

**5.01 QUADRIVALENT INFLUENZA VACCINE (SURFACE ANTIGEN, INACTIVATED, CELL-BASED),
Injection 15 microgram in 0.5 mL needle-free pre-filled syringe,
Injection 15 microgram in 0.5 mL pre-filled syringe with attached needle,
Flucelvax® Quad,
Seqirus (Australia) Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested listing on the National Immunisation Program (NIP) Schedule for a quadrivalent influenza virus vaccine, surface antigen, inactivated, cell-based (QIVc, Flucelvax® Quad) for the prevention of influenza in children aged ≥2 to <5 years, Aboriginal and Torres Strait Islander people aged ≥2 to <65 years, people at increased risk of influenza disease complications aged ≥2 to <65 years and pregnant women. The pre-PBAC Response requested a change to the populations proposed for listing by excluding children aged 2 to 4 years (see Table 1).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus existing NIP-funded quadrivalent egg-based vaccines (QIVe).

Table 1: Key components of the clinical issue addressed by the submission¹

Component	Description
Population	Prevention of seasonal influenza in the following populations: <ul style="list-style-type: none"> All children aged ≥ 2 to < 5 years Aboriginal and Torres Strait Islander people aged ≥ 25 to < 65 years Persons aged ≥ 25 to < 65 years who have certain medical conditions that increase the risk of influenza disease complications Pregnant women.
Intervention	Quadrivalent influenza virus vaccine, surface antigen, inactivated, cell-based (QIVc).
Comparator	Quadrivalent influenza vaccines, egg-based, standard dose, currently listed on the NIP (QIVe).
Outcomes	Effectiveness: influenza like illness; laboratory confirmed influenza; influenza-related hospital and primary care encounters. Safety: local reactions; systemic reactions; serious adverse events; non-serious reactions; adverse events of special interest.
Clinical claim	The submission made the following clinical claim for the population aged ≥ 2 to < 65 years: <ul style="list-style-type: none"> QIVc is superior to QIVe in effectiveness against clinically relevant influenza-related outcomes QIVc has a comparable safety profile to QIVe.

Source: Table 1.1.1, p31 of the submission

NIP = National Immunisation Program

¹ Changes requested by the sponsor in the pre-PBAC response (p1) are added in italics and deletions are crossed out with strikethrough.

- 1.3 The PICO table in the ATAGI pre-submission advice to PBAC proposed that QIVe be NIP-listed “as contingency” in the ≥ 65 years age group, as with the other “standard dose” QIVe vaccines. This population had been included on advice from the Department of Health, to maximise consistency with the existing QIVe vaccines on the NIP, minimise confusion among providers and enable its use as a contingency. It was not included in the PBAC submission.

2 Background

Registration status

- 2.1 QIVc was registered on the Australian Register of Therapeutic Goods on 1 September 2020 for use in adults and children ≥ 9 years of age for the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. An application to extend the indication to children aged ≥ 2 years of age was approved by the TGA on 10 November 2021.
- 2.2 QIVc is authorised for marketing by the US Food and Drug Authority (FDA) and the European Medicines Agency. QIVc is approved for use in adults and children from 6 months of age in the US and from 2 years of age in Europe.
- 2.3 The pre-PBAC Response stated that an indication for children aged 6 months and older is currently being considered by the TGA and that an expanded listing request for this population may be considered in the future.

3 Requested listing

- 3.1 The pre-PBAC Response requested a change to the populations proposed for listing by excluding children aged 2 to 4 years. The pre-PBAC Response also proposed a reduced price per dose of \$~~1~~. Additions requested by the sponsor in the pre-PBAC response are added in italics and deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Ex- Manufacturer Price	Proprietary Name and Manufacturer
CELL-CULTURED QUADRIVALENT INFLUENZA VACCINE (SURFACE ANTIGEN, INACTIVATED) 0.5mL, Injection, Prefilled syringe	\$ ■ \$ ■	Flucelvax® Quad Seqirus Australia Pty Ltd

Category/Program:	NIP
Requested populations:	All children aged ≥2 to <5 years Aboriginal and Torres Strait Islander people aged ≥25 to <65 years Persons aged ≥25 to <65 years who have certain medical conditions that increase the risk of influenza disease complications Pregnant women.

- 3.2 Under the National Health Act 1953, the PBAC makes recommendations to the Minister about vaccines it considers should be designated vaccines, and if such vaccines should only be provided under certain circumstances. The Minister may then determine that a vaccine is a designated vaccine via legislative instrument (the [National Health \(Immunisation Program – Designated Vaccines\) Determination 2014 \(No. 1\)](#) ('the Determination')). The Minister may then provide or arrange for the provision of such vaccines (via the NIP).
- 3.3 The secretariat proposes the following draft wording, noting that it is broadly consistent with the existing circumstances for Fluarix Tetra, FluQuadri, VaxiGrip Tetra and Afluria Quad, except that it is only for those aged 5 years and older and under 65 years (consistent with the proposed populations in the pre-PBAC Response).

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Number and timing of doses
Influenza	Flucelvax Quad	Injection (0.5mL)	For children older than 5 years but less than 9 years, 2 doses at least 1 month apart for the first vaccination and 1 dose per calendar year after that. For persons 9 years and less than 65 years, 1 dose per calendar year.

Circumstances

Vaccine may be provided to any of the following:

- (a) an Aboriginal or Torres Strait Islander person who is at least 5 years old but less than 65 years old; or
- (b) a person who is at least 5 years old but less than 65 years old and who:
 - (i) has cardiac disease including cyanotic congenital heart disease, coronary artery disease and congestive heart failure; or
 - (ii) has a chronic respiratory condition including suppurative lung disease, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease, chronic emphysema and severe asthma; or
 - (iii) has another chronic illness requiring regular medical follow-up or hospitalisation in the preceding year, including diabetes mellitus, chronic metabolic diseases, chronic renal failure, haemoglobinopathies and impaired immunity (including drug-induced immune impairment); or
 - (iv) has a chronic neurological condition, including multiple sclerosis, spinal cord injuries, seizure disorders or other neuromuscular disorders; or
 - (v) has impaired immunity, including HIV infection; or
- (c) a person who is at least 5 years old but is less than 11 years old and is receiving long-term aspirin therapy; or
- (d) a woman who is pregnant.

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

4 Population and disease

- 4.1 Influenza is a highly infectious disease that occurs in epidemics throughout the winter months of temperate climates but can occur year-round in tropical regions. Influenza illness is characterised by the abrupt onset of respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis (Monto et al. 2000). It can be a mild disease, although it can also cause serious illness in otherwise healthy people, with complications that may require hospitalisation and can lead to death (Australian Immunisation Handbook, 2020). Complications include pneumonia (primary viral and secondary bacterial pneumonia), bronchitis, sinus infections, ear infections, and exacerbation of many chronic conditions such as asthma, congestive heart failure, and chronic obstructive pulmonary disease. Secondary bacterial pneumonia is a common complication in people whose comorbidities make them vulnerable to influenza. Vulnerable people are at high risk during epidemics and may die of pneumonia or cardiac decompensation (Centers for Disease Control (CDC) 2020; Rajaram et al. 2020a; ATAGI 2021).
- 4.2 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. The

submission proposed that QIVc be available for the prevention of influenza caused by influenza virus, Types A and B.

