, 1809/1813 (99.8%) visited either a doctor (99.7%, mean 11.2 visits) or the same hospital (51.5%, mean 1.5 admissions) in the past one year; 1310/1850 (70.8%) had been admitted to the same hospital in the previous five years (mean 3.4 times).

Numbers of subject encounters with providers were generally similar for unvaccinated subjects (representing missed opportunities for vaccination) and vaccinated subjects for both 23vPPV and influenza vaccine. Exceptions were mean doctor visits in the past one year and 2-5 years prior to admission across almost all subcategories (Table 7.2). Restriction to periods of maximum influenza vaccination revealed no differences in numbers of provider encounters between vaccinated and unvaccinated subjects other than for influenza vaccine and the proportion of subjects visiting a doctor in the year or 2-5 years prior to admission (Table 7.2).
Table 7.2. Provider-subject encounters prior to admission: numbers and sites for vaccinated and unvaccinated subjects.

<table>
<thead>
<tr>
<th></th>
<th>Mean hospitalisations past 1 year* (95%CI)</th>
<th>Mean hospitalisations past 2-5 years* (95%CI)</th>
<th>Total hospitalisations past 5 years* (95%CI)</th>
<th>Mean minimum doctor visits past ly</th>
<th>Doctor visits past 2-5 yrs‡ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (range)</td>
<td>1.32 (range: 0-60, median: 0) n=4765</td>
<td>2.03 (range: 0-4, median: 1) n=4758</td>
<td>3.55 (range: 0-82, median: 2) n=4756</td>
<td>11.68 (0-20) n=3406</td>
<td>98.4 n=3501</td>
</tr>
<tr>
<td>Total (interview with subject only)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>10.56 (0-20) n=1878</td>
<td>98.3 n=1921</td>
</tr>
<tr>
<td>Difference: 95%CI§</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>1.12 (0.75-1.49)</td>
<td>0.003 (-0.006-0.008)</td>
</tr>
<tr>
<td>Total (alive at discharge)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>11.24 n=2862</td>
<td>98.5 n=2928</td>
</tr>
<tr>
<td>Difference: 95%CI§</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>0.44 (0.11-0.77)</td>
<td>0.007 (-0.004-0.02)</td>
</tr>
</tbody>
</table>

**Influenza vaccine**

<table>
<thead>
<tr>
<th></th>
<th>Mean hospitalisations past 1 year* (95%CI)</th>
<th>Mean hospitalisations past 2-5 years* (95%CI)</th>
<th>Total hospitalisations past 5 years* (95%CI)</th>
<th>Mean minimum doctor visits past ly</th>
<th>Doctor visits past 2-5 yrs‡ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>1.31 (1.20-1.42) n=2758</td>
<td>2.17 (2.02-2.31) n=2756</td>
<td>3.47 (3.26-3.68) n=2754</td>
<td>11.97 n=2275</td>
<td>99.1 (98.8-99.6) n=2332</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>1.50 (1.34-1.65) n=1139</td>
<td>1.96 (1.74-2.18) n=1137</td>
<td>3.45 (3.14-3.76) n=1137</td>
<td>11.20 n=848</td>
<td>97.4 (96.3-98.4) n=879</td>
</tr>
<tr>
<td>Difference</td>
<td>-0.19 (-0.38-0.007)</td>
<td>0.21 (-0.05-0.47)</td>
<td>0.02 (-0.36-0.40)</td>
<td>0.77 (0.25-1.29)</td>
<td>-0.02 (-0.03-0.007)</td>
</tr>
</tbody>
</table>

**Influenza vaccine**

<table>
<thead>
<tr>
<th></th>
<th>Mean hospitalisations past 1 year* (95%CI)</th>
<th>Mean hospitalisations past 2-5 years* (95%CI)</th>
<th>Total hospitalisations past 5 years* (95%CI)</th>
<th>Mean minimum doctor visits past ly</th>
<th>Doctor visits past 2-5 yrs‡ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>1.32 (1.16-1.47) n=1420</td>
<td>2.34 (2.12-2.56) n=1419</td>
<td>3.65 (3.34-3.96) n=1417</td>
<td>12.10 n=1165</td>
<td>99.1 (98.6-99.7) n=1187</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>1.40 (1.21-1.58) n=638</td>
<td>2.01 (1.71-2.30) n=638</td>
<td>3.41 (3.00-3.82) n=638</td>
<td>11.27 n=477</td>
<td>97.8 (96.5-99.1) n=495</td>
</tr>
<tr>
<td>Difference</td>
<td>-0.08 (-0.34-0.18)</td>
<td>0.33 (0.05-0.71)</td>
<td>0.24 (-0.29-0.77)</td>
<td>0.83 (0.12-1.54)</td>
<td>-0.14 (-0.03-0.002)</td>
</tr>
</tbody>
</table>

**23vPPV**

<table>
<thead>
<tr>
<th></th>
<th>Mean hospitalisations past 1 year* (95%CI)</th>
<th>Mean hospitalisations past 2-5 years* (95%CI)</th>
<th>Total hospitalisations past 5 years* (95%CI)</th>
<th>Mean minimum doctor visits past ly</th>
<th>Doctor visits past 2-5 yrs‡ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>1.31 (1.19-1.43) n=2108</td>
<td>2.05 (2.37) n=2104</td>
<td>3.50 (3.26-3.74) n=2103</td>
<td>12.19 n=1793</td>
<td>99.2 (98.8-99.6) n=1826</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Unvaccinated</th>
<th>1.46 (1.33-1.59)</th>
<th>1.99 (1.82-2.16)</th>
<th>3.44 (3.19-3.68)</th>
<th>11.17</th>
<th>98.0 (97.3-98.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1851</td>
<td>n=1851</td>
<td>n=1850</td>
<td>n=1367</td>
<td>n=1425</td>
<td></td>
</tr>
</tbody>
</table>

Difference (95%CI): 
-0.15 (-0.32-0.02) 0.22 (-0.02-0.46) 0.06 (-0.28-0.40) **1.02 (0.56-1.48)** **-0.01 (-0.02--0.004)**

### CAP versus non-CAP

<table>
<thead>
<tr>
<th>Hospitalisation with CAP</th>
<th>1.22 (1.11-1.32)</th>
<th>2.12 (1.95-2.29)</th>
<th>3.34 (3.11-3.56)</th>
<th>12.53</th>
<th>98.7 (98.1-99.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1948</td>
<td>n=1948</td>
<td>n=1947</td>
<td>n=1351</td>
<td>n=1388</td>
<td></td>
</tr>
</tbody>
</table>

Difference (95%CI): **-0.16 (-0.32- -0.04)**

<table>
<thead>
<tr>
<th>Hospitalisation with Non-CAP</th>
<th>1.38 (1.27-1.48)</th>
<th>1.97 (1.83-2.10)</th>
<th>3.34 (3.14-3.53)</th>
<th>11.11</th>
<th>98.2 (97.6-98.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2924</td>
<td>n=2917</td>
<td>n=2916</td>
<td>n=2128</td>
<td>n=2188</td>
<td></td>
</tr>
</tbody>
</table>

Difference (95%CI): 0.15 (-0.06-0.36) 0.15 (-0.30-0.30) **1.42 (0.97-1.87)** **0.004 (-0.003-0.01)**

---

*Based on hospital record review; influence of self-report not applicable
†Based on self-report: using lower bound of categories: 0-4, 5-9, 10-14, 15-19, 20 or more”; 128 of 3534 subjects consenting to questionnaires excluded for “don’t know or can’t remember” response
‡ Based on self-report, Yes/No variable
§ Difference in proportions for median category versus total study sample row2 (with 95%CIs)
║ Examining only admissions during periods of “peak influenza vaccination” a=autumn plus winter (Mar-Aug); b=autumn only (Mar-May)
¶ Significant difference between subcategories
7.5.5 Risk factors for being unvaccinated prior to admission

7.5.5.1 Influenza non-vaccination: variables for inclusion in multivariate analyses

Of 27 variables examined in univariate analysis, 12 were retained for multivariate analysis based on p-values<0.20 (Table 7.3). Three (smoking habit, doctor visits in the past one or 2-5 years) were added only to the final model due to excessive amounts of missing data (17-20%) for which appropriate adjustments could not be made. Excluded variables were gender, excessive alcohol intake, history of diabetes, immunosuppression, renal disease, liver disease, aspiration, pneumonia (past year, or ever), previous hospitalisations (total, past 1 or 2-5 years) and presence of comorbidity.

Table 7.3. Variables for inclusion in multivariate analysis; for prediction of unvaccinated status.

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Influenza vaccine</th>
<th>23vPPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Live in own home</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Rheumatological disease</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>First language English</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Marital status</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Pneumonia past 2-5y (n)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Smoking habit*</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dr visits past 1y (n)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dr visits past 2-5y (yes/no)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Aspiration</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Prior hospitalisations past 1y (n)</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Pneumonia ever</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Pneumonia past 1y(n)</td>
<td>x</td>
<td>✓</td>
</tr>
</tbody>
</table>
7.5.5.2 Influenza non-vaccination: final model of prognostic variables

Nine variables were predictive of being unvaccinated with influenza vaccine prior to hospital admission (Table 7.4). Subjects who had English as a first language, were married or in a defacto relationship, had visited a doctor in the past 2-5 years, and those with a history of ischaemic heart disease or rheumatological disease were less likely to be unvaccinated with influenza vaccine. Those living in their own homes, who were younger or had visited a doctor less often in the past year were more likely to be unvaccinated (Table 7.4). Factors not predictive of being unvaccinated with influenza vaccine were a history of other respiratory disease (non-pneumonia), cerebrovascular disease, pneumonia in the past 2-5 years and smoking habit.

Table 7.4. Risk factors predictive of incomplete vaccination status; final logistic regression model.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unvaccinated for influenza vaccine</th>
<th>Unvaccinated for 23vPPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group† (decreasing by 5y per age group)</td>
<td>1.01 (1.0-1.02) 0.06</td>
<td>1.01 (1.00-1.02) 0.03</td>
</tr>
<tr>
<td>Live in own home</td>
<td>1.39 (1.11-1.75) 0.004</td>
<td>2.75 (2.23-3.40) &lt; 0.001</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>0.80 (0.68-0.93) 0.005</td>
<td>0.78 (0.67-0.90) 0.001</td>
</tr>
<tr>
<td>Rheumatological disease</td>
<td>0.65 (0.52-0.81) &lt; 0.001</td>
<td>0.76 (0.63-0.92) 0.005</td>
</tr>
<tr>
<td>First language English</td>
<td>0.73 (0.62-0.87) &lt; 0.001</td>
<td>0.63 (0.54-0.74) &lt; 0.001</td>
</tr>
<tr>
<td>Married/defacto</td>
<td>0.73 (0.62-0.87) &lt; 0.001</td>
<td>- -</td>
</tr>
<tr>
<td>Pneumonia past 2-5y†: (single units)</td>
<td>1.09 (0.91-1.30) 0.35</td>
<td>- -</td>
</tr>
<tr>
<td>Dr visits past 1y*†: (decreasing by 5/group)</td>
<td>1.11 (1.03-1.19) 0.002</td>
<td>1.13 (1.06-1.20) &lt; 0.001</td>
</tr>
<tr>
<td>Dr visits past 2-5y*</td>
<td>0.29 (0.14-0.58) 0.001</td>
<td>0.47 (0.23-0.93) 0.03</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>- -</td>
<td>0.60 (0.51-0.69) &lt; 0.001</td>
</tr>
<tr>
<td>Hospitalisations past 1y† (increasing single units)</td>
<td>- -</td>
<td>1.04 (1.01-1.07) 0.01</td>
</tr>
<tr>
<td>Pneumonia ever</td>
<td>- -</td>
<td>0.71 (0.58-0.87) 0.001</td>
</tr>
</tbody>
</table>

* “Excluded” variable added only to final model following completion of the backward stepwise process due to missing data
† Categorical variables; test for trend provided
### 7.5.5.3 23vPPV non-vaccination: variables for inclusion in multivariate analyses

Twenty seven variables were examined in univariate analysis, of which 20 were retained for multivariate analysis based on p-values<0.20. Two were subsequently excluded from the starting model due to colinearity. The same three variables as for the influenza vaccine analysis were added separately only to the final model (smoking habit, doctor visits in the past one or 2-5 years) (see 7.5.5.1). The 18 variables included in the initial backward stepwise model are shown in Table 7.3 and were the same for the starting model for being unvaccinated with influenza vaccine plus a history of immunosuppression, aspiration, number of hospitalisations in the past year, comorbidity or previous pneumonia (ever, number of episodes in the past year). Excluded variables were gender, history of diabetes, renal disease, liver disease, excessive alcohol intake and hospital admissions in the past 2-5 years.

