7.09 HIGH DOSE INACTIVATED TRIVALENT INFLUENZA VACCINE (SPLIT VIRION), pre-filled syringe, 0.5 mL, Fluzone® High-Dose, Sanofi-Aventis Australia Pty Ltd

1 Purpose of Application

1.1 To seek support for the cost-effectiveness of the trivalent influenza vaccine high dose (TIV-HD) vaccine listing on the National Immunisation Program (NIP) schedule from the 2019 influenza season onwards, for people aged ≥65 years, at a price higher than approved for the minor submission recommended by PBAC in January 2018.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults aged 65 years and older
Intervention	TIV-HD (Fluzone High-Dose)
Comparator	QIVs (FluQuadri, Fluarix Tetra, Afluria Quad)
Outcomes	Clinically diagnosed & laboratory confirmed influenza, cardiorespiratory hospitalisation
Clinical claim	Reduction in cases of clinically diagnosed & laboratory confirmed influenza Reduction in cardiorespiratory hospitalisations Acceptable safety profile

HD= high dose; QIV= quadrivalent influenza vaccine; TIV= Trivalent influenza vaccine.
Source: Table 1.1.1, p10 of the submission.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Approved ex-manufacturer price	Proprietary Name and Manufacturer	
INACTIVATED TRIVALENT INFLUENZA VACCINE (SPLIT VIRION), 0.5ML, INJECTION, PREFILLED SYRINGE	1	0	$[redacted]	Fluzone High-Dose	Sanofi-Aventis Australia Pty Ltd

Category/Program:	NIP
NIP indication:	A single injection against influenza disease caused by influenza virus types A and B contained in the vaccine for use in persons 65 years of age and older

2.1 The NIP indication in the current submission was the same as the current NIP listing.

2.2 The submission proposed an approved ex-manufacturer price of $[redacted], which is [redacted] higher than the current price of $[redacted].

3 Background

Registration status

3.1 The TIV-HD was TGA registered on 20 December 2017 for active immunisation against influenza disease caused by influenza virus types A and B contained in the vaccine for use in persons 65 years of age and older.

3.2 TIV-HD (Fluzone High-Dose) for intramuscular injection is an inactivated influenza virus vaccine. It contains 180 micrograms (µg) haemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 60 µg HA of each of the three strains recommended for the 2018 influenza season:

- A/Michigan/45/2015 (H1N1) pdm09-like virus (A/Michigan/45/2015 X-275)
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus (A/Singapore/INFIMH-16-0019/2016 NIB-104)
- B/Phuket/3073/2013-like virus (B/Phuket/3073/2013; Yamagata lineage).

Previous PBAC consideration

3.3 The PBAC recommended listing TIV-HD on the NIP in late January 2018 based on a minor submission using a cost-minimisation approach. In that submission, TIV-HD was recommended at the same price as the quadrivalent influenza vaccine standard dose (QIV-SD).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

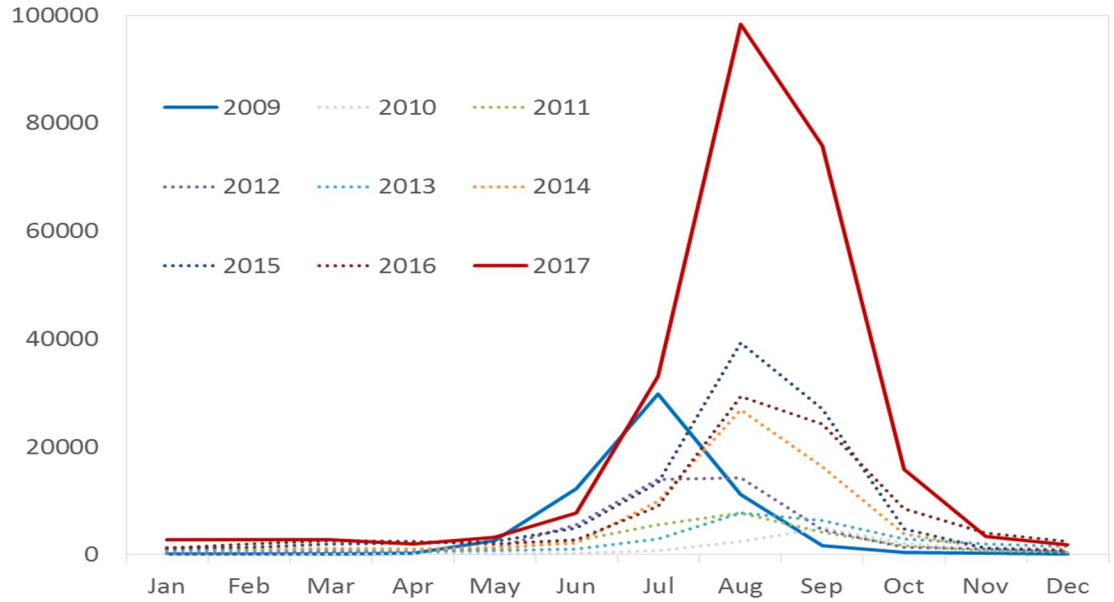
4.1 Influenza is an acute viral infection of the respiratory tract. Beyond the acute symptoms, influenza is also associated with complications including (but not limited to) acute bronchitis, pneumonia (both primary viral and secondary bacterial pneumonia), and cardiovascular complications including myocarditis and pericarditis. There are four types of influenza viruses: influenza A, B, C, and D but only influenza A and B viruses cause clinically important human disease and seasonal epidemics.

4.2 There was a peak of laboratory confirmed influenza in the 2017 influenza season (see Figure 1). Among the notified laboratory confirmed cases of influenza in all ages, a higher proportion was caused by influenza A/H3 in the older adults. However, recent high incidence seasons are likely to have increased community awareness. The ESC noted that the laboratory confirmed influenza data for 2017 likely also reflected improvements in access to testing for viruses.

4.3 There were 233,453 laboratory confirmed notifications of influenza in 2017 up to November 2017 (National Notifiable Diseases Surveillance System, NNDSS); of which

22% were people aged ≥65 years, around 29,000 hospital admissions, and 745 deaths[1].

Figure 1: Number of laboratory confirmed cases of influenza 2009-2017

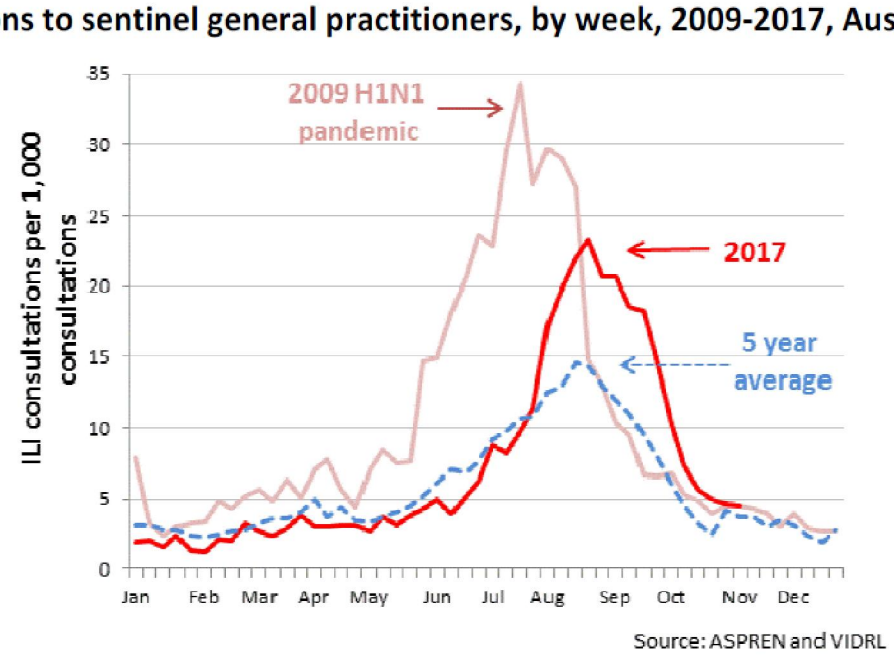


Source: National Notifiable Diseases Surveillance System (as of 7th Jan 2018). Figure 1.1.1, p9 of the submission.

4.4 The ESC considered there was considerable uncertainty with predicting the likely rates of influenza like illness and associated morbidity in future influenza seasons, and the assumed attack rates of influenza will impact the cost-effectiveness of the TIV-HD vaccine. The ESC noted that additional data sources, see Figure 2, suggested that influenza like illness was more common in 2009 than 2017, although these data were not laboratory confirmed cases.

[1] Australian Government Department of Health (2017), 2017 Influenza Season in Australia: A summary from the National Influenza Surveillance Committee

Figure 2: Influenza-like illness presented in general practice 2009-2017, ASPREN and VIDRL



Source: Australian Government Department of Health (2017) 2017 Influenza Season in Australia: A summary from the National Influenza Surveillance Committee

4.5 The ESC considered there were a number of factors relating to the increase in laboratory confirmed cases in 2017, potentially including increased community awareness. Although there was an increase in general practitioner and emergency department presentations for influenza like illness, there was no increase in emergency department presentations for pneumonia.

