Influenza Vaccination For ‘At Risk’ Australian Adults Aged Between 18 to 64

(Part 1: Literature review of influenza vaccination for the ‘at risk’ Australian adults)

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The National Institute of Clinical Studies has developed a website of influenza resources:

www.fightflu.com.au

The National Institute of Clinical Studies (NICS) is Australia's national agency for improving health care by helping close important gaps between best available evidence and current clinical practice.

NICS is funded by the Australian Government.
1. Introduction

Influenza is a highly contagious, seasonal viral infection that is typically characterised by symptoms such as malaise, feverishness, chills, headache, loss of appetite, muscle aches, cough and nasal discharge (The Australian Technical Advisory Group on Immunisation (ATAGI), 2003). The illness caused by influenza can last for up to 10 days. Whilst most healthy adults recover from influenza without further complications, influenza constitutes a significant risk factor for persons aged over 65 years, children and those with concomitant illness such as cardiopulmonary diseases and metabolic diseases such as diabetes mellitus. In addition, people with medical conditions that compromise their immuno-competency are also at greater risk than healthy people in developing serious complications. The complications of influenza include conditions such as primary viral or secondary bacterial pneumonia, pleurisy and even death. The prevalent period for influenza virus in non-tropical areas generally lasts for 14 weeks or longer, between late autumn and early spring.

Due to the high infectivity and the potential for serious consequences, especially in the elderly and persons with increased medical risk, influenza is one of the major causes of morbidity and mortality in many countries, including Australia. It is estimated that the annual attack rate of influenza in the general community is about 5 to 10 per cent and may rise up to 20 per cent during an epidemic year (The Australian Technical Advisory Group on Immunisation (ATAGI), 2003).

One of the most effective strategies in averting influenza at the population level is the use of influenza vaccination. Whilst the Australian Immunization Handbook 2003 has recommended various target groups in addition to those aged over 65 years for annual influenza vaccination, currently, the Australian government only provides funding for the annual vaccination of Australian residents aged 65 years or older through The National Influenza Vaccine Program for Older Australians. For Aboriginal and Torres Strait Islanders, the National Indigenous Pneumococcal and Influenza Immunisation Program provides free annual influenza vaccines for the following target populations:

- all Indigenous people over 50 years; and
- Indigenous people in the 15-50 year age group who are in high risk groups according to the NHMRC recommendations.

1.2 Objective and Tasks

This report presents the findings from the first part of a commissioned study by the National Institute of Clinical Studies (NICS). The overall objective of this study is to investigate the cost and cost effectiveness of the provision of influenza vaccination to Australians aged between 18 to 64 years who are “at risk” of contracting influenza or developing complications arising from influenza infection (i.e. the provision of influenza vaccination to the currently non-eligible population for the government program). The specific tasks involve:

- A review of relevant literature which identifies and summarises any existing studies on cost and cost effectiveness for influenza vaccination in the at risk population group aged between 18-64 years (current non-funded population); and
- Estimating the cost of the disease burden of influenza and the cost of vaccination for at risk groups aged 18-64 years.

The study perspective is set from the Australian government perspective which is in line with the organisational role for NICS. Nonetheless, this study will also extend to a societal perspective in order to capture a broader concept of benefits and costs in the full economic evaluation (should the study proceed to that stage).
1.2 Definitions

For the purpose of the current study, the “at risk” population aged between 18 to 64 years is defined in concordance with the current recommendations outlined in the Australian Immunization Handbook [8th edition]. The definition specifies the following populations (The Australian Technical Advisory Group on Immunisation (ATAGI), 2003):

- Adults with chronic cardiac conditions;
- Adults with chronic suppurative lung disease;
- Adults with chronic illnesses requiring regular medical follow-up or hospitalization in the preceding year, including diabetes mellitus and chronic renal failure;
- Persons with immunodeficiency, including HIV, malignancy and chronic steroid use;
- Residents of nursing homes and other long-term care facilities; and
- Contacts of high risks patients.

In addition, the Australian Immunization Handbook [8th edition] also suggested influenza vaccination in the following groups of patients even though the evidence is less conclusive. This includes patient groups with the following conditions or in the following situations:

- Asthma (influenza vaccine is most likely to benefit those with severe asthma that requires frequent hospitalization);
- Pregnancy;
- Workplace (eg. Health care professionals, healthy working adults); and
- Travellers.

This ATAGI definition hence defines “at risk” individuals as those who are at higher risk of contracting influenza and also those who are at higher risk of having more severe complications of influenza. Whilst this definition is intended to be all-encompassing, it poses significant data requirements for any evaluation. In addition, while in this report we refer to the term “influenza” as defined in section 1, it is acknowledged that the symptoms of influenza are similar to other influenza-like illness (ILI) and that the true efficacy of influenza vaccination can only be determined by virological tests that are rarely performed in daily clinical practice. The current literatures on influenza mostly include virologically confirmed influenza as well as ILI to reflect the effectiveness of the chosen vaccine. It is important to note these complexities in considering the application of information presented in this report on the available literature.

Finally, whilst there is a reported difference in the efficacy between the inactivated and attenuated virus used for vaccination in the literature, all the currently approved vaccines used in Australia contain inactivated influenza virus. Where possible, data specific to inactivated influenza vaccine is used for the purpose of this study.
2. Methods for Literature Review

2.1 Search strategy

Using electronic databases up to February 2006, we searched for primary studies on the effectiveness and cost effectiveness of vaccinating adults aged between 18 to 64 years who are at higher risk of influenza as previously defined. The electronic databases used in this review include the following:

- Cochrane Library;
- MEDLINE;
- PUBMED;
- NHS Economic Evaluation Databases (NHS EED); and
- Influenza Bibliography in the National Institute for Medical Research.

Combinations of the following search terms were used in search strategies:

- Influenza(e);
- Vaccination; Immunisation, Immunization
- cost(s);
- cost-effectiveness;
- economic(s);
- at risk;
- asthma;
- COPD;
- Pulmonary;
- Diabetes; and
- Cardiovascular.

