PUBLIC SUMMARY DOCUMENT
Product: INFLUENZA VACCINE, injection, 0.5 mL, Fluarix®, Fluvax®, Influvac®, Vaxigrip®
Sponsor: Influenza Specialist Group
Date of PBAC Consideration: November 2007

1. Purpose of Application
The submission sought to extend the current National Immunisation Program (NIP) listing of influenza vaccination to include all Australians over the age of 50 years.

2. Background
Influenza vaccination is currently funded by the Commonwealth Government as part of the NIP for all Australians aged 65 years and over, Aboriginal and Torres Strait Islander persons aged 50 years and over and at-risk Aboriginal and Torres Strait Islander persons aged 15-49 years. Influenza vaccination has also been available on the PBS since the early 1980's as a restricted benefit for persons at special risk of adverse consequences from infections of the lower respiratory tract.

3. Registration Status
Influenza vaccination is registered for the prevention of influenza caused by Influenza Virus, Types A and B.

4. Listing Requested and PBAC's View:
Funding under the NIP for universal vaccination of all persons aged 50 years and older in Australia.

The PBAC did not comment on the requested restriction.

5. Comparator
The submission nominated current influenza vaccination practice in persons aged 50 – 64 years as the main comparator. This includes influenza vaccination in this age group through the PBS, private prescribing and leakage through the NIP.

6. Clinical Trials
The submission presented the results of sixteen randomised controlled trials comparing influenza vaccination to placebo or to no intervention. Of these sixteen trials, four trials were performed in high risk patients (asthma, chronic obstructive pulmonary disease, multiple myeloma, and multiple sclerosis) and one trial was a single arm study. A Cochrane review (2007) included 48 trials. Eleven trials in the submission were included in the Cochrane review. On the other hand, the review excluded a paper by Wilde et al, but the submission included it. A list of the trials presented in the submission is shown below:

Publications presented in the submission

Trial/First author	Protocol title	Publication citation
Randomised controlled trials		
Abadoglu et al 2004	Influenza vaccination in patients with asthma: Effect on the frequency of upper respiratory tract infections and exacerbations	Journal of Asthma 41: 279–283
Allsup et al 2003	Cost-benefit evaluation of routine influenza immunisation in people 65-74 years of age,	Health Technology Assessment 7: 65–78

Trial/First author	Protocol title	Publication citation
Allsup et al 2004	Is influenza vaccination cost effective for healthy people between ages 65 and 74 years? A randomised controlled trial,	Vaccine 23: 639–645
Allsup et al 2001	Side effects of influenza vaccination in healthy older people: A randomised single-blind placebo-controlled trial	Gerontology 47: 311-314
Bridges et al 2000	Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomised controlled trial	Journal of the American Medical Association 284: 1655–1663
Cohen et al 2003	Influenza vaccination in an occupational setting: Effectiveness and cost-benefit study	Journal of Occupational Health and Safety Australia and New Zealand 19: 167–182
Edwards et al 1994	A randomised controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease,	Journal of Infectious Diseases 169: 68–76
Govaert et al 1994	The efficacy of influenza vaccination in elderly individuals: A randomised double-blind placebo-controlled trial	Journal of the American Medical Association 272: 1661–1665
Govaert et al 1993	Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial	British Medical Journal 307: 998–990
Mesa Duque et al 2001	[Effectiveness of an influenza vaccine in a working population in Colombia]	Revista panamericana.de salud pública Pan [American Journal of Public Health 10: 232–239]
Miller et al 1997	A multicenter, randomised, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis	Neurology 48: 312–314
Mixeu et al 2002	Impact of influenza vaccination on civilian aircrew illness and absenteeism	Aviation Space and Environmental Medicine 73: 876–880
Musto et al 1997	Vaccination against influenza in multiple myeloma	British Journal of Haematology. 97: 505–506
Nichol et al 1995	The effectiveness of vaccination against influenza in healthy, working adults,	New England Journal of Medicine 333: 889–893
Nichol et al 1996	Side effects associated with influenza vaccination in healthy working adults: A randomised, placebo-controlled trial,	Archives of Internal Medicine 156: 1546-1550
Powers et al 1995	Influenza A virus vaccines containing purified recombinant H3 hemagglutinin are well tolerated and induce protective immune responses in healthy adults	Journal of Infectious Diseases 171: 1595–1599
Praditsuwan et al 2005	The efficacy and effectiveness of influenza vaccination among Thai elderly persons living in the community	Journal of the Medical Association of Thailand 88: 256–264
Weingarten et al 1988	Do hospital employees benefit from the influenza vaccine? A placebo-controlled clinical trial	Journal of General Internal Medicine 3: 32–37
Wilde et al 1999	Effectiveness of influenza vaccine in health care professionals: A randomised trial	Journal of the American Medical Association 281: 908–913
Wongsurakiat et al 2003	Economic evaluation of influenza vaccination in Thai chronic obstructive pulmonary disease patients	Journal of the Medical Association of Thailand 86: 497–508