4.6 The ESC noted the 2017 influenza season used QIV-SD and that vaccine effectiveness estimates based on GP presentations (33%) and hospital presentations (16%) were low compared to other vaccinations for which vaccine effectiveness estimates are typically around 90%. The ESC considered that the 2017 QIV-SD had poor vaccine effectiveness against A/H3N2, the predominant strain, with 10% vaccine effectiveness based on GP presentation compared to 50% and 57% respectively for A/H1N1 and influenza B. Similarly, vaccine effectiveness was higher in adults ≤65 (43%) compared to ≥65 (12%).

4.7 The ESC also considered other factors contributing to lower vaccine effectiveness in 2017 included genetic diversity of dominant strains, that the elderly have reduced responses to vaccines, and persistent problems with A(H3) candidate vaccine viruses which, when propagated in eggs, rapidly acquire adaptive changes which alter antigenicity.

4.8 The ESC considered that it may be possible that those aged ≥65 years require more immunological support and that the timing of vaccination may have impacted immunity throughout the influenza season which is longer than the duration of effect.

4.9 The ESC noted the advice of the Australian Technical Advisory Group on Immunisation (ATAGI) (pre-submission advice) that given variance in strain proportions every year, the relative efficacy of TIV-HD will vary year to year, indicating that a single season of poor vaccine performance should not be focused on for evaluation as they are not consistent, and also noted that influenza vaccines are more effective when there is a high level of influenza activity.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated the current standard of care, the QIV-SD, as the main comparator. The QIV-SD (Fluzone) strains for the 2017-2018 season were: A/Michigan/45/2015 X-275 (H1N1)pdm09-like strain, A/Hong Kong/4801/2014 X-263B (H3N2)-like strain, B/Phuket/3073/2013-like strain and B/Brisbane/60/2008-like strain.

5.2 The nomination of the main comparator is consistent with ATAGI advice (ATAGI February 2018 pre-submission advice), as QIV-SD is current standard of care. The evaluation considered that aTIV-SD vaccine may be a near-market comparator given it was listed on the NIP for the 2018 influenza season. The Pre-Sub-Committee Response (PSCR) questioned the applicability of aTIV-SD as a near-market comparator citing the TGA's view that immunogenicity data available for aTIV-SD was insufficient to demonstrate increased efficacy in prevention of influenza compared to non-adjuvanted standard dose TIV and the outcomes of a recent literature review[2]. The ESC acknowledged there did not appear to be patient-relevant outcomes data on the clinical effectiveness aTIV-SD.

5.3 The ESC noted that should aTIV-SD remain on the NIP after the 2018 season at the current price, it would be [redacted] cheaper than the requested price for TIV-HD in this resubmission. The ESC considered that the ongoing head-to-head RCT of TIV-HD to aTIV-SD in older adults in the US using secondary outcomes (e.g. medical care utilisation, unsolicited adverse events, etc) may be informative[3].

For more detail on PBAC's view, see section 7 PBAC outcome.

[2] Literature Review Update on the Efficacy and Effectiveness of High-Dose (Fluzone® High-Dose) and MF59-Adjuvanted (Fluad®) Trivalent Inactivated Influenza Vaccines in Adults 65 Years of Age and Older. National Advisory Committee on Immunization. 2018. Available at: https://www.canada.ca/en/public-health/services/publications/healthy-living/executive-summary-literature-review-update-efficacy-effectiveness-fluzone-high-dose-fluad-trivalent-inactivated-influenza-vaccines-adults-65-older.html

[3] FLUAD vs. Fluzone High-Dose Study (ClinicalTrials Identifier: NCT03183908). https://clinicaltrials.gov/ct2/show/NCT03183908?term=fluad&age=2&rank=2.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from an individual (1), a health care professional (1) and two organisations (2), the Lung Foundation Australia and Diabetes Australia, via the Consumer Comments facility on the PBS website. The comments were supportive of TIV-HD and noted the severity of the 2017 influenza season, the low levels of vaccine effectiveness in 2017 and the need for improvements in the influenza burden in older Australians, who made up the majority of influenza associated mortality for 2017. The comments also noted the increased risk of influenza for older Australians with chronic diseases, the increased rates of morbidity and mortality in older Australians as well as the increased risk of complications including pneumonia and delayed recovery from influenza for those with diabetes.

Clinical trials

6.3 The submission presented studies which directly assessed measures of laboratory-confirmed influenza and associated cardio-respiratory events. A comparison of immunogenicity endpoints was not considered informative because there are considerable uncertainties in translating immunogenicity data into clinical benefits (p27 of the submission). However, surrogate outcomes have been used previously for PBAC decision-making[4]. The submission did not present any head-to-head randomised controlled trials (RCTs) comparing TIV-HD and QIV-SD. The submission discussed the results of trials comparing TIV-HD to TIV-SD relative to the PBAC's previous conclusion of non-inferiority of QIV-SD versus TIV-SD[5].

6.4 The submission was based on two clinical trials comparing TIV-HD to TIV-SD:

- FIM12: A Phase III/IV, large-scale, multi-centre, randomised, double-blind, active-controlled trial comparing the efficacy and safety of TIV-HD to TIV-SD in adults aged ≥65 years in the US and Canada (N=31,989).
- Gravenstein: A large cluster RCT of nursing home residents aged ≥65 years (N=92,269 were recruited, N=53,008 met the inclusion criteria).

[4] Influenza Vaccine (quadrivalent); 0.5 mL pre-filled syringe; Fluarix tetra® Public Summary Document, March 2015 PBAC meeting. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/fluarix-tetra-psd-03-2015

[5] Influenza Vaccine (quadrivalent); 0.5 mL pre-filled syringe; Fluarix tetra® Public Summary Document, March 2015 PBAC meeting. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/fluarix-tetra-psd-03-2015

6.5 In addition the submission presented DiazGranados et al. 2015, who conducted a supplementary analysis of FIM12 evaluating the effectiveness of TIV-HD compared to TIV-SD in preventing all-cause hospitalisations and serious cardiorespiratory events possibly related to influenza infection.

6.6 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
FIM12	DiazGranados CA et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults	N Engl J Med. 2014 Aug 14;371(7):635-45.
	CSR: Efficacy Study of Fluzone High-Dose Vaccine Compared With Fluzone Vaccine In Elderly Adults	21 November 2013
	DiazGranados CA et al. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty	Vaccine. 2015 Aug 26;33(36):4565-71.
	DiazGranados CA et al. Effect of Previous-Year Vaccination on the Efficacy, Immunogenicity, and Safety of High-Dose Inactivated Influenza Vaccine in Older Adults	Clin Infect Dis. 2016 May 1;62(9):1092-1099.
	DiazGranados CA et al. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines.	Vaccine. 2015 Sep 11;33(38):4988-93
Gravenstein	Gravenstein et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial	Lancet Respir Med 5 (9): 738-746, (2017).

Source: Table 2.2.1, p34 of the submission.

6.7 The key features of the randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	Number of participants	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
TIV-HD versus TIV-SD						
FIM12	TIV-HD (year 1): 7,254 TIV-SD (year 1): 7,243 TIV-HD (year 2): 8,738 TIV-SD (year 2): 8,748	2 years	Low	Healthy adults aged ≥65 years	Occurrences of culture- or PCR confirmed influenza; Rates of all-cause hospitalisations and selected cardiorespiratory events reported by DiazGranados	Used
Gravenstein	TIV-HD: 26,639 TIV-SD: 26,369	1 year	Moderate	Nursing home residents	Hospital admissions related to pulmonary and influenza-like illness	Not used

TIV-HD: High dose trivalent influenza vaccine; TIV-SD: Standard dose trivalent influenza vaccine
Source: Table 2.4.2, p41 of the submission; Table 2.4.4, p42 of the submission; Table 2.4.5, p43 of the submission.

6.8 Gravenstein was a single-blinded RCT – the researchers were blinded to the allocation of the nursing homes during the analysis, however the nursing home residents receiving the vaccine and the facility staff were not blinded. It was not reported whether the outcome assessors were blinded. Consequently, the risk of bias is moderate.

6.9 Studies for estimating the vaccine efficacy were conducted in North America. Translating the results to Australia remains uncertain given year to year variability in

influenza strains and severity of the season. The PSCR stated it was reasonable to consider the conclusions as an appropriate proxy for unpredictable future Australian influenza seasons. The ESC considered in the context of variable influenza seasons, the applicability to the Australian population was less relevant than the internal validity of the studies. On balance, the PBAC remained concerned that the year to year variation in predominant strain and severity made the impact of the loss of protection against the alternative B lineage uncertain.