Specific internet sites (including the National Centre for Immunization Research and Surveillance of Vaccine Preventable Disease), search engines and citation lists were also manually checked. We have also attempted to obtain any preliminary data from Ontario, Canada where universal immunization has been implemented since July 2000 (Kurji, 2004). However, there was no evaluation data available specific to our current evaluation question.

2.2 Inclusion and exclusion criteria

We included primary studies of any design, where the intervention was the vaccination of adults aged between 18 to 64 years who have any of the “at risk” medical conditions as previously defined. For cost-effectiveness analysis, we also included all quantitative data relating to influenza or pneumonia or other respiratory infections, morbidity or mortality, or all-cause mortality, or measures of cost effectiveness.

We excluded studies where the primary study populations were children or adolescents below 18 years of age, or elderly age above 65 years. However, for comparison purpose, we briefly reported on the literature relating to these population subgroups that are not within the current study objective. These include the elderly and healthy working adults.
3. Findings of the Literature Review

The effectiveness and cost-effectiveness of influenza vaccination have been extensively studied in various target populations especially in the elderly. This section presents the summary of relevant literature on the cost and the cost-effectiveness of influenza vaccination in populations aged between 18 and 64 years who are at higher risk of influenza due to their underlying medical conditions. This section takes a narrative approach in reporting the review findings. For clarity, we first present the evidence for the “at risk” population as a whole. This is followed by the evidence in individual conditions that pose higher risk for the individuals.

Except for children (which is not within the age specification), the literature on the effectiveness and cost-effectiveness of the present study population is relatively scarce. Therefore, in addition to presenting all relevant literatures specifically addressing the current study question, this section also briefly summarizes the evidence of influenza vaccination in other populations. The purpose of presenting this evidence is to highlight the variability in study design, outcome measures and findings, in both the effectiveness and cost-effectiveness literature.

3.1 Effectiveness, cost of influenza and cost-effectiveness of influenza vaccination in the ‘at risk’ populations

3.1.1 Persons at higher risk of contracting influenza

Effectiveness

One population based nested case-control study in the Netherlands - the PRISMA study - was identified during the literature search (Hak et al., 2005). According to the author, this was the first study that provided adequately powered analysis of influenza vaccination among high-risk persons younger than 65 years. In this study, cases were defined as all patients younger than 65 years with high-risk medical conditions. The definition for “high-risk” adopted in this trial by Hak et al (2005) was in accordance to the Dutch guidelines for influenza vaccination which are consistent with the definition adopted in this review. High-risk medical conditions include all cardiopulmonary diseases, diabetes mellitus, chronic renal disease, chronic staphylococcal infection, and immune-related diseases and patients in nursing homes and homes for the elderly. On the other hand, the study excluded healthy children aged 6 to 24 months, pregnant women, and health care workers. The study was conducted over the 1999 to 2000 influenza type A epidemics during which, all-cause mortality, hospitalizations or general practitioner (GP) visits for influenza, pneumonia, other acute respiratory disease, acute otitis media, myocardial infarction, heart failure and stroke were observed within a nested cohort of 75,227 primary care patients. During the study period, 47 deaths, 23 hospitalizations, and 363 GP visits were observed among high-risk adults aged between 18 and 64 years (n= 24,928; 33% of the total study population). After adjusting for confounders, influenza vaccination prevented 78% of deaths (95% CI: 39%-92%), 87% of hospitalizations (95% CI: 39%-97%) and 26% of GP visits (95% CI: 7%-47%).

This study was well controlled for participant characteristics such as age, sex, vaccination rates between the vaccinated and unvaccinated subjects. In addition, recollection bias was minimised by the prospective data collection strategy. The use of a nested case control design also reduced the potential bias due to inappropriate selection of controls.

However, as noted by the author, there was a higher number of people with risk factors among the vaccinated than the unvaccinated persons. The authors took three measures to reduce the impact of this bias, involving both design and data analysis, viz:

- Admitting patients for vaccination only by indications as verified by the doctors;
Frequency-matching cases and controls on age and the presence of risk factors by sampling in subgroups controlled for confounding effects in the analyses; and

Collecting information on many additional potential risk factors and making adjustments accordingly using logistic regression analysis.

The second primary study identified on effectiveness was also conducted in the Netherlands. It was a retrospective cohort study that examined the impact of influenza vaccination in high risk patients on primary care contact rates during the 1999 – 2000 epidemics (Tacken et al., 2004). Two samples of 25,533 high-risk patients from 30 GPs (1999-2000) and 38,483 high-risk patients from 40 GPs (2001-2002) were observed. Data were extracted from the National Information Network of GPs (LINH) – a computerised database used for annual monitoring of vaccination rates in the Netherlands.

In general, it was found that vaccination only reduced the contact rate in cardiovascular [-0.26 (95% CI: -0.44 to -0.08)] and diabetic patients [-0.29 (95% CI: -0.55 to -0.03)]. For “at risk” adults less than 65 years, the adjusted difference in the mean number of contacts was found to be statistically non-significant [-0.06 (95% CI: -0.14 to 0.02)]. No economic data was described in this study.

Cost of Illness & Cost Effectiveness

Two economic studies with sub-population analyses specifically addressing the use of influenza vaccination in the “at risk” adult population aged between 15 to 65 years were identified (Piercy and Miles, 2003, Meltzer et al., 1999).

In the first study by Piercy and Miles (2003), a decision analytic approach was used to determine the cost of influenza and the cost-effectiveness of several strategies, including influenza vaccination in various population groups. Whilst the perspective of this study was set as societal, sub-analysis using the health sector perspective was also assessed. The comparator for the cost-effectiveness analysis was a “do nothing” strategy.

The study by Piercy and Miles (2003) was predominantly based on local population data from Switzerland. The estimate for effectiveness of the influenza vaccine was obtained from epidemiological studies which reflected closely the reality of suboptimal field conditions i.e. degree of matching for viral strains, vaccine storage, handling and administration. Resource utilization incorporated in the modelling process included GP consultations, hospitalizations and drug use; and average income for the working population was used to calculate production gains/losses (sometimes referred to as ‘indirect’ cost). The data were derived from various baseline years depending on availability. For example, 1999 was the year used for estimating the number of persons in the subpopulations considered in the analysis, whereas the GP consultation and hospitalization data were based on average data from 1990-1999 and 1988-1999, respectively. Where necessary, the study also included evidence obtained from the literature.