Trial/First author	Protocol title	Publication citation
Wongsurakiat et al 2004	Adverse effects associated with influenza vaccination in patients with COPD: A randomised controlled study	Respirology 9: 550–556
Wongsurakiat et al 2004	Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: A randomised controlled study	Chest 125: 2011–2020
Meta-analysis		
Demicheli et al 2004	Vaccines for preventing influenza in healthy adults	Cochrane Database of Systematic Reviews Issue 3: 1–66
Jefferson et al 2007	Vaccines for preventing influenza in healthy adults	Cochrane Database of Systematic Reviews Issue 2: 1-81

7. Results of Trials

The main outcome discussed in the submission was influenza like illness (ILI) which was a primary or secondary outcome of all trials. Other Secondary outcomes included serologically confirmed influenza and hospitalisations due to ILI.

The results of the key trials are summarised in the tables below.

Results of influenza-like illness cases across the direct randomised trials

Trial ID	Vaccine n/N (%)	Placebo or no intervention n/N (%)	Risk difference (95% CI)	Relative risk (95% CI)
Key evidence				
Allsup 2003	5/552 (0.9)	2/177 (1)	0.00 [–0.02, 0.02]	0.80 [0.16, 4.10
Bridges 2000a	161/595 (27)	132/589 (22)	0.05 [0.00, 0.10]	1.21 [0.99, 1.47]
Bridges 2000b	82/587 (14)	128/604 (21)	–0.07 [–0.12, –0.03]	0.66 [0.51, 0.85]
Cohen 2003	104/296 (35)	101/301 (34)	0.02 [–0.06, 0.09]	1.05 [0.84, 1.31]
Edwards 1994a	75/878 (8.5)	92/878 (10)	–0.02 [–0.05, 0.01]	0.82 [0.61, 1.09]
Edwards 1994b	89/1060 (8)	119/1064 (11)	–0.03 [–0.05, 0.00]	0.75 [0.58, 0.97]
Edwards 1994c	122/1126 (11)	125/1125 (11)	0.00 [–0.03, 0.02]	0.98 [0.77, 1.23]
Edwards 1994d	75/1016 (7)	93/1016 (9)	–0.02 [–0.04, 0.01]	0.81 [0.60, 1.08]
Govaert 1994	17/927 (2)	31/911 (3)	–0.02 [–0.03, 0.00]	0.54 [0.30, 0.97]
Mesa Duque 2001	194/247 (79)	225/246 (91)	–0.13 [–0.19, –0.07]	0.86 [0.80, 0.93]
Mixeu 2002	86/405 (21)	98/408 (24)	–0.03 [–0.09, 0.031]	0.88 [0.69, 1.14]
Nichol 1995	249/424 (59)	287/425 (68)	–0.09 [–0.15, –0.02]	0.87 [0.78, 0.96]
Powers 1995	4/26 (15)	6/24 (25)	–0.10 [–0.32, 0.13]	0.62 [0.20, 1.92]
Praditsuwan 2005	13/330 (4)	26/305 (9)	–0.05 [–0.08, –0.01]	0.46 [0.24, 0.88]
Case specific definition, studies with high risk patients excluded				

