

**The association between influenza vaccination  
and hospitalization rates of respiratory and  
cardiovascular conditions among elderly  
members of a private medical scheme  
during the winter season  
of 2004 in South Africa**

**by**

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## ***DECLARATION***

I hereby declare that the work which I hereby submit as partial fulfilment for the Master of Science in Clinical Epidemiology degree, on which this thesis is based, is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been submitted, or is being submitted, for another degree at this or any other university.

## ***ABSTRACT***

**Objective:** The objective of this nested case-control study was to investigate the association between influenza vaccination and hospitalisation rates for acute respiratory illness or cardiovascular disease and death from any cause among elderly population of a medical scheme in South Africa during the winter season of 2004. The study also reported on further sub-groups with different risk profiles within this elderly population.

**Method:** All data were obtained from a computerised database containing information on a cohort of 45 700 elderly members. Cases were identified from hospital records and membership data between May and July 2004, and for each case four controls were chosen randomly from the cohort. Data on baseline characteristics were compared between cases and controls. Variables that may be potential confounders were identified and multivariate conditional logistic regression analysis was carried out to establish the vaccine effectiveness independent of confounding factors for the combined endpoints as well as for each endpoint separately. Analysis was done to confirm potential effect modification. Patients were classified as high-risk or low-risk according to their chronic illness profiles. Sub-group analysis was performed to determine the vaccine effectiveness in specific sub-groups of elderly patients.

**Results:** In total 1 282 (2.81%) elderly had an outcome; 627 died from any cause, and 428 and 227 were hospitalised for cardiovascular conditions and respiratory conditions respectively. Analysis showed a 19.3% (95% CI, 3.1 to 32.9) reduction in the incidence of combined outcomes in the vaccinated group. All-cause mortality was reduced

significantly by 23.6% (95%CI, 1.0 to 41.0) but there was no statistically significant reduction in either respiratory or cardiovascular hospitalisations. With statistical analysis, presence of chronic respiratory disease was identified as a potential effect modifier. Sub-group analysis was performed and after adjusting for confounding, vaccine effectiveness was determined as 56,3% (95% CI, 19.2 to 76.3) for all-cause mortality, 24.7% (95% CI, -37.7 to 58.8) for respiratory hospitalisation, and 44.4% (95% CI, -7.5 to 71.2) for cardiovascular hospitalisation in the sub-group of patients with chronic respiratory disease. After adjusting for confounding, vaccination was associated with a statistically significant reduction in all outcomes of 19.9% (95% CI, 2.2 to 34.4) in the high-risk sub-group of elderly, while in the low-risk sub-group of elderly there was a non-significant increase of 48.4% (95% CI, -289.7 to 43.4 ) in the outcomes.

**Conclusion:** In this population of elderly influenza vaccination was associated with a statistically significant reduction in the combined outcomes. Estimates of effectiveness differ substantially between different sub-groups of high- and low-risk patients implying a possible greater benefit from vaccination in the high-risk elderly population.

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## **CHAPTER 1**

### ***Background***

Influenza is a largely preventable communicable viral illness that affects the respiratory system, causing acute bouts of myalgia, cough and headaches [1]. It is considered a seasonal epidemic disease because of the high level of infection and transmission that occurs in colder months in temperate climates and throughout the year in tropical and sub-tropical climates with seasonal spikes of increased occurrence [2]. Treatment of influenza and its complications consume considerable resources that could otherwise be used for other essential healthcare needs.

Influenza vaccination is one way of preventing or decreasing this viral infection and its complications. As complications related to influenza occur more often in certain sub-groups, there are worldwide surveillance and recommendations as to which sub-groups are at higher risk and should thus receive preference in situations where there may be limited resources, such as poor availability of vaccine.

The elderly population is one of the sub-groups in which influenza vaccination is recommended worldwide [3]. For this purpose, inactivated influenza virus vaccines have been available for more than 50 years. As the elderly are also at a higher risk for serious complications of influenza such as secondary bacterial pneumonia and exacerbations of underlying chronic medical conditions that may result in hospitalisation or death, many studies have been undertaken to ascertain the efficacy, effectiveness and cost-effectiveness of the influenza vaccines in this population. Most of the studies have been undertaken in the northern

hemisphere (Europe and USA) but very few in the southern hemisphere (South America, Southern Africa, Australia and New Zealand). The winter season, when the level of transmission of influenza is the highest, is at a different time of the year from the northern hemisphere and the occurring virus strains can also be different from those that occurred in the northern hemisphere during the previous winter season. The question may thus be asked whether studies done on influenza vaccination effectiveness in the northern hemisphere can be generalised for countries in the south.

This viral infectious disease also has the ability to cause a pandemic, as was experienced at least three times during the last century. The World Health Organization (WHO) has been monitoring the possibility of a new pandemic of human influenza since 1968, when the last pandemic began. Following reports that a new highly pathogenic strain of avian influenza was spreading across Asia in 2004, the WHO drew up an action plan in order, first, to reduce the opportunities for this new virus to improve its pandemic potential and, second, to be prepared for a pandemic, should these efforts fail [4]. One of the concerns that may arise in the early stages of an influenza pandemic is the demand for vaccines and the decisions that will have to follow about who should receive vaccination. Many factors will be considered when prioritising sub-groups for influenza vaccination in a pandemic outbreak and some of these factors would certainly be the level of risk that the sub-group may have of contracting the disease, and the risk of serious complications and possible death resulting from the infection.

## **The aim of the study**

This study investigates the association between influenza vaccination and hospitalisation rates for acute respiratory illness or cardiovascular disease and death from any cause among elderly population of Medihelp Medical Scheme members. The study also reports on further sub-groups with different risk profiles within this elderly population.

## ***Literature Review***

### **Influenza: Biology**

There are two types of influenza viruses that cause epidemic human disease, namely influenza A and influenza B. Influenza A viruses are further categorised into subtypes on the basis of two surface antigens: hemagglutinin and neuraminidase. Influenza B viruses are not categorised into subtypes [3].

Influenza A (H1N1), influenza A (H3N2) and influenza B viruses have circulated globally since 1977. In 2001, influenza A (H1N2) viruses that probably emerged after genetic re-assortment between human A (H1N1) and A (H3N2) viruses began circulating widely [3].

Immunity to the surface antigens, particularly the hemagglutinin, reduces the likelihood and severity of disease. However, antibodies against one influenza virus type or subtype confer limited or no protection against another type or subtype of influenza [3].

Antigenic drift involves minor antigenic changes in the HA and NA that occur by accumulation of point mutations, resulting in amino acid

substitutions in antigenic sites [5]. Antigenic shifts result from genetic re-assortment within cells dually infected by human and animal influenza viruses [5]. Influenza A viruses undergo antigenic drift more rapidly than do influenza B viruses [3].

Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual incorporation of one or more new strains in each year's influenza vaccine. More dramatic antigenic changes, or shifts, occur less frequently and can result in the emergence of a novel influenza virus with the potential to cause a pandemic. Antibodies to one antigenic variant of influenza virus might not completely protect against a new antigenic variant of the same type or subtype [3].

The H5N1 strain of avian influenza, a highly pathogenic strain, infecting both birds and people has raised substantial concerns worldwide about its potential to undergo genetic changes, develop the capacity for sustained human-to-human transmission and to cause a pandemic influenza outbreak [5].

## **Influenza: Clinical signs and symptoms**

Influenza viruses are spread from person to person, primarily through respiratory droplet transmission. The typical incubation period for influenza is one to four days, and adults can be infectious from the day before symptoms begin through approximately five days after illness onset [3].

Uncomplicated influenza A syndrome is characterised by the abrupt onset of general and respiratory signs and symptoms such as fever, myalgias, headache, malaise, dry cough and chills [5]. It typically

resolves after three to seven days for the majority of people. After the fever and upper respiratory tract symptoms resolve, cough and weakness can persist for another one to two additional weeks [5].

Among certain people, influenza can exacerbate underlying medical conditions such as pulmonary or cardiac disease, lead to secondary bacterial pneumonia or primary influenza viral pneumonia, or occur as part of a co-infection with other viral or bacterial pathogens. Respiratory illnesses caused by influenza viruses are difficult to distinguish from illnesses caused by other respiratory pathogens on the basis of signs and symptoms alone [3].

## **Hospitalisations and deaths from influenza**

Risk factors for severe post-influenza complications include immune-related factors, such as ageing or the presence of respiratory tract disease, immune suppression, proneness to exacerbation of concomitant high-risk disease, residence in closed communities with a high transmission rate and potential adverse effects with long-term drug use [6].

The risks for complications, hospitalisations, and deaths from influenza are higher among people over the age of 65, young children, and people of any age with certain underlying health conditions than among healthy older children and younger adults [3].

Influenza-related deaths can result from pneumonia and from exacerbations of cardiopulmonary conditions and other chronic diseases. In addition, influenza seasons in which influenza A (H3N2) viruses predominate are associated with higher mortality [3].

## **Influenza Surveillance**

The WHO Global Influenza Surveillance Network was established in 1952 and comprises four WHO Collaborating Centers (WHO CCs) and 116 National Influenza Centers (NICs) in 87 countries. These NICs collect specimens in their own country and perform primary virus isolation and preliminary antigenic characterisation. These specimens are then shipped to WHO CCs for high-level antigenic and genetic analysis. The result of these analysis forms the basis for WHO recommendations on the composition of influenza vaccine for the northern and southern hemispheres each year [3].

The WHO Influenza Surveillance Network serves also as a global alert mechanism for the emergence of influenza viruses with pandemic potential [3].

Two of the National Influenza Centres are based in South Africa. They are respectively headed by Dr Terry Besselaar in Sandringham and Dr Girish Kotwal in Cape Town. In South Africa, influenza activity is monitored on an ongoing basis to provide public health authorities and healthcare practitioners with information as to when an epidemic has commenced as well as the extent and effect of the epidemic on the population [7].

## **Pandemic influenza**

Three worldwide (pandemic) outbreaks of influenza occurred in the 20th century: in 1918, 1957, and 1968. They are now known to represent three different antigenic subtypes of influenza A virus: H1N1, H2N2, and H3N2, respectively. Major influenza epidemics show no predictable periodicity or pattern, and all differ from one another. Evidence suggests

that true pandemics with changes in hemagglutinin subtypes arise from genetic re-assortment with animal influenza A viruses [5].

## **Influenza vaccination**

The primary method for preventing influenza is vaccination, which should aim at reducing the burden of post-influenza complications among persons who need it most. At all ages, vaccination is associated with less influenza-related respiratory illness and fewer physician visits. It is also associated with fewer hospitalisations and lower mortality rates in high-risk groups, less otitis media among children, and less work absenteeism among adults [3].

The rate of distribution of vaccine in South Africa in 1995 was estimated to be 12.5 per 1000 population. At this time the rate was low compared to the approximately 145 per 1000 in the USA and Canada [8]. It appears that there are no published data on the rate of distribution of vaccine among the elderly population of South Africa.

## **Vaccination recommendations in 2004**

The virus strains recommended by the WHO for the influenza vaccine formulation for the southern hemisphere's 2004 influenza season were the influenza A H3N2 A/Fujian/411/02-like viruses, the H1N1 A/New Caledonia/20/99-like viruses and B/Hong Kong/330/01-like viruses. The most commonly used H3N2 vaccine strain during the 2004 season was A/Wyoming/3/02, an a/Fujian/411/02-like virus, while the B viruses included either the B/Shangdong/7/97 or B/Brisbane/32/02 strains [9].

## Influenza activity in South Africa in 2004

Influenza activity was sporadic during the South African 2004 winter season. According to surveillance data, the influenza virus was isolated from 38 patients attending Viral Watch Centres and private pathologists between May to August of that year. Also, the school absenteeism programme, monitoring approximately 8 000 children at primary and high schools, rose to above the mean (calculated over a five year period), on weeks 26 and 29. However, these were the weeks that winter school holidays started and ended in government schools [9].

The vast majority of the South African viruses isolated in 2004 were influenza A viruses (97,3%) with only one influenza B virus identified. Antigenic sub-typing of the Johannesburg influenza A virus isolates by the haemagglutination inhibition (HI) assay revealed that 33 were subtype H3N2 while the remaining four could not be sub-typed. Some of the H3N2 viruses reacted well with the A/Fujian/411/02-like reference antisera in the WHO HI Kit while others reacted at lower titres. Subsequent data obtained from a number of South African H3N2 strains and sent to the WHO Collaborating Centres (WHO CCs) for Influenza Reference and Research in Melbourne and London for further serological characterisation by HI showed that the strains were antigenically similar to the more recent A/Christchurch/28/03 and the A/Wellington/1/04 reference strains [9].

Results of the phylogenetic analysis of representative South African influenza A H3N2 HA1 sequences showed that the 2004 isolates exhibited genetic drift from the A/Fujian/411/02 and A/Wyoming/3/02 strains and the majority were grouped with the more recent A/Wellington/1/2004 reference strain [9].

Amino acid analysis of the HA1 subunit of the Johannesburg influenza A H3N2 viruses with the A/Fujian/411/02 strain sequence revealed that the isolates shared three common amino acid changes at positions 159 (tyrosine to phenylalanine), 189 (serine to asparagine) and 227 (serine to proline). The former two positions map to the influenza antigenic site B and the latter to the receptor binding site of the HA. These mutations were also seen in many 2004 isolates from other areas of the world (WHO data). Other substitutions were observed in some of the South African isolates at position 188 (aspartic acid to tyrosine) in antigenic site B and 199 (serine to proline). Several H3N2 isolates had the same amino acid changes at 145 (lysine to asparagines) and 226 (valine to isoleucine) that were seen in some of the viruses isolated from New Zealand, Australia and Asia isolated later in the 2004 season (WHO data, Melbourne). One of these isolates (A/Johannesburg/31/04) was recovered from a patient who returned ill from a trip to Australia and Singapore [9].

The 2004 B/Johannesburg/22/04 isolate reacted with the B/Hong Kong/330/01-like reference antiserum in the HI test and was confirmed to be antigenically similar to the B/Shandong/7/97 and B/Brisbane/32/02 strains by the WHO CCs. The molecular characterisation of the Johannesburg influenza B isolate showed that it was closely related to a 2004 strain from Israel and was typical of other recent viruses of the B/Victoria/2/87 lineage. This is unlike the situation that prevailed the previous year in South Africa, where all the B strains had evolved from the B/Yamagata/16/88 lineage [9].

Based on the antigenic drift noted in the influenza A H3N2 strains observed in South Africa and other areas in the world during March to October 2004, the H3N2 vaccine component was updated to an A/Wellington/1/2004(H3N2)-like virus for the 2005 southern hemisphere vaccine. The recommended influenza B strain was a

B/Shanghai/361/2002-like virus where the actual vaccine viruses included the B/Shanghai/361/2002, B/Jilin/20/2003 and B/Jiangsu/10/2003 strains. The recommended H1N1 strain remained unchanged [9].

## **Efficacy, effectiveness and cost-effectiveness of the influenza vaccine**

Epidemiological studies on the impact of vaccines distinguish two measures of impact, i.e. efficacy and effectiveness. Vaccine efficacy is usually calculated from pre-marketing randomised, double-blind, placebo-controlled clinical trials and uses as clinical endpoints the post-vaccination protective antibody titres as a measure of indirect protection or influenza infection rates as a measure of direct protection [10]. The naturally occurring influenza virus strain often varies from year to year and, although the vaccine strain frequently matches the epidemic strain, sometimes it does not. Vaccine efficacy is thus expected to vary according to the match between the epidemic and vaccine strains.