### 7.5.5.4 23vPPV non-vaccination: final model of prognostic variables

Ten variables were predictive of being unvaccinated with 23vPPV prior to hospital admission, of which seven were the same as those predictive of being unvaccinated with influenza vaccine (Table 7.4). Subjects who had English as a first language, who had visited a doctor in the past 2-5 years, and those with a history of ischaemic heart disease, rheumatological disease, obstructive respiratory disease or previous pneumonia were less likely to be unvaccinated with 23vPPV. Those living in their own homes, who were younger and who had fewer doctor visits in the past year or who been hospitalised more often in the past year were more likely to be unvaccinated (Table 7.4). Factors not predictive of being unvaccinated with 23vPPV were a history of cerebrovascular disease, marital status, comorbidity, pneumonia in the past year, pneumonia in the past 2-5 years, smoking habit, immunosuppression and aspiration.

### 7.5.6 Opportunistic vaccination rate during hospitalisation

Of the 4772 subjects with records available for review, 447 died during admission and 461 were discharged to a hospital, leaving 3864 eligible subjects (vaccinated and unvaccinated). Of these, 912 (24%) were able to be confirmed as unvaccinated with influenza vaccine, and 1526 (40%) for 23vPPV. All five of the subjects who received vaccines in hospital did not require them based on confirmation of positive vaccination status by their providers: three subjects (<0.1%) received 23vPPV, and three (<0.1%) received influenza vaccine, with one of these subjects receiving both vaccines. All five of these subjects were admitted with a first presentation of CAP, representing 5/1417 (0.3%) of first presentation cases of CAP. Restriction to the period of peak influenza vaccination (winter plus autumn) resulted in only two influenza vaccinations (one also vaccinated with 23vPPV). Restriction to winter only resulted in only one influenza vaccination.
Inclusion of repeat admissions resulted in no further vaccinations.

It was not possible to examine risk factors for missed vaccination opportunities in hospital since no subject in need of vaccination was vaccinated.

### 7.5.7 Recording of vaccination status by hospital staff

4770/4772 eligible subjects had information extracted from hospital records on vaccination status for 23vPPV and influenza vaccine. 108/4770 (2.3%) subjects had vaccination status for either or both vaccines recorded in their hospital records: 91/4770 (1.9%) had influenza vaccination status recorded and 59/4770 (1.2%) had 23vPPV status recorded. Subjects hospitalised with CAP were more likely to have influenza vaccination status recorded than those without CAP (difference 2.0%, 95%CI 1.1-2.9%). This was not the case for 23vPPV (difference 0.6%, 95%CI -0.06-1.3%). Information was available on place of vaccination in fewer than 45% of records with vaccination status recorded (Table 7.5). Very few vaccinations were recorded as being given in hospitals.

<table>
<thead>
<tr>
<th>Total (%)</th>
<th>Site of vaccination recorded (%)</th>
<th>GP provider recorded (%)</th>
<th>Hospital provider recorded (%)</th>
<th>Other provider recorded (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine recorded</td>
<td>91/4770 (1.9)</td>
<td>40/91 (44)</td>
<td>33/40 (82)</td>
<td>2/40 (6)</td>
</tr>
<tr>
<td>23vPPV recorded</td>
<td>59/4770 (1.2)</td>
<td>22/59 (37)</td>
<td>20/22 (91)</td>
<td>2/22 (9)</td>
</tr>
</tbody>
</table>

### 7.5.8 Acceptability of vaccination among those reporting to be unvaccinated

Of those who reported being unvaccinated, 39% and 41% reported they would have accepted influenza or 23vPPV vaccination respectively if offered (Table 7.6). Case status did not impact on acceptability of either influenza vaccine (difference -2.1%, 95%CI -20.1-15.9) or 23vPPV (difference -0.06%, 95%CI -6.3-6.2).

Approximately half of all subjects were potentially in favour of accepting vaccination if those who reported being unsure were also included (for example, if they were able to be influenced by a vaccine provider in favour of vaccination) (Table 7.6).
Table 7.6. Self-reported acceptability of vaccination among those reporting as unvaccinated (one year prior to admission).

<table>
<thead>
<tr>
<th></th>
<th>Report not vaccinated (%)</th>
<th>Report not offered vaccine* (%)</th>
<th>Report would have accepted vaccine (%)</th>
<th>Report unsure if would have accepted vaccine (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine</td>
<td>289/1896 (15)</td>
<td>149/269 (55)</td>
<td>58/149 (39)</td>
<td>14/149 (9)</td>
<td>72/149 (48)</td>
</tr>
<tr>
<td>23vPPV</td>
<td>1236/1645 (75)</td>
<td>1113/1165 (96)</td>
<td>458/1113 (41)</td>
<td>147/1113 (13)</td>
<td>605/1113 (54)</td>
</tr>
</tbody>
</table>

* "Don’t know" response excluded from denominator

7.6 Discussion

7.6.1 Missed opportunities to vaccinate prior to admission

This study is the largest to date to quantify missed opportunities for vaccination with 23vPPV and influenza vaccine among hospitalised elderly patients with and without pneumonia. While it demonstrates that large numbers of elderly Victorian inpatients have received 23vPPV (53%) and influenza vaccine (71%) as recommended, these figures remain suboptimal. Virtually all (99.8%) incompletely vaccinated inpatients in this study had experienced at least one opportunity to be vaccinated prior to admission. The greatest number of opportunities occurred as doctor visits outside the hospital setting (mean minimum estimate 11 visits) and raising awareness of vaccination opportunities in primary care settings remains a priority. However, half of all individuals unvaccinated with influenza vaccine had been admitted to the same hospital as the selected admission in the previous year (mean 1.5 times), and 70% of those unvaccinated with 23vPPV in the previous 5 years had been admitted to the same hospital over this period (mean 3.4 times). These results were robust when analyses were restricted to subjects providing self-reported data in person, those who were alive at discharge, those hospitalised with CAP and those admitted only during periods of peak influenza vaccination. They confirm that a systematic approach to updating vaccination in hospital could potentially reach a large proportion of those requiring 23vPPV or influenza vaccine.

Results from this study are consistent with international data reporting frequent missed opportunities for vaccination with influenza vaccine and 23vPPV. These data were all published subsequent to completion of the research for this thesis. Although no study is directly comparable (previous studies
have included only subjects with IPD, and subjects less than 65 years of age were eligible), three are relevant based on their hospitalised study populations.

Kyaw et al reported that 92% of 617 unvaccinated subjects aged ≥18 years with IPD and a prior vaccine indication had experienced opportunities for vaccination during the two years prior to their disease episode.\textsuperscript{236} “Main providers” were the most important in terms of the number of visits for potential opportunistic vaccination among unvaccinated IPD cases. 76% of cases with a vaccine indication saw their main provider in the two years prior to infection (median 6 visits), compared with 58% visiting the emergency department (median one visit) and 54% experiencing hospitalisation at least once (median one visit). Only 18% of those aged ≥65 years (n= 262) had no contact with their main provider during this period.\textsuperscript{236}

Husain et al found that of 209 patients (mostly <65 years of age) with risk factors indicating a requirement for 23vPPV, 95% had contact with the hospital in the 4 weeks to 5 years prior to admission for pneumococcal bacteraemia (median visits: 2 to the emergency department, 5 to general medical clinics and 1.5 to inpatient wards).\textsuperscript{237} These researchers proposed that emergency department-based vaccination would be the most effective at reaching those at risk and estimated this would be cost effective. Doctor visits outside of hospital were not measured.

A third hospital-based study involved a 10 year retrospective chart survey of 101 adult and paediatric subjects aged over two years with pneumococcal bacteraemia.\textsuperscript{238} This found that 46 (52%) subjects were candidates for 23vPPV but only 3 (14%) had been vaccinated. Vaccination records were available for 33/43 (77%) remaining subjects, and 31/33 were unvaccinated. Of the unvaccinated subjects, 30/31 (97%) had the opportunity to be assessed for 23vPPV status and administered 23vPPV.

Although missed opportunities were not quantified, researchers from the Centers from Disease Control reported that of 5048/87 230 randomly selected inpatients aged ≥65 years with ICD-9 codes for pneumonia, only 12.3% (95%CI 11.2-13.4%) had received 23vPPV during the five years prior to admission and 29.4% (95%CI 26.5-32.3) of 1242 patients admitted during the autumn (Oct-Dec) peak influenza vaccination season had received influenza vaccine from September 1 until December 31, presumably indicating missed opportunities in the community.\textsuperscript{167} Similarly, Centers for Disease Control data show that among persons who reported at least one hospitalisation during the preceding year, 55% of those aged ≥65 years reported not receiving 23vPPV and 32% reported not receiving influenza vaccine.\textsuperscript{233}

Nowalk et al also reported missed opportunities to vaccinate with influenza vaccine or 23vPPV, but in diverse primary care settings.\textsuperscript{235} This study of 810 adults ≥66 years reported 24% coverage with influenza vaccine and 49% with 23vPPV despite an average of 1.3 +/- 1.9 acute visits (mean +/- standard deviation), 6.9 +/- 5.1 chronic visits and 0.48 +/- 0.91 preventive visits over the 27 month
study period. Missed opportunities to vaccinate occurred in 38 +/- 40% of visits for influenza vaccine and 47 +/- 48% of visits for 23vPPV, based on the proportion of visits during which vaccine was neither given, discussed or refused by the patient.235