Comparative effectiveness

6.10 Table 4 summarises key outcomes from the FIM12 trial.

Table 4: Efficacy of TIV-HD relative to TIV-SD against serious events possibly related to influenza (intent-to-treat analysis, Year 1 and Year 2 combined) in the FIM12 trial

Serious event category	TIV-HD (N = 15,990), n (rate)	TIV-SD (N = 15,993), n (rate)	Combined, rVE (95%CI) N=31,983
Associated with PD-ILI	**228 (1.43)**	**301 (1.88)**	**24.24 (9.71; 36.50)**
Influenza A	**190 (1.19)**	**250 (1.56)**	**23.99 (7.84; 37.39)**
A/H1N1	8 (0.05)	9 (0.06)	11.09 (-159.6; 70.15)
A/H3N2	**171 (1.07)**	**223 (1.39)**	**23.30 (5.97; 37.53)**
Influenza B	38 (0.24)	51 (0.32)	25.48 (-15.68; 52.36)
Victoria lineage	9 (0.06)	11 (0.07)	18.17 (-117.2; 70.03)
Yamagata lineage	24 (0.15)	36 (0.23)	33.32 (-14.89; 61.94)
All-cause hospitalisation	**1530 (95.68)**	**1643 (102.73)**	**6.9% (0.5 to 12.8)**
Serious cardiorespiratory events	**428 (26.77)**	**520 (32.51)**	**17.7% (6.6 to 27.4)**
Pneumonia events	**71 (4.44)**	**118 (7.38)**	**39.8% (19.3 to 55.1)**
Asthma/COPD/bronchial events	74 (4.63)	75 (4.69)	1.3% (-36.0 to 28.4)
Influenza events	4 (0.25)	6 (0.38)	33.3% (-136.2 to 81.2)
Coronary artery events	121 (7.57)	124 (7.75)	2.4% (-25.3 to 24.0)
Congestive heart failure	57 (3.56)	75 (4.69)	24.0% (-7.2 to 46.1)
Cerebrovascular events	72 (4.50)	77 (4.81)	6.5% (-28.9 to 32.1)
Other respiratory events	31 (1.94)	47 (2.94)	34.0% (-3.8 to 58.1)

Notes: rate = events per 1000 participant-seasons;
Events in **bold** denotes that the vaccine efficacy in that category was statistically significant.
PD-ILI: Protocol-defined influenza like illness; CI: confidence interval; COPD: chronic obstructive pulmonary disease; TIV-HD: high-dose inactivated influenza vaccine; TIV-SD: standard-dose inactivated influenza vaccine; rVE: relative vaccine efficacy.
Source: Table 2.5.1, p43-44 of the submission; Table 2.5.3, p45 of the submission.

6.11 The vaccine efficacy of TIV-HD relative to TIV-SD against lab-confirmed influenza caused by any viral types/subtypes was 24.24% (95% CI 9.71; 36.50) for Year 1 and Year 2 combined. The lower bound of the 95% CI exceeded 9.1%, the pre-defined superiority threshold for TIV-HD compared to TIV-SD.

6.12 ATAGI considered that an overall relative vaccine efficacy of 24.2% (95%CI: 9.7%–36.5%) is most appropriate for the base case assessment (ATAGI February 2018 pre-submission advice). However, the vaccine efficacy in terms of reduction in influenza events was not statistically significant for H1N1. Given there were only 8 and 9 H1N1 events in the TIV-HD and TIV-SD group respectively, the non-statistical significance might be due to the small number identified in each group. In addition, the lower bound of the 95% CI for H3N2 did not exceed the pre-defined superiority threshold

(i.e. 9.1%) and vaccine efficacy against influenza type B was not statistically significant.

6.13 Given the vaccine efficacy varied in different influenza strains, it is reasonable to conclude that the vaccine efficacy is likely to vary partially based on the dominant influenza strain of the season. The ESC noted that the vaccine efficacy was not statistically significant for H1N1 in the trials presented, however considered that this is also affected by how much H1N1 is circulating in a given year.

6.14 In the FIM12 trial a relative efficacy of 6.9% (95%CI: 0.5%-12.8%) was reported for the reduction in all-cause hospitalisations, and a composite outcome of 17.7% (95%CI: 6.6%-27.4%) was reported for the reduction in serious cardiorespiratory events (Table 4).

6.15 The reduction in all-cause hospitalisations in FIM12 did not reach the minimally clinically important relative reduction in the rate of hospitalisations set in the Gravenstein trial (15%). The evaluation considered that that 'all-cause hospitalisations' may overestimate the number of hospitalisations due to influenza. The ESC discussed that 'all-cause' hospitalisations associated with presentation of influenza will be for a range of disorders and the difference in this outcome may not be reasonably attributed solely to the vaccine efficacy. The PBAC considered this advice and noted that there was consistent evidence across the trials of some reduction of hospitalisation although not directly attributable to influenza in the TIV-HD cohort, which was plausible given the comorbidities of patients in this age group.

6.16 While the relative vaccine efficacy was statistically significant for the reduction in serious cardiorespiratory events as a composite outcome (0.177, 95% CI: 0.066, 0.274), the vaccine efficacy varied in different types of cardiorespiratory events; only the reduction in pneumonia events was statistically significant.

6.17 Table 5 summarises key outcomes from the Gravenstein study.

Table 5: Adjusted regression analysis results of primary outcome accounting for clustering by 817 nursing homes (intent-to-treat analysis) in the Gravenstein study

	Adjusted relative risk (95% CI)	p value
FFS group analysis (the primary endpoint)		
Hospital admissions for respiratory illness	0.873 (0.776–0.982)	0.023
FFS group analysis (the secondary outcomes)		
All-cause hospital admissions	0.915 (0.863–0.970)	0.0028
MDS group analysis (the secondary outcomes)		
All-cause mortality	0.985 (0.931–1.038)	0.57
All-cause hospital admissions	0.933 (0.884–0.985)	0.012
Functional decline (change in ADL score of at least four points)	0.996 (0.956–1.038)	0.86

ADL: activities of daily living; FFS: fee-for-service; MDS: minimum dataset
Source: Table 2.5.4, p47 of the submission; Table 2.5.5, p47 of the submission.

6.18 The relative risk of hospitalisation related to pulmonary and influenza-like conditions was significantly lower in facilities where residents received TIV-HD than in those that received TIV-SD [0.873 (95%CI: 0.776-0.982)].

6.19 The reduction in hospitalisation related to pulmonary and influenza-like conditions did not reach the minimally clinically important relative reduction (15%).

6.20 It should be noted that the mean age in the Gravenstein trial was approximately 10 years older than those in the FIM12 trial.

6.21 The PBAC noted NNDSS data[6] on laboratory confirmed influenza strains showing variation in B strain prevalence from 2013 to 2017 of 26%, 10%, 39%, 7% and [redacted] respectively. The PBAC noted that there was an average of B strain prevalence of [redacted] across those years, however this varied annually.

6.22 The PBAC noted additional data (see Table 6) from ATAGI (Pre-submission advice) which showed that over the six years, 2011 to 2016, B strain was responsible for an average of 18% of hospitalisations in the proposed population, again with high variation across years. The PBAC noted the variation in B strain prevalence over this period and ATAGI's advice that there does not appear to be a regular pattern over time in the proportions of A and B strains.

Table 6: Proportion of cases attributable to influenza types A and B among hospitalised influenza cases aged ≥65 years, 2011-2016 (Unpublished data from FluCAN)

	2011	2012	2013	2014	2015	2016
Influenza activity level	Moderate	High	Moderate	High	High	Moderate*
All hospitalisations						
% Type A	83.8%	92.7%	68.0%	93.1%	56.7%	96.5%
% Type B	16.3%	7.3%	32.0%	6.6%	42.7%	3.4%

Source: ATAGI Pre-submission advice

6.23 The PBAC also noted additional data (see Table 7) from ATAGI (Pre-submission advice) which included data across 2002 to 2016 showing the proportion of B strain influenza, distribution of B lineage and vaccine matching success over that time. These data showed that the predominant B lineage over time has varied and that the match between the lineage and vaccine inclusion has varied.

[6] http://www9.health.gov.au/cda/source/pub_influ.cfm, Influenza (laboratory confirmed) public dataset
The data provided were extracted from the NNDSS on 3 July 2018. Due to the dynamic nature of the NNDSS, data in this extract are subject to retrospective revision and may vary from data reported in published NNDSS reports and reports of notification data by states and territories.