Table 1, adapted from the study by Piercy and Miles (2003), lists the findings from the cost-of-illness study for high risk adults aged between 15 to 65 years (assuming a vaccine coverage of 36%) for the low, high and mean (base case) epidemic seasons in Switzerland. The corresponding figures for the elderly from the same study were also listed for reference.

In determining the cost-effectiveness of current influenza vaccination in the “high risk” adults in comparison to a situation without vaccination (i.e. the “do nothing” scenario), the authors made the following assumptions:

All relevant costs are incurred within a 12 month period and hence no discounting was applied;

Discounting is applied to life years gains that extend beyond a one year period;

The vaccination was fully funded by the Government and no co-payment was considered; and
Based on evidence from the literature and anecdotal evidence from the GPs, it was assumed that 0.5% of vaccines made a specific GP consultation for side effects.

Table 2 summarizes the cost-effectiveness of influenza vaccination according to cost per life year gained and cost per death averted in the high risk adults aged between 15 to 65 years and the elderly for reference purposes. Converting to Australian dollars, the cost-effectiveness ratio of AUD$19,968 (CHF 19,017) for the high risk group aged 15-65 yrs, would normally be regarded as “value-for-money” in an Australian policy context.

Table 1: Cost of illness in the high risk adults (aged 15-65 years) and the elderly in Switzerland

<table>
<thead>
<tr>
<th></th>
<th>High risk adults (aged 15-65 years)</th>
<th>The elderly (aged 66+ years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Cases</td>
<td>10,227</td>
<td>58,266</td>
</tr>
<tr>
<td>GP visits</td>
<td>6,560</td>
<td>67,551</td>
</tr>
<tr>
<td>Hospitalisations</td>
<td>869</td>
<td>1,769</td>
</tr>
<tr>
<td>Bed days</td>
<td>8,012</td>
<td>16,310</td>
</tr>
<tr>
<td>Deaths</td>
<td>29</td>
<td>54</td>
</tr>
<tr>
<td>Discounted LYL</td>
<td>510</td>
<td>950</td>
</tr>
<tr>
<td>Direct costs1 §</td>
<td>11.1 M</td>
<td>20.5 M</td>
</tr>
<tr>
<td>Indirect costs2 §</td>
<td>4.9 M</td>
<td>26.7 M</td>
</tr>
<tr>
<td>Total costs</td>
<td>16.0 M</td>
<td>47.3 M</td>
</tr>
</tbody>
</table>

Key: LYL-Life year loss, M-Million § All monetary values are expressed in Swiss Francs (CHF). According to current conversion rate, 1 CHF is approximately equivalent to 1.05 Australian Dollar.


2. ‘Indirect costs’, sometimes referred to as “productivity costs”, are the costs associated with lost or impaired ability to work or to engage in leisure activities due to morbidity and the lost economic productivity due to premature death.
Table 2: Cost-effectiveness of influenza vaccination in high-risk adults aged 15 to 65 years and the elderly

<table>
<thead>
<tr>
<th></th>
<th>High risk adults (aged 15-65 years)</th>
<th>The elderly (aged 66+ years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost per case averted</strong></td>
<td>7,308</td>
<td>14,469</td>
</tr>
<tr>
<td><strong>Cost per death averted</strong></td>
<td>331,653</td>
<td>96,569</td>
</tr>
<tr>
<td><strong>Cost per life year gained</strong></td>
<td>19,017</td>
<td>10,888</td>
</tr>
</tbody>
</table>

§ All monetary values are expressed in Swiss Francs (CHF). According to current conversion rate, 1 CHF is approximately equivalent to 1.05 Australian Dollar.

The second cost-benefit analysis was set in the United states (Meltzer et al., 1999). The authors built a Monte Carlo mathematical simulation model to estimate the number and the associated costs of deaths, hospitalizations, out-patient visits based on various scenarios of pandemic influenza. The authors then examined various immunization strategies in different groups of patients and suggested vaccination priorities and distributions. In this study, patients at high risk are defined as “persons with a pre-existing medical condition making them more susceptible to complications from influenza” (p.660, (Meltzer et al., 1999).

It was found that 15% of the American population were at high risk and would account for approximately 84 per cent of all deaths from pandemic influenza (estimated total number of deaths ranged from 89,000 to 207,000 during the pandemic scenario). At $21 per vaccinee (including costs of administration, time costs and management of adverse events) and 40% compliance, the authors projected a net savings to society if high risk patients between 20-64 years were vaccinated. At a cost of $62 per vaccinee and gross attack rates of less than 25 per cent, the authors still found that vaccinating populations at high risk would generate positive returns (Meltzer et al., 1999).

In contrast, vaccinating populations not at high risk would result in a net loss (i.e. positive cost per health gain) to society (Meltzer et al., 1999). In prioritising different vaccination strategies, vaccinating high risk group aged between 20–64 years was found to be the dominating strategy when the criteria for prioritization were set to avert the total number of deaths and maximise the total cost-offsets due to vaccination.

Although one economic evaluation conducted in the Australian context was identified, the full report is yet to be published (Andrews et al., 2003). The preliminary results of this evaluation presented in a PowerPoint presentation are presented in Table 3.

It is difficult to comprehensively assess the overall quality of this particular study due to the condensed nature of the information in the PowerPoint presentation. The large discrepancy between the incremental cost-effectiveness ratios in the Australian study ($146,691 per life year gained) and the Swiss study (AUD $19,968) are hard to explain with the present data available to us. It may be a reflection of differences in the economic methods adopted; in the population groups analysed; in the influenza epidemiology assumptions; in the socio-demographics; and/or health care systems between the two countries. What is even more puzzling is that the selection of the higher age group (50-64 yr olds) in the Australian study by Andrews et al (2003),
should bias the results in a favourable way, because more of the study participants are likely to be at higher risk than the younger population of 18 to 49 years.