- 4.3 Influenza viruses are coated with two proteins, haemagglutinin (HA) and neuraminidase (NA). Antibodies against these proteins provide protection against infection. As influenza viruses replicate, there are continual changes from mutations in the genes encoding the HA and NA surface proteins, called antigenic drift. These changes accumulate and existing antibodies become less effective at neutralizing the virus, and within a relatively short time they are no longer protective. Therefore, protection by vaccination requires annual dosing with updated vaccines. In Australia, vaccine composition is decided by the TGA, with advice from the Australian Influenza Vaccine Committee (AIVC), which examines, among other things, epidemiology, antigenic and genetic characteristics of recent influenza isolates circulating in Australia and the southern hemisphere. The AIVC meets after the annual World Health Organization (WHO) strain composition meeting and its advice generally aligns with the WHO recommendations, unless there are scientific or practical reasons for variations¹. Antigenic drift, and mismatch in vaccine and circulating viruses, means vaccine effectiveness can vary across (and within) seasons.
- 4.4 The traditional manufacturing process for influenza vaccines utilises fertilised chicken eggs. During this process, mutations can occur in the receptor binding region of HA, that allow influenza viruses to infect avian cells more efficiently. However, this can also lead to antigenic mismatch to circulating viruses, and reduced vaccine effectiveness. When this occurs, it is called egg adaptation, and it is a particular problem for influenza A/H3N2 and B viruses. Manufacturing influenza vaccines in cell-culture, from cell-derived candidate vaccine viruses, is designed to avoid this issue. Cell derived influenza vaccines have been developed recently and are not currently on the NIP in Australia. In the US 2017-18 influenza season, an influenza vaccine containing one cell derived component (H3N2) and three egg derived components was used, with production of cell derived components increasing in the US over the seasons until all strains came from cell-based production in the US 2019-20 season. Different viruses, which have similar antigenic properties, are sometimes recommended by WHO/AIVC for inclusion in egg-based and cell-based vaccines. This is because influenza viruses do not always replicate equally well in the egg- and cell-based vaccine production systems.²

5 Comparator

- 5.1 The nominated comparator was egg-based quadrivalent subunit influenza virus vaccine (QIVe), which is currently funded by the NIP for the proposed populations. The ESC considered that the comparator was appropriate. The QIVe vaccines funded

¹ <https://www.tga.gov.au/aivc-terms-reference>

² https://cdn.who.int/media/docs/default-source/influenza/who-influenza-recommendations/vcm-southern-hemisphere-recommendation-2022/202109_qanda_recommendation.pdf

across the proposed populations in the 2021 season were Vaxigrip Tetra, Fluarix Tetra and Afluria Quad.

- For the clinical comparisons, the submission compared QIVc with US-licensed QIVe for influenza seasons from 2017 to 2020 (see Table 3).
- For the economic model, the sponsor used the ~~\$~~Nationally Negotiated Price for Afluria Quad, another Seqirus product registered for use in those aged 5 and over, which was recommended for NIP listing on a cost-minimisation basis to Fluarix Tetra (Afluria Quad, Public Summary Document (PSD), August 2016 PBAC meeting).

- 5.2 The proposed algorithms assumed a complete switching from QIVe to QIVc for the proposed populations. This assumption may not be appropriate. ATAGI considered that QIVe will also likely remain available.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The sponsor representative stated that egg adaptation, the process by which virus strains are optimised for traditional egg-based influenza vaccine manufacturing, occurs in most seasons. The sponsor representative noted the clinical impact associated with egg adaptation and emphasised the 14–19% improvement in relative vaccine efficacy (rVE) of QIVc versus QIVe observed during 2017–2018 (US-based data). The sponsor representative acknowledged the clinical impact associated with egg adaptation is variable and noted that the rVE of QIVc was lower during 2018–2019 and 2019–2020 (US-based data). The sponsor representative stated that the variability observed in rVE had been incorporated into the economic evaluation and claimed that when taken as an average across seasons, listing QIVc at the proposed price is associated with a reduction in illness and clinical presentations and is cost-effective. The sponsor representative stated that the sponsor is willing to collect additional data to support the clinical and cost-effectiveness claims made in the submission. The PBAC noted that the hearing did not add substantively to the evidence presented in the submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from the Lung Foundation Australia, via the Consumer Comments facility on the PBS website.
- 6.3 Lung Foundation Australia noted that availability of Flucelvax® Quad through the NIP would provide Australians with an alternate supply of influenza vaccine, ensuring access when needed. Lung Foundation Australia noted the benefits of reducing the risk of disease associated with influenza outbreaks and minimising the economic and social burden associated with illness. Lung foundation Australia emphasised the

potential wider benefits of reducing the burden of illness experienced by children and their families and working Australians.

Clinical studies

- 6.4 The submission was based on 6 retrospective cohort observational studies comparing QIVc to QIVe for the clinical claim of superior effectiveness, and one head-to-head trial for the non-inferior safety claim (n=2,414 randomised, V130_10).
- 6.5 Details of the key observational studies and head-to-head trial presented in the submission are provided in Table 2. Supportive evidence was provided from 4 non-randomised observational studies with a test-negative design (TND), 1 retrospective cohort study with a TND case-control sub-analysis, and 3 randomised controlled trials examining immunogenicity and not designed to evaluate efficacy or demonstrate superiority.

Table 2: Trials/observational studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised controlled trials (immunogenicity outcomes and safety <4 years of age)		
V130_10 (NCT04074928)	A phase 3, randomised, observer-blind, multicenter, noninferiority study to evaluate safety and immunogenicity of a cell-based quadrivalent subunit influenza virus vaccine (QIVc) and a United States-licensed quadrivalent influenza virus vaccine (QIV) in healthy subjects 6 months through 47 months.	November 2020
Observational studies (pivotal to the clinical claim of superiority)		
US season 2017 – 2018		
Boikos 2020	A Retrospective Cohort Study Evaluating the Relative Effectiveness of QIVc Compared to Standard, Egg-based QIV: Study Report (Version 2.0). Boikos, C., et al. Relative Effectiveness of the Cell-Cultured Quadrivalent Influenza Vaccine Compared to Standard, Egg-derived Quadrivalent Influenza Vaccines in Preventing Influenza-like Illness in 2017–2018	November 2018 Clinical Infectious Diseases 2020; 71(10): e665–e671
Divino 2020	Divino, V., et al. A real-world study evaluating the relative vaccine effectiveness of a cell-based quadrivalent influenza vaccine compared to egg-based quadrivalent influenza vaccine in the US during the 2017-18 influenza season.	Vaccine 2020; 38(40): 6334-6343
US season 2018 – 2019		
Boikos 2021	Relative effectiveness of the cell-based, quadrivalent influenza vaccine compared to egg-based seasonal influenza vaccines in preventing influenza-related medical encounters in U.S. individuals ≥4 years during the 2018-19 influenza season. Seqirus CORE study, 20RWE02 Boikos, C., et al. Relative Effectiveness of the Cell-derived Inactivated Quadrivalent Influenza Vaccine Versus Egg-derived Inactivated Quadrivalent Influenza Vaccines in Preventing Influenza-related Medical Encounters During the 2018-2019 Influenza Season in the United States. Boikos, C., et al. Effectiveness of the Cell-Derived Inactivated Quadrivalent Influenza Vaccine in Individuals at High Risk of Influenza Complications in the 2018–2019 United States Influenza Season.	September 2020 Clinical Infectious Diseases 2021; 73(3): e692-e698 Open Forum Infectious Diseases 2021; 8 (7)

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Trial ID	Protocol title/ Publication title	Publication citation
Krishnarajah 2021	Krishnarajah, G., et al. Clinical and Economic Outcomes Associated with Cell-Based Quadrivalent Influenza Vaccine vs. Standard-Dose Egg-Based Quadrivalent Influenza Vaccines during the 2018-19 Influenza Season in the United States.	Vaccines (Basel) 2021; 9(2): 80
US season 2019 – 2020		
Seqirus 2021 (CSR)	Relative effectiveness of the cell-derived versus egg-derived quadrivalent influenza vaccines in the US during the 2019-20 influenza season.	March 2021
Divino 2021 (Submitted; published online 4 December 2021)	Divino, V. A Real-World Clinical and Economic Analysis of Cell-derived Quadrivalent Influenza Vaccine Compared to Standard Egg-derived Quadrivalent Influenza Vaccines During the 2019-20 Influenza Season in the United States	Open Forum Infectious Diseases 2020, Submitted; published online 4 December 2021

Source: Adapted from Table 2.2.1, p63-64 of the submission.