7.6.2 Risk factors for being unvaccinated at admission

This study found that subjects more likely to have received influenza vaccine prior to hospitalisation had English as a first language, were married or in a defacto relationship, had visited a doctor in the past 2-5 years, and had a history of ischaemic heart disease or rheumatological disease. Those less likely to be vaccinated were younger, living in their own homes and had fewer doctor visits in the past year. Factors not predictive of vaccination status for influenza vaccine were a history of other (non-pneumonia) respiratory disease, cerebrovascular disease, smoking habit, and a history of pneumonia in the past 2-5 years (plus variables not significant in univariate analysis: previous hospitalisation, alcohol intake, gender, history of diabetes, immunosuppression, renal disease, liver disease, aspiration or comorbidity). It is encouraging that increasing numbers of primary care doctor visits were associated with vaccination; a finding similar to that confirmed by Nowalk et al in their study of missed opportunities for vaccination in the primary care setting.235 It is also plausible that having a stable partner or English as a first language improves the chances of having an up to date vaccination status compared with living in a private residence (presumably with fewer health services prompts). However, it is not clear why having certain comorbidities might be helpful in terms of achieving influenza vaccination whilst others had the opposite or no impact. In particular, it is concerning that those with a recent history of pneumonia, other respiratory disease or current smoking habit were not more likely to be vaccinated since the presence of these factors in an individual should prompt providers to vaccinate. Similarly, it is of concern that the number of previous admissions to hospital did not predict vaccination with influenza vaccine. Contrary to results of this thesis, Parsons et al found that 438 subjects aged ≥65 years unvaccinated against influenza were significantly less likely to have asthma or diabetes.239 This study was conducted amongst a representative sample of community-based persons in South Australia. A national computer-assisted telephone interview (CATI) survey conducted in Australia found that an independent predictor of vaccination for the 78% of those aged ≥65 years reporting influenza vaccination was the presence of chronic disease (OR=1.6, 95%CI 1.3-2.0).135 Also contrary to this thesis, Nowalk et al found that missed opportunities for vaccination in the primary care setting were significantly less likely for both influenza vaccine and 23vPPV with decreasing age and male gender, in addition to use of health maintenance flow sheets and increased numbers of preventive visits.235

Similar factors to those predicting vaccination with influenza vaccine predicted vaccination with 23vPPV, with the encouraging exception of other respiratory disease being associated with vaccination. However, admission to hospital in the previous year was significantly more likely to be associated with being unvaccinated with 23vPPV. Kyaw et al found an association with vaccination
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with 23vPPV for 613 persons aged ≥65yrs and history of alcohol abuse, malignancy with metastases or no underlying high risk conditions (lower vaccination), and non-HIV immune disorders (eg Crohn’s disease, immune thrombocytopenic purpura, scleroderma, multiple sclerosis) and chemotherapy (higher vaccination).\textsuperscript{236} By contrast, this thesis did not find comorbidity, alcohol abuse or immunosuppression were associated with vaccination with 23vPPV; chemotherapy patients were excluded due to their very frequent rate of short-stay admissions, and malignancy was not examined as a risk factor.

Available comparative data regarding risk factors associated with vaccination status with either vaccine are limited, and all relevant comparisons are discussed above.\textsuperscript{235,236,239} Two of these studies come from the USA and were published after the completion of the research for this thesis, and the other was conducted in South Australia.\textsuperscript{239} Many of the risk factors included for examination in this thesis were not assessed by the above studies. The fact that those few risk factors for vaccination that were assessed in common were found to have contrary associations suggests that local differences may be important. Data from this thesis nonetheless suggest that the primary care setting remains an important and effective site for improving vaccination coverage with both influenza vaccine and 23vPPV. However, health providers working in the hospital setting are not vaccinating those at risk for whom current policy recommends vaccination. In addition, the data on risk factors for incomplete vaccination suggest that future vaccination strategies might consider targeting those not in a stable relationship, living in their own home, without English as a first language and with a prior history of pneumonia.

7.6.3 Opportunistic vaccination rate during hospitalisation

No subject in need of either influenza vaccine or 23vPPV was vaccinated during their selected hospital admission. These findings are consistent with a number of studies from the USA showing very low rates of opportunistic vaccination within the hospital setting despite national recommendations to update both influenza vaccine and 23vPPV prior to discharge.

Greci et al studied 160 patients (mean age 72 years) admitted to hospital with pneumonia of whom 97% were unvaccinated with both influenza vaccine and 23vPPV and found none were vaccinated during hospitalisation. No patient had a listed contraindication to either vaccination and none had recommendations to vaccinate documented in their hospital charts.\textsuperscript{166}

Dexter et al assessed the effectiveness of computerised reminders versus no intervention for hospitalised patients with at least one indication for vaccination with 23vPPV and found that no intervention resulted in 0.8% of 1696 unvaccinated patients (mean age 53 years) receiving 23vPPV and 1% of 1033 unvaccinated patients receiving influenza vaccine.\textsuperscript{240}

Husain et al retrospectively studied 287 patients aged ≥16 years with a first episode of pneumococcal bacteraemia in an inner-city hospital and found that only 2/98 with complete
vaccination records indicating they were unvaccinated received vaccination at discharge from the selected admission.\textsuperscript{237}

Bratzler et al studied a national sample of 107,311 fee-for-service high-risk Medicare inpatients aged \( \geq 65 \) years admitted with heart failure, pneumonia, myocardial infarction or stroke in the USA.\textsuperscript{165,167} Although vaccination status was not determined and adjustment for confounders was not made for the 104,976 patients aged \( \geq 65 \) years with a single hospitalisation, using claims-based data, the study found that only 444 (0.4%; 95%CI 0.2-0.6%) subjects received 23vPPV in hospital (34% were vaccinated prior to hospitalisation, and 1% within 30 days of discharge).\textsuperscript{165} Of the 40,488 patients discharged from October-December (the peak influenza vaccination season), only 755 (1.9%) were vaccinated in hospital (32% were vaccinated prior to hospitalisation and 11% in the 30 days after discharge).

Researchers from the Centers from Disease Control reported that of 5048/87,230 randomly selected inpatients aged \( \geq 65 \) years with ICD-9 codes for pneumonia, 0.4% (95%CI 0.2-0.6%) received 23vPPV during hospitalisation, and of 1242 patients admitted during Oct-Dec, 0.7% (95%CI 0.2-1.2%) received influenza vaccine during admission.\textsuperscript{167} For influenza vaccine, it was noted that this is likely to be an underestimate by up to 20% based on Medicare billing data and that vaccination withheld for legitimate reasons was also not able to be determined from the medical record.

This thesis was unable to examine risk factors for missed opportunities to vaccinate as no patient in need of vaccination received either influenza vaccine or 23vPPV. One recent study has examined risk factors for missed opportunities to vaccinate in hospital among high risk patients (admitted with heart failure, pneumonia, myocardial infarction or stroke).\textsuperscript{165} This study population was very different to the population studied for this thesis given the high risk status of patients plus the fact that a number were vaccinated in hospital, allowing examination of risk factors. The results are therefore not likely to be directly comparable to those of this thesis. Nonetheless, Bratzler et al reported an association between inpatient opportunistic vaccination for 23vPPV and increasing age, and influenza vaccine and male gender. In addition, Bratzler et al reported that those admitted more than once were three times more likely to have received 23vPPV than those admitted only once, although this was not the case for influenza vaccination.\textsuperscript{165}

Although this study did not seek to examine reasons for low rates of opportunistic vaccination with both influenza vaccine and 23vPPV, there are a number of possible explanations. Hospital provider or patient factors such as doubt regarding the effectiveness or safety of the vaccines could play a role. However, it is well known that side effects of both vaccines are uncommon and almost always mild.\textsuperscript{147} In addition, published data are in favour of benefit from influenza vaccine against influenza-like illness and mortality within influenza seasons (see 1.5.2) and observational trials show effectiveness of 23vPPV against IPD (see 1.5.1). Reluctance to vaccinate hospital inpatients by some hospital providers has been suggested by Dexter et al, who showed great individual variation
in physician acceptance of computerised reminders for vaccination with 23vPPV and influenza vaccine among eligible inpatients in a randomised controlled trial. This could be due, for example, to competing priorities in a busy hospital setting. Alternatively, Dexter et al also reported extremely low compliance rates in their control group suggested some of the non-compliance was attributable to long-established habits of vaccinating patients only in the outpatient setting. Concern about a possible reduction in vaccine effectiveness after acute illness may play a role, however, this possible reduction is unproven. Perceived or actual difficulty in confirming vaccination status could also be a problem for hospital providers caring for elderly inpatients. This argument lends support to the concept of a whole-of-life immunisation register encompassing adult vaccinations. Hospital providers’ knowledge of vaccination requirements in Australia is unknown.

At this point in time, potential barriers to hospital-based immunisation with influenza vaccine and 23vPPV require formal assessment in Australia if successful implementation of current vaccination policy is to occur for the elderly population.

### 7.6.4 Recording of vaccination status by hospital staff

This study found a very low rate of recording vaccination status for hospital inpatients, with only 2% having vaccination status for either influenza vaccine or 23vPPV recorded in their hospital records. This estimate is similar to those from studies in the USA despite recommendations being in place to assess vaccination for all inpatients in that country. Greci et al reported previous vaccination history for 23vPPV and influenza vaccine was listed for <0.5% of inpatients with pneumonia, researchers from the Centers for Disease Control reported a rate of 4.7% (3.4-5.9%) for admission histories among patients with pneumonia; and Bratzler et al found 8% and 13% of inpatients admitted with heart failure, pneumonia, myocardial infarction or stroke had 23vPPV and influenza vaccination status recorded respectively. Failure to review vaccination status has been previously cited as the primary cause of missed opportunities to vaccinate in primary care settings, and it clearly also plays an important role in hospitals. As for opportunistic vaccination discussed above, non-compliance with assessing vaccination status may also be related to long-established habits of leaving vaccination to the outpatient setting, low prioritisation given to vaccination, or perceived or actual difficulty regarding confirmation of vaccination status for hospitalised elderly inpatients.

### 7.6.5 Acceptability of vaccination among those reporting to be unvaccinated

Data from this study confirm the importance of provider support for vaccination among hospitalised patients. Approximately 40% of all unvaccinated subjects reported they would have accepted 23vPPV or influenza vaccination respectively if offered by their provider, and approximately another 10% were unsure. This finding is consistent with a previous study by Horby et al who
reported that for interviews conducted with 7681/25 518 (30%) households for Australians aged 40 years or older, 41% of those aged ≥65 years who were unvaccinated said they would have accepted vaccination if their doctor had recommended it, and among those vaccinated with influenza vaccine aged ≥65 years, 35% had been prompted to have the vaccine by the recommendation of their doctor.\textsuperscript{135} Similarly, a study from South Australia found 59% of 547 subjects selected from four Omnibus Surveys (1993-1996) stated they were influenced to have influenza vaccination by the recommendation by their doctor.\textsuperscript{239} Nichol et al also confirmed the importance of provider endorsement as an independent risk factor for vaccination with both influenza vaccine and 23vPPV in their cross sectional survey of 700 patients randomly selected from the outpatient roster of a medical centre.\textsuperscript{243} This study had a higher (68%) participation rate after three mail-outs of the self-administered questionnaire compared with the 30% reported by Horby et al. \textsuperscript{135} Nowalk et al also reported a low rate (9% or less) of documented refusal for either influenza vaccine or 23vPPV in primary care settings.\textsuperscript{235}

Reasons for vaccinations to be unacceptable to the remaining 50-60% of subjects were not examined in this thesis. However, published data suggest a positive attitude towards vaccination is important for both 23vPPV and influenza vaccination.\textsuperscript{243} Concerns about effectiveness and safety have been shown to be important.\textsuperscript{244} Among Australians aged ≥65 years, Horby et al reported the main reasons for non-vaccination with influenza vaccine were that subjects did not feel they were at risk (65%), were concerned about side effects (21%), and thought the vaccine did not work (14%).\textsuperscript{135} However, the same survey found only 2% of persons aged ≥65 years believed influenza vaccine is not at all effective at preventing influenza, with 79% believing it is somewhat or very effective.\textsuperscript{135} Parsons et al reported that of 438 South Australians unvaccinated against influenza vaccine, 46% believed they did not need the vaccine because they rarely became sick.\textsuperscript{239} MacIntyre et al conducted an intervention study comparing hospital and community-based reminder systems to improve 23vPPV and influenza vaccination in one of the hospitals forming the study base for this thesis (RMH).\textsuperscript{186} They reported that among 70 consenting patients in the hospital intervention arm, the most common patient factors for not receiving vaccination were patient refusal (21%), and a preference to be vaccinated by their general practitioner.\textsuperscript{186} Gill et al also reported from a survey of South Australian nursing home residents, that of the 5% who had not received an influenza vaccine, reasons why a resident did not have an influenza vaccination were reported by directors of nursing as refusal and allergy.\textsuperscript{234} There remains a relative lack of data on attitudes towards 23vPPV among the elderly in Australia.