Vaccine effectiveness is defined as the overall protective clinical effect on reducing post-influenza complications in routine medical practice. During a season with low influenza activity and high incidence of other respiratory viruses, the vaccine effectiveness would be small, even if the vaccine efficacy approaches 100%. As influenza cannot be distinguished on clinical grounds from other causes of respiratory illness, the effects of vaccine prophylaxis are 'diluted' in vaccine effectiveness estimates where clinical outcomes without virological confirmation are regarded [11].

Post-marketing observational studies such as cohort and case-control studies incorporating clinical endpoints relevant to the individual patient can be used to estimate vaccine effectiveness, providing that there is sufficient control for ‘confounding by indication’ in these studies [10].

According to Nichol (1999), influenza vaccine is underused worldwide and one barrier to optimal use is the uncertainty about its benefits. In particular, this uncertainty may contribute to lower rates of use among healthy elderly persons than among those with high-risk medical conditions [12].

A few small-scale studies on the clinical benefits of influenza vaccination among working-age patients with COPD have failed to demonstrate any effectiveness from annual vaccination [13]. In studies among young asthmatic children influenza vaccination has been shown to reduce otitis media, acute respiratory disease and the number of febrile influenza episodes and reduce hospitalisation rates [10].

In a summary of 20 cohort studies carried out by Gross et al. among the elderly in 1995, the pooled estimates of vaccine effectiveness were 56% (95% CI, 39 to 68%) for preventing respiratory illness, 50% (95% CI, 28 to -76%) for preventing hospitalisation, and 68% (95% CI, 56 to 76%) for preventing death [14].

Subsequent studies among the elderly measured the vaccine’s effectiveness in reducing serious complications, such as a need for hospitalisation for influenza or pneumonia, or death, with estimates varying from 30 to 60% [10]. In addition, acceptable cost effectiveness of immunising elderly persons aged 65 years or over against influenza has been indicated by several studies in countries with different healthcare systems [10].

In a randomised controlled trial carried out in the United Kingdom in 1999 to determine the cost effectiveness of influenza vaccination for healthy people between 65 and 74 years of age, the outcomes suggested that influenza vaccination in this population would not be cost effective. The results of this study demonstrated no significant difference between the groups for the primary outcomes of frequency of influenza diagnosis [15].

In 1997 a benefit:cost evaluation of influenza vaccination in South Africa was published, focusing primarily on direct medical cost. The study provided an attempt at estimating the economic burden of influenza [8]. In this study analysis of the data showed that the benefit:cost ratio was 1.6:1 (assuming a vaccine efficacy of 80%). The researchers concluded that more widespread influenza vaccination is likely to be an extremely cost-beneficial option and recommended increased efforts be made to increase vaccine uptake among elderly and high- risk groups [8].

Other studies have assessed the economic benefits of vaccination in the elderly and these studies suggest that it is highly cost effective and, in many cases, cost saving in this population [16].

## **Study design influences**

### **Case definition and outcomes**

Nichol and Mendelman (2004) examined the influence of clinical case definitions with differing levels of sensitivity and specificity on estimates of the relative and absolute health benefits of influenza vaccination.

According to the authors, there is currently no gold standard for a clinical case definition of influenza-like illness, and studies have reported widely varying degrees of sensitivity, specificity and predictive value for differing case definitions. By using different outcome periods and case definitions, the authors concluded that the case definitions can have a profound effect on estimates of the relative and absolute health and economic consequences of vaccination. Failing to match the best clinical case definition and outcome period to the appropriate question could result in dramatic underestimates of the benefits of influenza vaccination [17].

### **Bias and confounding**

**Selection bias** is a systematic error that may occur in studies where subjects are selected by using a procedure or by factors that may influence the participation in a study [18]. This type of bias comes about when the association between exposure and disease differs between those who participate and those who do not participate in the study. However, the use of the nested case-control design reduces to a large extent selection bias due to the inappropriate selection of cases.

The misclassification of subjects can lead to information bias if the information collected from study subjects is erroneous [18]. When using a categorical scale, a person may be placed in the incorrect category or misclassified as a result of this error.

As there is no random allocation of vaccination in non-experimental studies, there may be confounding due to patient factors that are also related to clinical endpoints as patients with poor prognoses may be more likely to be vaccinated. This is called “confounding by indication”

and may lead to invalid estimates of vaccine effectiveness if not sufficiently controlled for. Hak et al. (2002) discuss different ways to prevent or limit confounding by indication in cohort and case-control studies in the design and data analytical phases [19].

### **Study design choice**

In the absence of randomised controlled trials (RCTs) with clinical endpoints relevant to the individual patient, to evaluate the effectiveness and safety of the influenza vaccines post-marketing non-experimental studies have been applied [20]. Prospective and retrospective cohort studies have been used as well as case-control and nested case-control designs. Of these, the prospective cohort study has consistently been regarded as the strongest design [20]. Case-control studies are usually more economical, especially when medical records have to be reviewed to retrieve valid information on large numbers of people. By using a case-control study design, one can assess the effectiveness of influenza vaccination on endpoints such as hospitalisations for conditions associated with influenza and all-cause mortality. There are advantages of case-control studies over RCTs, including lower costs, enhanced timelines, larger power, and improved generalisability [20].

In a nested case-control study (or case-control in a cohort study), cases of a disease that occur in a defined cohort are identified and for each case a specified number of matched controls is selected from among those in the cohort who have not developed the disease by the time of the disease occurrence in the case [21]. The number of controls selected per case may vary but four or five controls per case is commonly used. In addition, the controls should be matched on time. A cohort member who at one stage served as a control may at a later

point in time become a case and a cohort member may be selected as a control for more than one case [21].

Nested case-control studies can be conducted on large medical databases where the study is nested in full cohorts. By comparing the estimates of associations between a cohort and nested case-control study design, Hak et al. (2004) concluded that nested case-control studies provide a cost-effective alternative to full-cohort analyses. When the case-control ratio was 1:4, the adjusted estimates were virtually the same, using both designs [20].

### **Propensity score method**

Observational studies assessing the effect of a particular treatment or exposure may be subject to bias, which can be difficult to eliminate using standard analytic techniques. When there are large differences in important prognostic characteristics between the treatment groups, adjusting for these differences with conventional multivariable techniques may not adequately balance the groups, and the remaining bias may limit valid causal inference.

Use of a propensity score, described as a conditional probability that a subject will be treated based on an observed group of covariates, may better adjust covariates between the groups and reduce bias. These propensity scores are used to create matched pairs, sets or strata that balance many observed covariates [23].

Propensity score methods, however, also have limitations. One of these limitations is that despite broad utility when addressing causal questions

from nonrandomised studies, propensity score can only adjust for observed confounding covariates and not for unobserved ones [23].

A study to determine the comparison of logistic regression with propensity score found that propensity score estimates were less biased than logistic regression estimates when there were six or fewer events per confounder and were adequate up to seven or fewer effects per confounder but decreased substantially afterwards. According to the researchers, logistic regression is the technique of choice when there are at least eight events per confounder. In such circumstances, analyses using logistic regression are precise and less biased than the propensity score estimates [24].

### ***Motivation and aim of the study***

Influenza vaccination rates are high in European countries and the United States and are usually >50% in the elderly population. Vaccination rates amongst the elderly population in South Africa have not been previously reported. This study could give an indication of the vaccination rate in an insured population of elderly people (a high-risk population) in South Africa.

Although randomised controlled trials (RCTs) are the preferred method for studying clinical effects of the influenza vaccine, they are expensive to carry out and there might be ethical concerns about carrying out a placebo controlled trial, especially in a high-risk population. Such a study would also have to be conducted across several influenza seasons because of the differences in virulence of the circulating viral types. This study could provide an indication whether a nested case-control study would be an acceptable alternative method to determine

the association between influenza vaccination and influenza related illnesses or all cause mortality.

Hospitalisation costs are high. Knowing whether influenza vaccination could decrease the rate of hospitalisation may lead to higher awareness among service providers, health care funders and patients and an increased rate of influenza vaccination of members of this population, whether they are insured or not.

Stratification and sub-group analysis may shed light on particular groups of patients that may benefit more from others from influenza vaccination. These sub-groups will need to be targeted in order that better use can be made of the limited resources available in South Africa. This data may also be helpful should the need arise to prioritise sub-groups for influenza vaccination in an epidemic outbreak.

## **CHAPTER 2**

### **Methods**

#### **Setting**

The study was performed on a private medical scheme population in South Africa consisting of a cohort of 28% (45700) elderly (older than 65) members, at the time of the study (Jan 2003 – Aug. 2004). This medical scheme covers institutionalised individuals (i.e., those who live in nursing homes), as well as community-dwelling individuals.

#### **Study design**

A nested case-control study using a medical scheme's claims data was chosen as the design for this study.

#### **Sample size**

The cohort consisted of all members of Medihelp Medical Scheme older than 65 who were active members of the scheme at least for the period 1 January 2003 to 30 Aug 2004. The number of cases that would give a statistical power of more than 80% to detect an odds ratio of 0.65 (i.e. a reduction of 35% in hospitalisations) if the case:control ratio were 1:4 at a 95% level of confidence was calculated with Win Episcope 2.0 to be 393 if the estimated exposure rate of controls were 20%.

## **Exclusion criteria**

All members without benefits (medication limit exceeded) for influenza vaccination during February to May of either 2003 or 2004 were excluded from the study.

## **Patient selection and sampling frame**

### **Identification of cases**

Subjects in the cohort qualified as cases if they were hospitalised for an acute respiratory condition (influenza or pneumonia) or cardiovascular condition during the period May to July 2004 as confirmed by hospital claims data or if they died during or within two weeks after the influenza season from any cause. The ICD-10 codes were used to define a hospital claim for a respiratory condition (influenza or pneumonia) or a cardiovascular condition. Patients who were hospitalised once for a respiratory condition or cardiovascular condition were not eligible to become a case again if they were hospitalised for a second time. The membership database was used to identify patients who died during the influenza season. Hospitalisations where pre-authorisation for the admission was done more than one day before the admission of the patient were not classified as cases as they were more likely to be elective procedures rather than emergency hospitalisations.

## **Coding of hospitalisation cases**

South Africa utilises the International Classification of Diseases, tenth revision (ICD-10) coding system, published by the WHO.

A cross-map developed for the South African market was used to crosslink the codes of the ninth revision (ICD-9 codes) used in previous similar studies to the relevant ICD-10 codes used in this study. This cross-map enabled comparison of results of this study with previously published studies. The details of the ICD-9 codes and descriptions used in previous studies and the ICD-10 codes and descriptions used for this study are listed in Annexure A.

## **Identification of controls**

For each case, four controls were chosen randomly from the cohort, making use of the incidence density sampling technique. The case data was converted to survival data and four controls for each case, matching on the date on which the case was identified, was selected from the cohort with Stata 9.2 software [25]. Some patients thus acted more than once as controls and some cases were chosen as controls earlier in the timeframe of the study before they became cases.

## **Measurement of covariates**

The following data was retrieved from the membership, medicine pre-authorisation and medicine and hospitalisation claims databases for each of the cases and controls:

## **Demographic covariates**

- Age (measured on the 1<sup>st</sup> of January 2004 in years)
- Gender (male or female)

## **Covariates for healthcare consumption**

- The number of times the patient was hospitalised during January 2003 to December 2003 (N)
- The number of doctor consultations during January 2003 to December 2003 (N)

## **Covariates indicating co-morbid conditions**

These covariate data were determined from chronic medication authorisations and are non-mutually exclusive (0 = condition not registered; 1 = condition registered):

1. Respiratory conditions - ICD-10 codes: J00 – J99
2. Hypertension and heart disease – ICD-10 codes: I00 – I509
3. Diabetes – ICD-10 codes: E10.0 –E14.9
4. Rheumatologic conditions - ICD-10 codes = M05.x, M06.x, M07.x, M08.x, M09.x, M30.x, M31.x, M32.x, M33.x, M34.x, M35.x and M36.x, (where x=0-9)
5. Stroke and dementia - ICD-10 codes = F03, I63.9, I64
6. Other chronic diseases - determined from pre-authorisation data after all the previously mentioned chronic conditions has been subtracted from pre-authorisation data of chronic medication.

## Covariates for medication utilisation

Data for these covariates were determined from medication claims history (0=No, 1=Yes):

- Use of certain medications that may alter the immune status of the patient at least once during the period of January 2003 to April 2004, i.e.
  - Immunoglobulin,
  - Coldvac Berna (oral medication containing Haemophilus influenza, Pneumococci, Streptococci and Staphylococci organisms) or Relenza (antiviral medication containing zanamivir)
- The following covariates were measured as positive if a patient utilised the medication at least three times during the period January 2003 to April 2004 (0=No; 1=Yes):
  - Statin therapy
  - Therapy for hypertension or heart disease
  - Alzheimer's therapy
  - Therapy for respiratory conditions
  - Central analeptic therapy
  - Cytostatic therapy
  - Antidepressant therapy
  - Anti-psychotic therapy
  - Antiparkinson's therapy
  - Nasal corticosteroid therapy
  - Insulin therapy
  - Oral antidiabetic therapy
  - Cox1&2 inhibitor therapy

### **Covariates related to the severity of disease**

Data for these covariates were determined from medication claims history during the period of January 2003 to April 2004:

- Number of therapeutic classes of medication claimed for hypertension or heart disease (N)
- Number of therapeutic classes of medication claimed for respiratory illness (N)

### **Covariates indicating vaccination status**

Data for this covariates were determined from medication claims history (1=vaccinated; 0=unvaccinated):

- Pneumococcal vaccination status in 2003
- Pneumococcal vaccination status of other family members in 2003
- Influenza vaccination status in 2003
- Influenza vaccination status of other family members in 2003
- Influenza vaccination status of other family members in 2004

### **Covariates combined**

To avoid correlation between covariates, the chronic authorisation and claims data related to the following conditions were combined (0=No; 1=Yes):

- Hypertension or heart disease
- Chronic respiratory disease
- Diabetes Mellitus (insulin- and non-insulin-dependent diabetes)

## Measurement of exposure

Influenza vaccination status during February to April 2004.

(1=vaccinated; 0=unvaccinated)

### Influenza vaccination available in South Africa in 2004

Medication claims were extracted for the following products containing inactivated subunit influenza virus strains as recommended by the WHO.

**Table 1. Product list for influenza vaccines in 2004**

| PRODUCT CODE | INFLUENZA VACCINE BRAND NAME |
|--------------|------------------------------|
| 818623       | Fluvirin                     |
| 732842       | Influvac 5ml                 |
| 732826       | Influvac subunit             |
| 838853       | Mutagrip                     |
| 812307       | Agrippal S-1                 |
| 813338       | Vaxigrip                     |
| 825670       | Vaxigrip                     |
| 813346       | Vaxigrip                     |
| 836591       | Vaxigrip                     |
| 813265       | X-Flu M/Dose 5ml             |
| 702733       | X-Flu Prefilled              |
| 813257       | X-Flu Single Dose            |

## Data analysis

Stata 9.2 software was used to perform the data analysis [25]. The controls were compared in terms of exposure status, and the variables where a significant difference was shown were eligible to be used in the models as potential confounders if they also differed significantly between cases and controls.

Baseline characteristics for cases and controls were compared using chi-square and Student's t-test for categorical and continuous variables. Explanatory models were used to determine the influence of the different variables on the odds ratios estimating influenza vaccine effectiveness.

Multivariate conditional logistic regression analysis was used to assess the vaccine effectiveness independent of confounding factors for the combined endpoint.

The following different endpoints in the study were also analysed separately i.e.:

- a. hospitalisation for a respiratory (influenza and pneumonia) illness;
- b. hospitalisation for a cardiovascular condition;
- c. all cause mortality; and
- d. hospitalisation for either respiratory (influenza and pneumonia) illness or a cardiovascular condition.