Abbreviations: CSR = Clinical Study Report; QIVc = cell-based quadrivalent subunit influenza virus vaccine; QIVe = egg-based quadrivalent subunit influenza virus vaccine; US = United States

6.6 The key features of the observational studies are summarised in Table 3. The key features of the randomised trial V130_10 are discussed in paragraph 6.22 (under ‘Comparative harms’).

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Table 3: Key features of the included evidence

Study	N	Adjustment	Risk of bias	Data source	Outcome(s)	Use in modelled evaluation
QIVc versus QIVe						
US season 2017-2018						
Boikos 2020	QIVc: 92,187 QIVe: 1,261,675	PSM analysis ¹ and logistic regression	Moderate	Electronic medical records from primary care (AllScripts database)	ILI within primary care ³	Not used
Divino 2020	QIVc: 555,538 QIVe: 2,528,524	IPTW and Poisson regression	Moderate	Administrative claims data (IQVIA Real-World Data Adjudicated Claims – US Database)	Influenza related hospitalisations or emergency room visits ⁴	Not used
US season 2018-2019						
Boikos 2021	QIVc: 2,125,430 QIVe: 8,000,903	Doubly robust ²	Moderate	Electronic medical records linked to pharmacy and medical claims data from primary care and hospitals (AllScripts plus Komodo Health databases)	ILI within primary care or hospital ³	Not used
Krishnarajah 2021	QIVc: 665,047 QIVe: 3,062,843	IPTW and Poisson regression	Moderate	Administrative claims data (IQVIA Real-World Data Adjudicated Claims – US Database)	Influenza related hospitalisations or emergency room visits ⁴	Not used
US season 2019-2020						
Seqirus 2021	QIVc: 1,559,695 QIVe: 5,367,253	Doubly robust	Moderate	Electronic medical records linked to pharmacy and medical claims data from primary care and hospitals (AllScripts plus Komodo Health databases)	ILI within primary care or hospital ³	Not used
Divino 2021	QIVc: 1,138,969 QIVe: 3,926,357	IPTW and doubly robust	Moderate	Administrative claims data (IQVIA Real-World Data Adjudicated Claims – US Database)	Influenza related hospitalisations or emergency room visits ⁴	Not used
Meta-analyses						
A meta-analysis was conducted for each season, combining presentations to primary care and hospitals, to generate a relative vaccine effectiveness (rVE) estimate for each season.						rVE

Source: Compiled from Table 2.4.2, p51, Table 2.3.1, p69, Table 2.4.3, p90, Table 2.4.4, p93, and text p85 of the submission.

PSM = propensity score matching, IPTW = inverse probability of treatment weighting, ILI = influenza-like illness, QIVc = cell-based quadrivalent subunit influenza virus vaccine, QIVe = egg-based quadrivalent subunit influenza virus vaccine.

1. A post hoc PSM analysis was conducted as well as a pre-specified multivariate logistic regression analysis. The PSM analysis was considered more robust by the sponsor and is presented as the main result of this study.
2. A post hoc doubly robust analysis was conducted as well as a pre-specified multivariate logistic regression analysis. The doubly robust analysis was considered more robust by the sponsor and is presented as the main result of this study.
3. Defined by ICD-9 and ICD-10 diagnostic codes specific to influenza: J09*-J11* in any diagnostic position as per "Code Set B", definition published and validated by US Armed Forces Health Surveillance Center (AFHSC).
4. Defined as ICD-9 487.x, 488.x, ICD-10 J09.x, J10.x, J11.x in any position.

6.7 The submission claimed that the use of 'real world evidence' (RWE) represents the only feasible approach for comparing the performance of different influenza vaccines in settings that are reflective of clinical practice. The submission considered that data from RWE studies are more representative of population use and outcomes than RCTs, which are generally conducted in a restricted number of study subjects over short time

periods. The ESC noted that influenza vaccine efficacy RCTs may also be conducted across influenza seasons, but it recognised that the large sample sizes required for statistical significance (given the rarity of the outcomes of laboratory confirmed influenza/medical treatment) may limit the practicality of such designs.

- 6.8 Using the ROBINS-I tool, the six retrospective cohort studies were scored by the submission as having an overall moderate risk of bias, on the basis of a moderate risk of confounding. The sponsor presented analyses that statistically adjusted for the potential confounding effect of possible differences in age, comorbidities, ethnicity, geographic area, payer-type, health-plan type, and healthcare seeking behaviour. However, a moderate risk-of-bias remained due to confounding given the non randomised design. The studies were scored as having a low risk of bias in the six other domains of the ROBINS-I tool (i.e. selection bias, misclassification of exposure, deviation from intended vaccine, missing data, misclassification of outcomes, reporting bias). Specifically, for misclassification of outcomes, primary endpoints were influenza-like illness (ILI) primary-care or emergency-room visits or ILI hospitalisations as identified by ICD codes. These could be affected by ICD coding errors. However, it could be argued that these measurement errors possibly affect both groups equally. A limitation is the lack of laboratory (PCR) confirmed influenza as an endpoint. One of the studies (Boikos, 2021) looked at the concordance between laboratory-confirmed influenza and ILI as identified by ICD codes and reported “concordance between trends”. Also, the ICD code set used to identify ILI primary care visits was validated in the dependents of military personnel¹.
- 6.9 The submission was concerned that the ATAGI advice “dismisses the value of RWE studies for the evaluation of QIVc on the basis of ‘risk of unrecognised and uncontrolled confounding in these studies based on their design”. The submission stated that the Seqirus-sponsored retrospective cohort studies were of particularly robust design and applied advanced epidemiological and statistical methodology to control for confounding. While these studies have used a number of methods to adjust for measured confounders, and are more robust than those which do not, the potential for confounding/bias does exist, albeit at a reduced level compared to if those methods had not been used. The ability to control confounding depends on the completeness and validity of the recorded information on confounding factors, which can be an issue in the datasets used in the submission’s key studies, particularly in administrative data. Three of six studies (Krishnarajah 2021, Seqirus 2021, and Divino 2021) included a negative control outcome (urinary tract infection, UTI) to address the likelihood of unmeasured confounding. The ESC noted the arguments raised in the Pre-Sub-Committee Response (PSCR) that confounding was mitigated by the urinary tract infection (UTI) negative control outcomes. The ESC also noted the four test negative design (TND) studies, which might provide reassurance about confounding

¹ Eick-Cost AA, Hunt DJ. Assessment of ICD-9-based case definitions for influenza-like illness surveillance. *MSMR* 2015; 22:2-7

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due to health-seeking behaviour. The ESC further noted the PSCR comments as to why missing data on race/ethnicity was not likely to bias the results.

6.10 The submission stated that estimates of rVE were presented separately for each season because:

- The advantage of QIVc over QIVe is due to the elimination of egg-adaptation, and the number of strains in the QIVc vaccine that were cell derived increased over the seasons (Table 4).
- There is seasonal variation in the circulating influenza strains, the vaccine match or mismatch due to antigenic drift, and egg-adaptation (Table 4).

Table 4: Northern Hemisphere influenza season characteristics and use of cell-derived candidate vaccine viruses in QIVc manufacturing

Season	QIVc candidate vaccine virus	Overall VE for any vaccine % (95% CI) ¹	Dominant circulating strain(s) ³	For predominant strain(s)		Season severity
				Antigenic drift	Egg-adaptation	
NH 2017-18	A(H3N2) only	38 (31, 43) ²	H3N2 (60%) B-Yam (26%)	No	Yes (H3N2) ⁴	High ⁸
NH 2018-19	A(H3N2), B/Victoria and B/Yamagata	29 (21, 35) ²	H1N1 (52%) H3N2 (42%)	Yes (H3N2)	Yes (H3N2) ⁵	Moderate ⁹
NH 2019-20	A(H1N1), A(H3N2), B/Victoria and B/Yamagata	39 (32, 45) ²	H1N1 (54%) B-Vic (40%)	No ^{6,7}	Yes (B-Vic) ^{6,7}	Moderate ¹⁰

Source: Table 2.5.1, p101 of the submission.