### 7.6.6 Study limitations and strengths

There are a number of limitations of this study that warrant consideration. Recall bias may have occurred when asking subjects to estimate prior (non-hospital) doctor visits. However, estimates are likely to be conservative (underestimates) since subjects were only asked about doctor visits rather
than other potential vaccine providers, and the lower bound of the nominated category was allocated (for example, for the category 1-4, only one visit was allocated). As hospitalisations were determined by chart review, these estimates are unlikely to have been affected by bias, except for the fact that no attempt was made to include hospitalisations outside that of the hospital of the selected admission. Therefore, this too may be an underestimate of total hospitalisations.

Excluded cases may have affected the generalisability of estimates for doctor visits and acceptability of vaccination. Based on those with records for review and who gave consent for self-report, 72% of eligible subjects were able to provide information on these two questions. When those excluded from calculations of doctor visits were compared with those who were included, the former group were more likely to be older, to live in their own homes, and less likely to be male (Table 7.1).

Estimates for the opportunistic vaccination rates with 23vPPV or influenza vaccine related to hospitalisation may have been underestimates since this study was not designed to account for outpatient vaccine administration prompted by recent hospitalisation. Similarly, the denominator did not account for vaccinations withheld for legitimate reasons (although there are few contraindications; for example allergy to a vaccine component) or patient refusals. Nonetheless, with a zero opportunistic vaccination rate in hospital for both vaccines based on review of actual medical records, 29% and 47% of subjects being unvaccinated for influenza vaccine and 23vPPV respectively, and relatively high reported acceptability of vaccination, these results provide compelling evidence for the need for improving opportunistic vaccination by hospital staff. Any unvaccinated patient discharged from hospital should be regarded as a missed opportunity for updating vaccination status. Of note, vaccination occurring after hospital discharge has been shown by others to be relatively infrequent. Bratzler et al examined vaccination within 30d of discharge for high risk patients and 1% were vaccinated with 23vPPV and 11% with influenza vaccine. Greci et al found that less than 5% of inpatients with pneumonia had documented vaccinations during the three years after discharge.

Defining the unvaccinated population eligible for opportunistic vaccination in hospital using complete dates of vaccination from nominated vaccine providers is likely to have been more accurate than for studies defining vaccination according to claims-based data, hospital record review or patient report of vaccination. Coverage estimates are likely to be generalisable to the elderly population since they are similar to previously published estimates for Victoria. As discussed in 5.5.3, based on data from a 1999/2000 survey of community-based elderly persons in Victoria who had their vaccination status confirmed by vaccine providers, vaccination coverage was similar (or slightly higher) in the community sample than that experienced by the hospitalised subjects analysed in this thesis (23vPPV: 58% versus 53% (95%CI 52-55), influenza vaccine 78% versus 71% (95%CI 69-72) respectively). More recently, Andrews reported further results for 23vPPV after additional time with the funded population program in Victoria and estimated coverage to be 50.5% (95%CI 44.8-56.1). Of note, coverage for 23vPPV after four years of the funded program in
Chapter 7: Opportunistic vaccination

Victoria was similar to that reported by Vila-Còrcoles et al (53.1%), four years into a funded 23vPPV program in Catalonia, Spain. Of interest, a further Australian survey was conducted in October 2004 (2.5 years subsequent to the completion of the research for this thesis) to establish baseline 23vPPV coverage prior to the introduction of a national 23vPPV program for elderly Australians in 2005. Data from this study are not directly comparable since adults aged ≥40 years were included, only approximately 1000 residents from each state or territory were included, vaccination coverage was established by self-report and residents from institutions such as aged-care facilities were excluded. The study found 23vPPV coverage for Victorians was 62% compared with 42-53% for all other jurisdictions, suggesting that the funded Victorian program has had lasting effects on increasing coverage. Influenza vaccine coverage was 82% compared with a national estimate of 79%.

Although potential bias could have arisen in this thesis from over-sampling cases if vaccines were effective in preventing hospitalisation with CAP (that is, if cases were less likely to be vaccinated, resulting in over-representation of those with missed opportunities for vaccination), since this study found no evidence of benefit against hospitalisation with CAP (see Chapter 5), this bias, if present, should not be of any quantitative importance.

7.6.7 Strategies and challenges for improving vaccination coverage

This study shows that hospitalised elderly patients currently receive 23vPPV and influenza vaccines only outside the hospital setting despite many opportunities for vaccination in hospital, relatively high acceptability of hospital-based vaccination among the unvaccinated, and recommendations for providers to vaccinate at every opportunity.

Although primary care will remain a key setting for vaccination, with the greatest number of opportunities for vaccination and current vaccinations occurring there, and a preference by some patients to receive their vaccinations there, from a practical point of view, both primary care and hospital settings are important. Hospitals capture high risk patients for whom vaccination is recommended in addition to age criteria. There are relatively few hospitals compared with primary provider settings, making implementation of interventions to improve vaccination coverage relatively more simple and potentially able to reach many unvaccinated individuals at higher risk of influenza and pneumococcal disease. In general, those well enough to be discharged should be well enough to be vaccinated given the very limited number of contraindications to vaccination.

Vaccination in hospital presents a number of challenges. Barriers require formal study in Australia, but previous research suggests a number of hurdles need to be overcome as discussed above, including concerns regarding safety and effectiveness (including after acute illness), reluctance to vaccinate due to competing priorities and long-established habits of vaccinating only in the
outpatient setting, and perceived or actual difficulty in confirming vaccination status (supported by the very low rates of documentation of vaccination status in only 2% of subjects in this study).

Strategies for vaccination in hospitals have been suggested by previous research and include systems based approaches such as prompts for screening vaccination status coupled with standing orders for vaccination prior to discharge (computer, nurse or pharmacist-based). Findings from this thesis would support such an approach given poor documentation of vaccination and an in-hospital vaccination rate of zero. Automated prompts for the recording of vaccination histories in hospital records could potentially improve assessment of vaccination status above the 2% rate seen in this study. For example, admission proformas or flow sheets including vaccination status could improve documentation.

Dexter et al provide compelling evidence for computer-generated reminders for hospitalised patients for vaccination with both 23vPPV and influenza vaccine. This intervention study found that those in the intervention group were significantly more likely to be vaccinated with 23vPPV (36% of the patients in the intervention group versus 1% of those in the control group, \(P<0.001\)), and influenza vaccine (51% versus 1%, \(P<0.001\)). These improvements were also sustainable, with further increases 15 months after completion of the study with continued use of reminders. Reminders were presented as full pre-written orders that appeared automatically up to four times during an admission and only required acceptance by pressing the “enter” key, thus minimising effort required from the responsible physician. Such an approach is likely to be better compared with manual reviewing of hospital charts, patient-directed interventions and physician-directed continuing education where considerably more input is required from individuals. Other US studies also support standing orders for the vaccination of hospitalised patients to improve vaccination coverage with 23vPPV and influenza vaccine. Data from the study by Herman et al provide strong evidence for organisational changes that involve non-physician personnel to enhance vaccination rates among older adults.

One small Australian study examined 131/368 (36%) eligible Royal Melbourne Hospital unvaccinated inpatients aged ≥65 years who were able to consent and have their vaccination history verified. Although excluded patients could have biased results, this study suggests that simple prompts for both general practitioners (reminder letter) and hospital staff (memo in hospital record plus a face-to-face reminder for physicians) could improve vaccination coverage. After implementation of randomly allocated hospital or general practitioner alerts for unvaccinated patients, 23vPPV coverage was 55% for a GP alert and 67% for a hospital alert at follow-up (day of discharge for the hospital arm, phone call at one and three months for the GP arm). These differences were not statistically significant. For influenza vaccine, coverage was 63% for a hospital alert compared to 53% for a GP alert.
In addition to inpatient wards, the emergency department has also been proposed by some researchers as an appropriate hospital setting in which to vaccinate patients at risk for pneumococcal bacteraemia with 23vPPV. Husain et al reported from their retrospective cohort study of 300 cases of pneumococcal bacteraemia that vaccination based in the emergency department would protect most patients at risk compared with other hospital settings (inpatient wards or outpatient clinics), with a best case scenario showing cost savings, particularly since the ill, elderly, poor and members of ethnic minorities are over-represented among patients attending emergency departments, and more likely to be unvaccinated. A pilot study conducted in the same emergency department found that the median extra time required for screening and vaccinating with 23vPPV or influenza vaccine was 4 minutes per patient (range 2-10 minutes) without additional personnel, and that of high risk patients screened, 76% accepted and received the vaccines. The group noted, however, that intense supervision was necessary to ensure implementation, and that there was extreme variation in individual performance.

Since provider recommendation has been shown by a number of studies to be one of the most important determinants of vaccine uptake, and data from this thesis indicate relatively high acceptability of vaccination among the unvaccinated hospitalised elderly, education of providers is also important. Data from this thesis also indicate certain groups are at greater risk of being unvaccinated, including those not in a stable relationship, those living in their own home, those without English as a first language, those with a prior history of pneumonia and for 23vPPV, those previously admitted to hospital. These factors should also be considered in undertaking education of providers, along with well described risk factors for influenza and pneumococcal disease described in the international literature. However, as for patient education, provider education is unlikely to have a major impact if not coupled with efficiencies in implementation of vaccination such as automated reminder systems.

7.6.8 Conclusions

Implementation of current recommendations to vaccinate patients aged ≥65 years with influenza vaccine and 23vPPV is suboptimal in both the hospital and primary care setting despite many opportunities for vaccination and relatively high acceptability of vaccination among unvaccinated patients. While there were many missed opportunities outside the hospital setting, there was evidence of primary care visits impacting positively on vaccination status. By contrast, previous hospitalisation was a risk factor for being unvaccinated with 23vPPV, and not associated with vaccination status for influenza vaccine. The practice of non-vaccination in hospital is likely to be longstanding given its completeness, and barriers to vaccination among both the hospitalised elderly and providers require further study in Australia, along with costs associated with failure to vaccinate. It is likely however, that an easily implementable systems approach will be necessary to improve opportunistic vaccination in the hospital setting. Available evidence suggests that any intervention should carry a minimal additional work load, prompt recording of vaccination status and provide
(preferably automated) standing orders for vaccination prior to discharge. For those not vaccinated at discharge due to factors such as unavailability of vaccine or patient refusal, a reminder sent to the patient’s general practitioner and/or inclusion of vaccination status on the discharge summary might be helpful. In addition, for 23vPPV in particular, hospital-based providers need additional education regarding current vaccination policy. Poor documentation of vaccination status in hospital may be due to perceived or actual difficulty in confirming vaccination status and lends support to the concept of a whole-of-life immunisation register encompassing adult vaccinations. Consideration should be given to systems changes that enable standing orders for vaccination to be carried out by other providers, particularly if physician endorsement of hospital-based vaccination cannot be achieved.
Chapter 8 Concluding Discussion

8.1 Key outcomes

8.1.1 Vaccine effectiveness against hospitalisation with CAP

The research described in this thesis is the first from the southern hemisphere to assess vaccine effectiveness for 23vPPV or influenza vaccine against hospitalisation for CAP in the elderly and did not demonstrate benefit to individuals from either vaccine against this outcome across a range of analyses, during a period of usual organism activity. This was despite excellent participation rates and adequate power. Although the study was not designed to examine the outcome of death, exploratory analyses suggested moderate benefit from influenza vaccine and minor benefit from 23vPPV against deaths associated with hospitalisation with CAP and all-cause mortality, however estimates were imprecise and just failed to reach statistical significance. The study did not seek to confirm the established benefits of vaccination in reducing the more specific outcomes of confirmed influenza or invasive pneumococcal disease. However, these results indicate that the current program funding these vaccines in this population is having no discernable impact on hospitalisation for CAP. Evidence favours reduced emphasis on prevention of pneumonia in recommendations to vaccinate persons aged ≥65 years with 23vPPV or influenza vaccine. Economic assessments of these vaccines should include a benefit against pneumonia of zero in sensitivity analyses.