For these analyses, all the controls selected initially were used each time to increase the power of the analysis. The odds ratios were determined for the different types of outcomes using unconditional logistic regression analysis.

Effect modification was tested by creating multiplicative interaction terms and entering them into the model. An *a priori* decision was made to test for effect modification by age categories, hypertension/heart disease, diabetes and respiratory conditions. Stratified analysis was used to determine odds ratios where effect modification was shown.

In addition, the patients were categorised into high-risk patients and low-risk patients in accordance with how categorisation was done by previous researchers, and the sub-group analysis was performed by running the model while excluding the particular relevant underlying medical conditions used to classify the patients in subgroups in order to determine the effect estimates. Patients with hypertension or heart disease, a chronic respiratory condition, diabetes, rheumatologic condition, dementia and stroke, and patients utilising citostatic drugs were classified as high-risk patients and the rest of the patients were classified as low-risk. This sub-group analysis was also performed for the different outcomes separately.

To assess the fit of the models, post-estimation statistics in STATA 9.2 software were used [25].

Finally, the vaccine effectiveness was calculated as  $1 - (\text{odds ratio})$  as determined by the logistic regression models.

## **CHAPTER 3**

### ***Results***

#### **Vaccination rate**

In the Medihelp population, an average of 15.4% of the elderly members were vaccinated during the influenza season of 2004.

#### **Incidence rates of outcomes**

Among the 45,700 elderly subjects there were 627 deaths from any cause, 428 hospitalisations for cardiovascular conditions and 227 hospitalisations for acute respiratory conditions. In total, 1 282(2.81%) of the medical scheme's elderly population had an outcome during the outcomes periods of either 1 May to 31 July 2004 for hospitalisations or 1 May to 15 August 2004 for all-cause mortality. The incidence rates for the different outcomes were calculated in numbers of events per 10 000 person-years and the corresponding figures were 561 deaths, 382 cardiovascular hospitalisations and 202 respiratory hospitalisations in the study period. The incidence of rate of all possible outcomes in this study was 1 145 per 10 000 yr<sup>-1</sup>.

#### **Univariate analysis**

The purpose of measuring covariates in this study was to establish potential confounding factors that may influence the results. For

confounding to occur, a covariate must be imbalanced between the cases and controls, as well as across exposure categories [13].

The number of covariates measured was reduced by grouping some of them into larger categories that showed similar patterns with regard to distribution; e.g. chronic authorisation for medication for respiratory conditions and regular utilisation of asthma medication was combined. Grouping covariates into categories was also done to avoid correlation between covariates that could be very similar to one another.

Healthcare consumption variables measured, namely the number of hospitalisations and consultations during 2003, were also converted into dichotomous variables; i.e. did any hospitalisation or doctor's consultation occur for the patient during 2003? (1 = Yes, 0 = No)

Firstly, it was established which covariates varied significantly across exposure categories in this study. Table 2 describes the controls in terms of exposed and unexposed to the influenza vaccination during the influenza season of 2004. Covariates with a statistically significant difference ( $p\text{-value} \leq 0.05$ ) between exposed and unexposed (exposure status) could have been potential confounders in a statistical model if they were also associated with the outcomes.

**Table 2. Description of controls in terms of exposure status (influenza vaccination)**

| COVARIATE                                 | CONTROLS<br>EXPOSED (790) | CONTROLS<br>UNEXPOSED<br>(4338) | P-VALUE |
|-------------------------------------------|---------------------------|---------------------------------|---------|
| <b>DEMOGRAPHIC VARIABLES</b>              |                           |                                 |         |
| Age                                       | 74.8±6.5                  | 74.9±7.1                        | 0.910   |
| Gender (F%)                               | 316/474(60.0%)            | 1483/2855<br>(65.8%)            | 0.002   |
| <b>HEALTHCARE-CONSUMPTION VARIABLES</b>   |                           |                                 |         |
| Hospitalised - 2003                       | 261(33.04%)               | 1346(31.03%)                    | 0.263   |
| Doctor consultations – 2003               | 770(97.47%)               | 3841(88.54%)                    | < 0.001 |
| Number of hospitalisations<br>(range)     | 0.5 (0-5) ±0.86           | 0.5(0-12) ±0.96                 | 0.965   |
| Number of doctor consultations<br>(range) | 6.3(0-30) ±4.37           | 4.8(0-31) ±4.11                 | < 0.001 |
| <b>CO-MORBIDITY-INDICATING VARIABLES</b>  |                           |                                 |         |
| Hypertension or heart disease             | 582(73.7)                 | 2837(65.4)                      | < 0.001 |
| Chronic respiratory conditions            | 146(18.5)                 | 436(10.1)                       | < 0.001 |
| Diabetes Mellitus                         | 85(10.8)                  | 344(7.9)                        | 0.009   |
| Rheumatological condition                 | 27(3.4)                   | 111(2.6)                        | 0.172   |
| Stroke or dementia                        | 16(2.0)                   | 49(1.1)                         | 0.041   |
| Any other chronic condition               | 733(92.8)                 | 3549(81.8)                      | < 0.001 |
| <b>MEDICATION-UTILISATION VARIABLES</b>   |                           |                                 |         |
| Alzheimer's therapy                       | 5(0.6)                    | 24(0.6)                         | 0.784   |
| Antidepressant therapy                    | 182(23.0)                 | 699(16.1)                       | < 0.001 |
| Antiparkinson's therapy                   | 21(2.7)                   | 91(2.1)                         | 0.323   |
| Anti-psychotic therapy                    | 21(2.7)                   | 98(2.3)                         | 0.494   |
| Central analeptic therapy                 | 9(1.1)                    | 33(0.8)                         | 0.281   |

| COVARIATE                                                                        | CONTROLS<br>EXPOSED (790) | CONTROLS<br>UNEXPOSED<br>(4338) | P-VALUE |
|----------------------------------------------------------------------------------|---------------------------|---------------------------------|---------|
| Oral immunisation and antiviral therapy                                          | 1(0.1)                    | 4(0.1)                          | 0.777   |
| Cox1&2 inhibitor therapy (excl. aspirin)                                         | 291(36.8)                 | 1121(25.8)                      | < 0.001 |
| Cytostatic therapy                                                               | 8(1.0)                    | 30(0.7)                         | 0.336   |
| Immunoglobulin therapy                                                           | 9(1.1)                    | 6(0.1)                          | < 0.001 |
| Nasal corticosteroid therapy                                                     | 66(8.3)                   | 173(4.0)                        | < 0.001 |
| Statin therapy                                                                   | 231(29.2)                 | 787(18.1)                       | < 0.001 |
| <b>SEVERITY OF DISEASE-INDICATING VARIABLES</b>                                  |                           |                                 |         |
| Number of therapeutic classes utilised for asthma (range)                        | 0.2(0-5)                  | 0.1(0-6)                        | < 0.001 |
| Number of therapeutic classes utilised for hypertension or heart disease (range) | 1.4(0-6)                  | 1.2(0-8)                        | < 0.001 |
| <b>PREVIOUS VACCINATION STATUS OF PATIENT OR FAMILY</b>                          |                           |                                 |         |
| Influenza vaccination – 2003                                                     | 482(61.0)                 | 430(9.9)                        | < 0.001 |
| Influenza vaccination of family - 2003                                           | 218(27.6)                 | 207(4.8)                        | < 0.001 |
| Influenza vaccination of family - 2004                                           | 323(40.9)                 | 79(1.8)                         | < 0.001 |
| Pneumococcal vaccination – 2003                                                  | 31(3.9)                   | 20(0.5)                         | < 0.001 |
| Pneumococcal vaccination of family - 2003                                        | 14(1.8)                   | 12(0.3)                         | < 0.001 |

The following variables were not significantly different between the exposed and unexposed categories and are not be included in the statistical model for this reason:

1. Any hospitalisations during 2003
2. Number of hospitalisations in 2003
3. Rheumatological conditions
4. Use of oral immunisation and antiviral therapy
5. Utilisation of Alzheimer's therapy
6. Utilisation of central analeptic therapy
7. Utilisation of cytostatic therapy
8. Utilisation of antipsychotic therapy
9. Utilisation of antiparkinson's therapy

Although age was not significantly different between the exposure categories, it was included in the subsequent explanatory models as it is biologically plausible that age could be a potential confounder. As the two covariates for doctor consultations, namely, “any doctor consultation during 2003” and “number of doctor consultations during 2003” were both statistically significant, it was decided to use only the latter in the model to avoid potential correlation between the two covariates.

A comparison of the baseline characteristics for the cases and controls of the combined outcomes (all-cause mortality and hospitalisations) is presented in Table 3.

**Table 3. Baseline characteristics for cases and controls**

| COVARIATE                                | CASES (1282)    | CONTROLS (5218)    | OR (95% CI)        | P-VALUE |
|------------------------------------------|-----------------|--------------------|--------------------|---------|
| <b>EXPOSURE TO INFLUENZA VACCINATION</b> |                 |                    |                    |         |
| Influenza vaccination - 2004             | 199 (15.52%)    | 790 (15.41%)       | 1.01 [0.85, 1.19]  | 0.918   |
| <b>DEMOGRAPHIC VARIABLES</b>             |                 |                    |                    |         |
| Age                                      | 78.8±7.8        | 74.9± 7.0          | 1.07 [ 1.07, 1.08] | < 0.001 |
| Gender (Female %)                        | 559/723 (56.4%) | 1799/3329 (64.92%) | 0.70 [0.62, 0.79]  | < 0.001 |
| <b>HEALTHCARE-CONSUMPTION VARIABLES</b>  |                 |                    |                    |         |
| Number of doctor consultations (range)   | 6.8 (0-59)      | 5.1 (0-31)         | 1.08 [1.07, 1.09]  | < 0.001 |
| <b>CO-MORBIDITY-INDICATING VARIABLES</b> |                 |                    |                    |         |
| Hypertension or heart disease            | 1048 (81.8%)    | 3419 (66.7%)       | 2.22 [1.90, 2.58]  | < 0.001 |
| Chronic respiratory conditions           | 256 (20.0%)     | 582 (11.4%)        | 1.92 [1.64, 2.26]  | < 0.001 |
| Diabetes Mellitus                        | 181 (14.1%)     | 429 (8.4%)         | 1.79 [1.49, 2.16]  | < 0.001 |
| Stroke or dementia                       | 54 (4.2%)       | 65 (1.3%)          | 3.40 [2.36, 4.90]  | < 0.001 |
| Any other chronic condition              | 1189 (92.8%)    | 4282 (83.5%)       | 2.52 [2.02, 3.16]  | < 0.001 |
| <b>MEDICATION-UTILISATION VARIABLES</b>  |                 |                    |                    |         |
| Antidepressant therapy                   | 321 (25.0%)     | 881 (17.2%)        | 1.60 [1.38, 1.85]  | < 0.001 |
| Cox1&2 inhibitor therapy (excl. aspirin) | 383 (29.9%)     | 1412 (27.5%)       | 1.12 [0.98, 1.28]  | 0.095   |
| Immunoglobulin therapy                   | 3 (0.2%)        | 15 (0.3%)          | 0.80 [0.23, 0.720] |         |

| COVARIATE                                                                        | CASES (1282) | CONTROLS (5218) | OR (95% CI)        | P-VALUE |
|----------------------------------------------------------------------------------|--------------|-----------------|--------------------|---------|
|                                                                                  |              |                 | 2.79]              |         |
| Nasal corticosteroid therapy                                                     | 59 (4.6%)    | 239 (4.7%)      | 0.99 [0.74, 1.32]  | 0.929   |
| Statin therapy                                                                   | 241 (18.8%)  | 1018 (19.9%)    | 0.93 [0.80, 1.09]  | 0.396   |
| <b>SEVERITY OF DISEASE-INDICATING VARIABLES</b>                                  |              |                 |                    |         |
| Number of therapeutic classes utilised for asthma (range)                        | 0.3 (0-5)    | 0.1 (0-6)       | 1.42 [1.31, 1.55]  | < 0.001 |
| Number of therapeutic classes utilised for hypertension or heart disease (range) | 1.9 (0-7)    | 1.2 (0-8)       | 1.41 [1.35, 1.48]  | < 0.001 |
| <b>PREVIOUS VACCINATION STATUS OF PATIENT OR FAMILY</b>                          |              |                 |                    |         |
| Influenza vaccination - 2003                                                     | 229 (17.9%)  | 912 (17.8%)     | 1.005 [0.86, 1.18] | 0.948   |
| Influenza vaccination of family - 2003                                           | 111 (8.7%)   | 425 (8.3%)      | 1.05 [0.84, 1.30]  | 0.670   |
| Influenza vaccination of family - 2004                                           | 96 (7.5%)    | 402 (7.9%)      | 0.95 [0.76, 1.20]  | 0.677   |
| Pneumococcal vaccination - 2003                                                  | 20 (1.6%)    | 51 (1.0%)       | 1.58 [0.94, 2.66]  | 0.086   |
| Pneumococcal vaccination of family - 2003                                        | 5 (0.4%)     | 26 (0.5%)       | 0.77 [0.30, 2.00]  | 0.591   |

## Conditional logistic regression analysis

The unadjusted odds ratio between the exposure (influenza vaccination in 2004) and combined outcomes was 1.01 [95% CI, 0.85, 1.19]. There was no difference in the rate of exposure between the cases and the controls (15.52% vs. 15.48%).

Then the variables that differed between the exposed and the non-exposed group (see Table 2) were entered into the model one at a time. Variables that were not statistically significantly different ( $p\text{-value} \leq 0.05$ ) between cases and controls were not entered into the explanatory model.

After entering demographic variables, i.e. age and gender, the variables for healthcare consumption, other co-morbidities, drug use and, finally, the variables relating to the severity of asthma and hypertension or heart disease were entered into the model one by one.

After entering all the variables that differed between exposed and non-exposed in the control group into the model, the OR was 0.807 and the  $p\text{-value}$  0.031 with 95% CI [0.67;0.97].

The following variables were adjusted for in the explanatory model:

- Age;
- Gender;
- Number of doctor consultations during 2003;
- Hypertension and/or heart disease;
- Respiratory conditions;
- Diabetes Mellitus;
- Stroke and/or dementia;
- Other chronic condition/s;
- Utilisation of antidepressant therapy;
- Number of therapeutic classes utilised of medication for hypertension and/or heart disease; and
- Number of therapeutic classes utilised of medication for asthma therapy.

The main results of the explanatory model are given in Table 4.

**Table 4. Unadjusted and adjusted odds ratios (combined outcomes)**

| EXPLANATORY MODEL                                                                   | ODDS RATIO   | CI (95%)            |
|-------------------------------------------------------------------------------------|--------------|---------------------|
| Unadjusted                                                                          | 1.008        | [0.85, 1.19]        |
| After adjusting for demographic variables (age, gender)                             |              |                     |
| Age                                                                                 | 1.030        | [0.87, 1.22]        |
| Gender                                                                              | 1.002        | [0.84, 1.19]        |
| After adjusting for healthcare-consumption variable                                 |              |                     |
| Doctor consultations - 2003                                                         | 0.900        | [0.75, 1.08]        |
| After adjusting for co-morbidities:                                                 |              |                     |
| Hypertension and heart disease                                                      | 0.883        | [0.74, 1.06]        |
| Respiratory conditions                                                              | 0.851        | [0.71, 1.02]        |
| Diabetes Mellitus                                                                   | 0.844        | [0.71, 1.01]        |
| Stroke and dementia                                                                 | 0.833        | [0.70, 1.00]        |
| Other chronic conditions                                                            | 0.827        | [0.69, 0.99]        |
| After adjusting for variables relating to drug use                                  |              |                     |
| Use of antidepressant therapy                                                       | 0.823        | [0.69, 0.99]        |
| After adjusting for variable relating to severity of asthma                         | 0.820        | [0.68, 0.98]        |
| After adjusting for variable relating to severity of hypertension and heart disease | 0.807        | [0.67; 0.97]        |
| <b>Final odds ratio for combined cases</b>                                          | <b>0.807</b> | <b>[0.67; 0.97]</b> |

## Analysing different endpoints

In the main results of the study, the different cases, i.e. hospitalisation and mortality cases were combined for the analysis. The same analysis was then performed, using the different type of cases each time with all controls that were randomly chosen to increase statistical power.