Pooled result from random effects model	–0.02 [–0.04, –0.01]	0.87 [0.79, 0.95]
p value	0.002	0.002
Chi square (Q) for heterogeneity: p = I2 statistic with 95% uncertainty interval =	0.0002 65.2%	0.02 49.1%

In the analysis of case specific definition for all studies, there was a significant difference in the number of patients with influenza-like illness (ILI) in the vaccine group compared with the placebo/no intervention group (p <0.002). The analysis shows there to be a risk difference (RD) of –2% (95% CI: [–4%, –1%]) and relative risk (RR) of 87% (95% CI: [79%, 95%]) with vaccination. However, significant heterogeneity was detected between the studies (p = 0.005).

The Jefferson 2007 Cochrane review found a RR for ILI of 77% (95% CI: [68%, 87%]) for inactivated parenteral vaccine versus placebo or no intervention.

Results of influenza cases serologically confirmed across the direct randomised trials

Trial ID	Vaccine n/N (%)	Placebo or no intervention n/N (%)	Risk difference (95% CI)	Relative risk (95% CI)
Key evidence				
Bridges 2000a[1]	3/595 (0.5)	6/589 (1)	–0.01 [–0.02, 0.00]	0.49 [0.12, 1.97]
Bridges 2000b[1]	2/587 (1)	14/604 (10)	–0.02 [–0.03, –0.01]	0.15 [0.03, 0.64]
Edwards 1994a[2]	6/878 (0.7)	28/878 (3)	–0.03 [–0.04, –0.01]	0.21 [0.09, 0.51]
Edwards 1994b[2]	9/1060 (0.8)	29/1064 (3)	–0.02 [–0.03, –0.01]	0.31 [0.15, 0.65]
Edwards 1994c[2]	8/1126 (0.7)	32/1125 (3)	–0.02 [–0.03, –0.01]	0.25 [0.12, 0.54]
Edwards 1994d[2]	4/1016 (0.4)	18/1016 (2)	–0.01 [–0.02, 0.00]	0.22 [0.08, 0.65]
Govaert 1994[1]	41/927 (4)	80/911 (9)	–0.04 [–0.07, –0.02]	0.50 [0.35, 0.73]
Powers 1995[2]	0/26 (0%)	3/24 (13)	–0.13 [–0.27, 0.02]	0.13 [0.01, 2.44]
Praditsuwan 2005[1]	7/330 (2)	19/305 (6)	–0.04 [–0.07, –0.01]	0.34 [0.15, 0.80]
Wilde 1999a[1]	2/52 (4)	14/50 (28)	–0.24 [–0.38, –0.11]	0.14 [0.03, 0.57]
Wilde 1999b[1]	0/51 (0)	4/52 (8)	–0.08 [–0.16, 0.00]	0.11 [0.01, 2.05]
Wilde 1999c[1]	1/78 (1)	7/78 (9)	–0.08 [–0.15, –0.01]	0.14 [0.02, 1.13]
Pooled result from random effects model			–0.03 [–0.04, –0.01]	0.32 [0.25, 0.41]
p value			<0.00001	<0.00001
Chi square (*Q*) for heterogeneity: *p* = I^2 statistic with 95% uncertainty interval =			<0.00001 75.7%	0.39 5.9%

Wilde 1999, serological cases of A and B influenza combined [1] Influenza confirmed from blood samples pre and post vaccination [2] Influenza confirmed from vaccines presenting with influenza like illness

A significantly greater proportion of patients were diagnosed with laboratory confirmed influenza in the placebo/no intervention group compared with the vaccine group

(p<0.0001). For patients receiving the vaccine compared with those patients who did not receive the vaccine, the analysis shows there to be a RD of –3% (95% CI: [–4%, –1%]) and RR of 32% (95% CI: [25%, 41%]) of contracting laboratory confirmed influenza. No heterogeneity was detected between the studies when an analysis of risk difference was performed (p = 0.39), although an analysis of relative risk did detect a significant amount of between-study variance (p<0.00001).