Table 3: Cost-effectiveness of influenza vaccination in high-risk adults aged 50-64 years old in Australia

<table>
<thead>
<tr>
<th></th>
<th>‘At Risk’ 50-64 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per case averted</td>
<td>$1,330</td>
</tr>
<tr>
<td>Cost per death averted</td>
<td>$2.1 Million</td>
</tr>
<tr>
<td>Cost per life-year gained</td>
<td>$146,691</td>
</tr>
<tr>
<td>Cost per DALY averted</td>
<td>$133,019</td>
</tr>
</tbody>
</table>

3.1.2 Patients with chronic lung diseases

The effectiveness and cost-effectiveness of influenza vaccination have also been studied in patients with various chronic lung diseases. Whilst some studies have studied patients with any chronic lung disease as a group, studies that examined more patients with chronic obstructive pulmonary disease (COPD), asthma and cystic fibrosis (CF) have also been conducted.

Chronic pulmonary disease

In a cohort study from the Netherlands, Hak and colleagues found no effectiveness for the immunisation programme in reducing the occurrence of any complication in patients with chronic pulmonary diseases aged between 18 to 64 years (Hak et al., 1998). In this study, data on immunization, general health status, and other relevant data of 1066 patients aged between 18-64 years were collected from The Utrecht University computer network. The patients were observed over the influenza season to identify outcomes of interest such as the GP visiting rate, the hospitalization rate and so on. After adjustments for prognostic confounding factors, the odds ratio was found to be 0.95 (95% CI: 0.62 -1.48).

COPD

Effectiveness

One review by the Cochrane collaboration was identified (Poole et al., 2000). In this review, nine randomized controlled trials (RCTs) that compared live or inactivated influenza vaccines with placebo in persons with COPD were included to assess the outcome measures of interest; namely, the exacerbation rates, hospitalizations, mortality, lung function and adverse effects. Of the nine RCTs included, only four were specifically focusing on COPD patients. The reported mean age of patients in three of these four RCTs was 57.9 years, while the percentage of males ranged from 64% to 100%.

This review found a reduction in the exacerbation rates for COPD symptoms over the study period, although this finding was based mainly on one RCT by Howells (1961) (cited in Poole et al, 2000). Vaccine effectiveness was established for a reduction in the exacerbations of 0.45 per patient (95% CI: -0.75 to -0.15) over the study period. In contrast, another study included in the study (Fell et al, 1977, cited...
in Poole et al, 2000) found that the vaccinated group was in fact at higher risk of exacerbations in comparison to those unvaccinated. The reviewers noted the main difference between the two studies was that the study by Fell (1977) was conducted during a non-epidemic year and the trialled vaccine used attenuated virus. Indeed, the reviewers found that the result by Howells (1961) was consistent with parallel evidence from an observational study of 1900 elderly subjects with chronic lung disease.

The reviewers did not find any evidence of significant effect of influenza vaccination in terms of hospitalizations, mortality rates, or lung function change amongst COPD patients. In regards to adverse events, the reviewers concluded that “there are significantly more local side-effects and wheeze reported with intramuscular influenza vaccine than with placebo, however; these effects are self limiting and are outweighed by the longer term benefits of the vaccination.” (Pg.13) (Poole et al., 2000)

Cost-of-illness and cost-effectiveness

The cost-effectiveness of influenza vaccination in COPD patients was reported in one study (Wongsurakiat et al., 2003). This was a cost-benefit study conducted alongside a randomised controlled trial conducted in Thailand. The authors extrapolated and reported the cost savings for 100 vaccinated patients with severe COPD in comparison to patients receiving placebo as 680,647 baht per year (approximately equivalent to AUD $23,000 using current conversion rate). Of note, the mean ages were 67.6 (±8) years and 69.1 (±7.5) years amongst the vaccinated and placebo group, respectively.

Caution should be exercised in using this study, however, as the economic methods are questionable. For example, one of the main cost-drivers identified in the study was the hospitalization rate, yet in the example given by the author, the cost data for patients with moderate COPD was based on 1 observed episode involving a 48-day hospitalization. This was also the case for other key observations, such as outpatient visits and ventilatory support, where results were based on an inadequate number of episodes. This reflected a more general problem, that the study was not adequately powered to detect statistically significant differences in cost between the vaccinated and placebo groups; nor to produce cost results with sufficient accuracy. This deficiency was compounded by the absence of either sensitivity or uncertainty analyses to test the impact of uncertainty on the study results.

Asthma

Effectiveness

One systematic review by the Cochrane collaboration was conducted to examine the efficacy and safety of influenza vaccination in asthmatic children and adults (Cates et al., 2004). Following two updates, the review has included a total of 14 trials. The mean age of the trial participants included in the review was not described in the report. Subgroup analysis according to age was not performed. The authors noted that the “included studies covered a wide diversity of people, settings and types of influenza vaccination” (p. 1). The authors concluded that while influenza vaccination in asthmatics does not increase the risk of asthma exacerbations (Risk difference 0.01; 95% CI -0.02 to 0.04), the protective effect of influenza vaccination against influenza-related asthma exacerbations remains uncertain.

Cost-of-illness and cost-effectiveness

No economic study specifically examining the cost-effectiveness of asthmatic patients was identified during literature search.
Cystic Fibrosis (CF)

Effectiveness

One review article that assessed the effectiveness of influenza vaccination for people with CF was identified (Bhalla et al., 2000). After the most recent search of the literature in May 2005, four studies enrolling a total of 179 participants were included in this review. However, 80 per cent of these participants were children aged 1 to 16 years (which is not surprising, given the natural disease course of CF). Whilst all study influenza vaccinations generated a satisfactory serological antibody response, no study reported other clinically important benefits.

Cost-of-illness and cost-effectiveness

No evidence was identified.