The analysis was performed using unconditional logistic regression for the different types of cases. All-cause mortality cases, cases hospitalised for cardiovascular conditions and, finally, cases hospitalised for respiratory (influenza and pneumonia) illness were analysed separately.

## All-cause mortality cases

**Table 5. Baseline characteristics for all-cause mortality cases and controls**

| COVARIATE                                | CASES (627)  | CONTROLS (5102) | OR (95% CI)       | P-VALUE |
|------------------------------------------|--------------|-----------------|-------------------|---------|
| <b>EXPOSURE TO INFLUENZA VACCINATION</b> |              |                 |                   |         |
| Influenza vaccination - 2004             | 87 (13.89%)  | 785 (15.4%)     | 0.89 (0.70, 1.13) | 0.321   |
| <b>DEMOGRAPHIC VARIABLES</b>             |              |                 |                   |         |
| Age                                      | 80.82±7.80   | 74.83±6.98      | 1.11              | <0.001  |
| Gender (Female %)                        | 345 (55.02%) | 3315 (64.97%)   | 0.66              | < 0.001 |
| <b>HEALTHCARE-CONSUMPTION VARIABLES</b>  |              |                 |                   |         |

| COVARIATE                                                                        | CASES (627)  | CONTROLS (5102) | OR (95% CI)       | P-VALUE |
|----------------------------------------------------------------------------------|--------------|-----------------|-------------------|---------|
| Number of doctor consultations (range)                                           | 6.6 (0-45)   | 5.1 (0-31)      | 1.07 [1.06, 1.09] | < 0.001 |
| <b>CO-MORBIDITY-INDICATING VARIABLES</b>                                         |              |                 |                   |         |
| Hypertension or heart disease                                                    | 510 (81.3%)  | 3397 (66.58%)   | 2.19 [1.77, 2.70] | < 0.001 |
| Chronic respiratory conditions                                                   | 108 (17.22%) | 576 (11.3%)     | 1.64 [1.31, 2.05] | < 0.001 |
| Diabetes Mellitus                                                                | 84 (13.4%)   | 428 (8.4%)      | 1.69 [1.32, 2.17] | < 0.001 |
| Stroke or dementia                                                               | 40 (6.38%)   | 63 (1.2%)       | 5.45 [3.63, 8.17] | < 0.001 |
| Any other chronic condition                                                      | 577 (92.0%)  | 4256 (83.4%)    | 2.29 [1.70, 3.09] | < 0.001 |
| <b>MEDICATION-UTILISATION VARIABLES</b>                                          |              |                 |                   |         |
| Antidepressant therapy                                                           | 168 (26.8%)  | 871 (17.0%)     | 1.78 [1.47, 2.15] | < 0.001 |
| Cox1&2 inhibitor therapy (excl. aspirin)                                         | 168 (26.8%)  | 1404 (27.52%)   | 0.96 [0.80, 1.16] | 0.701   |
| Immunoglobulin therapy                                                           | 2 (0.32%)    | 15 (0.29%)      | 1.08 [0.25, 4.76] | 0.914   |
| Nasal corticosteroid therapy                                                     | 22 (3.5%)    | 237 (4.7%)      | 0.75 [0.48, 1.16] | 0.198   |
| Statin therapy                                                                   | 73 (11.6%)   | 1015 (19.9%)    | 0.53 [0.41, 0.68] | 0.000   |
| <b>SEVERITY OF DISEASE-INDICATING VARIABLES</b>                                  |              |                 |                   |         |
| Number of therapeutic classes utilised for asthma (range)                        | 0.3 (0-5)    | 0.14 (0-6)      | 1.36 [1.23, 1.52] | < 0.001 |
| Number of therapeutic classes utilised for hypertension or heart disease (range) | 1.8 (0-7)    | 1.2 (0-8)       | 1.36 [1.28, 1.45] | < 0.001 |

| COVARIATE                                               | CASES (627) | CONTROLS (5102) | OR (95% CI)       | P-VALUE |
|---------------------------------------------------------|-------------|-----------------|-------------------|---------|
| <b>PREVIOUS VACCINATION STATUS OF PATIENT OR FAMILY</b> |             |                 |                   |         |
| Influenza vaccination - 2003                            | 107(17.07%) | 907 (17.78%)    | 0.95 [0.76, 1.19] | 0.659   |
| Influenza vaccination of family - 2003                  | 52 (8.29%)  | 425 (8.33%)     | 1.00 [0.74, 1.34] | 0.975   |
| Influenza vaccination of family - 2004                  | 43 (6.86%)  | 401(7.86%)      | 0.86 [0.62, 1.20] | 0.376   |
| Pneumococcal vaccination - 2003                         | 7 (1.12%)   | 51 (1.00%)      | 1.12 [0.51, 2.47] | 0.783   |
| Pneumococcal vaccination of family - 2003               | 2 (0.32%)   | 26 (0.51%)      | 0.62 [0.15, 2.64] | 0.522   |

### Explanatory model

Covariates that were found to statistically be significant ( $p\text{-value} \leq 0.05$ ) as shown in Table 2 and in Table 5 were added one by one to the unconditional logistic regression model in order to adjust the odds ratio for potential confounding variables.

**Table 6. Unadjusted and adjusted odds ratios (all-cause mortality)**

| EXPLANATORY MODEL                                     | ODDS RATIO | CI (95%)     |
|-------------------------------------------------------|------------|--------------|
| Unadjusted                                            | 0.886      | [0.70, 1.13] |
| After adjusting for demographic variables:            |            |              |
| Age                                                   | 0.927      | [0.72,1.19]  |
| Gender                                                | 0.886      | [0.69,1.14]  |
| After adjusting for healthcare-consumption variables: |            |              |
| Number of doctor consultations in 2003                | 0.803      | [0.62,1.03]  |
| After adjusting for co-morbidities:                   |            |              |
| Hypertension and heart disease                        | 0.788      | [0.61,1.01]  |

| EXPLANATORY MODEL                                                                   | ODDS RATIO | CI (95%)    |
|-------------------------------------------------------------------------------------|------------|-------------|
| Respiratory conditions                                                              | 0.765      | [0.59,0.99] |
| Diabetes Mellitus                                                                   | 0.766      | [0.59,0.99] |
| Stroke and dementia                                                                 | 0.755      | [0.58,0.97] |
| Other chronic conditions                                                            | 0.749      | [0.58,0.97] |
| After adjusting for variables relating to drug use                                  |            |             |
| Antidepressant therapy                                                              | 0.743      | [0.57,0.96] |
| Statin therapy                                                                      | 0.770      | [0.60,1.00] |
| After adjusting for variable relating to severity of hypertension and heart disease | 0.770      | [0.59,0.99] |
| After adjusting for variable relating to severity of asthma                         | 0.764      | [0.59,0.99] |
| <b>Final odds ratio for all cause mortality cases</b>                               | 0.764      | [0.59,0.99] |

## Hospitalised cases: Cardiovascular conditions

**Table 7. Baseline characteristics for cardiovascular hospitalised cases and controls**

| COVARIATE                            | CASES (428)  | CONTROLS (5085) | OR (95% CI)       | P-VALUE |
|--------------------------------------|--------------|-----------------|-------------------|---------|
| <b>INFLUENZA VACCINATION</b>         |              |                 |                   |         |
| Influenza vaccination status in 2004 | 71(16.59%)   | 783 (15.4%)     | 1.09 [0.84, 1.43] | 0.513   |
| <b>DEMOGRAPHIC VARIABLES</b>         |              |                 |                   |         |
| Age                                  | 76.43±7.09   | 74.80±6.94      | 1.03 [1.02, 1.05] | < 0.001 |
| Gender (F%)                          | 244 (57.01%) | 3269 (64.82%)   | 0.72 [0.59, 0.88] | 0.001   |

| COVARIATE                                                                        | CASES (428)  | CONTROLS (5085) | OR (95% CI)       | P-VALUE |
|----------------------------------------------------------------------------------|--------------|-----------------|-------------------|---------|
| <b>HEALTHCARE-CONSUMPTION VARIABLES</b>                                          |              |                 |                   |         |
| Number of doctor consultations (range)                                           | 6.93 (0-59)  | 5.06 (0-31)     | 1.08 [1.06, 1.10] | 0.001   |
| <b>CO-MORBIDITY-INDICATING VARIABLES</b>                                         |              |                 |                   |         |
| Hypertension or heart disease                                                    | 358 (83.64%) | 3388 (66.63%)   | 2.56 [1.97, 3.33] | < 0.001 |
| Chronic respiratory conditions                                                   | 70 (16.36%)  | 573 (11.27%)    | 1.54 [1.17, 2.02] | 0.002   |
| Diabetes Mellitus                                                                | 70 (16.36%)  | 425 (8.36%)     | 2.14 [1.63, 2.82] | < 0.001 |
| Stroke or dementia                                                               | 8 (1.87%)    | 61 (1.20%)      | 1.57 [0.75, 3.30] | 0.235   |
| Any other chronic condition                                                      | 379 (92.76%) | 4240 (83.38%)   | 2.55 [1.75, 3.71] | < 0.001 |
| <b>MEDICATION-UTILISATION VARIABLES</b>                                          |              |                 |                   |         |
| Antidepressant therapy                                                           | 92 (21.50%)  | 865 (17.01%)    | 1.33 [1.05, 1.70] | 0.019   |
| Cox1&2 inhibitor therapy (excl. aspirin)                                         | 138 (32.24%) | 1400 (27.53%)   | 1.25 [1.01, 1.55] | 0.037   |
| Immunoglobulin therapy                                                           | 1 (0.23%)    | 15 (0.29%)      | 0.79 [0.10, 6.01] | 0.821   |
| Nasal corticosteroid therapy                                                     | 20 (4.67%)   | 237 (4.66%)     | 1.00 [0.63, 1.60] | 0.991   |
| Statin therapy                                                                   | 127 (29.67%) | 1015 (19.96%)   | 1.69 [1.36, 2.11] | < 0.001 |
| <b>SEVERITY-INDICATING VARIABLES</b>                                             |              |                 |                   |         |
| Number of therapeutic classes utilised for asthma (range)                        | 0.20 (0-5)   | 0.14 (0-6)      | 1.16 [1.00, 1.34] | 0.049   |
| Number of therapeutic classes utilised for hypertension or heart disease (range) | 2.09 (0-6)   | 1.22 (0-8)      | 1.57 [1.46, 1.68] | < 0.001 |

| COVARIATE                                               | CASES (428)    | CONTROLS (5085) | OR (95% CI)       | P-VALUE |
|---------------------------------------------------------|----------------|-----------------|-------------------|---------|
| <b>PREVIOUS VACCINATION STATUS OF PATIENT OR FAMILY</b> |                |                 |                   |         |
| <b>Influenza vaccination - 2003</b>                     | 73<br>(17.06%) | 903<br>(17.76%) | 0.95 [0.73, 1.24] | 0.715   |
| <b>Influenza vaccination of family - 2003</b>           | 35 (8.18%)     | 424<br>(8.34%)  | 0.98 [0.68, 1.40] | 0.908   |
| <b>Influenza vaccination of family - 2004</b>           | 38 (8.88%)     | 400<br>(7.87%)  | 1.14 [0.81, 1.62] | 0.457   |
| <b>Pneumococcal vaccination - 2003</b>                  | 7 (1.64%)      | 51 (1%)         | 1.64 [0.74, 3.64] | 0.223   |
| <b>Pneumococcal vaccination of family - 2003</b>        | 1 (23%)        | 26 (0.51%)      | 0.46 [0.06, 3.37] | 0.441   |

### Explanatory model

Covariates that were found to be statistically significant ( $p\text{-value} \leq 0.05$ ) as per Table 2 and Table 7 were added one by one to the unconditional logistic regression model in order to adjust the odds ratio for potential confounding variables.

**Table 8. Unadjusted and adjusted odds ratios (cardiovascular hospitalisations)**

| EXPLANATORY MODEL                                     | ODDS RATIO | CI (95%)    |
|-------------------------------------------------------|------------|-------------|
| Unadjusted                                            | 1.093      | [0.84,1.43] |
| After adjusting for demographic variables:            |            |             |
| Age                                                   | 1.101      | [0.84,1.44] |
| Gender                                                | 1.074      | [0.82,1.40] |
| After adjusting for healthcare-consumption variables: |            |             |

|                                                                                     |       |             |
|-------------------------------------------------------------------------------------|-------|-------------|
| Number of doctor consultations in 2003                                              | 0.961 | [0.73,1.26] |
| After adjusting for co-morbidities:                                                 |       |             |
| Hypertension and heart disease                                                      | 0.932 | [0.71,1.22] |
| Respiratory conditions                                                              | 0.916 | [0.70,1.20] |
| Diabetes Mellitus                                                                   | 0.908 | [0.69,1.19] |
| Other chronic conditions                                                            | 0.905 | [0.69,1.19] |
| After adjusting for variables relating to drug use                                  |       |             |
| Antidepressant therapy                                                              | 0.902 | [0.69,1.19] |
| Statin therapy                                                                      | 0.865 | [0.66,1.14] |
| After adjusting for variable relating to severity of hypertension and heart disease | 0.853 | [0.64,1.13] |
| After adjusting for variable relating to severity of asthma                         | 0.854 | [0.65,1.13] |
| <b>Final odds ratio for cardiovascular cases</b>                                    | 0.854 | [0.65,1.13] |