Results of hospitalisations across the direct randomised trials

Trial ID	Vaccine n/N (%)	Placebo or no intervention n/N (%)	Risk difference (95% CI)	Relative risk (95% CI)
Key evidence				
Allsup 2003[2]	0/552 (0)	0/177 (0)	0.00 [–0.01, 0.01]	Not estimable
Bridges 2000a[2]	1/595 (0.2)	0/589 (0)	0.00 [0.00, 0.01]	2.97 [0.12, 72.75]
Bridges 2000b[2]	0/587 (0)	0/604 (0)	0.00 [0.00, 0.00]	Not estimable
Supportive trials				
Musto 1997[1, 3]	2/25 (8)	12/25 (48)	–0.40 [–0.62, –0.18]	0.17 [0.04, 0.67]
Wongsurakiat 2004[1,2]	2/62 (3)	5/63 (8)	–0.05 [–0.13, 0.03]	0.41 [0.08, 2.02]
High risk excluded				
Pooled result from random effects model			0.00 [0.00, 0.00]	2.97 [0.12, 72.75]
p value			0.63	0.50
Chi square (*Q*) for heterogeneity: *p* = I^2 statistic with 95% uncertainty interval =			0.83 0%	n/a
All studies				
Pooled result from random effects model			0.00 [-0.02, 0.01]	0.32 [0.13, 0.78]
p value			0.74	0.01
Chi square (*Q*) for heterogeneity: *p* = I^2 statistic with 95% uncertainty interval =			<0.00001 92.5%	0.25 28.4%

[1] High risk study; [2]Hospitalisation due to influenza like illness; [3]Reason for hospitalisation not reported

A significant relative risk of hospitalisation (32%; 95% CI: [13%, 78%]) was detected in the vaccine group compared with the placebo/no intervention group, in the analysis of all studies (p = 0.01). However, when high risk studies (Musto and Wongsurakiat) were excluded from the analysis, no significant difference between the two groups was detected (p = 0.50).

The Jefferson 2007 Cochrane review showed a relative risk of 89% (95% CI: [65%, 120%]) in hospitalisation attributed to vaccination. This effect was largely driven by a study from 1970 which was undertaken during the 1968/1969 pandemic in the USA. Without this study included, there were no differences in hospitalisations between the treatment arms.

In the analysis of all studies, there was no significant difference in the number of patient deaths between the vaccine group and the placebo/no intervention group (p = 0.98). Moreover, there was no significant difference between the two treatment arms when the high risk studies were excluded (p = 0.41).

Adverse events were localised, not systemic reactions. There was no evidence to suggest that the rare adverse reactions that occurred were a result of influenza vaccination. Four types of local adverse events were experienced by a significantly greater proportion of patients in the vaccine group compared to the comparator. Arm soreness/tenderness differed significantly between the two groups ($p<0.00001$) as well as erythema ($p=0.001$), induration (hardening of soft tissue) ($p<0.00001$) and warm feeling ($p=0.0002$). Significant heterogeneity was detected between the studies for each of these events. Some individual studies showed significant differences in the relative risk of further adverse events, such as itching, numbness, oedema, myalgia, fever, headache, sore throat, fatigue or indisposition, coryza, chills, nausea, diarrhoea, cough, rhinorrhea, rash, malaise and other, undescribed adverse events.

For the PBAC's comments on these results, see Recommendation and Reasons.

8. Clinical Claim

The submission claimed that influenza vaccine is therapeutically superior to placebo. The PBAC considered that there was some uncertainty about this clinical claim, *see Recommendation and Reasons*.

9. Economic Analysis

The submission presented a stepped economic evaluation as the modelled evaluation. The choice of a cost-utility approach was considered valid. The resources included were vaccine costs, vaccine administration costs, hospital services and diagnostic tests and imaging.