3.1.3 Patients with diabetes mellitus or cardiovascular diseases

The effectiveness of influenza vaccination in patients with diabetes mellitus or cardiovascular diseases is mainly derived from epidemiological evidence. It has been shown that those patients with diabetes mellitus, congestive heart failure and other cardiac diseases are associated with excess mortality during influenza epidemics (Stephenson and Zambon, 2002). Of note, these observations include diabetic elderly patients above 65 years in the analysis.

In a protection study conducted in the UK, Colquhoun et al (1997) used a case control design to examine the effectiveness of influenza vaccination in reducing hospital admissions in people with diabetes. It was found that the adjusted odds ratio for hospital admission was 0.21 (95% CI: 0.05-0.81) when comparing patients vaccinated during the immunization season immediately preceding the epidemic and the controls. This gives an estimated vaccine effectiveness of 79% (95% CI: 19%-95%) (Colquhoun et al., 1997). In another study that was described previously (pg. 3), Tacken et al (2004) found that influenza vaccination in the Dutch population reduced the primary care contact rate in cardiovascular patients [-0.26 (95% CI: -0.44 to -0.08)] and diabetic patients [-0.29 (95% CI: -0.55 to -0.03)].

In another study conducted in Israel, the authors have further demonstrated that annual influenza vaccination in elderly diabetic patients decreased the rate of hospital admission by 12.2% when compared with non-vaccinated diabetic patients (Heymann et al., 2004). In contrast to the previous evidence, the authors found a smaller relative reduction in hospitalization among vaccinated patients with diabetes when compared with the reference population. In other words, influenza vaccination was not more effective in reducing hospitalization in diabetic patients than in the reference population. It was pointed out, however, that this observation may have been confounded by the higher use of pneumococcal vaccination in patients than in the reference population.

No economic evaluation or cost of illness study directly addressing the current research question of interest was identified.

3.1.4 Health care professionals

The effectiveness of influenza vaccination in health care professionals was examined in three studies (Potter et al., 1997, Wilde et al., 1999, Carman et al., 2000).

The study by Potter et al (1997) examined the impact of influenza vaccination of health care workers in long-term-care hospitals on the mortality of elderly patients in Glasgow. It was found that vaccination of health care workers (61% of 1078 trial participants) was associated with reductions in total patient mortality from 17 per cent to 10 per cent [Odds ratio=0.56 for non-cluster analysis (95% CI: 0.40-0.80)] and in ILI [OR=0.57, 95% CI: 0.34-0.94].

The study conducted by Carman et al (2000) was a follow-up of the pilot study conducted by Potter et al (1997). Uncorrected mortality was reported as 13.6% in comparison with 22.4% in the controls [Odds ratio= 0.58 (95% CI: 0.40-0.84)].
adjusted for possible confounding factors individually, the results remained statistically significant. The results were of borderline statistical significance when the potential confounders were analysed together. These two studies were included in a systematic review conducted for the European Scientific Working Group on Influenza (Jordan et al., 2004).

In the third study, the double blinded RCT examined the effectiveness of influenza vaccine in reducing infection, illness, and absence from work in young, healthy health care professionals (Wilde et al., 1999). Based on 359 person-winters of serologic surveillance and 4746 person-weeks of illness surveillance, influenza vaccination reduced the cumulative days of reported febrile respiratory illness from 40.6 per 100 subjects in controls to 28.7 per 100 subjects in the vaccine arm. The days of absence were 9.9 per vaccinee versus 21.1 per 100 subjects in controls. However, the reductions in both outcome measures were not statistically significant.

One abstract of a full economic evaluation conducted in Amsterdam (Parlevliet et al., 2002) was identified in the literature search. Due to the incompleteness of the abstract, we rely on the report by Jordan et al (2004) for the overall quality of this evaluation. Under baseline assumptions, this cost-benefit analysis showed a net benefit of EUR 125 per vaccination (i.e. EUR125 cost saving) from the hospital employer perspective. In multivariate sensitivity analysis, vaccine cost and lost time per vaccination resulted in a net cost for the vaccination program only if the worst case scenario was simulated.

Jordan et al (2004) has also conducted an evaluation based on the study by Carman et al (2000). From the base-case analysis, influenza vaccination in health care workers working in a 72-bed hospital was found to produce a cost-saving of £1400.

3.1.5 Patients with other ‘at risk’ conditions

Renal Disease

Due to the compromised state of the immune system in patients with renal disease, it is thought that influenza vaccination in this group of patients may not produce an immune response sufficient to prevent influenza (Kausz and Pahari, 2004). However, in a case control study from the United States, it was demonstrated that influenza vaccination was associated with decreased mortality in patients with end-stage renal disease (ESRD) who were either undergoing haemodialysis or peritoneal dialysis (Gilbertson et al., 2003).

Whilst the results from the study showed consistency in decreased mortality and morbidity in the vaccinated patients, it was also acknowledged that the study was not able to adjust for tobacco use and socioeconomic status due to unavailability of the data. Given the limited evidence, we are unable to confidently summarise the evidence of effectiveness for influenza vaccination in this group of patients.

No economic study specific to this at-risk patient group was identified.

Cancer

We identified one study conducted in the US that examined the epidemiology and outcomes of serious influenza-related infections in the cancer population (Cooksley et al., 2005). In this study, excess influenza-related hospitalizations were estimated by subtracting the number of hospitalization records indicating a diagnosis of either bronchopneumonia or pneumonia caused by an unspecified organism during influenza season (October-March) from that during a non-influenza season (April-September). The estimated weighted total of the study ‘population’ was > 64,000 influenza-related hospital discharges of patients with cancer during the 4 years studied. The majority of these discharges occurred among adults with lung (24%) or haematological (20%) malignancies. Patients aged more than 65 years comprised more than 75% of the study population.

It was found that the estimated rates of hospitalization and death per 100,000 in the prevalent cancer population aged less than 65 years were 219 and 17.4,
respectively. Including all age groups, patients with cancer admitted for an influenza-related infection incur hospitalization costs ranging from US$2,673 to US$7,083 with the mean length of stay ranging from 2.8 to 6.6 days. It is important to note that baseline vaccination status of the cancer patients included in this study was not analysed. The authors “suspect” that many of the patients “were likely not vaccinated at all” (p. 626) (Cooksley et al., 2005).