## Hospitalised cases: Respiratory illness

**Table 9. Baseline characteristics for respiratory hospitalised cases and controls**

| Covariate                                   | Cases<br>(227) | Controls<br>(5081) | OR (95%<br>CI)     | p-value |
|---------------------------------------------|----------------|--------------------|--------------------|---------|
| <b>INFLUENZA VACCINATION</b>                |                |                    |                    |         |
| <b>Influenza vaccination status in 2004</b> | 41 (18.06)     | 784 (15.43%)       | 1.21[0.85, 1.71]   | 0.285   |
| <b>DEMOGRAPHIC VARIABLES</b>                |                |                    |                    |         |
| <b>Age</b>                                  | 77.76±7.43     | 74.80±6.96         | 1.06 [1.04, 1.08]  | < 0.001 |
| <b>Gender (F%)</b>                          | 134 (59.03%)   | 3302 (64.99%)      | 0.78 [ 0.59, 1.02] | 0.067   |

| Covariate                                                                              | Cases<br>(227) | Controls<br>(5081) | OR (95%<br>CI)       | p-value |
|----------------------------------------------------------------------------------------|----------------|--------------------|----------------------|---------|
| <b>HEALTHCARE-CONSUMPTION VARIABLES</b>                                                |                |                    |                      |         |
| Number of doctor consultations<br>(range)                                              | 7.08 (0-29)    | 5.05 (0-31)        | 1.09 [1.07,<br>1.12] | < 0.001 |
| <b>CO-MORBIDITY-INDICATING VARIABLES</b>                                               |                |                    |                      |         |
| Hypertension or heart disease                                                          | 180 (79.30%)   | 3384 (66.60%)      | 1.92 [1.39,<br>2.66] | < 0.001 |
| Chronic respiratory conditions                                                         | 78 (34.36%)    | 573 (11.28%)       | 4.12 [3.09,<br>5.49] | < 0.001 |
| Diabetes Mellitus                                                                      | 27 (11.89%)    | 424 (8.34%)        | 1.48 [0.98,<br>2.24] | 0.062   |
| Stroke or dementia                                                                     | 6 (2.64%)      | 63 (1.24%)         | 2.16 [0.96,<br>5.05] | 0.075   |
| Any other chronic condition                                                            | 215 (94.71%)   | 4236 (83.37%)      | 3.57 [1.99,<br>6.42] | < 0.001 |
| <b>MEDICATION-UTILISATION VARIABLES</b>                                                |                |                    |                      |         |
| Antidepressant therapy                                                                 | 61 (26.87%)    | 865 (17.02%)       | 1.79 [1.32,<br>2.42] | < 0.001 |
| Cox1&2 inhibitor therapy (excl.<br>aspirin)                                            | 77 (33.92%)    | 1,398 (27.51%)     | 1.35 [1.02,<br>1.79] | 0.036   |
| Immunoglobulin therapy                                                                 | 0 (0%)         | 15 (0.30%)         | -                    | -       |
| Nasal corticosteroid therapy                                                           | 17 (7.49%)     | 237 (4.66%)        | 1.65 [0.99,<br>2.76] | 0.054   |
| Statin therapy                                                                         | 41(18.06%)     | 1012 (19.92%)      | 0.89 [0.63,<br>1.25] | 0.493   |
| <b>SEVERITY-INDICATING VARIABLES</b>                                                   |                |                    |                      |         |
| Number of therapeutic classes<br>utilised for asthma (range)                           | 0.63 (0-5)     | 0.14 (0-6)         | 1.88 [1.66,<br>2.12] | < 0.001 |
| Number of therapeutic classes<br>utilised for hypertension or<br>heart disease (range) | 1.73 (0-6)     | 1.22 (0-8)         | 1.34 [1.22,<br>1.47] | < 0.001 |

| Covariate                                               | Cases<br>(227) | Controls<br>(5081) | OR (95%<br>CI)       | p-value |
|---------------------------------------------------------|----------------|--------------------|----------------------|---------|
| <b>PREVIOUS VACCINATION STATUS OF PATIENT OR FAMILY</b> |                |                    |                      |         |
| <b>Influenza vaccination - 2003</b>                     | 49 (21.59%)    | 904 (17.79%)       | 1.27 [0.92,<br>1.76] | 0.146   |
| <b>Influenza vaccination of family -<br/>2003</b>       | 24 (10.57%)    | 424 (8.34%)        | 1.30 [0.84,<br>2.01] | 0.239   |
| <b>Influenza vaccination of family -<br/>2004</b>       | 15 (6.61%)     | 401 (7.89%)        | 0.83 [0.48,<br>1.41] | 0.482   |
| <b>Pneumococcal vaccination -<br/>2003</b>              | 6 (2.64%)      | 51 (1.0%)          | 2.68 [1.14,<br>6.31] | 0.024   |
| <b>Pneumococcal vaccination of<br/>family - 2003</b>    | 2 (0.88%)      | 26 (0.51%)         | 1.73 [0.41,<br>7.33] | 0.458   |

### Explanatory model

Covariates that were found statistically significant ( $p\text{-value} \leq 0.05$ ) as per Table 2 and Table 9 were added one by one to the unconditional logistic regression model in order to adjust the odds ratio for potential confounding variables.

**Table 10. Unadjusted and adjusted odds ratios (respiratory illness)**

| EXPLANATORY MODEL                                                                       | ODDS RATIO | CI (95%)    |
|-----------------------------------------------------------------------------------------|------------|-------------|
| Unadjusted                                                                              | 1.208      | [0.85,1.71] |
| After adjusting for demographic variables                                               |            |             |
| Age                                                                                     | 1.233      | [0.87,1.75] |
| Gender                                                                                  | 1.212      | [0.86,1.72] |
| After adjusting for healthcare-consumption variables                                    |            |             |
| Number of doctor consultations in 2003                                                  | 1.058      | [0.74,1.51] |
| After adjusting for co-morbidities:                                                     |            |             |
| Hypertension and heart disease                                                          | 1.042      | [0.73,1.48] |
| Respiratory conditions                                                                  | 0.918      | [0.64,1.31] |
| Diabetes Mellitus                                                                       | 0.916      | [0.64,1.31] |
| Stroke and dementia                                                                     | 0.906      | [0.63,1.30] |
| Other chronic conditions                                                                | 0.895      | [0.62,1.28] |
| After adjusting for variables relating to drug use                                      |            |             |
| Use of Cox1&2-inhibitors                                                                | 0.894      | [0.62,1.28] |
| Antidepressant therapy                                                                  | 0.889      | [0.62,1.28] |
| Nasal corticosteroids                                                                   | 0.893      | [0.62,1.28] |
| After adjusting for the variable relating to severity of hypertension and heart disease | 0.885      | [0.62,1.27] |
| After adjusting for the variable relating to severity of asthma                         | 0.880      | [0.61,1.27] |
| After adjusting for pneumococcal vaccination 2003                                       | 0.862      | [0.60,1.25] |
| <b>Final odds ratio for respiratory cases</b>                                           | 0.862      | [0.60,1.25] |

## Hospitalised cases: Respiratory illness or Cardiovascular illness

### Explanatory model

Baseline characteristics were not repeated for this group and the covariates that were used in the models for each separate outcome were combined in this model. Covariates that were found to be statistically significant ( $p\text{-value} \leq 0.05$ ) as per Table 2 and Table 7 or Table 9 were added one by one to the unconditional logistic regression model in order to adjust the odds ratio for potential confounding variables.

**Table 11. Unadjusted and adjusted odds ratios (combined hospitalisations)**

| EXPLANATORY MODEL                                    | ODDS RATIO | CI (95%)     |
|------------------------------------------------------|------------|--------------|
| Unadjusted                                           | 1.131      | [0.91; 1.41] |
| After adjusting for demographic variables            |            |              |
| Age                                                  | 1.148      | [0.92; 1.43] |
| Gender                                               | 1.125      | [0.90; 1.40] |
| After adjusting for healthcare-consumption variables |            |              |
| Number of doctor consultations in 2003               | 1.001      | [0.80; 1.25] |
| After adjusting for co-morbidities:                  |            |              |
| Hypertension and heart disease                       | 0.975      | [0.78; 1.22] |
| Respiratory conditions                               | 0.924      | [0.74; 1.16] |
| Diabetes Mellitus                                    | 0.920      | [0.74; 1.15] |
| Stroke and dementia                                  | 0.916      | [0.73; 1.15] |

|                                                                                         |       |              |
|-----------------------------------------------------------------------------------------|-------|--------------|
| Other chronic conditions                                                                | 0.909 | [0.73; 1.14] |
| After adjusting for variables relating to drug use                                      |       |              |
| Use of Cox1&2-inhibitors                                                                | 0.908 | [0.73; 1.14] |
| Antidepressant therapy                                                                  | 0.906 | [0.72; 1.13] |
| Statin therapy                                                                          | 0.889 | [0.71; 1.11] |
| Nasal corticosteroids                                                                   | 0.892 | [0.71; 1.12] |
| After adjusting for the variable relating to severity of hypertension and heart disease | 0.883 | [0.70; 1.11] |
| After adjusting for the variable relating to severity of asthma                         | 0.880 | [0.70; 1.11] |
| After adjusting for pneumococcal vaccination 2003                                       | 0.869 | [0.69; 1.10] |
| <b>Final odds ratio for respiratory cases</b>                                           | 0.869 | [0.69; 1.10] |

## Effect modification

An *a priori* decision was made to test for effect modification by age categories, hypertension/heart disease, diabetes and respiratory conditions.

Effect modification between exposure and four age categories was tested and the p-value was 0.222. This result indicated that there was no evidence of multiplicative interaction between exposure and the age category variables.

The test was also performed for effect modification between exposure and the hypertension or heart disease variable, and exposure and diabetes combined variable without any evidence of effect modification. P-values were respectively 0.821 and 0.699.

Significant multiplicative interaction ( $p = 0.033$ ) was found between exposure and the respiratory conditions combined variable and therefore stratification was indicated on this variable.

## Stratification

The full explanatory models were rerun, stratified on a chronic respiratory condition being either present (1) or not present (0) in the patients. In the conditional logistic regression model representing all cases combined, 558 and 256 groups were respectively dropped as a result of all positive or all negative outcomes.

As shown in Table 12, the OR for influenza vaccination in patients with chronic respiratory conditions was 0.564 [95% CI, 0.252,1.260] and the OR in patients without chronic respiratory conditions was 0.934 [95% CI, 0.754,1.156].

Odds ratios and confidence intervals for each of the preliminary and final models were reported in Table 12.

**Table 12 . Summary of odd ratios for sub-groups of patients with or without chronic respiratory conditions**

| ENDPOINT MEASURED                      | UNADJUSTED ODDS RATIO | P-VALUE      | ADJUSTED ODDS RATIO | 95% CONFIDENCE INTERVAL | P-VALUE      |
|----------------------------------------|-----------------------|--------------|---------------------|-------------------------|--------------|
| <b>All endpoints combined</b>          |                       |              |                     |                         |              |
| All elderly                            | <b>1.009</b>          | <b>0.918</b> | <b>0.807</b>        | <b>[0.671; 0.969]</b>   | <b>0.022</b> |
| With chronic respiratory conditions    |                       |              | 0.564               | [0.252; 1.260]          | 163          |
| Without chronic respiratory conditions |                       |              | 0.934               | [0.754; 1.156]          | 0.535        |
| <b>All-cause mortality</b>             |                       |              |                     |                         |              |
| All elderly                            | <b>0.886</b>          | <b>0.321</b> | <b>0.764</b>        | <b>[0.590; 0.990]</b>   | <b>0.042</b> |
| With chronic respiratory conditions    |                       |              | 0.437               | [0.237; 0.808]          | 0.008        |
| Without chronic respiratory conditions |                       |              | 0.890               | [0.670; 1.182]          | 0.421        |
| <b>Hospitalised - Cardiovascular</b>   |                       |              |                     |                         |              |
| All elderly                            | <b>1.093</b>          | <b>0.513</b> | <b>0.854</b>        | <b>[0.646; 1.128]</b>   | <b>0.266</b> |
| With chronic respiratory conditions    |                       |              | 0.556               | [0.288; 1.075]          | 0.081        |
| Without chronic respiratory conditions |                       |              | 0.943               | [0.694; 1.282]          | 0.709        |
| <b>Hospitalised - Respiratory</b>      |                       |              |                     |                         |              |
| All elderly                            | <b>1.208</b>          | <b>0.285</b> | <b>0.862</b>        | <b>[0.597; 1.246]</b>   | <b>0.430</b> |
| With chronic respiratory conditions    |                       |              | 0.753               | [0.412; 1.377]          | 0.357        |
| Without chronic respiratory conditions |                       |              | 0.960               | [0.607; 1.518]          | 0.860        |

| ENDPOINT MEASURED                                   | UNADJUSTED ODDS RATIO | P-VALUE      | ADJUSTED ODDS RATIO | 95% CONFIDENCE INTERVAL | P-VALUE      |
|-----------------------------------------------------|-----------------------|--------------|---------------------|-------------------------|--------------|
| <b>Hospitalised - Respiratory or cardiovascular</b> |                       |              |                     |                         |              |
| All elderly                                         | <b>1.13</b>           | <b>0.266</b> | <b>0.869</b>        | <b>[0.690; 1.100]</b>   | <b>0.238</b> |
| With chronic respiratory conditions                 |                       |              | 0.681               | [0.426; 1.089]          | 0.109        |
| Without chronic respiratory conditions              |                       |              | 0.954               | [0.733; 1.243]          | 0.729        |

### Sub-group analysis (High- versus low-risk)

The full explanatory models were rerun, after the data had been divided into high-risk and low-risk sub-groups based on the medical conditions and utilisation of relevant chronic medication. The relevant medical conditions were excluded from the model as potential confounders. The number of outcome events in the high-risk group was 1107(23.22%), while the number of outcome events in the low-risk group was 175(10.65%).

The percentage of people vaccinated in the high-risk group was 16.9% and in the low-risk group 1.2%.

**Table 13 . Summary of odd ratios for high- and low-risk sub-groups**

| ENDPOINT MEASURED                                   | UNADJUSTED ODDS RATIO | P-VALUE      | ADJUSTED ODDS RATIO | 95% CONFIDENCE INTERVAL | P-VALUE      |
|-----------------------------------------------------|-----------------------|--------------|---------------------|-------------------------|--------------|
| <b>All endpoints combined</b>                       |                       |              |                     |                         |              |
| All elderly                                         | <b>1.009</b>          | <b>0.918</b> | <b>0.807</b>        | <b>[0.671; 0.969]</b>   | <b>0.022</b> |
| High-risk sub-group                                 |                       |              | 0.801               | [0.656; 0.978]          | 0.030        |
| Low-risk sub-group                                  |                       |              | 1.484               | [0.565; 3.897]          | 0.423        |
| <b>All-cause mortality</b>                          |                       |              |                     |                         |              |
| All elderly                                         | <b>0.886</b>          | <b>0.321</b> | <b>0.764</b>        | <b>[0.590; 0.990]</b>   | <b>0.042</b> |
| High-risk sub-group                                 |                       |              | 0.729               | [0.552; 0.964]          | 0.026        |
| Low-risk sub-group                                  |                       |              | 1.256               | [0.656; 2.406]          | 0.423        |
| <b>Hospitalised - Cardiovascular</b>                |                       |              |                     |                         |              |
| All elderly                                         | <b>1.093</b>          | <b>0.513</b> | <b>0.854</b>        | <b>[0.646; 1.128]</b>   | <b>0.266</b> |
| High-risk sub-group                                 |                       |              | 0.827               | [0.615; 1.113]          | 0.210        |
| Low-risk sub-group                                  |                       |              | 1.381               | [0.624; 3.055]          | 0.425        |
| <b>Hospitalised - Respiratory</b>                   |                       |              |                     |                         |              |
| All elderly                                         | <b>1.208</b>          | <b>0.285</b> | <b>0.862</b>        | <b>[0.597; 1.246]</b>   | <b>0.430</b> |
| High-risk sub-group                                 |                       |              | 0.974               | [0.668; 1.420]          | 0.892        |
| Low-risk sub-group                                  |                       |              | 0.536               | [0.122; 2.352]          | 0.408        |
| <b>Hospitalised - Respiratory or cardiovascular</b> |                       |              |                     |                         |              |
| All elderly                                         | <b>1.13</b>           | <b>0.266</b> | <b>0.869</b>        | <b>[0.690; 1.100]</b>   | <b>0.238</b> |
| High-risk sub-group                                 |                       |              | 0.886               | [0.696; 1.128]          | 0.325        |
| Low-risk sub-group                                  |                       |              | 1.071               | [0.531; 2.160]          | 0.847        |

## Post-estimation statistics

The fit of the conditional logistical models was assessed according to the method presented by Hosmer and Lemeshow [26]. After examining the descriptive statistics and inspecting the associated graphs, values of

cases and their corresponding controls that were outliers were deleted from the dataset. However, as one could expect with a large dataset, deletion of these outliers did not change the odds ratios or the p-values significantly and the fit of the conditional logistical models were thus found acceptable.

The Hosmer-Lemeshow goodness-of-fit test for the logistic regression models was done with Stata 9.2 software [25], and is shown in Table 14. The Receiver-Operator-Curves (ROC) and estimates of the area-under-the-curve (AUC) were determined for each model and the tabulated.