Table 7: Proportion of B subtypes out of all notified cases with subtype information, and different B lineages in Australians aged ≥65 years, by year, 2002-2016

Year	Proportion of influenza due to influenza B % (*N*)*	Distribution of B lineages#		Lineage of influenza B component in the TIV for the season	Match between B lineage in vaccine and circulating lineage
		Proportion of B that is of Victoria lineage % (*N*)	Proportion of B that is of Yamagata lineage % (*N*)		
2002	13.0 (56)	100 (11)	0	Yamagata	Poor
2003	7.4 (27)	0	0	Victoria	N/A
2004	16.0 (54)	7 (1)	93 (13)	Victoria	Poor
2005	15.4 (85)	31 (8)	69 (18)	Yamagata	Good
2006	16.6 (76)	100 (1)	0	Victoria	Good
2007	12.8 (146)	0	100 (22)	Victoria	Poor
2008	40.2 (436)	49 (23)	51 (24)	Yamagata	Partial
2009†	3.1 (61)	50 (1)	50 (1)	Yamagata	Partial
2010	11.3 (106)	100 (10)	0	Victoria	Good
2011	21.3 (544)	94 (50)	6 (3)	Victoria	Good
2012	12.2 (860)	55 (30)	45 (25)	Victoria	Partial
2013	25.9 (987)	5 (4)	94 (80)	Yamagata	Good
2014	9.9 (1108)	7 (4)	93 (52)	Yamagata	Good
2015	39.6 (6201)	37 (116)	63 (200)	Yamagata	Partial
2016§	6.6 (1388)	19 (12)	81 (51)	Victoria	Poor

N/A = not applicable

* Proportional burden of influenza due to influenza B based on notifications to NNDSS with subtype information, 2002–2016

\# Proportion of influenza B attributable to Victoria or Yamagata lineages obtained from WHO CC data, 2002–2016

† 2009 was a pandemic year with H3N2 being the dominant strain

§ QIV was the only type of influenza vaccine used under the NIP during the 2016 influenza season

6.24 The PBAC noted ATAGI's advice (Pre-submission advice) regarding the unpredictable variation in strain prevalence over time, the likely impact of the lost B strain in the proposed population, cross-protection in a mismatched vaccine, and the risk of B strain mismatch. The Committee considered that although some factors favoured the argument that TIV-SD may be a suitable proxy for QIV-SD, other factors did not.

Benefits/harms

6.25 A summary of the comparative benefits and harms for TIV-HD versus TIV-SD is presented in Table 8. The benefit results were only derived from the FIM12 trial as results from the Gravenstein study were not used in the economic model as the Gravenstein study was conducted in the aged care setting (a sub-set of the NIP population).

Table 8: Summary of comparative benefits and harms for TIV-HD and TIV-SD

Trial	TIV-HD (n)	TIV-SD (n)	rVE (95% CI)	Event rate/1000 patients*		RD/1000 patients
				TIV-HD	TIV-SD	
Benefits: FIM12						
Associated with PD-ILI	228	301	24.24% (9.71% to 36.50%)	14.3	18.8	-4.5
All-cause hospitalisation	1530	1643	6.9% (0.5% to 12.8%)	95.68	102.73	-7.05
Pneumonia events	71	118	39.8% (19.3% to 55.1%)	4.44	7.38	-2.94
Harms						
	TIV-HD (n)	TIV-SD (n)	RR (95% CI)	Event rate/100 patients		RD
				TIV-HD	TIV-SD	
FIM12						
SAE	1323	1442	NA	8.27	9.02	-0.75%
Death	83	84	NA	0.52	0.53	-0.01%
AE of Special Interest	3	6	NA	0.02	0.04	-0.02%
SAE leading to study discontinuation	99	103	NA	0.62	0.64	-0.02%
Related SAE	3	0	NA	0.02	0	0.02%
FIM05 **						
Solicited reaction (D0 to D7)	1378	556	NA	53.6	44.1	9.5%
Solicited injection site reaction	1076	394	NA	41.8	31.3	10.5%
Solicited systemic reaction	882	370	NA	34.3	29.4	4.9%

* Duration of follow-up: FIM12: 2 years

** As FIM12 did not capture immediate reactions or non-serious AEs, the submission reported data on injection site reactions and low grade systemic reactions such as fever, headache, malaise, and myalgia from the FIM05 trial.

CI: confidence intervals; NA: not applicable; PD-ILI: Protocol-defined influenza like illness; TIV-HD: High dose trivalent influenza vaccine; TIV-SD: Standard dose trivalent influenza vaccine; RD: risk difference;

Source: Table 2.5.1, p43-44 of the submission; Table 2.5.3, p45 of the submission; Table 2.5.6, p48 of the submission, Table 2.5.7, p50 of the submission and calculated during evaluation.

6.26 On the basis of direct evidence presented by the submission, for every 1,000 patients treated with TIV-HD in comparison to TIV-SD and over a 2 years duration of follow-up:

- Approximately 4 fewer patients would have the protocol-defined influenza like illness;
- Approximately 7 fewer patients would have all-cause hospitalisation;
- Approximately 3 fewer patients would have pneumonia events;
- Approximately 8 fewer serious adverse events;
- Approximately 95 additional solicited reactions;
- Approximately 105 additional solicited injection site reactions; and
- Approximately 4.9 additional solicited systemic reactions.

6.27 This benefits/harms information relates to the comparison of TIV-HD to TIV-SD, not the comparator for the submission, QIV-SD.

6.28 The PBAC noted that the benefits/harms table relied on data from influenza seasons in North America with a low prevalence of B strain influenza, which increased uncertainty around the impact of TIV-HD on B strains in terms of relative efficacy given the loss of a B strain in TIV versus the QIV-SD comparator.

Clinical claim

6.29 The submission claimed that, based on the evidence available:

- TIV-HD is superior to TIV-SD in terms of reductions in cases of clinically diagnosed and laboratory confirmed influenza
- TIV-HD is superior to TIV-SD in terms of reduction in cardiorespiratory hospitalisations
- TIV-HD is well tolerated with an acceptable safety profile
- When comparing with the QIV-SD, the absence of the additional lineage in TIV-HD is not expected to result in substantially reduced protection from influenza infection in the proposed NIP patient population.

6.30 The ESC considered it was reasonable to claim that TIV-HD is superior to TIV-SD in terms of reductions in cases of clinically diagnosed and laboratory confirmed influenza, and that TIV-HD is well tolerated with an acceptable safety profile. However, the claim that TIV-HD is superior to TIV-SD in terms of reducing cardiorespiratory hospitalisations as a composite outcome is not adequately supported given that the vaccine efficacy was only significant in reducing pneumonia but not in other cardiorespiratory events.

6.31 The ATAGI pre-submission advice noted that the key question associated with the submission was whether the additional protection of the high-dose formulation of TIV is greater than the protection conferred by the additional antigenically distinct alternative B lineage included in QIV. The evaluation considered that without head-to-head comparison between TIV-HD to QIV-SD, it remained uncertain whether TIV-HD was superior compared to QIV-SD given the previous finding that QIV-SD might be superior in immunogenicity results compared to TIV-SD against the influenza B strain not included in the TIV-SD vaccine[7]. The PSCR suggested the loss of the alternate B lineage will likely be less relevant given most infections in the target population are A/H3N2. The ESC sought additional verbal advice from ATAGI during

[7] Influenza Vaccine (quadrivalent); 0.5 mL pre-filled syringe; Fluarix tetra® Public Summary Document, March 2015 PBAC meeting. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/fluarix-tetra-psd-03-2015

the meeting on this issue and was advised that there is sufficient evidence that the effect of TIV-HD compared to TIV-SD could be a proxy for the effect of TIV-HD compared to QIV-SD. The value of the additional benefit of TIV-HD compared to QIV-SD beyond 12 months is unclear.

6.32 The PBAC noted the ATAGI verbal advice and considered that although the clinical trials supported benefit of TIV-HD compared to TIV-SD, the extrapolation of this effect to QIV-SD was uncertain given the marked variation in B strain prevalence across different influenza seasons and there was therefore insufficient evidence on which to determine cost effectiveness.

6.33 The PBAC considered that the claim of an acceptable comparative safety profile was reasonable, noting the increased frequency of mild to moderate injection site reactions.

Economic analysis – cost-utility

6.34 A cost-effectiveness (cost per life year gained) and cost-utility (cost per quality adjusted life year (QALY) gained) analysis comparing a national TIV-HD immunisation program with QIV-SD immunisation across the Australian population aged ≥ 65 years was conducted. Health benefits for the vaccinated cohort were estimated directly using a 1-year static Markov model and no indirect herd immunity benefits were included.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	1 year, with the loss of future years of life due to premature mortality were discounted to the 1-year horizon of the model.
Outcomes	Confirmed influenza cases, hospitalisations, fatal influenza events prevented, years of life and QALYs.
Methods used to generate results	Decision analysis.