3.2 Effectiveness and cost effectiveness of influenza vaccination in other populations

Whilst the objective of this study is to focus on patients aged between 18 to 64 years who have medical conditions that subject them to higher risk of contracting influenza, the evidence in other populations may be helpful in interpreting the limited effectiveness and cost-effectiveness evidence of influenza vaccination in the target groups of interest.

This section briefly presents the evidence of influenza vaccination in elderly aged people over 65 years old and in healthy working adults.

Elderly aged over 65 years old

Influenza vaccination in the elderly aged over 65 years has been widely recommended over the past four decades. In 2000, 40 of 51 developed or rapidly developing countries recommended vaccination for all individuals aged over 60 to 65 years or older (Jefferson et al., 2005). Whilst this recommendation was based on ample literatures which have demonstrated the efficacy and effectiveness of influenza vaccination in reducing mortality and morbidity, some recent studies have questioned the high estimate for the effectiveness.

In a recent systematic review by Jefferson et al (2005), it was found that the effectiveness of influenza vaccination in preventing ILI in homes for elderly individuals was 23 per cent (95% CI: 6-36) and that the effect against influenza was not significant (RR=1.04, 0.43-2.51). In addition, the authors found that influenza vaccination was not effective in preventing influenza (RR=0.19, 0.02-2.01), ILI (RR=1.05, 0.58-1.89), or pneumonia (RR=0.88, 0.64-1.20). After adjustment for confounders, vaccine prevented hospital admissions for influenza and pneumonia decreased by 27% (95% CI: 21-33), respiratory diseases by 22% (15-28), cardiac diseases by 24% (18-30) and all-cause mortality by 47% (39-54). These effectiveness estimates were lower in comparison to the previously reported figures (Nichol, 2003). It was suggested that the previously reported high effectiveness of influenza vaccination might be due to an unrecognised bias in cohort studies (Simonsen et al., 2005).

The economic impact of influenza vaccination in the elderly has also been widely studied. In a report by Nichol (2003), except for one study from Hong Kong, all other 13 studies included in the report concluded ‘cost saving/ effective’ for influenza vaccination. This is consistent with the conclusion of another review of the pharmacoeconomic evidence of influenza vaccination in the elderly (Postma et al., 2000). However, it must be noted that some of the studies included in these reviews have used vaccine effectiveness as high as 80%.

Healthy working adults

Effectiveness

The effectiveness of influenza vaccination in healthy working adults has been evaluated extensively. In a review by the Cochrane collaboration, 25 reports of studies involving 59,566 people were included (Demicheli et al., 2004). It was found that inactivated influenza vaccines had a vaccine efficacy of 70% (95% CI: 56-80). However, the yearly recommended vaccines had low effectiveness of 25% (95% CI: 13-35) against clinical influenza cases. Whilst the vaccine was found to be statistically significant in reducing work absenteeism, the pooled number of days off
work averted was only 0.16 days (95% CI: 0.04-0.29) for each influenza episode. Accordingly, the authors concluded that whilst influenza vaccination in healthy adults is effective in reducing serologically confirmed cases, clinical influenza and work absenteeism is not reduced by influenza vaccination.

Cost Effectiveness

Despite the lack of support from current evidence in terms of vaccine effectiveness, pharmacoeconomic studies have been conducted to estimate the economic implications of vaccinating healthy working adults. In a review of the pharmacoeconomic evidence in vaccinating healthy working adults, Postma et al (2002) found that “(influenza vaccine) may be an intervention with favourable cost-effectiveness and cost-saving potentials if indirect benefits of averted production losses are included” (p.1014). Of the eleven studies included in this review, eight studies indicate a benefit-to-cost ratio of greater than 1, ranging from 2.0 to 3.6 (Postma et al., 2002).

On the other hand, three cost-benefit studies from the same review found that costs exceeded the benefits. However, it was noted that company-specific features may have significant influence the cost-effectiveness of vaccination for healthy workers.

The evidence is further established in three recent cost-effectiveness analyses (Rothberg and Rose, 2005, Postma et al., 2005, Turner et al., 2006). In the study by Rothberg et al (2005), a Markov model was constructed to examine the effectiveness of influenza vaccination for healthy working adults. It was found that vaccination results in a marginal cost-effectiveness ratio of $113 per quality-adjusted day gained or $41,000 per quality-adjusted life-year saved when compared with antiviral therapy from a societal perspective.1

However, the results were sensitive to work day loss to influenza, vaccination costs, annual probability of influenza and vaccine effectiveness. Whilst the values for average work day loss from influenza and the vaccine efficacy against matched strain were obtained from reliable sources (1.9 days and 72% respectively), the values are higher than that from the abovementioned Cochrane review.

In the second economic evaluation of influenza vaccination for healthy working adults by Postma et al (2005) conducted from a societal perspective in the Netherlands, the authors consistently found that influenza vaccination produces net cost savings. The model input values for the vaccine effectiveness and average absenteeism were 71% and 1.5 days respectively. Again, these figures are significantly higher than what was concluded in the Cochrane review cited above.

The third economic evaluation published by Turner et al (2006) set out to determine the cost-effectiveness of extending the influenza vaccination strategy in the UK to include healthy 50-64 year olds from both a “National Health Service only” and a societal perspective. According to the decision analytic model, the expansion of the vaccination program resulted in a cost per QALY of £6,174 and £10,766 (2002 £) for NHS and societal perspectives, respectively.

Several elements of this evaluation are worth-noting. Firstly, the authors endeavoured to assess the effects of influenza vaccination only on the number of influenza cases (and the consequences) but not influenza-like illness. However, as previously discussed, most of the influenza cases are unlikely to have been confirmed virologically from epidemiological studies. It is not clear from the paper how the authors disentangled the data on the excess number of GP consultations/hospitalizations/mortality due to influenza from that of influenza-like illness.