**Table 14. Goodness-of-fit statistics for the final logistic regression models**

| LOGISTIC REGRESSION MODEL                     | HOSMER -<br>LEMESHOW<br>GOODNESS-OF-FIT<br>STATISTIC (P-VALUE) | ROC CURVE<br>(AUC) |
|-----------------------------------------------|----------------------------------------------------------------|--------------------|
| <b>All-cause mortality endpoint</b>           |                                                                |                    |
| All elderly                                   | 0.3210                                                         | 0.7768             |
| With chronic respiratory conditions           | 0.2475                                                         | 0.7565             |
| Without chronic respiratory conditions        | 0.1939                                                         | 0.7710             |
| High-risk sub-group                           | 0.0267                                                         | 0.7698             |
| Low-risk sub-group                            | 0.6440                                                         | 0.7334             |
| <b>Hospitalised - Cardiovascular endpoint</b> |                                                                |                    |
| All elderly                                   | 0.9618                                                         | 0.6961             |
| With chronic respiratory conditions           | 0.7085                                                         | 0.6761             |
| Without chronic respiratory conditions        | 0.9884                                                         | 0.6941             |
| High-risk sub-group                           | 0.2507                                                         | 0.6907             |
| Low-risk sub-group                            | 0.8881                                                         | 0.5464             |
| <b>Hospitalised - Respiratory endpoint</b>    |                                                                |                    |
| All elderly                                   | 0.1438                                                         | 0.7452             |
| With chronic respiratory conditions           | 0.0912                                                         | 0.7139             |

| LOGISTIC REGRESSION MODEL                                          | HOSMER -<br>LEMESHOW<br>GOODNESS-OF-FIT<br>STATISTIC (P-VALUE) | ROC CURVE<br>(AUC) |
|--------------------------------------------------------------------|----------------------------------------------------------------|--------------------|
| Without chronic respiratory conditions                             | 0.9687                                                         | 0.7006             |
| High-risk sub-group                                                | 0.7345                                                         | 0.6962             |
| Low-risk sub-group                                                 | 0.7771                                                         | 0.6151             |
| <b>Hospitalised - Respiratory and<br/>cardiovascular endpoints</b> |                                                                |                    |
| All elderly                                                        | 0.1065                                                         | 0.7014             |
| With chronic respiratory conditions                                | 0.1520                                                         | 0.6779             |
| Without chronic respiratory conditions                             | 0.3902                                                         | 0.6882             |
| High-risk sub-group                                                | 0.0135                                                         | 0.6884             |
| Low-risk sub-group                                                 | 0.5595                                                         | 0.5906             |

An AUC estimate of 1.0 indicates perfect discrimination whereas an estimate of 0.5 indicates no discrimination [20]. The discriminative power of the multivariate models, all with reliable fit (goodness-of-fit test  $p > 0.05$ ), was acceptable (between 0.54 and 0.78).

## Summary of estimated vaccine effectiveness

Translated by the formula  $1 - \text{OR}$  times 100, the vaccine effectiveness was calculated and is shown in Table 15.

**Table 15. Estimates of vaccine effectiveness**

| Endpoint                                                       | % Vaccine effectiveness | 95% Confidence interval |
|----------------------------------------------------------------|-------------------------|-------------------------|
| <b>All endpoints</b>                                           |                         |                         |
| All elderly                                                    | 19.3                    | [3.1, 32.9]             |
| With chronic respiratory conditions                            | 43.6                    | [-26, 74.8]             |
| Without chronic respiratory conditions                         | 6.6                     | [-15.6, 24.6]           |
| High-risk sub-group                                            | 19.9                    | [2.2; 34.4]             |
| Low-risk sub-group                                             | -48.4                   | [43.5; -289.7]          |
| <b>All-cause mortality endpoint</b>                            |                         |                         |
| All elderly                                                    | 23.6                    | [1.0, 41.0]             |
| With chronic respiratory conditions                            | 56.3                    | [19.2, 76.3]            |
| Without chronic respiratory conditions                         | 11                      | [-18.2, 33.0]           |
| High-risk sub-group                                            | 27.1                    | [3.6; 44.8]             |
| Low-risk sub-group                                             | -25.6                   | [-140.6; 34.4]          |
| <b>Hospitalised - Cardiovascular endpoint</b>                  |                         |                         |
| All elderly                                                    | 14.6                    | [-12.8, 35.4]           |
| With chronic respiratory conditions                            | 44.4                    | [-7.5, 71.2]            |
| Without chronic respiratory conditions                         | 5.7                     | [-28.1, 30.6]           |
| High-risk sub-group                                            | 17.3                    | [-11.3; 38.5]           |
| Low-risk sub-group                                             | -38.1                   | [-205.5; 37.6]          |
| <b>Hospitalised - Respiratory endpoint</b>                     |                         |                         |
| All elderly                                                    | 13.8                    | [-24.6, 40.3]           |
| With chronic respiratory conditions                            | 24.7                    | [-37.7, 58.8]           |
| Without chronic respiratory conditions                         | 4                       | [-51.8, 39.3]           |
| High-risk sub-group                                            | 2.6                     | [-42.0; 33.2]           |
| Low-risk sub-group                                             | 46.4                    | [-135.2; 87.8]          |
| <b>Hospitalised - Respiratory and Cardiovascular endpoints</b> |                         |                         |
| All elderly                                                    | 13.1                    | [-10.0; 31.0]           |
| With chronic respiratory conditions                            | 31.9                    | [-8.9; 57.4]            |
| Without chronic respiratory conditions                         | 4.6                     | [-24.3; 26.7]           |
| High-risk sub-group                                            | 11.4                    | [-12.8; 30.4]           |
| Low-risk sub-group                                             | -7.1                    | [-116.0; 46.9]          |

## **CHAPTER 4**

### ***Discussion of results***

#### **Main results**

This study was carried out to determine the association between influenza vaccination and hospitalisation rates for respiratory (pneumonia and influenza) illness and cardiovascular conditions, as well as all-cause mortality among the elderly members of a private medical scheme during the winter season of 2004 in South Africa. Despite a mismatch between the influenza A strain contained in the vaccine used in the 2004 influenza season and the predominant circulating strain that year, it can be concluded from the results of this study that, overall, the use of influenza vaccination showed a modest protective effect in this elderly population against becoming a case, as measured by the endpoints of hospitalisation for respiratory or cardiovascular conditions or death from any cause. There was a 19.3% (95% CI, 3.1 to 32.9) reduction in the incidence of cases in the vaccinated group.

After each of the *a priori* chosen variables, namely age, hypertension/heart disease, diabetes and respiratory disease, were tested for effect modification, chronic respiratory disease in patients was identified in this study as a potential effect modifier during statistical analysis. For this reason the analysis was stratified and estimates of effectiveness were determined separately for patients identified to be with or without chronic respiratory conditions. In the population of elderly patients with chronic respiratory disease, influenza vaccination showed

a protective effect against all-cause mortality. After adjusting for all measurable confounders, there seemed to have been a statistically significant reduction in the incidence of all-cause mortality in the vaccinated group of elderly patients by 56.3% (95% CI, 19.2 to 76.3). A trend towards reducing hospitalisation for respiratory (24.7% [95% CI, -37.7 to 58.8]) or cardiovascular (44.4% [95% CI, -7.5 to 71.2]) conditions was also seen in the population with chronic respiratory disease, although it was not statistically significant. The estimated reduction in events in the population without chronic respiratory disease ranged between 4 -11%, and none of the estimates were statistically significant.

From this study it seems that influenza vaccination in the elderly with underlying chronic respiratory illness is associated with a statistically significant reduction of 56.3% in all cause mortality. However, this inference is perhaps not biologically plausible and will be discussed in more detail in Section 3 of this Chapter. Furthermore, the trend toward effectiveness of the vaccination to protect against other endpoints, i.e. hospitalisations for respiratory and cardiovascular conditions, although not statistically significant, was always more pronounced in the population of elderly with underlying chronic respiratory conditions.

In order to compare the results of this study with those of other published studies, the data was divided into high-risk and low-risk sub-groups based on patients' chronic conditions and utilisation of regular medication. After adjusting for the additional variables, not included in the assessment of risk of each patient, it was found in the high-risk population that vaccination was associated with a statistically significant reduction in all outcomes of 19.9% (95% CI, 2.2 to 34.4), while in the low-risk group there was a non-statistically significant increase of 48.4% (95% CI, -289.7 to 43.5) in the outcomes.

When each type of outcomes was analysed separately, the statistical power seemed to be too low to produce statistically significant results. Even after the hospitalisation outcomes for acute respiratory and cardiovascular conditions were grouped together in an attempt to increase the statistical power, the results were still not statistically significant. However, in all the types of outcomes except in the endpoint of hospitalisations for acute respiratory conditions, in the high-risk group vaccination showed a trend towards decreasing of outcomes whereas in the low-risk group it showed a trend towards increasing the outcomes. The low-risk group showed a non-significant decrease in hospitalisations for an acute respiratory condition of 46.4% with a wide 95% confidence interval of -135.2% to 87.8%. The high-risk group, however, showed only a 2.6% (95% CI, -42.0 to 33.2) non-significant decrease in hospitalisations for acute respiratory conditions.

The incidence rates of outcomes in this study was 561/10 000 yr<sup>-1</sup> for all-cause mortality, 202/10 000 yr<sup>-1</sup> for acute respiratory hospitalisation, and 382/10 000 yr<sup>-1</sup> for cardiovascular hospitalisation. The total of 1282 (2.81%) events was higher than what was found in the Prisma study, a similar study that was conducted in the Netherlands stretching over three influenza seasons from 1999 to 2002 [27]. In the Prisma subgroup of subjects older than 65 (44366 subjects) 272 deaths were identified and 166 hospitalisations. The total number of events was, therefore, 428 or 0.99%. Furthermore, the influenza period of 1999-2000 during which these events were measured, had been described as an influenza A epidemic period and one would thus expect more events in this population than in the South-African population with a similar average age of between 74 and 75.7. However, the vaccination rate in the Netherlands population was 81%, while the vaccination rate in this study population was 15.4%. This difference may have an influence on the number of events either by way of direct or indirect association. The

rate of hospitalisation in South Africa was almost four times as high as that in the Netherlands population. It seems, therefore, as if the population in the Netherlands is in a generally more healthy state at a similar age than the population in this study. This conclusion is not surprising as the life expectancy at birth in South Africa, a developing country, is 48 years while in the Netherlands it is 79 years according to statistical data from the World Bank [28].

### **Possible limitations of the study**

The study was done in a population of elderly in South Africa that may be seen as representative of the population of elderly with healthcare insurance. In South Africa, around 7 million of the 46.9 million people in the country have healthcare cover and are not reliant on the public healthcare system. This population may differ substantially from the average South African population with respect to education level, economic status and other socio-economic factors. It is likely that the percentage of vaccinated people in the non-insured elderly would be even lower than in the insured population.

Misclassification of vaccination status was considered a possibility when data from a data-base was utilized. If patients failed to claim benefits for vaccination received, study results could have been biased. If such misclassification were non-differential, it could have biased the study toward negative findings. However, if it were differential, then the study findings may have been biased in either direction. In this nested case-control study one would expect some cases where vaccination did occur but was not claimed for, resulting in a patient being misclassified as unvaccinated. If underreporting occurred, depending on whether this patient experienced an outcome or not, the study findings could have

been either an overestimation or an underestimation of the efficacy of vaccination. However, as the medical scheme benefits make provision for influenza vaccination and patients who ran out of this particular benefit before the vaccination season were excluded from the study, it is believed that if such misclassification did occur, it could have had a modest influence at the most.

All but one of the estimates of vaccine effectiveness determined after stratification of the data between patients with and without chronic respiratory illness and subsequent logistic regression analysis, had large confidence intervals around the odds ratios. For this reason, the point estimates for these outcomes should be interpreted cautiously. These large confidence intervals could be an indication that the study did not have sufficient power to detect a statistically significant association between the vaccination status and the outcomes. Sample-size calculations done prior to the study were based on an estimated vaccination rate in the controls of 20%. The number of cases that would give statistical power of 80%, to detect an odds ratio of 0.65 if the case:control ratio was 1:4, at a 95% level of confidence, was 393. However, the actual vaccination rate in the controls was 17%. The combined endpoint yielded 1282 cases. A statistically significant odds ratio was determined for the combined endpoint but as effect modification was identified during statistical analysis, data needed to be stratified between patients with, or without, chronic respiratory illness. This stratification of the data resulted in fewer cases per stratum and a loss of statistical power. Further separation of the different endpoints and stratification of these sub-groups also resulted in smaller sample sizes and a loss of power. After stratification only the odds ratio for all-cause mortality in the sub-group of patients with chronic respiratory conditions was statistically significant. Although this resulted in estimates that were imprecise there is little that one can do as the total

number of cases within the cohort of patients older than 65 were used in the study. One could attempt to increase power by including data from more than one influenza season.

In the winter season of 2004 there were only sporadic cases of laboratory-proven influenza reported and, therefore, no epidemic outbreak of influenza occurred. During an epidemic, the effectiveness of influenza vaccine is usually more pronounced than when there is only a sporadic occurrence of infection. If this study had been carried out in a season where there had been an epidemic of influenza, the effectiveness of the vaccine could have been more pronounced and statistically significant results could have been obtained without an increase in the sample size.

The vaccinated and unvaccinated controls differed for important characteristics which were taken into account in the adjustment of potential confounders by using a logistic regression model. There may also be important additional variables such as smoking status and other lifestyle behaviours, functional status, socio-economical status and genetic factors which may be associated with both the decision to receive the vaccine (exposure) and with the outcomes of the study. These unknown variables can cause confounding if they differ between vaccinated and unvaccinated in the controls and it would not be possible to adequately adjust for them, rendering the explanatory models used in this study inadequate to determine the estimates of vaccine effectiveness.

Selection bias could also play a role in the under- or overestimation of the vaccine effectiveness. The population that elects to be vaccinated may have a different prognosis from those that do not elect to receive vaccination. One may attempt to determine a patient's prognostic factors

from his healthcare consumption variables, but it is not always the case that patients who utilise more healthcare benefits are necessarily worse off in terms of prognosis. It has been postulated that there may be an unrecognised sub-group of under-vaccinated frail elderly people in the studies that could have caused overestimation of vaccine effectiveness for a non-specific outcome such as all-cause mortality [29]. Perhaps selection bias could explain the apparent overestimation of influenza vaccine effectiveness to reduce all-cause mortality in the patients with chronic respiratory conditions in this study.

This study looked at the reduction in pseudo-markers (hospitalisations and all- cause mortality) for influenza. These pseudo-markers could also be totally unrelated to influenza virus infection and, for this reason, not all changes in these outcomes can be attributed to reduction in influenza virus infection or to immunity from influenza vaccination. To effectively judge the reduction in these outcomes it could be of value to first determine the percentage of excess occurrence of these outcomes found during the influenza seasons. In this way influenza effectiveness can be expressed in terms of the reduction in the excess of outcomes such as hospitalisations and mortality from any cause during the influenza season. Any reduction in the outcomes beyond the excess that is caused by influenza virus infection should be an indication of the need to examine the study methods or to examine the possibility that influenza vaccination may produce effectiveness beyond the scope of preventing influenza virus infection.

## **Comparison with other studies**

In an early meta-analysis of the efficacy of influenza vaccination, published in 1995, 20 studies were evaluated and it was concluded that

influenza vaccine reduced risk for pneumonia, hospitalisation and death in elderly persons during influenza epidemic seasons if the vaccine strain was identical or similar to the epidemic strain [14].