NH = Northern Hemisphere, VE = vaccine effectiveness, QIVc = cell-based quadrivalent subunit influenza virus vaccine

1. Vaccine effectiveness for any vaccine vs. any influenza strain.
2. United States Centers for Disease Control and Prevention. (2020, July 01). CDC Seasonal Flu Vaccine Effectiveness Studies. Retrieved November 03, 2020, from <https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm>
3. United States Centers for Disease Control and Prevention. (2018, July 06). FluView Interactive. Retrieved January 27, 2021, from <https://www.cdc.gov/flu/weekly/fluviewinteractive.htm>
4. WHO changes 2 strains for 2018-19 flu vaccine. CIDRAP. (2021). Retrieved 27 January 2021, from <https://www.cidrap.umn.edu/news-perspective/2018/02/who-changes-2-strains-2018-19-flu-vaccine>
5. Xu et al. (2019)
6. Dawood et al. (2020)
7. World Health Organization. (2020). Recommended composition of influenza virus vaccines for use in the 2020- 2021 northern hemisphere influenza season. Who.int. Retrieved 27 January 2021, from https://www.who.int/influenza/vaccines/virus/recommendations/202002_recommendation.pdf?ua=1
8. How CDC Classifies Flu Severity | CDC. Cdc.gov. (2021). Retrieved 27 January 2021, from <https://www.cdc.gov/flu/about/classifies-flu-severity.htm>
9. Estimated Influenza Illnesses, Medical visits, Hospitalizations, and Deaths in the United States — 2018–2019 influenza season | CDC. Cdc.gov. (2021). Retrieved 27 January 2021, from <https://www.cdc.gov/flu/about/burden/2018-2019.html>
10. Estimated Influenza Illnesses, Medical visits, Hospitalizations, and Deaths in the United States — 2018–2019 influenza season | CDC. Cdc.gov. (2021). Retrieved 27 January 2021, from <https://www.cdc.gov/flu/about/burden/2018-2019.html>

6.11 Because the outcomes of the 6 pivotal retrospective cohort studies were clinical and not laboratory confirmed, strain specific VE could not be calculated and only overall VE estimates were available. Therefore, the alignment, or otherwise, of the predominant circulating strain(s) and the cell-derived composition of QIVc in any given season requires consideration when interpreting overall relative effectiveness. Limiting the assessment of rVE to 2019–2020, when all four strains in the QIVc vaccine

were cell-derived would mean excluding four of six studies, and excluding 2017-2018, where there was a good match between the cell-derived vaccine strain and predominant circulating strain. Any impact of egg-derived components in the QIVc vaccine in 2017-18 and 2018-19 on the rVE estimate, would depend on the predominance and extent of egg adaptation in the egg-derived strains in those seasons.

Comparative effectiveness

6.12 The rVE estimates presented in the submission varied with each season, and each clinical outcome, but consistently favoured QIVc, with confidence intervals (CIs) that did not cross zero. The supporting test-negative design studies had rVE point estimates that also favoured QIVc however, there were large confidence intervals around the estimates, which may be due to small numbers in the test-negative design studies; for example, 8.5% (95% CI -75.9 to 52.3). The ESC noted that as the studies used very large datasets, some of the statistically significant results arise from relatively small differences between interventions.

Table 5: Estimated relative vaccine effectiveness (rVE) against any influenza strain in the retrospective cohort studies

Study	Primary outcome	Age (yrs)	QIVc		QIVe		Adjusted rVE [%] (95% CI)
			n/N	Rate per 1,000	n/N	Rate per 1,000	
US Season 2017-18 (cell-derived A(H3N2) CVV only)							
Boikos 2020	IRPCE	≥4	1,705/92,187	18.5	25,645/1,261,675	20.3	19.3% (9.5, 28.0)¹
Divino 2020	IRHE	4-64	1,142/551,544	2.07	6,230/2,528,966	2.46	14.4% (8.8, 19.6)
US Season 2018-19 (cell-derived A(H3N2), B/Victoria and B/Yamagata CVVs)							
Boikos 2021	IRME	≥4	34,520/2,125,430	16.2	192,845/8,000,903	24.1	7.6% (6.5, 8.6)²
Krishnarajah 2021	IRHE	4-64	1,049/669,030	1.6	5,151/3,062,797	1.7	6.5% (0.1, 12.5)
US Season 2019-20 (all QIVc components cell-derived)							
Seqirus 2021	IRME	≥4	22,368/1,559,695	14.3	138,386/5,367,253	25.8	17.2% (15.8, 18.6)²
Divino 2021	IRHE	4-64	2,011/1,150,134	1.75	7,248/3,924,819	1.85	6.8% (2.1, 11.3)⁴

Statistically significant results are presented in bold.

Source: Table 2.5.2 p101 of the submission and corrected during the evaluation (the numbers were a percentage rather than a rate per 1000 as per the heading for all Boikos/Seqirus papers i.e. 1.85 not 18.5; and for Divino 2021 0.175 instead of 1.75.)

CI = confidence interval, n = number of participants with event, N = total participants in group, CVV = candidate vaccine virus, rVE = relative vaccine effectiveness, IRHE = Influenza related hospital encounters, IRPCE = Influenza related primary care encounters, IRME = Influenza related medical encounters (primary care or hospital), QIVc = cell-based quadrivalent subunit influenza virus vaccine, QIVe = egg-based quadrivalent subunit influenza virus vaccine.

1. Propensity score matched (PSM) analysis.
2. Post hoc, "doubly robust" inverse probability treatment weighting (IPTW) analysis; n patients calculated from published rates.
3. Post-IPTW adjusted sample.
4. "Doubly robust" sensitivity analysis.

- 6.13 Seasonal variability: the rVE estimates in the 2017-2018 season were amongst the highest, when only the H3N2 strain was cell-derived. H3N2 was also the predominant circulating strain, and there was evidence of egg adaptation for this strain. Because of this, the estimates from 2017-2018 could be considered a best-case scenario for QIVc across these three seasons. The rVE estimates were the lowest in 2018-19, when H1N1 was more predominant than H3N2, and the QIVc vaccine did not contain a cell-derived H1N1 component. The pre-PBAC Response acknowledged that the rVE of QIVc will vary from year-to-year based on the season-specific characteristics of the circulating virus and its match to vaccine strains, including the degree of egg adaptation, and emphasised that this variability was incorporated into the economic model.
- 6.14 Egg adaptation and cell-derived vaccine: the submission stated that the studies were likely to underestimate the true benefit that would have been observed had a fully cell-derived vaccine been used. However, the magnitude of any impact would depend on the extent of egg adaptation in the predominant non-cell derived strains in these seasons. In 2018-19, for example, it would depend on the degree of egg adaptation in H1N1. The submission did not provide any data on egg-adaption for H1N1 in the northern hemisphere for this year, but public sources include more commentary on the emergence of considerable genetic diversity among H1N1 than on egg-adaption^{1,2}. An analysis of the degree of antigenic similarity between cell and egg-propagated vaccine reference viruses and the circulating viruses for the 2016-2020 Southern Hemisphere seasons was presented by the submission and indicated virtually no egg adaptation for H1N1 in Australia in the 2018 or 2019 influenza seasons. The pre-PBAC response referenced a study analysing data from annual and interim reports published by the Worldwide Influenza Centre, London. This data enabled retrospective assessment of antigenic similarity between circulating and WHO reference viruses propagated in either eggs or cells from the 2002 to 2018 Northern and Southern influenza seasons³. The pre-PBAC Response noted that the study showed evidence of egg-adaption for the A(H3N2), B/Yamagata, and B/Victoria strains for seasons varying between 2002 and 2018 across Northern and Southern influenza seasons. The pre-PBAC Response also noted that recent antigenic characterisation studies using post-vaccination human antisera suggest egg-adaptation may also occur in A(H1N1) strains.
- 6.15 Variability in outcome measures: the largest variation in rVE within a season was across the two different studies for 2019-2020. For Seqirus 2021 disaggregated

¹ World Health Organization (2019) 'Recommended composition of influenza virus vaccines for use in the 2019- 2020 northern hemisphere influenza season',

(https://www.who.int/influenza/vaccines/virus/recommendations/201902_recommendation.pdf?ua=1)

² Skowronski DM, Leir S, et al (2019) 'Interim estimates of 2018/19 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, January 2019'. Euro Surveill. 24(4):pii=1900055.