Secondly, several choices for the input data are questionable. For example, it was assumed that “ for those admitted to hospital, 4.9% would need an intensive treatment unit (ITU) therapy for an average of 28 days” (p.1036) (Turner et al., 2006). The 4.9% rate for ITU therapy was based on a small study (n = 35) in which 88% of

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3 Whilst it is impossible to stipulate the acceptable cost per QALY, generally, an incremental cost-effectiveness ratio below a shadow price of $50,000 per QALY is considered as acceptable.
the patients had “serious comorbid illnesses” (Oliveira et al., 2001). The surprisingly long ITU stay of 28 days was estimated from a study conducted in 1982-83 in the UK, the results of which are unlikely to be related to the present day resource utilization pattern in the UK (The British Thoracic Society and the Public Health Laboratory Service, 1987). Therefore, whilst the study is interesting, further modifications are needed for a more persuasive conclusion.
4. Discussion

This review shows that the present literature on the effectiveness, cost-of-illness and cost-effectiveness of influenza vaccination in “at risk” adults aged between 18 to 64 years is limited. This is despite the extensive literature on influenza vaccination in the elderly, which has led to the widespread adoption of a universal vaccination policy in this older age group.

In this review, all evidence for the effectiveness of influenza vaccination in the “at risk” adults aged between 18 to 64 years (Table 4, p.20) are provided by observational studies. This is because the vaccination guidelines in most countries (including Australia) currently recommend vaccination for patients with high risk conditions, making placebo-controlled trial an unethical study option.

Despite the less rigorous study approach, the balance of evidence from observational studies suggests that influenza vaccination is effective in reducing various clinical end-points. This includes reductions in the mortality rate and hospitalizations for the target population of the present study. However, in terms of primary care contacts, the two studies identified in this review presented different conclusions. The study by Hak et al (2005) showed that 26% of GP visits (95% CI: 7%-47%) was prevented whereas the study by Tacken et al (2004) found a non-significant result [OR= -0.06 (-0.14, 0.02)].

In this report, we have also presented the evidence of individual conditions that impose higher risk for our target study population (Table 4). Interestingly, despite the positive evidence from studies that analysed the “at risk” patients as an aggregated group, the evidence is less consistent from studies that examined influenza vaccine effectiveness in individual “at risk” conditions. For example, both Cochrane reviews for influenza vaccine effectiveness in patients with COPD or asthma have not demonstrated statistically significant differences between vaccinated and unvaccinated groups in terms of hospitalization and mortality rates. On the other hand, studies that included only patients with diabetes and other cardiovascular disease have indicated that influenza vaccination is very likely to reduce hospitalization and mortality in patients aged between 18-64 years. The evidence for other at risk conditions such as renal disease and cancers is even more limited.

These results perhaps reflect the inherent difficulties in interpreting the research findings from observational studies. Several issues need to be considered. Firstly, the epidemiology of influenza is highly variable from country to country. The incidence of influenza and the effectiveness of influenza vaccine are significantly dependent upon various factors such as the proportion of individuals who are “at risk”, the virulence of the circulating strains, the ‘match’ of the vaccine, seasonality and so on. Given that these factors are likely to differ considerably between countries, care must be taken when interpreting and “transferring” effectiveness results derived from other study populations (such as the Dutch population).

Secondly, whilst acknowledging the ethical difficulties in conducting placebo-controlled trials for influenza vaccines, observational studies are unfortunately prone to biases. For example, in a recent paper, it was found that the failure of many studies to adjust for the differences in underlying health status between the vaccinated and unvaccinated seniors had resulted in serious bias when estimating influenza vaccine effectiveness (Jackson et al., 2005). It was found that “the magnitude of bias demonstrated by the association before the influenza season was sufficient to account entirely for the association observed during influenza season” (p.1). This emphasises the need for careful interpretation of influenza vaccine effectiveness data, especially when the literature on the current study group is variable in quality/results and much more limited.

These issues are further reflected in our assessment for the evidence in the cost-of-illness and cost-effectiveness studies. For example, despite the fact that most of the studies have quoted the vaccine effectiveness from credible sources, we found that most studies have used a value of around 70% for the vaccine effectiveness. Given the issues associated with the bias in estimating vaccine effectiveness, it is quite possible that the cost effectiveness of influenza vaccination is currently over
estimated. Indeed, if the vaccine effectiveness was in fact lower than the inputted effectiveness value in the economic model, then the cost effectiveness ratio is likely to be higher than the reported values (i.e. less cost effective). Therefore, it is important to interpret the results with these issues in mind.

From the three economic studies that specifically address our current study question, the study by Meltzer et al. (1999) from the US concluded that influenza vaccination in “at risk” adults was ‘cost-saving’ and the study by Piercy and Miles (2003) suggested that vaccination in this group was ‘cost-effective’ (if we use a ‘shadow price’ of AUD$50,000 per life year gained). In contrast, the study conducted in Australia by Andrews et al (2003) showed that vaccination in “at risk” adults aged 50-64 years was not cost-effective (AUD$146,691 per life year gained). As discussed before, the dramatic difference in results is troubling and difficult to explain without further detail on the Andrews study. The difference may have arisen from the different age groups specified in the studies or a number of other methodological and parameter issues.

The economic literature for the individual “at risk” conditions is even more scarce and variable. This may be a consequence of the limited evidence for the effectiveness of influenza vaccination in individuals with the specified “at risk” conditions. Although it is intuitively appealing to conclude that influenza vaccination is likely to be cost-effective in the “at risk” populations aged between 18 to 64 years (using AUD$50,000 per life year gain), we are unable to conclude this with any level of certainty. Similarly, whilst influenza vaccination may offer benefits on an individual basis, we are unable to provide clear guidance from the literature from a broader societal or health sector perspective as to whether or not influenza vaccination policy should target the specified “at risk” populations. In short, given the limited evidence base, there is a pressing need for future evaluations in order to determine with greater certainty the likely “value-for-money” of influenza vaccination in specified “at risk” adults aged between 18 to 64 years.