Superior effectiveness was found in a retrospective, multi-season cohort study conducted from 1993-1996 among elderly members of a managed healthcare organisation who had a previous diagnosis of chronic lung disease. Nichol et al. (1999) found that influenza vaccination was associated with fewer hospitalisations for pneumonia and influenza (adjusted risk ratio, 0.48 [95% CI, 0.28 to 0.82]) and with lower risk of death (adjusted risk ratio, 0.30 [95% CI, 0.21 to 0.43]) during the influenza season [30]. One explanation for this superior effectiveness may be the fact that vaccination rates were 70% for each season whereas the vaccination rate in the South African population that was studied was around 15-17%. In a study by Looijmans-Van Den Akker et al. (2006), it was shown that the effectiveness of the influenza vaccine to reduce complications was only 47% in first-time vaccinated subjects but in subjects who have received vaccination in the year before, complications were reduced by 58% [31]. There would thus be a greater chance of any person in the cohort where vaccination rate is 70% of having had the vaccine the previous year than in a cohort where the vaccination rate is as low as 15%.

Another factor that could influence the effectiveness of the vaccine is whether the vaccine was well matched with the circulating viruses of the particular year. Nichol et al. (1999) reported a good to excellent match between the vaccine and circulating virus strain for the studied seasons [30]. In South Africa in 2004, the influenza vaccine was not a perfect match for the circulating viruses. Nichol et al. (1999) also reported significant activity of the influenza A in all three seasons and of influenza

B in the 1994 to 1995 season while in 2004 the activity reported in South Africa was that of sporadic cases of influenza A.

Between 1996 and 1998, data was analysed from three large managed-care organisations in the USA to determine influenza vaccination effectiveness in reducing hospitalisations for pneumonia and influenza and death in patients older than 65. The results from this cohort with a vaccination rate of 57.4% showed a decrease in hospitalisations of 19-20% in the first influenza season and 18-24% in the second influenza season and a decrease in deaths of 60-61% and 35-39% respectively in the two influenza seasons [32]. It is evident from this and other studies that influenza vaccine is usually associated with a higher rate of reduction in mortality, than in hospitalisations or morbidity. This was also found in this nested case-control study in the South African elderly population.

Another publication reported on the same population of the three large managed-care organisations. The absolute benefits of vaccination varied according to subgroup. Vaccination prevented 3.8 of 1000 healthy elderly from being hospitalised for pneumonia or influenza or death but in the persons with high-risk medical conditions, vaccination prevented 18.0 of 1000 from experiencing one of these complications during the first year. In that year the number-needed-to-treat in the high-risk group to prevent one outcome was between 26-56 persons while 264 healthy elderly needed to be vaccinated to prevent 1 outcome [33]. This outcome is similar to what the South African nested case-control study produced, where patients with chronic respiratory disease were shown to benefit more from the influenza vaccination than those without. Also in the South African study, the benefit from influenza vaccination in the high-risk sub-group of elderly people was significantly more than in the low-risk sub-group.

In another prospective cohort study, Hak et al. (1998) studied the cost effectiveness of immunising all adult patients in the Utrecht community in the Netherlands with chronic lung disease against influenza [34]. These researchers measured the overall attack rate of any complication including all cause death, low respiratory tract infection and acute cardiac disease. The results of the study showed that no effectiveness of the immunisation programme could be established in patients 18-64 years old, but in patients 65 years and older the occurrence of any complication was reduced by 50% (95% CI, 17 to 70%). Hak et al. (1998) estimated the economic benefit of vaccination in this population at £50 per elderly vaccinee [34]. Although it is beyond the scope of this study to determine the cost-effectiveness of vaccinating the elderly, this could be determined in a follow-up study to provide further economic motivation for vaccinating more widely, especially among populations such as the elderly.

In a recent review carried out by the Cochrane Collaboration, 64 studies were identified and included in the assessment of efficacy or effectiveness of influenza vaccination for preventing influenza in the elderly [35]. The Cochrane Collaboration identified five randomised controlled trials over a period of four decades. A meta-analysis of two of these trials showed that inactivated vaccines were more effective than a placebo against influenza-like illnesses (ILI) in conditions of high viral circulation among community-dwelling elderly individuals. Vaccine effectiveness was 43%. The authors also identified a few datasets that assessed the effectiveness of vaccines in preventing complications. In two studies, carried out in situations of low viral circulation and poor vaccine matching, the vaccine had a combined effectiveness of 65% in preventing pneumonia. In eleven data sets representing 27 283 observations during low viral circulation, the vaccines were 33%

effective in preventing ILI but had no significant effects in preventing influenza [35]. In the Cochrane Collaboration review the authors found six data sets from five case-control studies that assessed the effects of inactivated influenza vaccines on community-dwelling elderly. Before adjustment for confounding, the use of the vaccine was associated with an increased risk of admission for any respiratory disease (OR 1.08; 95% CI, 0.92 to 1.26), did not prevent hospitalisations for pneumonia and influenza (OR 0.89; 95% CI, 0.69 to 1.15), or affect mortality from influenza and pneumonia. After adjustment, however, the above outcomes were all reduced significantly with ORs being 0.71, 0.59 and 0.74 respectively [35]. In this South African nested case-control study, the unadjusted odds ratio to prevent any outcomes was 1.008 (95% CI, 0.85 to 1.19), for hospitalisations for acute respiratory conditions (influenza or pneumonia) it was 1.208 (95% CI, 0.85 to 1.71) and for all-cause mortality it was 0.886 (95% CI, 0.70 to 1.13). After adjustment, the odds ratios for any outcomes and all-cause mortality were reduced significantly with respective odds ratios of 0.807 (95% CI, 0.67 to 0.97) and 0.760 (95% CI, 0.59 to 0.99), while the adjusted odds ratio for hospitalisations for acute respiratory conditions (influenza or pneumonia) (OR 0.862; 95% CI, 0.60 to 1.25) were not statistically significant.

One of the covariates found to have a significant influence on the outcomes in this study, but that was not mentioned as a potential confounder in previous studies, was the use of antidepressants. This covariate differed significantly between cases and controls in all endpoints as well as between exposed and non-exposed. The exposure rate was higher in patients utilising antidepressant therapy regularly (23% vs. 16.1%) than in non-users. In univariate analysis the odds ratios for use of antidepressants were between 1.33 and 1.79, meaning that the odds of a patient being on an antidepressant if he had one of the

endpoints in this study was higher than 1. One possible explanation for this could be that, as was found in several previous studies, the use of antidepressant medication is associated with an increased risk of cardiovascular disease [36]. The study by Cohen et al. (2000) concluded that the association between the use of tricyclic antidepressants (TADs), but not between serotonin reuptake inhibitors (SSRIs), and the increased risk of myocardial infarction may be a long-term cardiovascular outcome, although this association has not been proven in previous short-term studies [36].

Jefferson et al. (2005) published a systematic review of data that was carried out as part of the abovementioned Cochrane Review, on the efficacy and effectiveness of influenza vaccines in elderly people [37]. These researchers concluded that vaccination was most effective against complications in elderly living in long-term care facilities but that the usefulness of vaccines in the elderly living in the community was modest. These researchers went on to discuss the potential bias caused by the non-randomised nature of the current evidence base and the likelihood of results being influenced by selection bias. Several factors are mentioned that can influence the uptake of influenza vaccine, e.g. anxiety over unwanted effects, disease threat perception, social and economic conditions, and education and health status. This differential uptake and resulting selection bias are therefore the most likely explanation for the high effectiveness of influenza vaccines in preventing all cause mortality, namely 47% in this systematic review [37].

A study carried out to assess the excess-mortality caused by influenza in the US elderly population concluded that the decline in influenza-related mortality among people aged 65 to 74 years in the decade after the 1968 influenza pandemic can be attributed to the acquisition of immunity to the emerging A(H3N2) virus [29]. After 1980, increasing

vaccination coverage could not be correlated with declining mortality in any age group. As fewer than 10% of all winter deaths were attributable to influenza in any season, it was concluded that observational studies of influenza vaccination effectiveness substantially overestimate vaccination benefit [29]. It was postulated that an unrecognised sub-population of under-vaccinated, frail elderly people in the cohort studies could have caused the serious overestimation of vaccine effectiveness for a non-specific outcome such as all-cause mortality [29].

In this nested case-control study the estimate of effectiveness of the influenza vaccination to decrease all-cause mortality in the sub-group of patients with chronic respiratory disease was found to be 56.3% and in the high-risk sub-group 27.1%. As it was an influenza season with a suboptimal match between influenza vaccine and the circulating virus and only sporadic occurrence of recorded influenza infection, it is not biologically plausible that such a high percentage of deaths could have been attributed to influenza or, in other words, could have been prevented by influenza vaccination. This result of 56.3% found in the group with chronic respiratory disease could be an artefact of the data or there could be, as postulated by Simonson et al. (2005), an unrecognised sub-population of under-vaccinated, frail elderly people that may cause a serious overestimation of the all-cause mortality outcomes [38].

In a more recently published historical cohort study carried out in the UK on individuals older than 64 over the period from 1989-1999 influenza vaccine was found to be effective in reducing hospitalisations for acute respiratory disease by 21% and death due to respiratory disease by 12%, but there was no clear reduction in death due to all causes [39]. The authors of this study were concerned that individuals who are vaccinated are healthier than individuals who are not vaccinated,

potentially biasing estimates of effectiveness upward. To control for the presence and severity of underlying illness in the vaccinated and unvaccinated populations, they used repeat prescription data for several conditions during the 12 months preceding the study. As the rates of hospitalisation increased with increasing numbers of prescriptions, it was confirmed that repeat prescriptions was a good marker of underlying ill health requiring hospital care [39].

### **Additional remarks**

The outcomes periods for the different outcomes in this study were chosen on the bases of the usual period in which influenza peaks in South Africa. As there is currently no gold standard for outcomes periods, the usual peak periods were seen to be a reasonable timeframe to use. However, it is known that different outcomes periods may have an effect on the estimates of a study. The influence of the outcomes periods on the estimated of effectiveness was, however, not part of the purpose of this study but could be explored in a subsequent study.

Follow-up studies to assess the effectiveness of influenza vaccination in other age groups, larger populations and over a number of influenza seasons could enhance the knowledge base of the effectiveness of influenza vaccines in South Africa. Caution should be exercised in order to ensure that a study design is used that could further minimise or eliminate possible selection bias or confounding. Pharmaco-economic studies may also be of value to assess the cost-effectiveness of influenza vaccination amongst the elderly and/or other age groups within the medical scheme population.

Despite the lack of proven benefit from vaccination in the elderly population with regards to hospitalisations for influenza and pneumonia or cardiovascular conditions, there was a significant reduction in all outcomes in the total population, which was found to be even more pronounced in the high-risk population. Although the absolute benefit of vaccination was highest among high-risk elderly people, the recommendation will remain at this time that all individuals older than 65 should be vaccinated against influenza every year. As the incidence of hospitalisation and all-cause mortality seems to be much higher in the South African population at a similar age than in the Netherlands population of similar age, it may be of value to explore the reasons for this difference, as well as what the influence of a higher rate of vaccination in this group of South African patients will be on the incidence of hospitalisation and mortality.

## Conclusion

The findings of this study add to the existing pool of data on vaccination rate, outcomes rate and effectiveness of influenza vaccination, especially in the South African setting where these outcomes for influenza vaccination has, to our knowledge, never been assessed previously. As some of the results found in this study were not completely biologically plausible, it alerted the researcher to important limitations of this study design. Absence of confounding and bias can only be guaranteed in large randomised controlled trials. In the absence of any randomised controlled trials on influenza vaccine effectiveness in this country, healthcare providers have had to rely on effectiveness data from trials and observational studies carried out in other settings. However, it has been found that estimates of effectiveness differ substantially between sub-groups of high- and low-risk patients implying

a possible greater benefit from vaccination in the former population of elderly high-risk patients. Should there, in future, be limited influenza vaccines available, the highest priority should be given to elderly with high-risk medical conditions.

## ***References***

1. Demicheli V, Rivetti D, Deeks JJ et al. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2004(3):CD001269
2. Ruben FL. Inactivated influenza virus vaccines in children. Clin infect Dis 2004;38(5):678-88
3. Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas, RA. Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). 2006; [41 pages]. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr55e628a1.htm>. Accessed November 12, 2006.
4. WHO activities in avian influenza and pandemic influenza preparedness. January – December 2006. 2007; [33 pages]. Available at: [http://www.who.int/csr/disease/avian\\_influenza/WHOactivitiesavianinfluenza/en/index.html](http://www.who.int/csr/disease/avian_influenza/WHOactivitiesavianinfluenza/en/index.html). Accessed May 24, 2007.
5. La Rosa AM, Whimbey E. Respiratory viruses. In: Cohen & Powderly: Infectious Diseases. 2nd ed. Mosby, An Imprint of Elsevier; 2004. p. 2077-80.
6. Hak E, Hoes AW, Verheij TJM. Influenza Vaccinations. Drugs 2002;62(17):2413-20.

7. Schoub BD. Influenza and influenza vaccination. *Geneeskunde The Medicine Journal* 2002;44(2)
8. Martin DJ, Schoub BD. Benefit:Cost evaluation of influenza vaccination in South Africa. *Occupational Health SA* 1997;3(1):23-8.
9. South African flu web. Scientific influenza information for South Africa. South African 2004 influenza season. Available at: <http://www.flu.co.za/scientif.htm>. Accessed November 13, 2006.
10. Szucs T. The socio-economic burden of influenza. *J Antimicrob Chemother* 1999;44(Suppl B):11-5.
11. Beyer WEP. Heterogeneity of case definitions used in vaccine effectiveness studies and its impact on meta-analysis. *Vaccine* 2006;24:6602-04.
12. Nichol KL. Complications of influenza and benefits of vaccination. *Vaccine* 1999;17:S47-S52.
13. Hak E, Hoes AW, Grobbee DE, Lammers JWJ, van Essen GA, van Loon AM et al. Conventional Influenza Vaccination Is Not Associated with Complications in Working-Age Patients with Asthma or Chronic Obstructive Pulmonary Disease. *Am J Epidemiol* 2003;157(8):692-700.
14. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. *Ann Intern Med* 1995;123(7):518-27.

15. Allsup S, Haycox A, Regan M, Gosney M. Is influenza vaccination cost effective for healthy people between ages 65 and 74 years? A randomised controlled trial. *Vaccine* 2004;23:639-45.
16. Nichol KL. The efficacy, effectiveness and cost-effectiveness of inactivated influenza virus vaccines. *Vaccine* 2003;21:1769-75.
17. Nichol KL, Mendelman P. Influence of clinical case definitions with differing levels of sensitivity and specificity on estimates of the relative and absolute health benefits of influenza vaccination among healthy working adults and implications for economic analyses. *Vaccine* 2004;103:3-8.
18. Rothman KJ. *Epidemiology: An Introduction*, 1<sup>st</sup> ed. New York: Oxford University Press, 2002.
19. Hak E, Verheij THJM, Grobbee DE, Nichol KL, Hoes AW. Confounding by indication in non-experimental evaluation of vaccine effectiveness: the example of prevention of influenza complications. *J Epidemiol Community Health* 2002;56:951-955.
20. Hak E, Wei F, Grobbee DE, Nichol KL. A nested case-control study of influenza vaccination was a cost-effective alternative to a full cohort analysis. *J Clin Epi* 2004;57:875-80.
21. Ernster VL. Nested case-control studies. *Preventive Medicine* 1994;23:587-90.