While a randomised trial of community-based elderly persons would have been an ideal design to examine vaccine effectiveness, this was neither ethical nor feasible, and limitations generally ascribed to a case-cohort study did not impact appreciably on the study estimates. Estimates for both univariate models adjusted for design variables, and multivariate models adjusted for known confounders were similar, and suggest that uncontrolled confounding is unlikely to have played a major role. Preferential vaccination of healthy subjects would have resulted in over-estimation of vaccination benefit. Since no benefit was found, this is unlikely to have occurred. While choice of hospitalised study subjects could potentially limit generalisability of results, independent data for community-based elderly Victorians support the coverage estimates described in this study, both vaccination status and CAP were reliably ascertained, adjustment was made for comorbitides and other known confounders, and inclusion or removal of frequently admitted subjects from analyses resulted in very similar estimates.

Although this study was large and robust, as the first study from the southern hemisphere to examine the question of VE against all-cause pneumonia, it would be helpful to have these findings confirmed by at least one further well-designed large study in this region. However, sufficient
evidence has now accumulated to strongly suggest a lack of benefit from influenza vaccine or 23vPPV against hospitalisation with pneumonia in elderly inpatients.

8.1.2 Validity of ICD-10 codes as a tool to retrospectively identify hospitalised CAP

This study is the largest to date, and the first from Australia to examine the validity of using ICD-10-AM codes to retrospectively identify cases of pneumonia among hospitalised patients, and adds to a very limited international knowledge base. It shows that when medical record notation of pneumonia is used as the standard, ICD-10 codes are a valid method and appear superior to use of complexes of symptoms and signs, or radiology reports. They are therefore an appropriate method for case ascertainment of all-cause pneumonia in the estimation of vaccine effectiveness where pneumonia is the outcome of interest. These results are reassuring for the many previous studies using this approach. Codes were not helpful in this setting for the identification of subcategories of pneumonia due primarily to low rates of laboratory investigation. Development of a standardised approach to the interpretation of adult CXRs may improve the usefulness of radiology reports as a comparator in the future.

While lack of a true reference standard for diagnosis of pneumonia against which to compare ICD-10 codes is problematic in this area of research, analyses were conducted using three comparators suggested by review of the literature and the study was large enough to exclude validity estimates for ICD-10 codes for pneumonia of less than 95% when compared with medical record notation of pneumonia. There were few missing data for any comparator, selection and measurement bias were minimised through aspects of design, and exploratory analyses indicated that repeat presentations were not coded differently and their exclusion from the primary analyses was unlikely to have biased the estimates of validity.

In the future, a large prospective study of the investigation of hospitalised CAP and its aetiology in Australia could potentially examine the validity of using ICD-10-AM codes to identify specific subcategories of pneumonia by causative organism.

8.1.3 Vaccination coverage and opportunistic vaccination

In addition to monitoring the impact of vaccination programs in reducing disease, assessment of program implementation is also an integral component of good public health practice. Assessment of vaccine coverage and missed opportunities to vaccinate can assist with future vaccination strategies. Prior to this study, data were limited regarding the evaluation of the Victorian and now national program of vaccination with 23vPPV and influenza vaccine in the elderly population.
This study provides the most comprehensive and largest data set thus far on vaccination coverage for influenza vaccine and 23vPPV for the Victorian elderly population. Estimates were based upon dates of vaccination confirmed by providers and were adjusted for selection probability. While they demonstrate that the vaccination program has been successful in Victoria in increasing vaccination coverage for both vaccines, at 71% coverage for influenza vaccine and 53% for 23vPPV for the periods of one and five years prior to admission respectively, these figures remain suboptimal.

Risk factors for being unvaccinated identified by this study can assist with future strategies for program implementation since the hospitalised elderly are a population at increased risk of subsequent disease due to influenza and *S. pneumoniae* and a key target group. Data from this thesis suggest certain groups are at greater risk of being unvaccinated (for example, those with a prior history of pneumonia). In addition, providers need greater awareness of those with a history of other respiratory disease or who are current smokers since these groups should be targeted for vaccination and were not more likely to be vaccinated than other inpatients. These factors should be considered in undertaking provider education, along with established risk factors for influenza and pneumococcal disease.

This study is also the largest study to quantify missed opportunities for vaccination with 23vPPV and influenza vaccine among hospitalised elderly patients with and without pneumonia and contributes to limited Australian and international data. Despite current recommendations to vaccinate this population at every opportunity, no incompletely vaccinated inpatient was vaccinated. This was despite relatively high levels of acceptance of vaccination and confirmation of the positive influence of provider endorsement. In addition, previous hospitalisation was a risk factor for being unvaccinated with 23vPPV and was not positively associated with influenza vaccination. Only two percent of inpatients had their vaccination status documented for either influenza vaccine or 23vPPV. While barriers to vaccination among patients and providers require formal study in Australia, available evidence suggests that any intervention aimed at improving vaccination with 23vPPV and influenza vaccine should carry minimal additional workload and include education of providers and the elderly about the benefits, safety and appropriateness of 23vPPV and influenza vaccine prior to discharge. Education of hospital providers is unlikely to have a major impact if not coupled with efficiencies in implementation of vaccination such as automated prompts for assessing vaccination status and standing orders for vaccination. Consideration should be given to systems changes that facilitate those orders being carried out by other providers, particularly if physician endorsement of hospital-based vaccination cannot be achieved. While primary care settings remain key to improvements in opportunistic vaccination in the elderly, hospitals remain important since they provide the opportunity to target those at greater risk of vaccine-preventable disease. A whole-of-life register including adult vaccinations could assist with determination of vaccination status, which may currently be too time-consuming or difficult to accurately determine, and therefore infrequently undertaken in the hospital setting in the presence of competing priorities.

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Although recall bias may have occurred when asking subjects to quantify prior (non-hospital) doctor visits, estimates of opportunities for vaccination were conservative given non-doctor vaccine providers were not included, the lower bound of the nominated category was allocated, and admissions to other hospitals were not included. Opportunistic vaccination during hospitalisation may have been underestimated since outpatient vaccine administration was not examined. In addition, vaccinations withheld for legitimate reasons and patient refusals were not assessed. Nonetheless, the study provides compelling evidence for the need to improve opportunistic vaccination.

Should future studies show improvements in opportunistic vaccination for the hospitalised elderly, it may be possible to examine for the first time risk factors for failing to vaccinate this population.

### 8.1.4 Validity of self-reported vaccination status

This study is the largest to date to examine the validity of self-reported vaccination status as an indicator of true status for influenza vaccine and 23vPPV and the first to adjust for confounders. It contributes to the further assessment of the current Australian program in persons aged ≥65 years, as well as similar programs in other countries, and clinicians vaccinating individuals. The study found that asking subjects their influenza vaccination status is generally likely to produce a correct response. While subject factors such as age, gender, admission with pneumonia, and comorbidity seem to have little influence on validity of self-report, increasing contact with medical personnel or institutions reduced validity. Contact with multiple medical personnel over a relatively short period might result in a degree of confusion regarding vaccination status, or alternatively, being unwell may reduce the ability to recall vaccinations accurately, particularly if received when unwell. Self-reported 23vPPV status for the previous five year period was found to be reasonably accurate, but was less likely to be correct where self-reported influenza vaccination status was known to be incorrect. Validity of recall of 23vPPV status in the past year was poor.

For policy makers assessing the impact of state or national programs, self-reported influenza vaccination coverage among the hospitalised elderly over-estimates true vaccination coverage by about 10%, while 23vPPV coverage is not dramatically under- or over-estimated. Although sensitivity of self-reported influenza vaccination status was high (98%), specificity was poor (56%) and this was lower again among those with frequent provider or hospital visits. For 23vPPV, sensitivity was high (86%) and specificity moderately high (78%).

Estimates for validity of self-report may have been affected by participation bias, as the group not providing consent to undertake the questionnaire comprised a quarter of those eligible, and although few differences were noted between the participants and non-participants, unmeasured factors may remain unaccounted for. Those who refused provider confirmation of vaccination status were few in number and their absence from analysis is unlikely to have introduced appreciable bias. Similarly,
restriction of the study population to only subjects completing interviews themselves produced similar results to analyses including all selected subjects, and restriction of the study population to first presentations or that reclassified “don’t know” responses to unvaccinated status also produced similar estimates.

In general, using self-report to measure vaccination coverage remains imperfect. These data support a whole-of-life immunisation register as a preferable goal. In addition, exploration of why contact with medical personnel or institutions could negatively influence accuracy of subject recall of vaccination status is warranted.

8.1.5 Epidemiology of hospitalisation with CAP

Prior to this study, Australian data on the epidemiology of CAP were limited to four small studies of less than 200 subjects, with none focussing on the elderly or examining risk factors. Data were therefore lacking for many aspects of basic epidemiology for CAP in elderly Australians. This research described the epidemiology of CAP, including burden of disease, outcomes and risk factors in elderly Victorian inpatients and provides the most comprehensive data for elderly Australians to date. Such information is useful for directing future management and preventive strategies.

This thesis confirms that hospitalisation with CAP among elderly Australians is common, frequently fatal and responsible for a considerable burden to the community that will increase with the growth of the elderly population. Those hospitalised with CAP represented 4% of all admissions for the elderly for the two hospitals of interest during the study period. They stayed in hospital on average 9 days, 14% required admission to an intensive care unit and 11% died within 30 days of admission. These estimates were all significantly more burdensome compared with those admitted without a diagnosis of CAP.

Investigation of hospitalised CAP in the elderly was ad hoc and the approach to management empiric in this setting. Approximately 30% of all those hospitalised with CAP had no laboratory investigations performed, and the remainder had very few. Almost all received antibiotics and these were generally consistent with antibiotic guidelines available during the study period. One third had three or fewer of seven frequently occurring symptoms and signs sought for pneumonia, confirming the less distinct clinical presentation often seen among elderly persons with CAP.

This thesis has produced the first Australian data on risk factors for CAP and associated mortality in the elderly. This is important since knowledge of risk factors at presentation or admission can direct health providers to better predict the risk of CAP and subsequent mortality. Data from this research indicate prior history of respiratory disease, previous pneumonia, aspiration, immunosuppression, diabetes, renal disease, excessive alcohol intake, those living in their own home and males are at increased risk of admission with CAP. Awareness of risk factors such as aspiration and alcoholism could potentially lead to implementation of preventive strategies and improved outcomes.
Importantly, influenza vaccination in the previous year protected substantially against mortality associated with CAP, supporting current recommendations to vaccinate persons aged ≥65 years. Death associated with CAP was more likely among those admitted to ICU, who were older, or who had a history of renal disease, immunosuppression, smoking, multilobar involvement on CXR or who lived in their own home.