Finally, the choice of study design for any further economic evaluation is also worth mentioning. Clearly, the current literature has shown that cost-benefit and cost-effectiveness analyses are the methods of choice for economic research in influenza vaccination. Cost-benefit analysis has the advantage of allowing the results to be presented as “cost saving” or not (i.e. expressing the outcomes in monetary terms). However, it requires the valuation of death and life years gained, which remains contentious in economic evaluation. Despite the controversy, various methods have been developed in valuing life years and death. On the other hand, cost-effectiveness analysis is also appropriate because it expresses the results in terms of the natural unit which is intuitively appealing for clinicians.

For the current research question, the use of a cost-benefit analysis design is challenging because of the wide age range included in the analysis of our “at risk” group. The wide age range means that assumptions must be made in terms of the age at which the patients die as a result of influenza in order to value the life-years gained/lost. Challenging methodological and ethical issues flow from this under the various methods available to measure/value these outcomes (i.e. “willingness-to-pay”; “human capital”; or the “frictional cost approach”). Clearly depending on the assumptions, the results will be affected. Therefore, a cost-effectiveness analysis using life years gained/QALYs, deaths averted, and hospitalizations averted as the outcome measures may be more appropriate for future economic evaluations in this area.
Table 4: Summary of the literature

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Study, Study Year &amp; Setting</th>
<th>Study design</th>
<th>Main Findings (Vaccine v Control) Value (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk adults</td>
<td>(Hak et al., 2005), The Netherlands</td>
<td>Nested case control</td>
<td>Deaths prevented: 78% (39%-92%)</td>
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<td>Hospitalizations prevented: 87% (39%-97%)</td>
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<td></td>
<td></td>
<td></td>
<td>GP visits prevented: 26% (7%-47%)</td>
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<tr>
<td>(Tacken et al., 2004), The Netherlands</td>
<td>Retrospective cohort</td>
<td></td>
<td>Number of primary care contacts: -0.06 (-0.14, 0.02)</td>
</tr>
<tr>
<td>(Piercy and Miles, 2003), Switzerland</td>
<td>COI &amp; Economic evaluation</td>
<td></td>
<td>Cost per case averted: CHF 7,308</td>
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<td></td>
<td></td>
<td></td>
<td>Cost per death averted: CHF 331,653</td>
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<td></td>
<td></td>
<td></td>
<td>Cost per life year gained: CHF 19,017</td>
</tr>
<tr>
<td>(Meltzer et al., 1999) US</td>
<td>Economic evaluation</td>
<td></td>
<td>Net savings for 2 tested vaccine price of $21 and $62 per dose</td>
</tr>
<tr>
<td>(Andrews et al., 2003), Australia</td>
<td>Economic evaluation</td>
<td></td>
<td>Cost per case averted: $1,330</td>
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<td></td>
<td></td>
<td></td>
<td>Cost per death averted: $2.1 Million</td>
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<td>Cost per life-year gained: $146,691</td>
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<td></td>
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<td></td>
<td>Cost per DALY averted:$133,019</td>
</tr>
<tr>
<td>Chronic Pulmonary Disease</td>
<td>(Hak et al., 1998), The Netherlands</td>
<td>Prospective Cohort</td>
<td>Odds ratio (OR) of complications of influenza: 0.95 (0.62-1.48)</td>
</tr>
<tr>
<td>Study Population</td>
<td>Study, Study Year &amp; Setting</td>
<td>Study design</td>
<td>Main Findings (Vaccine v Control) Value (95% Confidence Interval)</td>
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<tr>
<td>COPD</td>
<td>(Poole et al., 2000)</td>
<td>Cochrane review</td>
<td>Exacerbation rate of - 0.45 per patient (-0.75 to -0.15). However, the reviewer found no compelling evidence in terms of hospitalizations, mortality rates, or lung function change.</td>
</tr>
<tr>
<td>(Wongsurakit et al., 2003), Thailand</td>
<td>Economic evaluation</td>
<td>Incremental cost per life year: 680, 647 Thai baht (~AUD23,000) However, the results were most likely to be biased due to methodological flaws</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>(Cates et al., 2004)</td>
<td>Cochrane review</td>
<td>Risk difference in asthma exacerbations: 0.01 (-0.02 to 0.04) The protective effect of influenza vaccination against influenza-related asthma exacerbations remains uncertain</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>(Bhalla et al., 2000)</td>
<td>Cochrane review</td>
<td>Whilst all study influenza vaccinations mounted a satisfactory serological antibody response, no study reported clinically important benefits</td>
</tr>
<tr>
<td>Diabetes and Cardiovascular Disease</td>
<td>(Colquhoun et al., 1997),</td>
<td>Case control</td>
<td>OR for hospitalization: 0.21 (0.05-0.81)</td>
</tr>
<tr>
<td>Study Population</td>
<td>Study, Year &amp; Setting</td>
<td>Study design</td>
<td>Main Findings (Vaccine v Control) Value (95% Confidence Interval)</td>
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<td><strong>OR for hospitalization during winter months: 0.75 (0.75-0.80)</strong>&lt;br&gt;<strong>OR for mortality:</strong>&lt;br&gt;men 0.35 (0.25-0.49); women 0.32 (0.20-0.50)</td>
</tr>
<tr>
<td>Study Population</td>
<td>Study, Year &amp; Setting</td>
<td>Study design</td>
<td>Main Findings (Vaccine v Control) Value (95% Confidence Interval)</td>
</tr>
<tr>
<td>Health care professionals</td>
<td>(Potter et al., 1997), UK</td>
<td>RCT</td>
<td><strong>OR for reduction in mortality (non-clustered analysis): 0.56 (0.40-0.80)</strong></td>
</tr>
<tr>
<td>Renal disease</td>
<td>(Gilbertson et al., 2003), US</td>
<td>Case control</td>
<td><strong>OR for mortality and morbidity are mostly &lt;1 for haemodialysis patient</strong></td>
</tr>
<tr>
<td>Cancer</td>
<td>(Cooksley et al., 2005)</td>
<td>Observational &amp; COI</td>
<td><strong>Rates for influenza-related hospitalization and death were 219 and 17.4 in cancer patients &lt;65 years. Average costs&gt;$6300.</strong></td>
</tr>
</tbody>
</table>
5. References