22. Joffe MM, Rosenbaum PR. Invited commentary: Propensity Scores. *Ann Intern Med* 1999;150(4):327-333.
23. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;127(8S):757-63.
24. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of Logistic Regression versus Propensity Score When the Number of Events Is Low and There Are Multiple Confounders. *Am J Epidemiol* 2003;158(3):280-7.
25. StataCorp. 2006. Statistical Software: Release 9.2. College Station, TX: Stata Corp LP.
26. Hosmer DW, Lemeshow S. Applied logistic regression. 2<sup>nd</sup> Ed. New York: Wiley-Interscience Publication, 2000.
27. Hak E, Buskens E, van Essen GA, de Bakker DH, Grobbee DE, Tacken MAJB et al. Clinical Effectiveness of Influenza Vaccination in Persons Younger Than 65 Years with High-Risk Medical Conditions. *Arch Intern Med* 2005;165:274-80.
28. World Bank. 2005. Available at: <http://econ.worldbank.org/WBSITE/EXTERNAL/EXTDEC/0,,menuPK:476823~pagePK:64165236~piPK:64165141~theSitePK:469372,00.html>. Accessed May 20, 2007.
29. Simonson L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med* 2005;165:265-72.

30. Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalizations, and mortality in elderly persons with chronic lung disease. *Ann Intern Med* 1999;130(5):397-403.
31. Looijmans-Van den Akker I, Nichol KL, Verheij TJM, Rutten GEHM, Buskens E, Hak E. Clinical Effectiveness of First and Repeat Influenza Vaccination in Adult and Elderly Diabetic Patients. *Diabetes Care* 2006;29(8):1771-6.
32. Nordin J, Mullooly J, Poblete S, Strikas R, Petrucci R, Wei F et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: Data from 3 Health Plans. *J Infect Dis* 2001;184:665-70.
33. Hak E, Nordin J, Wei F, Mullooly J, Poblete S, Strikas R, Nichol KL. Influence of High-Risk Medical Conditions on the Effectiveness of Influenza Vaccination among Elderly Members of 3 Large Managed-Care Organizations. *Clin Infect Dis* 2002;35:370-7.
34. Hak E, Van Essen GA, Buskens E, Stalman W, De Melker RA. Is immunising all patients with chronic lung disease in the community against influenza cost effective? Evidence from a general practice based clinical prospective cohort study in Utrecht, the Netherlands. *J Epidemiol Community Health* 1998;52:120-5.
35. Rivetti D, Jefferson T, Thomas R, Rudin M, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in the elderly. *Cochrane Review* 2006. John Wiley & Sons, Ltd.



36. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. *Am J Med* 2000;108(1): 2-8.
37. Jefferson T, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. *Lancet* 2005;366:1165-74.
38. Simonson L, Viboud C, Taylor R. Influenza vaccination in elderly people. *Lancet* 2005;366:2086.
39. Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *J Infect Dis* 2004;190:1-10.

## ***Annexure A***

### **List of ICD-9 and ICD-10 codes**

#### **Respiratory conditions**

The following ICD-9 codes were used in previous published studies:

##### **Viral pneumonia**

- 480.0 Pneumonia due to adenovirus
- 480.1 Pneumonia due to respiratory syncytial virus
- 480.2 Pneumonia due to parainfluenza virus
- 480.3 Pneumonia due to SARS-associated coronavirus
- 480.8 Pneumonia due to other virus not elsewhere classified
- 480.9 Viral pneumonia, unspecified

##### **Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]**

- 481 Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]

##### **Other bacterial pneumonia**

- 482.0 Pneumonia due to Klebsiella pneumoniae
- 482.1 Pneumonia due to Pseudomonas
- 482.2 Pneumonia due to Hemophilus influenzae [H. influenzae]

##### **Other bacterial pneumonia- Pneumonia due to Streptococcus**

- 482.30 Streptococcus, unspecified
- 482.31 Group A



482.32 Group B

482.39 Other Streptococcus

**Other bacterial pneumonia- Pneumonia due to Staphylococcus**

482.40 Pneumonia due to Staphylococcus, unspecified

482.41 Pneumonia due to Staphylococcus aureus

482.49 Other Staphylococcus pneumonia

**Other bacterial pneumonia- Pneumonia due to other specified bacteria**

482.81 Anaerobes

482.82 Escherichia coli [E. coli]

482.83 Other gram-negative bacteria

482.84 Legionnaires' disease

482.89 Other specified bacteria

**Other bacterial pneumonia**

482.9 Bacterial pneumonia unspecified

**Pneumonia due to other specified organism**

483.0 Mycoplasma pneumoniae

483.1 Chlamydia

483.8 Other specified organism

**Pneumonia in infectious diseases classified elsewhere**

484.1 Pneumonia in cytomegalic inclusion disease

484.3 Pneumonia in whooping cough

484.5 Pneumonia in anthrax

484.6 Pneumonia in aspergillosis

484.7 Pneumonia in other systemic mycoses

484.8 Pneumonia in other infectious diseases classified elsewhere

### **Bronchopneumonia, organism unspecified**

485 Bronchopneumonia, organism unspecified

### **Pneumonia, organism unspecified**

486 Pneumonia, organism unspecified

### **Influenza**

487.0 With pneumonia

487.1 With other respiratory manifestations

487.8 With other manifestations

After cross-linking the ICD-9 codes to relevant ICD-10 codes, the following ICD-10 codes were used to extract data from the Medihelp Database.

**Table 16. ICD-10 codes for acute respiratory conditions**

|       |                                                                             |
|-------|-----------------------------------------------------------------------------|
| 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             |
| 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 <i>Streptococcus pneumoniae</i>                            |
| J14   | Pneumonia due to <i>Haemophilus influenzae</i>                              |
| J15.0 | Pneumonia due to <i>Klebsiella pneumoniae</i>                               |
| J15.1 | Pneumonia due to <i>Pseudomonas</i>                                         |
| J15.2 | Pneumonia due to <i>Staphylococcus</i>                                      |
| J15.3 | Pneumonia due to <i>Streptococcus</i> , Group B                             |
| J15.4 | Pneumonia due to other streptococci                                         |

|       |                                                       |
|-------|-------------------------------------------------------|
| J15.5 | Pneumonia due to Escherichia coli                     |
| J15.6 | Pneumonia due to other aerobic Gram-negative bacteria |
| J15.7 | Pneumonia due to Mycoplasma pneumoniae                |
| J15.8 | Other bacterial pneumonia                             |
| J15.9 | Bacterial pneumonia, unspecified                      |
| J16.8 | Pneumonia due to other specified infectious organisms |
| J17.0 | Pneumonia in bacterial diseases classified elsewhere  |
| J17.1 | Pneumonia in viral diseases classified elsewhere      |
| J17.2 | Pneumonia in mycoses                                  |
| J17.8 | Pneumonia in other diseases classified elsewhere      |
| J18.0 | Bronchopneumonia, unspecified                         |
| J18.8 | Other pneumonia, organism unspecified                 |

## **Cardiovascular conditions**

### **Chronic rheumatic pericarditis**

393 Chronic rheumatic pericarditis

### **Diseases of mitral valve**

394.0 Mitral stenosis

394.1 Rheumatic mitral insufficiency

394.2 Mitral stenosis with insufficiency

394.9 Other and unspecified mitral valve diseases

### **Diseases of aortic valve**

395.0 Rheumatic aortic stenosis

395.1 Rheumatic aortic insufficiency

395.2 Rheumatic aortic stenosis with insufficiency

395.9 Other and unspecified rheumatic aortic diseases

### **Diseases of mitral and aortic valves**

396.0 Mitral valve stenosis and aortic valve stenosis

- 396.1 Mitral valve stenosis and aortic valve insufficiency
- 396.2 Mitral valve insufficiency and aortic valve stenosis
- 396.3 Mitral valve insufficiency and aortic valve insufficiency
- 396.8 Multiple involvement of mitral and aortic valves
- 396.9 Mitral and aortic valve diseases, unspecified

#### **Diseases of other endocardial structures**

- 397.0 Diseases of tricuspid valve
- 397.1 Rheumatic diseases of pulmonary valve
- 397.9 Rheumatic diseases of endocardium, valve unspecified

#### **Other rheumatic heart disease**

- 398.0 Rheumatic myocarditis

#### **Acute myocardial infarction- Of anterolateral wall**

- 410.00 Of anterolateral wall- episode of care unspecified
- 410.01 Of anterolateral wall- initial episode of care
- 410.02 Of anterolateral wall- subsequent episode of care

#### **Acute myocardial infarction- Of other anterior wall**

- 410.10 Of other anterior wall- episode of care unspecified
- 410.11 Of other anterior wall- initial episode of care
- 410.12 Of other anterior wall- subsequent episode of care

#### **Acute myocardial infarction- Of inferolateral wall**

- 410.20 Of inferolateral wall- episode of care unspecified
- 410.21 Of inferolateral wall- initial episode of care
- 410.22 Of inferolateral wall- subsequent episode of care

#### **Acute myocardial infarction- Of inferoposterior wall**

- 410.30 Of inferoposterior wall- episode of care unspecified

410.31 Of inferoposterior wall- initial episode of care

410.32 Of inferoposterior wall- subsequent episode of care

**Acute myocardial infarction- Of other inferior wall**

410.40 Of other inferior wall- episode of care unspecified

410.41 Of other inferior wall- initial episode of care

410.42 Of other inferior wall- subsequent episode of care

**Acute myocardial infarction- Of other lateral wall**

410.50 Of other lateral wall- episode of care unspecified

410.51 Of other lateral wall- initial episode of care

410.52 Of other lateral wall- subsequent episode of care

**Acute myocardial infarction- True posterior wall infarction**

410.60 True posterior wall infarction- episode of care unspecified

410.61 True posterior wall infarction- initial episode of care

410.62 True posterior wall infarction- subsequent episode of care

**Acute myocardial infarction- Subendocardial infarction**

410.70 Subendocardial infarction- episode of care unspecified

410.71 Subendocardial infarction- initial episode of care

410.72 Subendocardial infarction- subsequent episode of care

**Acute myocardial infarction- Of other specified sites**

410.80 Of other specified sites- episode of care unspecified

410.81 Of other specified sites- initial episode of care

410.82 Of other specified sites- subsequent episode of care

**Acute myocardial infarction- Unspecified site**

410.90 Unspecified site- episode of care unspecified

410.91 Unspecified site- initial episode of care



410.92 Unspecified site- subsequent episode of care

**Other acute and subacute forms of ischemic heart disease**

411.0 Postmyocardial infarction syndrome

411.1 Intermediate coronary syndrome

**Other acute and subacute forms of ischemic heart disease- Other**

411.81 Acute coronary occlusion without myocardial infarction

411.89 Other

**Old myocardial infarction**

412 Old myocardial infarction

**Angina pectoris**

413.0 Angina decubitus

413.1 Prinzmetal angina

413.9 Other and unspecified angina pectoris

**Other forms of chronic ischemic heart disease**

414.8 Other specified forms of chronic ischemic heart disease

414.9 Chronic ischemic heart disease, unspecified

**Cardiomyopathy**

425.0 Endomyocardial fibrosis

425.1 Hypertrophic obstructive cardiomyopathy

425.2 Obscure cardiomyopathy of Africa

425.3 Endocardial fibroelastosis

425.4 Other primary cardiomyopathies

425.5 Alcoholic cardiomyopathy

425.7 Nutritional and metabolic cardiomyopathy

425.8 Cardiomyopathy in other diseases classified elsewhere

425.9 Secondary cardiomyopathy, unspecified

**Heart failure**

428.0 Congestive heart failure, unspecified

428.1 Left heart failure

428.20 Unspecified

428.21 Acute

428.22 Chronic

428.23 Acute on chronic

428.30 Unspecified

428.31 Acute

428.32 Chronic

428.33 Acute on chronic

428.40 Unspecified

428.41 Acute

428.42 Chronic

428.43 Acute on chronic

428.9 Heart failure, unspecified

429.0 Myocarditis, unspecified

429.1 Myocardial degeneration

429.2 Cardiovascular disease, unspecified

429.3 Cardiomegaly

429.4 Functional disturbances following cardiac surgery

429.5 Rupture of chordae tendineae

429.6 Rupture of papillary muscle

429.71 Acquired cardiac septal defect

429.79 Other

429.81 Other disorders of papillary muscle

429.82 Hyperkinetic heart disease

429.89 Other

#### 429.9 Heart disease, unspecified

ICD-10 codes used to extract data for hospitalisations due to cardiovascular disease:

**Table 17. ICD-10 codes for cardiovascular conditions**

|       |                                                            |
|-------|------------------------------------------------------------|
| I05.0 | Mitral stenosis                                            |
| I05.1 | Rheumatic mitral insufficiency                             |
| I05.2 | Mitral stenosis with insufficiency                         |
| I05.8 | Other mitral valve diseases                                |
| I06.0 | Rheumatic aortic valve diseases                            |
| I06.1 | Rheumatic aortic stenosis                                  |
| I06.2 | Rheumatic aortic insufficiency                             |
| I06.8 | Rheumatic aortic stenosis with insufficiency               |
| I07.9 | Other rheumatic aortic valve diseases                      |
| I08.0 | Disorders of both mitral and aortic valves                 |
| I09.0 | Rheumatic myocarditis                                      |
| I09.1 | Rheumatic diseases of endocardium, valve unspecified       |
| I09.2 | Chronic rheumatic pericarditis                             |
| I09.8 | Other specified rheumatic heart diseases                   |
| I20.0 | Unstable angina                                            |
| I20.1 | Angina pectoris with documented spasm                      |
| I20.8 | Other forms of angina pectoris                             |
| I20.9 | Angina pectoris, unspecified                               |
| I21.0 | Acute transmural myocardial infarction of anterior wall    |
| I21.1 | Acute transmural myocardial infarction of inferior wall    |
| I21.2 | Acute transmural myocardial infarction of other sites      |
| I21.3 | Acute transmural myocardial infarction of unspecified site |
| I21.4 | Acute subendocardial myocardial infarction                 |

|       |                                                                   |
|-------|-------------------------------------------------------------------|
| I23.8 | Other current complications following acute myocardial infarction |
| I24.0 | Coronary thrombosis not resulting in myocardial infarction        |
| I24.1 | Dressler's syndrome                                               |
| I24.8 | Other forms of acute ischaemic heart disease                      |
| I25.0 | Atherosclerotic cardiovascular disease, so described              |
| I25.2 | Old myocardial infarction                                         |
| I25.8 | Other forms of chronic ischaemic heart disease                    |
| I25.9 | Chronic ischaemic heart disease, unspecified                      |
| I42.1 | Obstructive hypertrophic cardiomyopathy                           |
| I42.3 | Endomyocardial (eosinophilic) disease                             |
| I42.4 | Endocardial fibroelastosis                                        |
| I42.6 | Alcoholic cardiomyopathy                                          |
| I42.8 | Other cardiomyopathies                                            |
| I42.9 | Cardiomyopathy, unspecified                                       |
| I43.0 | Cardiomyopathy in infectious & parasitic diseases                 |
| I43.2 | Cardiomyopathy in nutritional diseases                            |
| I50.0 | Congestive heart failure                                          |
| I50.1 | Left ventricular failure                                          |
| I50.9 | Heart failure, unspecified                                        |
| I51.0 | Cardiac septal defect, acquired                                   |
| I51.1 | Rupture of chordae tendineae, not elsewhere classified            |
| I51.2 | Rupture of papillary muscle, not elsewhere classified             |
| I51.4 | Myocarditis, unspecified                                          |
| I51.5 | Myocardial degeneration                                           |
| I51.7 | Cardiomegaly                                                      |
| I51.8 | Other ill-defined heart diseases                                  |
| I51.9 | Heart disease, unspecified                                        |
| I97.1 | Other functional disturbances following cardiac surgery           |