<https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2019.24.4.1900055>

³ Rajaram S, Suphaphiphat P, Boxmeer J van, Haag M, Leav B, Iheanacho I, et al. Retrospective Assessment of the Antigenic Similarity of Egg-Propagated and Cell Culture-Propagated Reference Influenza Viruses as Compared with Circulating Viruses across Influenza Seasons 2002–2003 to 2017–2018. Int J Environ Res Pu. 2020b;17(15):5423.

analyses by hospitalisation or primary care presentation were presented. The rVE for the hospitalisation outcome (5.7%, 95% CI 2.6% to 8.7%, any diagnosis; figures for admission diagnosis were very similar) was similar to that for the hospital-based Divino (2021) study, with a much larger rVE for primary care presentation (20.8%, 95% CI 19.2% to 22.4%).

6.16 Evaluation of rVE point estimates: point estimates of rVE from the observational studies ranged from 6.5% to 19.3% (Table 5).

- As most effect sizes across the studies are reasonably small, any potential for remaining confounding is of greater concern, as effect sizes larger than these in observational epidemiologic studies have been generated by residual and/or unmeasured confounding alone¹, and strong statistical associations in study results are considered less likely to be due to bias².
- It is unclear what these values of rVE mean in terms of a clinically important difference. ATAGI advice indicated, "It is unclear if these levels of rVE are clinically significant. With an estimated vaccine effectiveness (overall) of around 50% in Australia (as reported in WHO Collaborating Centre for Reference and Research on Influenza review of Australian 2019 influenza season), this level of rVE would increase the effectiveness of the influenza vaccine to between approximately 53% and 59%. This is within the range of normal vaccine effectiveness variation; for example, in 2018 influenza vaccine effectiveness was 58% against hospitalisation due to influenza and 68% against GP presentation due to influenza. Between 2012 and 2017, vaccine effectiveness for GP presentations ranged from 35-60%, and 13-50% for hospitalisation". The PSCR contended that the magnitude of incremental effectiveness of QIVc compared to QIVe was clinically relevant, noting that Lewis (2021) had shown that a 5% rVE can avert significant disease, especially in seasons when the absolute VE of the comparator is low. Lewis (2021) conducted a scenario analysis using data from adults ≥ 65 years, with absolute VE estimates ranging from a 30% to 60%. An impact of a 5% rVE was seen using data from people ≥ 65 years, and it was greatest in scenarios with lower absolute VE (11,700 additional hospitalisations averted at 30%, and 6,700 at 60%).³ The PSCR also re-presented data from the submission's static cohort modelling to assert the clinical relevance of the modelled rVE (0% to 15.6%) in terms of burden of disease presented, as shown in the table below. The ESC noted that in some years there will be no impact of QIVc.

¹ Fewell Z, Smith GD et al (2007) The Impact of Residual and Unmeasured Confounding in Epidemiologic Studies: A Simulation Study. *Am J Epi* 166:646-655

² Grimes DA and Schulz K (2002) Bias and causal associations in observational research. *Lancet* 359:248-252

³ Lewis, N. M., Chung, J. R., Uyeki, T. M., Grohskopf, L., Ferdinands, J. M., & Patel, M. M. (2021). Interpretation of Relative Efficacy and Effectiveness for Influenza Vaccines. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, ciab1016. Advance online publication.

<https://doi.org/10.1093/cid/ciab1016>

Table 6: Estimated absolute QIVc effectiveness and influenza burden averted in the context of the observed QIVe effectiveness and burden of illness in 2015-2019 in Australia

Year	VE QIVe ¹	Base case rVE	Estimated VE QIVc	Estimated burden averted in the proposed vaccinated NIP population		
				Medically attended influenza	Hospitalisations	Deaths
2015	54.0%	14.0%	60.4%	2,005	548	18
2016	40.0%	15.6%	49.4%	1,978	627	22
2017	33.0%	15.6%	43.5%	5,370	1,340	49
2018	68.0%	0.0%	68.0%	0	0	0
2019	47.6%	15.6%	55.8%	6,780	1,594	56

¹ VE estimate from primary care.

Source: Submission Tables 3.3.2, 3.3.3, 3.8.16, shown in Table 2 of the PSCR.

- The combined primary care and hospitalisation outcomes for 2019-20 have masked an apparent difference in rVE in these settings, with a small point estimate (5.7%) for hospitalisation and a larger estimate for primary care (20.8%) based on disaggregated analysis of Seqirus 2021. For 2018-19, the point estimates for hospital only (Krishnarajah 2021, 6.5%), and the hospital and primary care combined (Boikos 2021, 7.6%) are similar, which may suggest little difference between QIVe and QIVc in this season, though as disaggregated data are not available for 2018-2019, this cannot be confirmed. In general, overall VE estimates can differ by outcome (primary care versus hospitalisation encounters) and by season, and rVE may also differ between primary care and hospital settings in a variable way across influenza seasons, likely dependent on circulating strain, match/mismatch of vaccine, and severity of the season (as well as egg-adaptation). Disaggregated rVE results are more informative for this reason. The PSCR commented that there was no data to support a difference in vaccine effectiveness by severity, noting that if there were, it might be expected that the vaccine would be more effective at preventing severe outcomes, but that none of the studies had shown a trend towards greater effectiveness in the hospital setting. The ESC considered having one measure for all influenza outcomes meant that any factors influencing disease severity and types of medical encounters may be obscured (e.g. circulating strains), and it noted that effects in different settings were unable to be modelled separately. It was also unclear why the submission did not provide disaggregated data from these studies.

rVE estimates by age group

- 6.17 rVE estimates based on subgroup analyses by age also generally favoured QIVc over QIVe, although some confidence intervals crossed zero.
- 6.18 The rVE estimates were not always significant for the age subgroup analyses, particularly where the number of children vaccinated with QIVc with a medical encounter in either primary care or hospitalisation was low (IRPCE or IRHE, Table 7). The age groups specified in these studies for children, namely 4 to 17 years, do not reflect the proposed listing of the submission (two to five years). There is no data on effectiveness compared with QIVe for children aged two to four years. The TGA dossier for registration in this age group was based on Study V130_12, a phase 3/4 RCT in

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children 2 to <18 years of age, with a non-influenza vaccine comparator (Menveo®, Meningococcal ACWY vaccine).

Table 7: Estimated relative vaccine effectiveness (rVE) from the retrospective cohort studies against any influenza strain – subgroups stratified by age

Study	Primary outcome	Age (yrs)	QIVc		QIVe		Adjusted rVE [%] (95% CI)
			n/N	Rate (%)	n/N	Rate (%)	
US Season 2017-18 (cell-derived A(H3N2) CVV only)							
Boikos 2020	IRPCE	4-17	115/7,465	1.54	10,816/404,510	2.67	18.8 (-53.9, 57.2) ¹
		18-64	1,069/55,104	1.94	10,021/693,014	1.45	26.8 (14.1, 37.6) ¹
Divino 2020 ²	IRHE	4-17	131/54,419	0.240	2,245/798,415	0.281	13.1 (-3.7, 27.1)
		18-64	976/499,156	0.196	4,053/1,730,403	0.234	13.1 (6.79, 18.96)
US Season 2018-19 (cell-derived A(H3N2), B/Victoria and B/Yamagata CVVs)							
Boikos 2021	IRME	4-17	4,115/78,602	5.24	94,187/1,628,038	5.79	3.9 (0.9, 7.0) ³
	IRME	18-64	24,084/1,529,189	1.57	87,113/5,384,922	1.62	6.5 (5.2, 7.9) ³
Krishnarajah 2021 ²	IRHE	4-17	167/74,304	0.23	2,087/839,744	0.25	8.54 (-7.1, 21.9)
	IRHE	18-64	792/590,705	0.13	3,166/2,223,435	0.14	4.9 (-2.8, 12.1)
US Season 2019-20 (all components cell-derived)⁴							
Seqirus 2021	IRME	4-17	2,936/60,480	4.9	76,618/1,240,990	6.2	12.2 (7.5, 16.6) ³
	IRME	18-64	16,030/1,144,427	1.4	55,761/3,427,818	1.6	11.9 (10.2, 13.6) ³

Statistically significant results are presented in bold.