Component	Summary	
Health states	Well Confirmed influenza cases (resulting in GP visits, ED visits or neither) Hospitalisations (influenza-related and cardiovascular-related) Influenza related mortality Background mortality	The model estimated the number of influenza cases (resulting in GP visits, ED visits or neither) and the number of hospitalisations (influenza-related and cardiovascular-related) separately. This in theory is reasonable; however the estimated number of hospitalisations was greater than the number of confirmed influenza cases. This may be because of a) more than one hospitalisation per case or b) case confirmation and hospitalisation attribution approaches used in the FIM12 trial. The PSCR stated this was a deliberate decision given the supplementary analysis included influenza-related hospitalisations based on any hospital admission with a Medical Dictionary for Regulatory Activities (MEDRA) code independently adjudicated as being possibly related to influenza, irrespective of whether the patient met the relevant clinical or laboratory case definitions. The ESC considered that the submission did not verify the proportion of individuals in the FIM12 trial who had both a respiratory and a cardiovascular hospitalisation, and whether the model results accurately reflected this; the approach to modelling hospitalisation may overestimate those related to influenza, impacting the cost-effectiveness of TIV-HD. The Pre-PBAC Response stated that the number of individuals with both a respiratory and cardiovascular hospitalisation was not available. It added that the economic model considered the actual number of hospitalisations with a primary diagnosis determined to be possibly related to influenza.
Transition probabilities	Background incident rates of influenza: FIM12 trial. The same attack rates were applied to the unvaccinated QIV-SD and TIV-HD arms.	ATAGI recommended the FIM12 trial should be used given the systematic under reporting of influenza cases (ATAGI February 2018 pre-submission advice). The FIM12 trial was conducted over high and low incidence influenza seasons in North America, but with high influenza type A prevalence. Although undertaken in North America, the use of FIM12 trial data, as opposed to using assumed multiples of recorded Australian cases, provides real world data.
	Background influenza A subtypes strain prevalence: NNDSS time series 2002-2016 data	The data source is appropriate. Although ATAGI noted data on the proportion of influenza A disease attributable to A subtypes is generally not reliable in Australia (ATAGI February 2018 pre-submission advice). ATAGI also did not consider it appropriate to use a simple average estimate of the proportion of influenza due to different subtypes over a longitudinal period (ATAGI February 2018 pre-submission advice).
	Background influenza B lineage prevalence: WHO-CC time series data 2002-2015	The data source is appropriate. Although ATAGI did not consider it appropriate to use a simple average estimate of the proportion of influenza due to different subtypes over a longitudinal period (ATAGI February 2018 pre-submission advice).
	VE against confirmed cases: Estimated indirectly using strain specific VE from Clements et al., 2014 for TIV-SD and QIV-SD against Type A and matched/unmatched B lineages in Australia and weighted by prevalence of Type A and B lineages. Relative VE for TIV-HD vs TIV-SD (24.2%) was based on the FIM12 trial.	The proportion of influenza cases attributable to A and B strains varies with season, which confounds the weighted VE calculations.

Component	Summary	
	VE against hospitalisations: Supplementary analysis of the FIM12 trial. VE against respiratory hospitalisation outcomes for TIV-SD and QIV-SD: 30% VE against hospitalisation for cardiovascular events for TIV-SD and QIV-SD: 20% Relative VE against respiratory hospitalisation TIV-HD vs TIV-SD: 27.3%. Relative VE against cardiovascular hospitalisation TIV-HD vs TIV-SD: 9.4%	ATAGI considered that cardiovascular disease should not be included as a potential health benefit (ATAGI February 2018 pre-submission advice), and results from the FIM12 trial do not support the use of a relative risk reduction in cardiovascular hospitalisation being associated with TIV-HD vaccination – due to the effect being driven by pneumonia. It is inappropriate to include cardiovascular hospitalisation in the base case. The VE of TIV-SD against the risks of hospitalisation were based on rates of illness (influenza/pneumonia, respiratory and cardiorespiratory) from the supplementary analysis FIM12 trial. However, the submission did not use the rates of hospitalisations from trial FIM12. The basis for the assumed hospitalisation rates was unclear. The relative VE of TIV-HD for hospitalisations was based on the FIM12 trial. The PSCR stated that the absolute efficacy of influenza vaccines against hospitalisation is subject to considerable debate, and that available studies and meta-analyses have produced relatively heterogeneous results, and the sponsor is open to re-specification of assumptions if alternative data sources are identified. The submission also assumed QIV-SD and TIV-SD have the same vaccine efficacy against hospitalisations. Although the benefits of TIV-HD may outweigh the potential loss of protection against the mismatched B strain in QIV-SD compared to TIV-SD, the ESC considered there is likely to be some value in the alternative B strain not accounted for in the model. The results were sensitive to the TIV-HD vs comparator (TIV-SD or QIV-SD) VE relative risks against hospitalisation.
	Vaccine coverage: AIHW 2009 Adult vaccination survey	This may understate coverage given the survey is dated and recent high incidence seasons are likely to have increased community awareness.
	Herd immunity: None	This is most likely a conservative assumption as a large population (65+ year old Australians) would be targeted with a higher dose vaccine. This population has the highest incidence of influenza.
	Hospital case-fatality rate: AIHW national hospital morbidity database for Australia	This is appropriate.
	Background mortality: Australian Bureau of Statistics	This is appropriate.
Utilities	Published studies including Turner et al., 2003, McPhail and Haines, 2010 and Hawthorne et al., 2013	These sources are appropriate. The McPhail and Haines 2010 study used EQ-5D utility and VAS and Turner (2003) used VAS equivalent scores which were converted to TTO from a series of randomised trials. The method for the estimation of age-related disutilities for cases and hospitalisation was not clear. For example, disutilities per day in hospital of 0.2620 were subtracted from 'well' expected for 65+ year olds which differs from 0.2870 for conventional EQ-5D change in McPhail and Haines 2010 study. This issue only has a minor impact given 95% of incremental QALYs were associated with mortality impacts.
Costs	Direct medical costs, including vaccine administration costs, GP and ED treatment of confirmed cases, along with averaged AR-DRG costs for cardiovascular and respiratory-related influenza hospital admissions.	
Perspective	Australian health system	
Discount rate	The standard PBAC discounting approach of 5% per annum for estimated foregone QALYs as a result of premature mortality.	

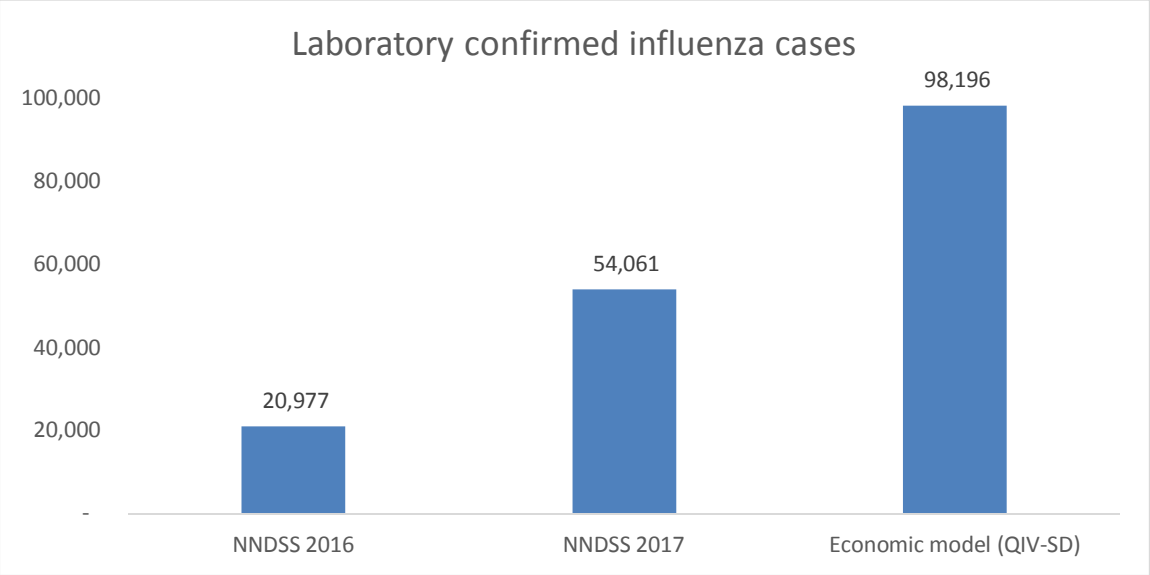
ED: Emergency department; GP: General practitioner; QALY: quality adjusted life years; QIV-SD: Standard dose quadrivalent influenza vaccine; TIV-HD: High dose trivalent influenza vaccine; TIV-SD: Standard dose trivalent influenza vaccine; TTO: time trade-off; VAS: visual analogue scale; VE: vaccine efficacy.

6.35 The ESC noted that the model estimated 98,196 influenza cases, 69,733 influenza-related hospitalisations and 2,427 influenza-attributable deaths for the QIV-SD arm using inputs estimated using FIM12 data for TIV-SD. These estimates are substantially higher than the National Notifiable Diseases Surveillance System estimates for 2017[8] and result in significant cost-savings. This approach favours TIV-HD. The ESC noted data (see Figure 3) presenting the number of influenza cases in Australia in 2016 and 2017 and the numbers estimated in the model and questioned whether the model had overestimated the number of cases at 98,196 compared to 54,061 in 2017, almost double the number seen in 2017. Similarly, the ESC questioned the number of influenza-related hospitalisations; given Australian data from 2017 reported 29,000 cases, compared to the model estimates of 69,733, over double the number seen in 2017, see Figure 4. NNDSS influenza-attributable death data was also substantially lower than estimated in the model (see Figure 5 below).