This thesis also highlights the disparity in ICU admission rates between older and younger elderly patients and raises the question of whether their similar ICU survival rates reflect preferential admission of older patients likely to have a good prognosis. Very old patients ≥80 years were less likely to be admitted to ICU but did not die significantly more often than younger patients aged 65-79 years.

While this study is the largest to date in Australia of CAP among elderly persons, it was not specifically designed to examine the epidemiology of this disease. Data were collected retrospectively from hospital records, and while some fields were well documented (basic epidemiology, burden of disease, risk factors and outcomes), others captured the non-uniform practices of staff investigating and managing such cases. Cases were defined using ICD-10 codes. Although it remains possible that some subjects did not have CAP, Chapter 4 examined the validity of using ICD codes to retrospectively identify cases of hospitalised pneumonia and indicates this is a valid practice in this setting. As previously outlined, the study population is also likely to have been representative of hospitalised elderly persons in Victoria.

In the future, a large prospective study examining investigation, aetiology and treatment of CAP in elderly Australians would make a valuable contribution to what is currently a knowledge vacuum. If clinical severity indices were also examined, it may be possible to also answer whether only those very old patients with a likely good prognosis are admitted to ICU. It may also be worthwhile to explore further why certain comorbid conditions such as rheumatological disease might protect against admission with CAP, while living in one’s own home or having English as a first language appear to increase risk of admission. A study of changes in the dependency level of residence after admission with CAP could also provide additional detail on burden of disease.

**8.2 Summary of health policy implications**

Evidence from this thesis favours:

- Reduced emphasis on prevention of pneumonia in current programs to vaccinate persons aged ≥65 years with 23vPPV or influenza vaccine.

- Inclusion of a benefit of zero against pneumonia in sensitivity analyses of economic assessments for these vaccines.
Chapter 8: Concluding Discussion

- Moderate protection against mortality from CAP by influenza vaccination, although the estimates were imprecise and just failed to reach statistical significance.
- Targeting vaccination at elderly individuals with risk factors for CAP.
- Identification of those at risk for CAP, potentially resulting in earlier diagnosis and treatment.
- Education of providers and the elderly about the benefits, safety and appropriateness of 23vPPV and influenza vaccine prior to discharge from hospital.
- Systems changes that improve efficiency of implementing inpatient vaccination.
- Use of ICD-10-AM codes as a valid tool for retrospective case ascertainment of all-cause pneumonia in the hospitalised elderly population.
- Development of a standardised approach to the interpretation of adult CXRs, which could contribute to the development of a reference standard for diagnosis of pneumonia in the future.
- The expansion of the current Australian Childhood Immunisation Register to a whole-of-life immunisation register.

8.3 Summary of implications for research

Findings from this thesis support conducting the following future research:

- A large, prospective study examining severity indices, investigation, aetiology and treatment of hospitalised CAP in elderly Australians. This could potentially also examine the validity of using ICD-10-AM codes to identify subcategories of pneumonia by causative organism.
- Further exploration of some factors predicting or negatively associated with hospitalisation with CAP, including rheumatological disease, living in one’s own home and having English as a first language.
- Study of changes in the dependency level of residence after admission with CAP in order to better define burden of disease.
- Formal study of barriers to vaccinating the elderly with 23vPPV and influenza vaccine among patients and providers in Australia, and costs associated with failure to vaccinate.
- A first study of risk factors for failing to vaccinate Australian elderly inpatients, provided future studies indicate improvements in opportunistic vaccination
Conclusions

Contrary to what might currently be considered popular opinion, this thesis did not confirm benefit from influenza vaccine or 23vPPV against hospitalisation with community-acquired pneumonia in elderly Australians. This finding has implications for both economic assessments of vaccine benefits and emphasis of current vaccination programs. This research also found ICD-10 codes were a valid method for retrospective ascertainment of hospitalised pneumonia when compared against the standard of medical record notation of pneumonia. Hospitalisation with CAP was confirmed to be a common and frequently fatal illness in the elderly population for which inpatient investigation is currently limited and treatment empiric. This burden of illness is likely to grow as the Australian population ages. It is possible that greater awareness of frequently occurring symptoms and signs among those at risk, and risk factors at presentation among physicians as described in this thesis could potentially improve outcomes if this knowledge resulted in timely commencement of appropriate treatment or implementation of preventive strategies.

Despite not finding benefit against hospitalisation with CAP, both influenza vaccine and 23vPPV have proven benefits against other outcomes, including mortality, which was confirmed by this thesis in the case of influenza vaccine. Although current Australian recommendations are to vaccinate all persons ≥65 years with both vaccines, there is currently a failure both to document vaccination status and provide vaccinations to inpatients. Education of providers and a whole-of-life immunisation register in Australia could positively impact on vaccination program implementation for the elderly population. A whole-of-life register would also improve ease and reliability of vaccination program assessment for this group. Future research should focus on better establishing costs, attitudes and risk factors associated with non-vaccination.
References


References


References


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References


# Appendices

## Appendix 1: ICD-10 codes J10-J18

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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| J10  | Influenza due to identified influenza virus  
J10.0 Influenza with pneumonia, influenza virus identified  
J10.1 Influenza with other respiratory manifestations, influenza virus identified  
J10.8 Influenza with other manifestations, influenza virus identified |
| J11.0 | Influenza with pneumonia, virus not identified  
J11.0 Influenza with pneumonia, virus not identified  
J11.1 Influenza with other respiratory manifestations, virus not identified  
J11.8 Influenza with other manifestations, virus not identified |
| J12  | Viral pneumonia, not elsewhere classified  
J12.0 Adenoviral pneumonia  
J12.1 Respiratory syncytial virus pneumonia  
J12.2 Parainfluenza virus 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 Pneumonia due to other bacterial pneumonia  
J15.9 Bacterial pneumonia, unspecified |
| J16  | Pneumonia in diseases classified elsewhere  
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 Hydropneumonia, unspecified  
J18.8 Other pneumonia, organism unspecified  
J18.9 Pneumonia, unspecified |
Appendix 2: Selected Subject Questionnaire

VECAP ID #

SELECTED SUBJECT QUESTIONNAIRE
(to be administered by telephone interview)

ATTACH TO DATA COLLECTION FORM

Hospital (circle)  UR number
RMH  WH

INTERVIEWER: Check discharge location on data collection form. If subject deceased, follow “next of kin” text.

Contact Log – to be completed for every call

No answer: allow at least 1 hour before re-dialling. Max 5 calls (include one after 6.00pm) – if still no answer note “no response”

Answering machine: leave message for subject to ring you. If no reply within 24 hours repeat for max 3 calls (include one after 6.00pm) – if still no reply note “no response”

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Consent: Complete this section on completion of interview

0 Questionnaire only
0 Vaccine Provider only (eg: GP, nursing home records)
0 Both Questionnaire and Vaccine Provider
0 Neither
0 Contact unsuccessful

AW / CR / JT
Who was the interview conducted with?

- Subject  → next page
- Relative
- Household member
- Staff member
- Other  → specify _______________________________

If the interview was not conducted with the subject, what was the reason?

- Deceased  Note: Follow “Next of kin” text in this group where appropriate
- Language
- Too frail
- Dementia
- Other  → specify _______________________________

Introduction

Hello, my name’s ___________ and I’m from the Royal Melbourne Hospital/Western Hospital. Can I please speak to ________________? (subject’s name).

**INTERVIEWER:**

- If subject unavailable or not convenient, make an appointment to call back later.
- If subject unavailable “long-term” (eg dementia, too frail) and a family/household or staff member is unable to represent them  → exclude from questionnaire (keep medical record data, attempt GP data collection)
- If subject deceased since discharge, explain reason for calling to next of kin, and if possible administer next of kin interview
- If the subject has moved, if possible, ask the person answering the telephone if they could provide you with a contact telephone number.
- If wrong number make a note in the contact log to this effect.

I hope you’ve received our letter in the last few days telling you about our study and that we’d be calling. We’d like to talk to you because you were recently a patient in the hospital. We’re interested in finding out about vaccinations against pneumonia in people 65 years or older.

This project has been approved by the Hospital Ethics Committee, and has the support of doctors who treat pneumonia and influenza at the hospital. Any information you provide will be strictly confidential. If you don’t wish to take part you’re under no obligation to do so.
You do not have to answer all the questions. Whether you decide to take part or not, will not affect your relationship with the Hospital or those treating you in any way.

We’d like to ask you a few questions about vaccination which will only take about 5 minutes. If it’s not convenient to talk now, we’d be very happy to call back at a better time.

1. Would you be willing to participate in our questionnaire?

☐ Yes (go to Q4)

☐ No

2. Would you allow us then to contact your local doctor or whoever usually immunises you to see if they have a record of you having flu or pneumococcal vaccine?

We will only ask for the dates of these vaccinations. Your doctor will receive our request in writing and may contact you if they want to confirm that you’ve given your permission.

☐ Yes

☐ No → thank the person for their time, terminate the interview

3. Can you tell me your doctor’s …

3a Name ________________________________

3b Suburb/Clinic ________________________________

3c Telephone no. ________________________________

thank the person for their time, terminate the interview

4. We will be asking you some questions about vaccination against flu and a particular type of pneumonia, then we’d like to contact your doctor or whoever usually immunises you to see if they have a record of having given you these vaccines.

We will only ask for the dates of these vaccinations. Your doctor will receive our request in writing and may contact you if they want to confirm that you’ve given your permission.

Would you allow us then to contact your doctor about this?

☐ Yes

☐ No (go to Q6)
5. Can you tell me your doctor’s…

5a Name _________________________
5b Suburb/Clinic _________________________
5c Telephone no. _________________________

6. I would like to start by confirming some details with you. Can you tell me your name, date of birth and postcode please: (see page 1 of Hospital Record Review, tick if confirmed otherwise note amendment below)

6a Subjects name _________________________

6b D.O.B _________________________

6c Postcode _________________________

7. You were admitted to (specify Royal Melbourne Hospital / Western Hospital) on _________ (insert admission date, page 1 of Hospital Record Review), is that correct?

☐ Yes

☐ No → when were you admitted? 7b Specify date or if not admitted _________

☐ Don’t know

8. Do you live in (read options)

☐ a private residence, for example a house or flat

☐ a lodge

☐ a hostel

☐ a retirement village

☐ a nursing home or

☐ another sort of accommodation? 8b specify _________________________
9. Do you currently smoke cigarettes or other tobacco?

☐ Yes → 9b how many years have you smoked cigarettes or other tobacco? _ 

☐ Don’t know

☐ No → 9c have you ever smoked in the past?

☐ Yes  ☐ No  ☐ Don’t know

10. Are you of Aboriginal or Torres Straight Islander descent?

☐ Yes → 10b are you ☐ Aboriginal  ☐ a Torres Strait Islander or ☐ Both

☐ No

Now, I would like to ask some questions about influenza vaccination; some people refer to it as the flu injection.

11. In the year before you were admitted to the Royal Melbourne Hospital/Western General Hospital, were you given the flu vaccination?