Source: Table 2.6.1, p109 of the submission

CI = confidence interval, n = number of participants with event, N = total participants in group, CVV = candidate vaccine virus, rVE = relative vaccine effectiveness, IRHE = Influenza related hospital encounters, IRPCE = Influenza related primary care encounters, IRME = Influenza related medical encounters (primary care or hospital), QIVc = cell-based quadrivalent subunit influenza virus vaccine, QIVe = egg-based quadrivalent subunit influenza virus vaccine

1. Propensity score matching (PSM) analysis.
2. Rates converted to % from rate per 1000.
3. "Doubly robust" analysis.
4. Note that Divino 2021 did not present data by age group.

rVE estimates for high risk population

6.19 Results for the high risk population (Table 8) were generally similar to the whole population. ATAGI stated that it was acceptable to apply vaccine effectiveness estimates from the general population to the group of people at increased risk of influenza disease and complications. For 2017-18 and 2019-20 the point estimates for rVE for the high risk population were lower than the rVE applied (results from meta-analysis) in the economic model (shown in Table 9).

Table 8: Estimated relative vaccine effectiveness in high-risk patients (aged 4 years and older)

Study	Outcome	Group	QIVc		QIVe		Adjusted rVE (95% CI)
US Season 2017-18 (cell-derived A(H3N2) CVV only)							
			n/N	Rate (%)	n/N	Rate (%)	
Divino 2020	IRHE	HR ^{1,2}	521/119,060	0.438	2,435/491,496	0.495	10.1% (1.1, 18.2)
	IRHE	All	1,142/551,544	0.207	6,230/2,528,966	0.246	14.4% (8.8, 19.6)
US Season 2018-19 (cell-derived A(H3N2), B/Victoria and B/Yamagata CVVs)							
			n/N	Rate	n/N	Rate	
Boikos 2021	IMRE	HR	8,362/471,301	1.77	40,956/1,641,915	2.49	13.4% (11.4, 15.4)
	IMRE	All	34,520/2,125,430	1.6	192,845/8,000,903	2.4	7.6% (6.5, 8.6)
Krishnarajah 2021	IRHE	HR ¹	454/142,150	0.32	1,891/584,959	0.32	0.91% (-0.98%, 10.6%)
	IRHE	All	1,049/669,030	0.16	5,151/3,062,797	0.17	6.5% (0.1, 12.5)
US Season 2019-20 (all components cell-derived)⁴							
			n/N	Rate	n/N	Rate	
Divino 2021	IRHE	HR ¹	755/247,172	0.306	2,622/767,973	0.341	10.5% (2.9, 17.4)
	IRHE	All	2,011/1,150,134	0.175	7,248/3,924,819	0.185	6.8% (2.1, 11.3)³

Statistically significant results are presented in bold.

Source: Table 2.6.2, p111 of the submission.

CI = confidence interval; n = number of participants with event; N = total participants in group; CVV = candidate vaccine virus; rVE = relative vaccine effectiveness; IRHE = Influenza related hospital encounters; IRPCE = Influenza related primary care encounters; IRME = Influenza related medical encounters (primary care or hospital); HR = high risk.

1. Patients considered at higher risk for influenza complications were identified based on ≥ 1 claim during the 6-month pre-index period with a diagnosis code, drug code or procedure code defining clinical risk groups where flu vaccination is indicated.
2. Numbers of high-risk patients in each cohort calculated from percentages stated in publication (14.3% and 11.5%, respectively).
3. "Doubly robust" analysis.
4. Note that Boikos 2020 and Seqirus 2021 did not present data by high-risk group

Meta-analysis by season

6.20 Results from the meta-analyses were used to translate rVE estimates measured in different clinical settings to the estimates used in the economic model. The meta-analyses were not presented as part of the clinical claim of superiority. The ESC noted the I^2 for the 2019-20 suggested significant heterogeneity (Seqirus 2021 17.2% vs Divino 2021 6.8%) and that pooling of the studies may not be appropriate.

Table 9: Random effects meta-analyses of real-world evidence studies against any influenza

Season	Study design	N studies	I^2 (%)	Q	df	p-value	Pooled OR/RR (95% CI)	Pooled rVE (%) (95% CI)
2017-18	Retrospective cohort	2	0.00	0.78	1	0.376	0.844 (0.799, 0.892)	15.6% (10.8, 20.1)
2018-19	Retrospective cohort	2	0.00	0.12	1	0.730	0.924 (0.914, 0.935)	7.6% (6.5, 8.6)
2019-20	Retrospective cohort	2	94.94	19.77	1	<0.001	0.876 (0.781, 0.984)	12.4% (1.6, 21.9)

Statistically significant results are presented in bold.

Source: Table 3.3.1, p147 of the submission.

df = degrees of freedom, CI = confidence interval, OR = odds ratio, RR = risk ratio, N= number of studies, rVE = relative vaccine effectiveness, I^2 = measure of heterogeneity.

- 6.21 The analyses were appropriately separated by season, but the outcomes (primary care or hospitalisation encounters) were combined. In the pre-submission advice ATAGI did not agree with the sponsor's justification that combining outcomes "is consistent with the application of the estimated relative vaccine effectiveness as a reduction in the risk of developing influenza". ATAGI also indicated that outcomes represent different severities of influenza, and "the reduction in influenza-related hospitalisations or primary health encounters may be due to a change in the severity of disease, as opposed to the risk of infection". ATAGI had requested further explanation to justify the combination of outcomes, and noted it was important as "this appears to be the basis on which the sponsor intends on presenting a dynamic transmission model as part of their cost-effectiveness analyses". Results from the meta-analyses were used to inform the economic model.
- 6.22 The submission did not address the potential for outcomes to vary across different settings due to change in severity of the dominating circulating virus, as opposed to the risk of infection. The submission justified the combination of outcomes by saying: that only two studies were available in each season, thus pooling was required; that Boikos 2021 and Seqirus 2021 already combined hospital and primary care presentations; and that the approach was supported by consistent rVE estimates, particularly in the 2017-18 season, when the outcomes were separate (primary care only in Boikos 2020 and hospital data in Divino 2020). However, in the 2019-20 season when the outcomes were disaggregated in Seqirus 2021, the rVE for primary care was substantially higher than that for hospitalisation, indicating rVE is not always consistent across outcomes. Disaggregating the data across all seasons would be more informative and allow outcomes to be modelled separately. Only disaggregated rVE estimates, not numbers of people with the event or total numbers (N) considered, were available in the Seqirus 2021 CSR (2019-20 season). Further, data were not disaggregated in the CSR or publication for the Seqirus-funded Boikos 2021 study (2018-19 season). The ESC considered that combining different influenza-like-illness outcomes in the meta-analysis introduced uncertainty. The ESC acknowledged that the meta-analysis was not pivotal to the clinical claim, however noted these combined estimates were used in the economic model.

Comparative harms

- 6.23 Safety data from RCT V130_10 was used to demonstrate the safety profile of QIVc compared to QIVe. Clinical trial V130_10 was a phase III, randomised, observer-blind, noninferiority study that was conducted to evaluate the safety and immunogenicity of QIVc and QIVe in healthy children six to 47 months of age. The trial was conducted in the US during the 2019-20 influenza season, at which time all four influenza strains in the QIVc formulation used in the trial were cell derived. A total of 2,414 participants were randomised 2:1 to QIVc or QIVe. A total of 334 (13.8%) enrolled subjects (QIVc = 235 (14.6%), QIVe = 99 (12.2%)) did not complete the study (Table 10).