6.36 The Pre-PBAC Response stated that given surveillance systems are widely acknowledged to under-ascertain the true influenza burden, use of the estimates of disease burden from a RCT with intensive follow up such as the FIM12 was a reasonable source of estimate of the true average burden of disease in Australia and the variation of this with the NNDSS data further highlights under ascertainment in the NNDSS. The PBAC acknowledged the issues of under-reporting in the surveillance data, however it was considered the modelled influenza illness and hospitalisation estimates were high compared to recent years in Australia and may be overestimated.

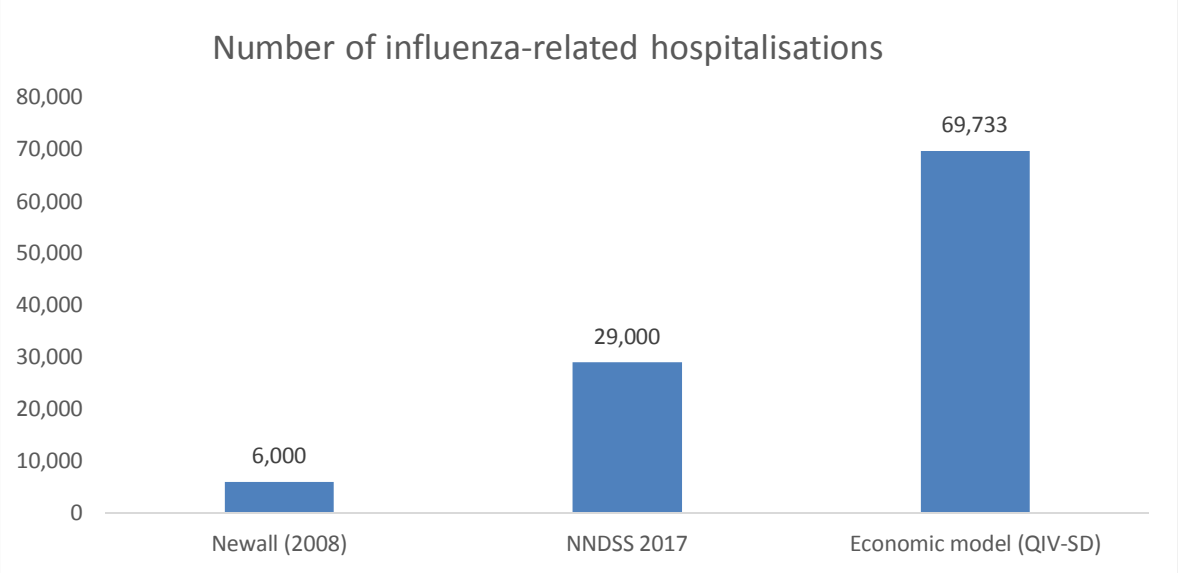
[8] National Notifiable Diseases Surveillance System (NNDSS), Department of Health www9.health.gov.au/cda/source/cda-index.cfm

Figure 3: Influenza cases identified by National Notifiable Diseases Surveillance Scheme (NNDSS) (2016–17) vs model



Source: constructed during the ESC[9]

Figure 4: Influenza-related hospitalisations — NDSS (2017) and Newell (2008) vs model

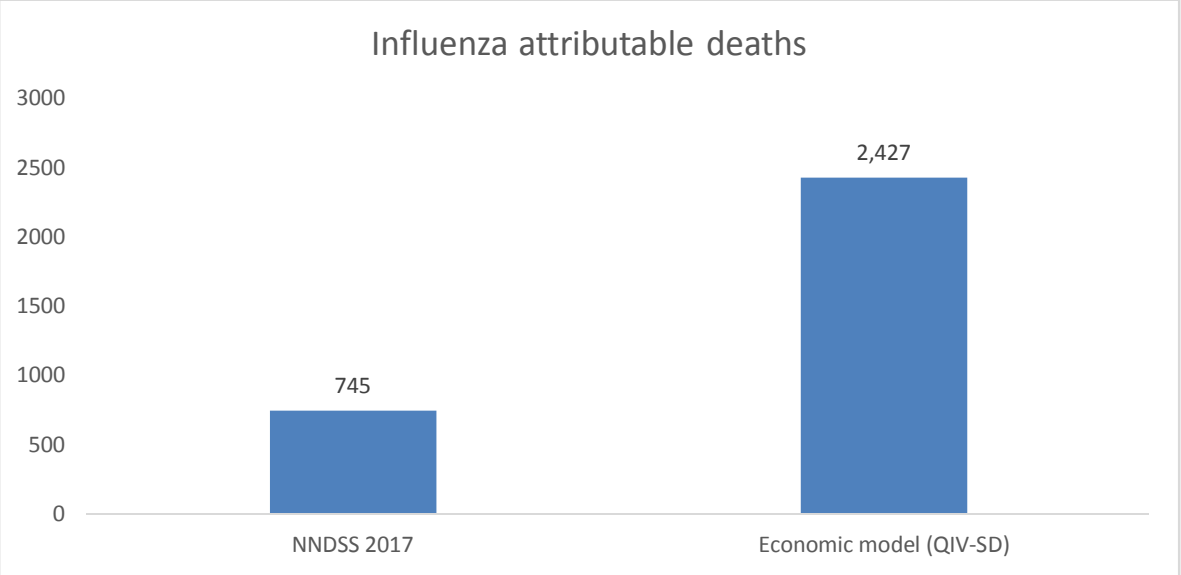


Source: constructed during the ESC[10]

[9] National Notifiable Diseases Surveillance System (NNDSS), Department of Health www9.health.gov.au/cda/source/cda-index.cfm

[10] Newall, A. T., Wood, J. G. & MacIntyre, C. R. 2008b. Influenza-related hospitalisation and death in Australians aged 50 years and older. *Vaccine,* 26**,** 2135-41; National Notifiable Diseases Surveillance System (NNDSS), Department of Health, www9.health.gov.au/cda/source/cda-index.cfm

Figure 5: Influenza-related hospitalisations — NDSS (2017) and Newell (2008) vs model



Source: constructed during the ESC[11]

[11] National Notifiable Diseases Surveillance System (NNDSS), Department of Health www9.health.gov.au/cda/source/cda-index.cfm

Table 10: Key drivers of the model

Description	Method/value	Impact
Increasing background influenza attack rates in Australia	The background attack rates were taken from the FIM12 trial in North America, where high and low influenza activity was evident, but with high influenza type A prevalence. The results of the economic model are confounded by the cyclical nature of low-moderate-high influenza seasons, and the proportion attributable to A and B strains. The PSCR argued that it is impossible to accurately predict the intensity and strain composition of future influenza seasons. The ESC considered this to be reasonable, however it was unclear whether 2017 is the peak of the influenza cycle and the incidence would return to lower levels in future years. The Pre-PBAC Response noted that the economic evaluation relied on two low and one moderate North American influenza season, not the Australian 2017 season.	High. Favours TIV-HD if Australian attack rates fall or the proportion due to influenza type B rises.
Inclusion of avoided cardiovascular hospitalisations	The model included the impact of TIV-HD on influenza related hospitalisations using data from the FIM12 trial. Differences in cardiovascular hospitalisations were only statistically significant for pneumonia, yet vaccine efficacy against other cardiorespiratory events were included in the model. The PSCR reiterated that three alternative case definitions based on hospitalised cases were modelled and all suggested TIV-HD was cost-effective. The complications from influenza are broad, however the ESC considered that the use of the broader category of all-cause hospitalisations was inappropriate as there was inadequate evidence of improved efficacy against serious cardiorespiratory events beyond pneumonia and the model would attribute benefits to the vaccine which may not be realised in clinical practice should patients be hospitalised for other causes which remain without the presence of flu-like illness. As noted above, the model has estimated substantially higher cases and costs for hospitalisations for QIV-SD than the NNDSS estimates from 2017.	High, favours TIV-HD
QIV-SD and TIV-SD VEs against hospitalisations assumed to the same	The submission assumed the VE of TIV-SD. The basis for this assumption was unclear. Furthermore, the submission also assumed QIV-SD and TIV-SD have the same vaccine efficacy against hospitalisations. This assumption ignores the benefit of the mismatched B strain in QIV-SD.	Moderate, favours TIV-HD.
High cost of respiratory hospital admission	Costs of respiratory and cardiovascular hospitalisations were estimated using averaged Round 19 Australian public hospital AR-DRGs. The distribution of severity was not discussed in the FIM12 trial, nor was the average number of days per admission. In the event there is a greater proportion of lower complexity admissions, the use of the average would overestimate avoided costs. The PSCR acknowledged the uncertainty around the estimates and argued as the AR-DRG data are not age specific, it would not be unreasonable to assume that those ≥65 might on average present with more complex admissions, which would reduce the ICER. The ESC considered that the estimate of avoided costs was uncertain, however it was possible that costs associated with respiratory hospital admissions due to influenza like illness and pneumonia are less severe and complex compared to the average AR-DRG.	Moderate, favours TIV-HD.