The submission calculated a base case modelled incremental discounted cost/extra discounted QALY of less than $15,000, increasing to $15,000 - $45,000 if the values of the Jefferson (2007) Cochrane review were used (23% ILI, 11% hospitalisation, 20% pneumonia, compared with 13%, 68% and 68% in the submission, respectively).

The PBAC considered that there was high sensitivity of the cost per QALY saved due to the assumptions used in the model, *see Recommendation and Reasons.*

10. Estimated PBS Usage and Financial Implications

The financial cost per year to the NIP excluding co-payments minus any cost due to the current policy was estimated to be in the range of $10 - $30 million in Year 5.

11. Recommendation and Reasons

The PBAC observed that the inclusion criteria for the trials included a wide and varied range of people of all ages and were therefore not representative of the group for whom listing in the NIP was sought.

The PBAC considered that, although not unreasonable, there is some uncertainty about the submission's clinical claim that influenza vaccination has significant advantages in effectiveness over placebo or no intervention and uncertain toxicity. This was because the claim was based on ILI (which was not confirmed in all the trials and its definition was variable from study to study) and laboratory-confirmed influenza, but there was no difference in hospitalisations or deaths between vaccinated and unvaccinated individuals, if patients at high risk were excluded from the meta-analyses.

The PBAC accepted that the model is driven by influenza-attributable mortality and hospitalisation and these are determined by laboratory-confirmed influenza rates rather than ILI. However, there were a number of problems with the assumptions used in the model. For example, similar efficacy was assumed for the 50-65 year-old age group as for 18-65 year-old age group based upon almost 'similar' immunogenicity response rate rather than geometric mean titres. Further, immunosenescence was assumed to not commence until a patient reaches 65 years and then to decline precipitously.

The PBAC considered that the pivotal assumption that amongst the additionally vaccinated Australian population a clinically observed 68% reduction in laboratory confirmed cases of influenza in healthy patients with vaccination leads to a 68% reduction in influenza related hospitalisations and deaths, was insufficiently substantiated. The PBAC considered that acceptance of this assumption implies that the mortality and hospitalisation rates from influenza are independent of immune response to vaccination. The PBAC agreed it is likely that the patients with no immune response to vaccination in the vaccination setting are also those who were more likely to have had a higher mortality rate and more severe cases in the non-vaccination setting – hence the rate of mortality amongst those who contract influenza in the vaccination arm may be expected to be higher than in those who contract influenza in the non-vaccination arm. Further, it is likely that the patients with no immune response to vaccination in the vaccination setting are also those who were more likely to be more severe cases and present to hospitals in the non-vaccination setting – hence the rate of hospitalisation and complexity of the hospitalised cases (higher cost per hospitalisation) amongst those who contract influenza in the vaccination arm may be expected to be higher than amongst those who contract influenza in the non-vaccination arm.

The PBAC also noted that the model was highly sensitive to hospitalisation rates post influenza.

The PBAC therefore rejected the submission because of uncertainty in clinical benefits in terms of hospitalisation and mortality and uncertainty about the results of the modelled economic evaluation, because of use of an insufficiently substantiated reduction in hospitalisation and mortality rates and the lack of inclusion of a decrement of response to the vaccine with age.

Despite rejecting the submission, the PBAC had some sympathy with the intention of immunising more at-risk individuals and recommended that consideration be given to establishing a subsidy arrangement 'between' the PBS and NIP mechanisms that would more effectively target this group.

12. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

13. Sponsor's Comment

The Influenza Specialist Group (ISG) applied for an extension of the National Immunisation Program (NIP) to include influenza vaccination for all Australians aged 50

- 64 years. This was based on its study indicating that this would constitute a cost-effective extension of the program and previous studies indicating that age-based targeting would be the most effective means of increasing vaccination in the substantial high-risk population within this age cohort.

Although the application was rejected by the Pharmaceutical Benefits Advisory Committee (PBAC), the ISG would like to reaffirm its strong focus on increasing vaccination uptake among Australians at risk of severe complications from influenza and will continue to work to this end.