Table 10: Number (%) of participants with at least one solicited adverse event¹ postvaccination (Day 1 through Day 7) in study V130_10 – solicited safety set²

Solicited adverse event n (%)	V130_10			
	30 minutes after any vaccination		Day 1 through 7 days after any vaccination	
	QIVc	QIVe	QIVc	QIVe
N	1,564	784	1,564	784
Any	192 (12.3)	104 (13.3)	940 (60.1)	491 (62.6)
Local	171 (10.9)	95 (12.1)	656 (41.9)	350 (44.6)
Systemic	30 (1.9)	18 (2.3)	681 (43.5)	358 (45.7)
Analgesic/Antipyretic use ³	8 (0.5)	2 (0.3)	240 (15.3)	136 (17.3)

Source: Table 2.5.5, p106 of the submission

QIVc = cell-based quadrivalent subunit influenza virus vaccine, QIVe = egg-based quadrivalent subunit influenza virus vaccine, n = number of patients with an event, N = number of study participants

1. Solicited AEs were reported through the first 30 minutes after vaccination (by clinical study staff) and from 30 minutes after vaccination through Day 7 using Subject Diary Cards. On Day 1, it was recommended to assess solicited AEs preferably in the evening, at approximately 6 hours postvaccination.
2. Solicited safety set: All subjects in the All Enrolled Set who were randomised and received a study vaccination who were not part of the Cell-Mediated Immunity (CMI) population and who received vaccine on Day 1 and provided serology specimens which yielded valid serology assay results from both Day 1 and Day 29 (previously vaccinated subjects) or Day 1 and Day 57 (not previously vaccinated subjects) with any solicited AE data.
3. Analgesic/antipyretic use was for prevention or treatment of pain/fever.

Table 11: Number (%) of participants with unsolicited adverse events after vaccination¹ in study V130_10 – unsolicited safety set²

	V130_10	
	QIVc	QIVe
N	1,597	805
Any AE, n (%)	418 (26.2)	207 (25.7)
Any AE by severity		
Mild, n (%)	308 (19.3)	164 (20.4)
Moderate, n (%)	98 (6.1)	41 (5.1)
Severe, n (%)	12 (0.8)	2 (0.2)
AE - possibly related, n (%)	70 (4.4)	36 (4.5)
SAE, n (%)	15 (0.9)	7 (0.9)
SAE - possibly related, n (%)	0	0
AE leading to premature withdrawal, n (%)	3 (0.2)	0
Medically attended AE, n (%)	222 (13.9)	97 (12.0)
New onset chronic disease, n (%)	22 (1.4)	13 (1.6)
Death, n (%)	2 (0.1)	0
Death - related, n (%)	0	0

Source: Table 2.5.7, p 107 of the submission

AE = Adverse event; SAE = Serious adverse event; n = number of participants with event, N = Number of participants; QIVc = cell-based quadrivalent subunit influenza virus vaccine, QIVe = egg-based quadrivalent subunit influenza virus vaccine

1. V130_10: All unsolicited AEs were collected during the treatment period (Day 1 to 29/57); SAEs, medically attended AEs, AEs leading to withdrawal from the study and New Onset Chronic Diseases were collected from Day 1 through Day 181/209.
2. Unsolicited Safety Set (V130_10): All subjects in the All Enrolled Set who were randomised and received a study vaccination who were not part of the Cell-Mediated Immunity [CMI] population and who received vaccine on Day 1 and provided serology specimens which yielded valid serology assay results from both Day 1 and Day 29 [previously vaccinated subjects] or Day 1 and Day 57 [not previously vaccinated subjects] with any unsolicited AE data.

6.24 The ESC noted that no notable differences in fever, incidences of anaphylactic reactions and/or hypersensitivity/drug hypersensitivity were reported. Children aged 24 to 47 months receiving QIVc were slightly more likely to have a fever $\geq 40^{\circ}\text{C}$,

however these were based on small numbers: 10 children (0.6% of children who received QIVc) versus 1 child (0.2% of children receiving QIVe).

- 6.25 ATAGI noted that, “Safety data are limited but there are no apparent concerns that the QIVc is less safe than the QIVe vaccine. Safety data are available for the trivalent cell-based vaccine, which is considered likely to be equivalent in terms of safety and reactogenicity to the egg-based comparator”.
- 6.26 The submission provided data on potential safety concerns beyond those identified in the clinical trial, including the Periodic Safety Update Report, the Risk Management Plan, the Seqirus pregnancy registry, and two publications on adverse event surveillance, one in healthcare workers in Italy and one in pregnant women in the US. The submission concluded that the extended safety assessment did not identify any additional AEs or suggest any increased concerns. The ESC considered this was reasonable, although there are no specific data for high risk populations.

Benefits/harms

- 6.27 The ESC considered it was not possible to reliably quantify the rVE for QIVc versus QIVe noting the extent of benefit would depend on egg-adaptation which can vary from year to year. The ESC noted the precise size of the benefit in any particular year would also be subject to some uncertainty because of the possibility of residual confounding, given the superiority claim is based on nonrandomised studies.
- 6.28 The results from the meta-analyses of rVE were used in the economic model in Section 3. Comparative harms have not been presented as the submission did not claim a safety difference.

Clinical claim

- 6.29 The submission claimed QIVc was superior to QIVe in effectiveness against clinically relevant influenza-related outcomes, and “comparable” in terms of safety compared to QIVe. The ESC noted that the effectiveness claim was based on non-randomised studies that used administrative data.
- 6.30 The ESC considered that while superior effectiveness of QIVc compared to QIVe was biologically plausible, this would depend on egg-adaptation which can vary from year to year. The pre-PBAC Response maintained that the superior effectiveness of QIVc compared to QIVc was well supported by the studies presented in the submission and emphasised that the variability in rVE, based on season-specific characteristics of the circulating virus and its match to vaccine strains, including the degree of egg adaptations, was incorporated into the economic model.
- 6.31 The PBAC considered that the claim of superior comparative effectiveness was plausible though any benefit was difficult to quantify from the available data. The PBAC considered that the extent of benefit if any, would be dependent on the degree to which antigenic drift and egg adaptation affected the differential match of vaccine

viruses to circulating strains and the severity of the flu season, which varies from year-to-year.

- 6.32 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.33 The submission presented a stepped economic evaluation implementing a modelled economic evaluation based on retrospective (observational) cohort studies. The stepped economic evaluation included cost-effectiveness analyses (cost per influenza case avoided and cost per life year gained; CEA) and cost-utility analysis (cost per quality adjusted life year (QALY) gained; CUA) comparing a QIVc vaccination program versus the current QIVe vaccination program for each of the four populations proposed in the submission. An updated economic evaluation was provided with the pre-PBAC Response which excluded children aged 2 to 4 years.

- 6.34 Two economic models were presented. They were:
- A dynamic transmission model that estimated the direct and indirect (herd immunity) impact of the alternative influenza vaccination programs.
 - A static cohort model that estimated the direct effect of the alternative vaccination programs.

- 6.35 The evaluation considered that given the difficulty in parameterising a dynamic model due to lack of data and uncertain impacts of herd immunity and force of infection, the use of a dynamic model may not be adequately supported. Previous base case models considered by the PBAC for influenza vaccinations were either expected cohort analysis or static (Markov) models where herd immunity was not considered (Quadrivalent influenza vaccine Vaxigrip Tetra, PSD, July 2019 meeting; Influenza Quadrivalent Adjuvanted Vaccine Fludax[®] Quad, Influenza Trivalent Adjuvanted Vaccine Fludax[®], PSD, July 2019 PBAC meeting; High Dose Inactivated Trivalent Influenza Vaccine (Split virion) Fluzone[®] High-Dose, PSD, July 2018 meeting). For the quadrivalent influenza vaccine Vaxigrip Tetra, the impact of herd immunity was presented as a scenario analysis. The PBAC did not consider these results because ATAGI had suggested that the proposed vaccination program would have little, if any, measurable population-level herd protection (Table 9, Quadrivalent influenza vaccine Vaxigrip Tetra, PSD, July 2019 PBAC meeting).