☐ Yes

☐ No (go to Q13)

☐ Don’t know / Can’t remember (go to Q13)

12. Who was it that gave you the flu vaccine? (Don’t read options)

12a Name   ____________________________

12b Suburb/Clinic  ____________________________

12c Telephone no.  ____________________________

☐ (if same as specified in Q5, don’t re-write just tick this box) (go to Q15)

☐ Don’t know / Can’t remember (go to Q15)

13. In the year before you were admitted to hospital, were you offered the flu vaccine?

☐ Yes (go to Q15)

☐ No

☐ Don’t know / Can’t remember
14. Would you have accepted the flu vaccine if it had been offered to you?
   - Yes
   - No
   - Don’t know / Can’t remember

I’d now like to ask you some questions about pneumococcal vaccination. This vaccine is given to provide protection against a type of pneumonia; some people call it the “pneumonia vaccine”.

15. In the year before you were admitted to the Royal Melbourne Hospital/Western General Hospital, were you given the pneumococcal vaccine?
   - Yes (go to Q20)
   - No
   - Don’t know / Can’t remember

16. In the year before you were admitted to hospital, were you offered the pneumococcal vaccine?
   - Yes (go to Q 18)
   - No
   - Don’t know / Can’t remember

17. Would you have accepted the pneumococcal vaccine if it had been offered to you?
   - Yes
   - No
   - Don’t know / Can’t remember
18. Apart from the year before your admission to hospital, have you ever received a pneumococcal vaccine?

☐ Yes

☐ No (go to Q21)

☐ Don’t know / Can’t remember (go to Q21)

19. Did you receive the pneumococcal vaccine within the last five years?

☐ Yes

☐ No (go to Q21)

☐ Don’t know / Can’t remember (go to Q21)

20. Who was it that gave you the pneumococcal vaccine?

☐ Name ___________________________

☐ Suburb/Clinic ___________________________

☐ Telephone no. ___________________________

☐ (if same as specified in Q5, don’t re-write just tick this box)

☐ (if same as specified in Q12, don’t re-write just tick this box)

☐ Don’t know / Can’t remember

21. During the year before you were admitted to hospital, how many times do you think you visited a doctor? Read out: None, 5, 10, 15, 20, or more than this?

☐ 0

☐ 1-4

☐ 5-9

☐ 10-14

☐ 15-19

☐ 20 or more

☐ Don’t know / Can’t remember
22. Had you visited a doctor during the 4 years before that?

☐ Yes

☐ No

☐ Don’t know

Thank you for your time. Do you have any questions for us?

INTERVIEWER NOTES:
Appendix 3: Subject Questionnaire - Next of kin

**SELECTED SUBJECT QUESTIONNAIRE**

*(to be administered by telephone interview to next of kin)*

<table>
<thead>
<tr>
<th>Admission Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(Note: these items are to be obtained from medical records prior to interview and checked during the interview if possible – see below)</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ID number:</th>
</tr>
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<tbody>
<tr>
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</table>

<table>
<thead>
<tr>
<th>Name of next of kin:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(to whom letter sent)</em></td>
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<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject Name:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Date of Birth:</th>
<th>≥65 years: □ Yes □ No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Sex:</th>
<th></th>
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<tbody>
<tr>
<td>□ Male</td>
<td>□ Female</td>
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</table>

<table>
<thead>
<tr>
<th>Telephone:</th>
<th>Post Code</th>
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</table>

<table>
<thead>
<tr>
<th>Hospital:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>□ RMH</td>
<td>□ Western</td>
</tr>
</tbody>
</table>

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<tr>
<th>Admission Date:</th>
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<table>
<thead>
<tr>
<th>Discharge Date:</th>
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<table>
<thead>
<tr>
<th>Deceased:</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>□ Yes</td>
<td>□ No</td>
</tr>
</tbody>
</table>

*if deceased use “next of kin” questionnaire*

---

**Contact Log**

<table>
<thead>
<tr>
<th>Date:</th>
<th>Time: (0-2400hrs)</th>
<th>Comment (Interviewer to initial):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Notes to Interviewer

Ask to speak to the person to whom the “next of kin” letter was addressed (listed above). If unavailable/not convenient, make an appointment to call back later.

Introduction

Hello, my name is ___________ and I’m from the Royal Melbourne Hospital/Western Hospital. Is this ______________? (name listed as next of kin). We’re sorry to call you at this time, but we hope you will have already received our letter in the last week or so telling you about our study and that we’d be calling. We’re calling because you are the next of kin for ____________(Subject’s name), who was recently admitted to the hospital. They were selected as part of a program at the hospital to find out about vaccinations in persons aged 65 years or older.

We would first like to let you know that the study has been approved by the Hospital Ethics Committee, and we can assure you that any information you provide will be strictly confidential. As with all research projects in the Hospital, your participation must be voluntary. If you don’t wish to take part you are under no obligation to do so. You can also choose not to answer all questions if you wish. Whether you decide to take part or not will not affect your relationship with the Hospital or those treating you in any way.

If you are willing, we would like to ask you to try and answer a few questions about ____________(Subject’s name)’s health and vaccinations if you can. It will only take about 5 minutes. If it’s not convenient to talk now, we’d be very happy to call back at a better time. We completely understand if you would rather not participate.

Would you be willing to participate?

☐ Yes ➔ note time and date: __:__ ___ / ___ / ___

☐ No ➔ thank the person for their time

Thank you. Please don’t worry if you don’t have answers to every question and just do the best you can.
1. I would like to start by confirming some details with you. Can you tell me if you know (Subject’s name)’s date of birth and postcode please: (see page 1, tick if confirmed otherwise note amendment below)

   D.O.B
   ________________________________

   Postcode
   ________________________________

2. Do you know what date (Subject’s name) was admitted to (specify if Royal Melbourne Hospital or Western Hospital)? (see admission date, page 1)

   □ Yes
   □ No, specify ______________
   □ Don’t know

3. Do you know what sort of accommodation (Subject’s name) lived in?

   □ House
   □ Retirement village
   □ Nursing home
   □ Other, specify ____________________________

4. Did (Subject’s name) smoke cigarettes or other tobacco?

   □ Yes → how many years? __________

   □ No → had they ever smoked in the past □ Yes □ No

5. Was (Subject’s name) of Aboriginal or Torres Straight Islander descent?

   □ No

   □ Yes → □ Aboriginal □ Torres Strait Islander □ Both
I would now like to ask you some questions about vaccinations that (Subject’s name) might have had.

6. In the 12 months before (Subject’s name) was admitted, do you know whether they received a flu vaccine?
   - [ ] Yes
   - [ ] No (go to Q8)
   - [ ] Don’t know (go to Q8)

7. Do you know where they received the flu vaccination?
   - [ ] at GP,
     specify GP/Clinic name ______________________(go to Q10)
   - [ ] at hospital,
     specify hospital name ______________________(go to Q10)
   - [ ] somewhere else
     specify _________________________________(go to Q10)
   - [ ] Don’t know (go to Q10)

8. Do you know whether (Subject’s name) was offered flu vaccination in the 12 months before they were admitted?
   - [ ] Yes (go to Q10)
   - [ ] No
   - [ ] Don’t know

9. Do you think (Subject’s name) would have accepted flu vaccination if it had been offered?
   - [ ] Yes
   - [ ] No
   - [ ] Don’t know
10. Do you know whether *(Subject's name)* ever received flu vaccine in previous years (apart from the 12 months prior to admission)?

☐ Yes

☐ No

☐ Don’t know

11. Do you know whether *(Subject's name)* received a pneumococcal vaccine in the 12 months prior to admission? *May prompt: “this is sometimes called pneumovax”*

☐ Yes

☐ No (go to Q13)

☐ Don’t know (go to Q13)

12. Do you know where they received the pneumococcal vaccination?

☐ at GP,

   specify GP/Clinic name ______________________ (go to Q15)

☐ at hospital,

   specify hospital name ______________________ (go to Q15)

☐ somewhere else

   specify ______________________ (go to Q15)

☐ Don’t know (go to Q15)

13. Do you know whether *(Subject's name)* was offered pneumococcal vaccination in the 12 months before he/she was admitted?

☐ Yes (go to Q15)

☐ No

☐ Don’t know
14. Do you think (Subject’s name) would have accepted pneumococcal vaccination if it had been offered?

☐ Yes
☐ No
☐ Don’t know

15. Do you know whether (Subject’s name) ever received a pneumococcal vaccine in previous years (apart from the 12 months prior to admission)?

☐ Yes, specify ______________ year if known otherwise state if < or >5yrs ago
☐ No
☐ Don’t know

16. In the 12 months before (Subject’s name) was admitted, would you be able to estimate how many times he/she visited a doctor?

☐ 0 • had he/she visited a doctor in the previous 5 yrs? Yes / No
☐ 1-3
☐ 4-7
☐ 8-12
☐ > 12
☐ Don’t know

Finally, we’d like your permission to contact (Subject’s name)’s GP/vaccine provider to see if they have a record of flu or pneumococcal vaccination. We won’t divulge any of the information that we’ve discussed in this survey. Do we have your permission to contact (patient’s) GP/vaccine provider (whomever they’ve specified)?

☐ Yes, specify

    GP name __________________ Suburb ____________

    Tel. ______________________

☐ No
If they would like to check first with you that we have your permission, do you give your permission for the doctor/vaccine provider to call you?

☐ Yes  ☐ No

Many thanks for your time. Do you have any questions for us?

INTERVIEWER NOTES:

Was this interview conducted with someone other than the subject.

☐ Conducted with subject

☐ Conducted with someone else → specify __________________________

Interview successfully completed?  ☐ Yes

☐ No

Interviewer __________________ Date _________ Time __________
# Appendix 4: Hospital Record Review

## Hospital Record Review – Data Collection Form

<table>
<thead>
<tr>
<th>1. VECAP ID #</th>
<th>2. RN (initials)</th>
<th>3. Date Record Reviewed</th>
<th>4. Admission Date</th>
<th>5. Discharge Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>___ / ___ / ___</td>
<td>___ / ___ / ___</td>
<td>___ / ___ / ___</td>
</tr>
</tbody>
</table>

6. Hospital (circle)
- RMH
- WH

6.b UR number

**Reviewer Note:**
If available, attach adhesive label from hospital record. Boxes which require information already included on the label can just be ticked, the remaining boxes should be completed.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13. Date of Birth

14. Age ≥65 years (circle)
- Yes
- No

15. Sex
- M
- F

16. ATSI Status
- Yes (ATSI)
- No
- Unknown/Not stated

16b. Language (specify if not ENG)

17. Usual Doctor Name

**Reviewer Note:**
If available, attach adhesive label with Dr details from hospital record. Boxes which require information already included on the label can just be ticked, the remaining boxes should be completed.

18a. Practice Name if available (Dr.)