QIV-SD: Standard dose quadrivalent influenza vaccine; TIV-HD: High dose trivalent influenza vaccine; TIV-SD: Standard dose trivalent influenza vaccine; VE: vaccine efficacy.
Source: compiled during the evaluation

Table 11: Results of the economic evaluation

Cost-Effectiveness Results (LYs)					
Vaccine	**Total Costs**	**Total LYs**	**Inc Costs**	**Inc LYs**	**ICER**
TIV-HD	$[redacted]	9.5299	-$[redacted]	0.0010	TIV-HD dominates QIV-SD: Cheaper and more effective
QIV-SD	$[redacted]	9.5288			
Cost-Effectiveness Results (QALYs)					
Vaccine	**Total Costs**	**Total QALYs**	**Inc Costs**	**Inc QALYs**	**ICER**
TIV-HD	$[redacted]	7.2500	-$[redacted]	0.0008	TIV-HD dominates QIV-SD: Cheaper and more effective
QIV-SD	$[redacted]	7.2492			

LY: Life years; QALYs: quality adjusted life years. ICER: incremental cost-effectiveness ratio; TIV-HD: Trivalent Influenza Vaccine – High Dose, QIV-SD: Quadrivalent Influenza Vaccine – Standard Dose.
Source: p82 of the submission

6.37 The trial evidence suggested a reduction in hospitalisations and deaths from influenza is associated with TIV-HD; however there is uncertainty around the model's hospitalisation estimates, its applicability to the Australian population and whether the influenza burden will continue to increase in time. The ESC noted that no stepped economic evaluation was conducted which made the results less transparent. The Pre-PBAC Response acknowledged the uncertainty around hospitalisation estimates but argued that the relative effect of TIV-HD in reducing hospitalisations associated with influenza is robust, applicable to the Australian setting, irrespective of absolute burden of influenza over time and is supported by the FIM12 and Gravenstein trials.

6.38 TIV-HD resulted in higher QALYs (0.0008) and was cost-saving. Correspondingly, TIV-HD was the dominant strategy.

Table 12: Health care resource items: disaggregated summary of cost impacts in the economic evaluation

Outcomes	**QIV-SD**	**TIV-HD**	**Net Difference**
Costs			
Vaccination	$[redacted]	$[redacted]	[redacted]
Vaccine administration	$[redacted]	$[redacted]	$[redacted]
Prescription meds	$433,493	$383,326	-$50,168
Influenza-related GP Visits	$1,829,263	$1,617,565	-$211,699
Influenza-related ED Visits	$1,340,333	$1,185,218	-$155,115
Influenza-related hospitalisations	$500,053,271	$408,110,173	-$91,943,098
Cardiovascular-related hospitalisations	$763,532,879	$713,187,811	-$50,345,068
Total Direct Healthcare	**$[redacted]**	**$[redacted]**	**-$[redacted]**
Outcomes			
Influenza cases	98,196	86,832	-11,364
Influenza-related GP Visits	49,373	43,659	-5,714
Influenza-related ED Visits	2,985	2,640	-345
Influenza-related hospitalisations	69,733	56,911	-12,822
Cardiovascular-related hospitalisations	72,106	67,352	-4,754
Deaths (All-cause)	79,393	78,956	-437
Deaths (Influenza-related hospitalisations)	2,427	1,981	-446
Deaths (CV-related hospitalisations)	0	0	0
Deaths (Other)	76,966	76,975	9
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]

ED: emergency department, GP: general practitioner, TIV-HD: Trivalent Influenza Vaccine – High Dose, QIV-SD: Quadrivalent Influenza Vaccine – Standard Dose. Source: Table 3.8.1, p81 of the submission

6.39 The combined total of respiratory (56,911 with TIV-HD) and cardiovascular (67,352 with TIV-HD) hospitalisations was higher than the number of confirmed cases (86,832) in the base case model results. This may be because of a) more than one hospitalisation per case or b) confirmed case definition and the approach taken to attributing hospital cases undertaken in the FIM12 trial and reported in DiazGrandos (2015) [12].

6.40 The evaluation considered that the results should be considered with caution due to:

- The model estimates appear to lack face validity. There are substantially more influenza cases as well as influenza- and cardiovascular hospitalisations when compared to the 2017 National Notifiable Diseases Surveillance System.
- Seasonal variations in influenza incidence and strain circulation.
- The impact of TIV-HD on cardiorespiratory hospitalisations other than pneumonia was included.
- The submission assumed the vaccine efficacy of TIV-SD against hospitalisations. The basis for this assumption was unclear.
- QIV-SD and TIV-SD vaccination was assumed to result in having the same vaccine efficacy against hospitalisation, which ignored the potential value in the alternative B strain protecting against some hospitalisations.
- The cost of respiratory hospitalisations may be overestimated.

6.41 The submission presented a number of one-way sensitivity analyses. The model results were most sensitive to assumed attack rates, hospitalisation rates, avoided hospitalisation costs and, to a lesser extent, averted mortality.

Table 13: Results of key univariate and scenario sensitivity analyses

Analysis	Inc Cost	Inc QALY	ICER $/QALY
Base case	**-$[redacted]**	**0.0008**	**Dominant**
Lower unvaccinated attack rates of 3% for confirmed influenza, along with proportional changes in the relative hospitalisation rates (66% of base) for respiratory-related influenza. No cardiovascular outcomes included	$[redacted]	0.0005	$[redacted]
Respiratory-related influenza hospitalisation limited to pneumonia, and no cardiovascular outcomes included	$[redacted]	0.0004	$[redacted]
A lower unit cost of $5,248 included for respiratory-related influenza hospitalisation, and no cardiovascular outcomes were included	$[redacted]	0.0008	$[redacted]

ACM: All-Cause Mortality; CFR: Case Fatality Ratio; CI: Confirmed Influenza; CV: Cardiovascular; ED: Emergency Department; GP: General Practitioner; H: Hospitalised; I: Incremental; I/P: Confirmed/Suspected Influenza and/or Pneumonia; TIV-HD: Trivalent Influenza Vaccine – High Dose, QIV-SD: Quadrivalent Influenza Vaccine – Standard Dose, RVE: Relative Vaccine Efficacy; PM: Prescription Medicines; R: Respiratory; VE: Vaccine Efficacy

Source: Submission Table 3.9.3, p85 and conducted during the evaluation.

[12] DiazGranados (2015) noted that attributing a hospital case to influenza was undertaken by "two physicians blinded to treatment group [who] independently reviewed all serious adverse events diagnostic categories that were reported during the study [although] adjudication was done without regard to influenza confirmation in the study" (p4989).

6.42 Increasing influenza attack rates have been reported in Australia. Background attack rates were taken from the FIM12 trial in North America for the economic model, where moderate and low influenza activity was evident, but with high influenza Type A prevalence. Since the year 2000, reported cases have increased more than 20-fold in Australia, so attack rates in the FIM12 trial could understate the evolving conditions in Australia without TIV-HD vaccination. Large increases in influenza incidence improve the cost-effectiveness of a more effective vaccine introduction. Estimating cost-effectiveness is complicated by the cyclical nature of low-moderate-high influenza seasons. There is uncertainty as to whether 2017 is the peak of influenza cycles and incidence would return to 1998-2005 levels, or whether the burden would continue to increase. A reduction in the unvaccinated confirmed influenza attack rates (from 4.5% to 3%), and no cardiovascular outcomes included, increased the ICER to less than $15,000 per QALY gained. The PSCR argued that it is impossible to accurately predict the intensity and strain composition of future influenza seasons. The ESC considered this reasonable, however it was unclear whether 2017 is the peak of the influenza cycle and if the incidence would return to lower levels in future years.

6.43 The submission included the impact of TIV-HD on influenza related hospitalisations using data from the FIM12 trial. Differences in hospitalisations were only statistically significant for pneumonia, yet vaccine efficacy against other cardiorespiratory events (e.g. asthma/COPD/bronchial, congestive heart failure etc) were included in the model. ATAGI indicated that it was "appropriate to include estimates of the additional cases of pneumonia prevented by TIV-HD over TIV-SD, but not for other cardiorespiratory outcomes" (ATAGI February 2018 pre-submission advice). A sensitivity analysis with only influenza/pneumonia hospitalisations was conducted during the evaluation. The ICER increased to $15,000 - $45,000 per QALY gained. The ESC considered that the use of the broader category of all-cause hospitalisations was inappropriate and as noted above, the model has estimated substantially higher cases and costs for hospitalisations for QIV-SD than the NNDSS estimates from 2017.