18b Practice Address (Dr)

19. Suburb (Dr.)

20. Post Code (Dr.)

21. Tel. (Dr.)

22. Fax. (Dr.)

23. Discharge Location (tick):
- Other hosp
- Home
- Hostel
- Same Hospital
- Died
- Other
- Nursing home
- Unknown

24. Admitted ICU?
- Yes
- No

Include CCU & HDU under ICU

25. ICU Admission Date

26. ICU Discharge Date

___ / ___ / ___

___ / ___ / ___

___ / ___ / ___
### Details for next of kin

<table>
<thead>
<tr>
<th>27. Surname (Next of Kin)</th>
<th>28. Given Names (Next of Kin)</th>
</tr>
</thead>
</table>

29a Relationship of NOK to Subject: 
29b Address (Next of Kin)

<table>
<thead>
<tr>
<th>30. Suburb (Next of Kin)</th>
<th>31. Post Code</th>
<th>32. Tel. (Next of Kin)</th>
</tr>
</thead>
</table>

33. Patient’s usual residence
   - [ ] Private residence
   - [ ] Retirement village
   - [ ] Nursing home
   - [ ] Other, specify ______________________
   - [ ] Unknown / Not stated

34. Current smoker
   - [ ] Yes
   - [ ] No ➔ [ ] Ex [ ] Never [ ] Unknown / Not stated
   - [ ] Unknown / Not stated

35. History of alcohol abuse (includes medical record comments such as “alcoholism”, “alcohol abuse”, “EtOH abuse” or alcohol consumption described as in excess of 4 standard drinks/day for men and 2 standard drinks/day for women)
   - [ ] Yes
   - [ ] No (record indicates no Hx of alcohol abuse, eg. teetotaler)
   - [ ] Unknown / Not stated

### Chest X-ray

*NOTE: 1st abnormal CXR if more than one; to be reviewed blinded to any other radiology reports*

<table>
<thead>
<tr>
<th>37. Performed</th>
<th>38. Radiologist’s report (RNs)</th>
<th>39. Final X-ray Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes ➔</td>
<td>[ ] Consistent with pneumonia</td>
<td>[ ] Not pneumonia</td>
</tr>
<tr>
<td>[ ] No (go to 40)</td>
<td>[ ] NOT consistent with pneumonia</td>
<td>[ ] Lobar pneumonia</td>
</tr>
<tr>
<td>[ ] Unknown</td>
<td>[ ] Unsure*</td>
<td>[ ] Bronchopneumonia</td>
</tr>
<tr>
<td>[ ] No report available after 3m</td>
<td></td>
<td>[ ] Other pneumonia_______</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[ ] Unsure</td>
</tr>
</tbody>
</table>

* If unsure refer for medical review

Additional radiology notes: (eg CT scan performed and consistent with CXR)
### Microbiology/Virology Results

*ONLY COLLECT FOR PATIENTS WITH PNEUMONIA AS DETERMINED BY Q64 – WILL BE USED TO DETERMINE THE PROPORTION OF PATIENTS THOUGHT TO HAVE PNEUMONIA WHO HAVE AN ORGANISM IDENTIFIED*

*eg. infection with Legionella pneumophila. Please indicate if any of the specimens listed below were collected and, if so, complete the relevant information*

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Lab Report</th>
<th>Test (eg MC&amp;S, PCR, IF)</th>
<th>Organism/Result (eg pneumococcus, gram positive cocci, influenza, Legionella)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40. Blood</td>
<td>41. Positive</td>
<td>42.</td>
<td>43.</td>
</tr>
<tr>
<td>- Yes</td>
<td>□ No (go to 44)</td>
<td>□ Negative (go to 44)</td>
<td>□ No report (go to 44)</td>
</tr>
<tr>
<td>44. CSF</td>
<td>45. Positive</td>
<td>46.</td>
<td>47.</td>
</tr>
<tr>
<td>- Yes</td>
<td>□ No (go to 48)</td>
<td>□ Negative (go to 48)</td>
<td>□ No report (go to 48)</td>
</tr>
<tr>
<td>(cerebrospinal fluid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>□ No (go to 48)</td>
<td>□ Negative (go to 52)</td>
<td>□ No report (go to 52)</td>
</tr>
<tr>
<td>52. NPA</td>
<td>53. Positive</td>
<td>54.</td>
<td>55.</td>
</tr>
<tr>
<td>- Yes</td>
<td>□ No (go to 56)</td>
<td>□ Negative (go to 56)</td>
<td>□ No report (go to 56)</td>
</tr>
<tr>
<td>(Nasopharyngeal aspirate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>□ No (go to 60)</td>
<td>□ Negative (go to 60)</td>
<td>□ No report (go to 60)</td>
</tr>
<tr>
<td>specify __________</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>□ No (go to 64)</td>
<td>□ Negative (go to 64)</td>
<td>□ No report (go to 64)</td>
</tr>
<tr>
<td>specify __________</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>63a. Other specimen</td>
<td>63b. Positive</td>
<td>63c</td>
<td>63d</td>
</tr>
<tr>
<td>- Yes</td>
<td>□ No (go to 64)</td>
<td>□ Negative (go to 64)</td>
<td>□ No report (go to 64)</td>
</tr>
<tr>
<td>specify __________</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* If unsure refer for medical review

Reviewer notes:
## Pneumonia

(Reviewer note: Please indicate whether the patient was diagnosed with pneumonia for the current admission. If unknown or unsure refer for medical review.)

<table>
<thead>
<tr>
<th>64. Diagnosed (current admission)</th>
<th>65. Date diagnosed (at or after admission)</th>
<th>66. Onset of illness (prior to admission)</th>
<th>67. Clinical signs &amp; symptoms of illness (tick one or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes →</td>
<td></td>
<td>□ Not prior</td>
<td>Fever $\geq 37.5^\circ C$ □ Y □ N □ Not recorded</td>
</tr>
<tr>
<td>□ No* (go to 72)</td>
<td></td>
<td>□ &lt; 1 day</td>
<td>Shortness of breath □ Y □ N □ Not recorded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 1-6 days</td>
<td>Cough □ Y □ N □ Not recorded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 7-13 days</td>
<td>Sputum production □ Y □ N □ Not recorded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ &gt;14 days</td>
<td>Crackles (creps) □ Y □ N □ Not recorded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Unknown</td>
<td>Pleuritic chest pain □ Y □ N □ Not recorded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspiration-related □ Y □ N □ Not recorded</td>
</tr>
</tbody>
</table>

* If unsure refer for medical review

### Reviewer notes

### Antimicrobial Treatment

(Reviewer note: This section should be completed for all patients with pneumonia. Please list all antimicrobials prescribed – name only, not doses or dates)

*USE GENERIC NAMES – Please refer to MIMS 2000*

<table>
<thead>
<tr>
<th>Name of Antimicrobial</th>
<th>68. Pre-admission (tick)</th>
<th>69. Current admission (tick)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
### History of previous admissions to RMH/WH for any reason
(Reviewer note: Check all volumes for the last five years. Do not include current admission)

<table>
<thead>
<tr>
<th>Question</th>
<th>Ever</th>
<th>Within &lt;1 yr</th>
<th>Within 1-5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>72. Ever</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Ever</th>
<th>Within &lt;1 yr</th>
<th>Within 1-5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>73. Never</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Ever</th>
<th>Within &lt;1 yr</th>
<th>Within 1-5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>74. Never</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

### History of previous pneumonia
(Reviewer note: include history of previous pneumonia (whether hospitalised or not), if hospitalised record the number of admissions in the appropriate column. Do not include current admission)

<table>
<thead>
<tr>
<th>Question</th>
<th>Ever</th>
<th>Within &lt;1 yr</th>
<th>Within 1-5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>75. Ever</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Ever</th>
<th>Within &lt;1 yr</th>
<th>Within 1-5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>76. Never</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Ever</th>
<th>Within &lt;1 yr</th>
<th>Within 1-5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>77. Never</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

### Other existing or pre-existing conditions
(Reviewer note: Based on the available medical history, please specify if the patient has or had any of the following conditions. Please specify the condition/s in the appropriate space)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ever</th>
<th>Evidence of Aspiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other respiratory disease (bronchitis, asthma, emphysema, other chronic obstructive airways disease (COAD))</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ever</th>
<th>Cerebrovascular disease (stroke, TIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (non-insulin dependent (NIDDM) or insulin dependent (IDDM))</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ever</th>
<th>Immunosuppression (AIDS, any cancer (excluding basal cell carcinoma and squamous cell carcinoma), chronic steroid Re, HIV infection before development of AIDS, organ transplantation, dysgammaglobulinaemia, sickle cell disease, asplenia (functional or anatomical), nephrotic syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease (eg. angina, myocardial infarction, coronary artery bypass grafting (CABG))</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ever</th>
<th>Liver disease (chronic infection (hepatitis), cirrhosis, liver failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

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Other existing or pre-existing conditions
(Reviewer note: Based on the available medical history, please specify if the patient has or had any of the following conditions. Please specify the condition/s in the appropriate space)

<table>
<thead>
<tr>
<th>Condition</th>
<th>99. Ever</th>
<th>102. Ever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease (particularly renal failure requiring dialysis. Note renal transplant included under immunosuppression)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rheumatological disease (rheumatoid arthritis, osteoarthritis, systemic lupus erythematosi (SLE), multiple connective tissue disease)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Reviewer notes

Vaccination History
(prior to admission)

Influenza vaccination within 12 months (prior to admission date)

<table>
<thead>
<tr>
<th>105. Record of Vaccine given</th>
<th>106. Date given</th>
<th>107. Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>____ / ____ / ____</td>
<td>GP</td>
</tr>
<tr>
<td>No (go to 108)</td>
<td>Date not recorded</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

Pneumococcal vaccination within 5 years (prior to admission date)

<table>
<thead>
<tr>
<th>108. Record of Vaccine given</th>
<th>109. Date given</th>
<th>110. Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>____ / ____ / ____</td>
<td>GP</td>
</tr>
<tr>
<td>No (go to 111)</td>
<td>Date not recorded</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

Vaccinations given during the current admission

<table>
<thead>
<tr>
<th>111. Influenza vaccine given</th>
<th>112. Pneumococcal vaccine given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>specify date ____ / ____ / ____</td>
</tr>
<tr>
<td>No</td>
<td>specify date ____ / ____ / ____</td>
</tr>
</tbody>
</table>

END NOTES:
Appendix 5: General Practitioner Questionnaire

Dr <Initial> <Surname>
<Address>
Victoria, <Postcode>
Facsimile <Fax Number>

Re: <Patients First Name> <Patient Surname> (Date of birth: <Patient's D.O.B>), admitted to <Royal Melbourne/Western Hospital> on <admission date>.

Dear Dr <Surname>

The next of kin of the above named patient has been interviewed as part of a research study aimed at evaluating the impact of influenza and pneumococcal vaccination among older Victorians. The study has been approved by the Clinical Research and Ethics Committee of the Royal Melbourne Hospital Research Foundation/North Western Health Care Network. As part of the study we are seeking confirmation of vaccination status for influenza and pneumococcal vaccine through the patient’s nominated general practitioner or vaccine provider (even if the patient said they were not vaccinated). The patient or their next of kin is aware that we are seeking this information and has granted consent for us to contact you. If you wish to confirm that this consent has been provided, they have also given their permission for you to contact them on (Ph): <subject’s or next of kin’s phone number>.

Please could you (or your practice manager) provide the following information:

1. In the 12 months prior to <admission date>, do your records indicate that the patient received influenza vaccination? | 
   □ Yes → please specify date given _________________
   □ No

2. In the 5 years prior to <admission date>, do your records indicate that the patient received pneumococcal vaccination? 
   □ Yes → please specify date given _________________
   □ No

Thank you for your co-operation.

Yours sincerely, pr

Dr Sue Skull
Principal Investigator
Victorian Infectious Diseases Service
Royal Melbourne Hospital
Phone: 9342 8897

PLEASE COULD YOU FAX OR MAIL THIS FORM BACK TO:
ATTENTION Anne-Marie Woods or Caroline Watts (Phone: 9342 8772)
FAX NUMBER (03) 9342 7060
Clinical Epidemiology and Health Services Evaluation Unit
Royal Melbourne Hospital
Grattan St, Parkville, 3052
Effectiveness of influenza and pneumococcal vaccination against hospitalisation for community-acquired pneumonia among persons >=65 years

2007


Unpublished

http://hdl.handle.net/11343/39333

Effectiveness of influenza and pneumococcal vaccination against hospitalisation for community-acquired pneumonia among persons >=65 years

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