6.44 The submission estimated the costs of hospitalised influenza management for respiratory and cardiovascular using averaged Round 19 Australian public hospital AR-DRGs. The distribution of severity was not discussed in the FIM12 trial, nor was the average number of days per admission. In the event there is a greater proportion of lower complexity admissions per separation, then use of the average would overstate avoided costs as a result of TIV-HD adoption. The ICER increased to less than $15,000 when lower unit costs are included. The ESC considered that estimate of avoided costs remained uncertain however, the costs associated with respiratory hospital submissions may be less severe and complex compared to the average AR-DRG.

Drug cost/patient/course

6.45 The proposed price for TIV-HD is $[redacted] per dose which would be administered once per 65+ year old patient per year at an administration cost of $[redacted] per subject. The ESC noted that this is approximately [redacted] the cost of the current QIV vaccine on the NIP.

Estimated NIP usage and financial implications

6.46 This submission was not considered by DUSC. The submission employed an epidemiological approach to estimate the financial implications from the substitution of QIV-SD vaccines (primarily used in the NIP for patients aged ≥65 years), with TIV-HD.

Table 14: Estimated use and financial implications

	2019	2020	2021	2022	2023	2024
Costs of TIV-HD						
Eligible subjects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake	74.6%	74.6%	74.6%	74.6%	74.6%	74.6%
Subjects vaccinated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doses per subject	1	1	1	1	1	1
Doses administered	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost per dose	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	$0	$0	$0	$0	$0	$0
Total cost the NIP	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net cost to NIP/MBS						
Net Cost to the NIP	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to the MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Overall net cost to government health budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

NIP: National Immunisation Program, TIV-HD: Trivalent Influenza Vaccine – High Dose
Source: Table 4.2.2, p87 of the submission

The redacted table shows that over 6 years, the estimated number of subjects vaccinated was over 200,000 per year.

6.47 The cost to the NIP from TIV-HD is likely to exceed $100 million per year in year 6, and the net cost $60 - $100 million when substitution with QIV-SD is considered.

6.48 The uptake rate of TIV-HD was based on the uptake rate reported in Australian Institute for Health and Welfare (AIHW) Adult Vaccination Survey (2009) (74.6%). This survey is dated and there is likely to be greater vaccination awareness with higher burdens of influenza disease in recent years. Vaccination coverage may have increased, which given the large population being targeted could result in a higher financial impact. The ESC considered that the uptake rate for influenza vaccine in the population may be underestimated.

6.49 Substitution of TIV-HD for the currently used QIV-SD was 100% from 2019. This assumed the current NIP would exclusively supply QIV-SD, and ignored the

availability of other influenza vaccines. Ignoring the availability of other influenza vaccines and the potential for QIV-SD to be used in some instances overstates the cost differential between projected NIP costs with TIV-HD and the current situation. The ESC considered that the substitution rate for TIV-HD may be overestimated as it was unlikely that 100% of use in the proposed population would be with TIV-HD given the increased frequency of mild to moderate injection site reactions associated with its use, and this overstated the cost differential.

Quality Use of Medicines

6.50 No quality of use of medicines information was provided in the submission.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the requested change to the price of the National Immunisation Program (NIP) listing of inactivated trivalent influenza vaccine (Fluzone® High-Dose, TIV-HD), for active immunisation against influenza in adults aged ≥65 years. This decision was made on the basis of the high financial implications of the proposed price increase, the uncertainty around the loss of protection against the alternative B lineage and the incremental benefit of the strains matched with the comparator vaccine, and the associated uncertainty in assessing the incremental cost-effectiveness of the vaccine. Given the very large opportunity cost of the proposed price change, the PBAC considered better modelling and scenario analyses around TIV-HD compared with QIV-SD using data from Australian experience over a longer time-frame was required.

7.2 The PBAC agreed with the proposed clinical place for TIV-HD, noting the high incidence of influenza, high mortality and hospitalisation rates associated with influenza and reduced vaccine efficacy against the predominant strain (A/H3N2) during the 2017 influenza season, as well as the typically lower vaccine effectiveness observed in the proposed population. The PBAC noted that community awareness and influenza testing have increased over time, making laboratory confirmed rates of influenza data difficult to compare over time.

7.3 The PBAC agreed that the proposed comparator, quadrivalent influenza vaccine (QIV-SD) currently listed on the NIP for use in the proposed population, was appropriate. The PBAC considered aTIV to be a near-market comparator as aTIV is listed on the NIP for 2018.

7.4 The PBAC noted the submission was based on two large randomised controlled trials (RCTs) comparing TIV-HD to TIV-SD (FIM12 and Gravenstein) and a supplementary analysis of FIM12 (DiazGranados). The PBAC noted that the studies were conducted in North America over two low and one moderate influenza season.

7.5 The PBAC considered that the clinical trials supporting the submission demonstrated benefits of TIV-HD compared to TIV-SD in laboratory-confirmed influenza and associated cardio-respiratory events. The PBAC noted that in the FIM12 study TIV-HD demonstrated a relative vaccine efficacy of 24.2% against protocol defined influenza like illness, a relative efficacy against A/H3N2 of 23.3%, a 6.9% relative reduction in all-cause hospitalisation and a 39.8% relative efficacy against pneumonia events. The PBAC noted that reductions were seen in a range of other cardiorespiratory diagnoses in FIM12 although these were not statistically significant in isolation. The PBAC noted that the data from the Gravenstein trial demonstrated a reduction in hospitalisations for respiratory illnesses and all-causes.

7.6 The PBAC noted that in the absence of data comparing TIV-HD with the comparator QIV-SD, the submission referred to the PBAC's previous conclusion of non-inferiority of QIV-SD to TIV-SD. The PBAC considered ATAGI's pre-submission advice that most years the potential additional disease burden due to the alternative B lineage not included in the TIV-HD is likely to be offset by the potential additional protection provided by the TIV-HD against the common vaccine strains, due to the superior protection afforded by the vaccine against the A/H3 strain, relative to TIV-SD. However, the PBAC considered that the extent to which the benefits of TIV-HD outweighed the potential loss of protection against the mismatched B strain in QIV-SD compared to TIV-SD remained uncertain given year to year variability in influenza strains and severity of the season. The PBAC noted the NDSS data and ATAGI pre-submission advice (see paragraphs 6.21 – 6.24) that the variation in B strain prevalence, proportion of cases attributable to influenza types A and B among hospitalised influenza cases in the eligible population, and different lineages of B strain all varied substantially from year to year. Thus, while the Committee accepted that TIV-HD is likely to be superior to QIV-SD in the target population on average, the Committee was not confident of the size of any additional benefit of TIV-HD given the loss of the additional B stain.

7.7 The PBAC considered the claim of acceptable comparative safety was reasonable. The PBAC considered that although there was an increased frequency of injection site reactions, these were mild to moderate in nature. The PBAC recalled that in January 2018 it accepted that TIV-HD had an acceptable safety profile, albeit with a higher frequency of mild to moderate of injection-site reactions compared with TIV-SD[13].

7.8 The PBAC considered the incremental cost-effectiveness presented to be unreliable given the clinical issues above and considered scenario analyses comparing TIV-HD and QIV-SD over a longer time-frame and using Australian age-specific burden and

[13] Inactivated trivalent influenza vaccine (split virion), suspension for injection, 180mcg single dose in 0.5mL, Fluzone® High-Dose, Public Summary Document, March 2018 PBAC meeting, available at http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-03/Inactivated-trivalent-influenza-vaccine-%28Split%20Virion%29-suspension-for-injection-psd-march-2018

influenza type prevalence data over the last decade, as well as data on the frequency of TIV-SD B-strain mismatch over that time, would be informative.

7.9 The PBAC noted that the proposed price was [redacted] higher than the price for the comparator QIV-SD, and the financial implications of the proposed listing were significant. The PBAC considered the proposed price unreasonable based on the evidence provided to support incremental comparative cost-effectiveness.

7.10 The PBAC considered the uptake rate estimates may be underestimated as they were based on 2009 survey data, and the substitution rates may be overestimated as it would be unlikely that 100% of use in the proposed population would be with TIV-HD given the increased frequency of mild to moderate injection site reactions associated with its use.

7.11 The PBAC considered that any future resubmission would need to be a major submission. The PBAC considered that the provision of further data and modelling comparing TIV-HD to QIV-SD under a range of scenarios using longer-term Australian data to address the uncertainties around the loss of the alternate B strain and the incremental benefit of TIV-HD to QIV-SD directly would be required.

7.12 The PBAC noted that this submission is not eligible for independent review as independent review is only relevant to PBS listing.

Outcome:

Rejected

8 Recommended listing

No change to the existing NIP listing.

9 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.

10 Sponsor's Comment

Sanofi is disappointed with the Committee's decision not to recommend the change to the current NIP listing for Fluzone High Dose. Large scale clinical trials, supported by emerging data from real world surveillance have demonstrated the benefit that Fluzone High Dose delivers to adults aged 65 and older by reducing the burden of the severe consequences which can result from influenza infection in this population. As such we will ensure we make this important vaccine available to the Australian people.