- 6.36 ATAGI indicated that the improvement in vaccine effectiveness was not likely to result in measurable population herd protection and therefore the presentation of a transmission model was inadequately justified. The submission nor the post-submission documents provided additional clinical evidence to support the claim of herd immunity based on the vaccine effectiveness observed. The ESC agreed with the evaluation and ATAGI advice that a QIVc vaccination program was not likely to produce significant changes in the force of infection and the presentation of a dynamic model was not justified.

- 6.37 The dynamic transmission model presented in the submission incorporated an epidemiological module and an economic module. The epidemiological module consisted of the classic 'Susceptible-Exposed-Infectious-Recovered' (SEIR) model to provide estimates of the epidemiological impact of the switch from QIVe to QIVc. The SEIR model captures the natural history of influenza and is commonly applied in infectious disease modelling. The economic module was described to have the same overall structure, morbidity and mortality inputs as the static cohort model, with the number of influenza cases per age-group estimated by the epidemiological model included as inputs.
- 6.38 There were a number of issues identified with the dynamic transmission model, particularly with the assumptions in the epidemiological module which were likely to have overstated the indirect benefits of the vaccination program thus over-estimating the benefits conferred by QIVc. Some issues included:
- The choice of susceptibility profile in the epidemiological module is a key determinant of the estimated effective reproduction number. By imposing a low value of prior immunity (27%) the model calibration yielded very low estimates of the effective reproduction number (R_{eff}), which indicated that (a) the existing immunisation program was estimated to provide significant indirect protection, appearing to almost prevent the 2018 epidemic from occurring (5.67 million cases in the No Vaccine scenario and only 115,386 symptomatic cases in the vaccinated scenarios); and (b) a small increase in vaccine effectiveness, such as routinely occurs from one season to the next, will necessarily provide a substantial increase in indirect protection in the epidemiological module. These outcomes are a direct result of the chosen susceptibility profile, and both the outcomes and the assumed susceptibility profile were highly improbable. The PSCR maintained that at 50% prior immunity, the QIVc program remained highly cost-effective.
 - The model calibration process could not be sufficiently verified during the evaluation.
 - Reliability of the rVE applied in the model. The sensitivity analyses presented in the submission indicated that rVE was the key driver of the ICER for the dynamic model. The ICER increased to \$0 to < \$5,000 per QALY gained from \$0 to < \$5,000 per QALY gained (base case for all seasons combined) when rVE estimates were varied from 12.2% to 8.2%.
 - The dynamic model presented in the submission did not reasonably account for major sources of uncertainty. Apart from pre-existing immunity as described above, other sources of uncertainty include vaccine coverage and the linear assumptions around this parameter. These assumptions were not tested by the submission.
 - The model included the general population in the vaccination program (beyond the 4 population subgroups proposed for NIP funding, i.e. including NIP-funded

and non-NIP private market coverage) to estimate the indirect effect (herd immunity). Therefore, it was unclear what proportion of the overall change in number of cases was attributed to the populations requested for NIP listing.

- The specification of the impact of non-fatal disease on QALYs was likely incorrectly implemented in the Shiny model (the model was developed in R and C++, with a Shiny package interface). The model appeared to be solely driven by the “qaly_loss_per_case” variable and the two remaining variables (“qaly_loss_per_outpatient_case” and “qaly_loss_per_hosp”) did not have any impact (over the base case) in the number of QALYs reported. The application of the model deviates from the model design described in the submission, both in terms of the magnitude of the QALY decrement applied to non-fatal cases and the fact that the same decrement is applied to both outpatient and hospitalised cases.
- There were a number of assumptions made in the dynamic model which were unsupported and inconsistent with those stated in the submission. These include: the assumption that 100% of outpatients are prescribed antivirals, which is implausible; the proportion of hospitalised cases transported by ambulance; and the cost of ambulance services, which was likely overestimated. These issues, however, were considered to have a lower impact on the results compared to the issues described above.

- 6.39 There was substantial difference in the cost-effectiveness results presented between the two economic models. Given the concerns regarding the underlying assumptions, structural issues and the lack of availability of evidence to populate the dynamic model, the evaluation considered the static cohort model more reliable than the dynamic model and it was the focus of the evaluation.
- 6.40 The static cohort model simulates population and age-specific cohorts over one cycle, representing one year or one influenza season. This structure was appropriate.
- 6.41 Inputs for the static cohort model were season specific using the 2015 to 2019 Australian seasons. The model also included an additional scenario reflecting the average over 2015-2019 seasons. The results averaged over seasons understate the variability from season to season as it does not capture the distribution around the mean value. For example, in the 2018 season (rVE=0%), the cost-effectiveness result was dominated (i.e. QIVc more expensive with less/same effectiveness) whereas in the 2019 season (rVE=15.6%) the ICER was \$5,000 to < \$15,000 per QALY gained.
- 6.42 Table 12 presents the key components of the economic (static cohort) model.

Table 12: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	QIVc vs QIVe
Time horizon	1 year, with full life expectancy applied for deaths avoided.
Outcomes	Outpatient influenza cases, Hospitalised influenza cases, Influenza deaths, Life years (LYs), Quality adjusted life years (QALYs)
Methods used to generate results	A static cohort model capturing the direct effect of the alternative vaccination programs
Health states	Well (No Influenza), Influenza, Outpatient Influenza, Hospitalised Influenza, Treated/ Recovered from Influenza, Influenza death The "Influenza" health state was structured to represent medically attended influenza. This evaluation considered this was reasonable as inputs were based on age-specific notification rates of laboratory confirmed influenza in Australia as a proxy.
Cycle length	1 year
Transition probabilities	<p><u>Background incidence of influenza (age and season specific)</u>: season- and age-specific laboratory confirmed influenza notifications reported for 2015-2019 through the NNDSS.</p> <p><u>Influenza hospitalisations</u>: calculated based on age and season-specific ratio between the influenza hospitalisation rate (sourced from National Hospital Morbidity Database) and the influenza notification rate. Adjusted to proposed populations using rate ratios and proportions sourced from literature.</p> <p><u>Influenza-related deaths (case-fatality ratio)</u>: calculated from modelled influenza associated respiratory and cardiovascular hospitalisations and deaths from Leung et al (2021). Adjusted to proposed populations using rate ratios and proportions sourced from literature.</p> <p><u>Other inputs used to calculate population-specific incidence, hospitalisation and CFR</u>:</p> <ul style="list-style-type: none"> • Ioannides et al, 2019 – source of rate ratio of notification rates in Aboriginal and Torres Strait Islander populations versus non-Indigenous populations. • Cromer et al, 2014 – source of rate ratio of hospitalisation rates and CFRs in the high risk versus non-high risk populations. • MedicineInsight 2014 – source for proportion of population with medical conditions that increase the risk of influenza complications. • Australian Institute of Health and Welfare 2018 – source for the distribution of mothers. • Prasad et al, 2019 – source of rate ratio of hospitalisation rates in the pregnant population.
Relative vaccine effectiveness	Estimated from meta-analyses of retrospective cohort (observational) studies presented as evidence to demonstrate clinical effectiveness.
Vaccine coverage	Age and population specific rates from Beard et al. 2021, FluCAN annual reports 2015-2018, Kaufman et al. 2021 and ATAGI pre-submission advice. These estimates were used to re-weight results from the static cohort model for the Aboriginal and Torres Strait Islander and high-risk populations.
Extrapolation method	Full life expectancy was applied to the surviving population to estimate the differential impact of QIVc compared to QIVe on influenza-related deaths. QALYs were also modelled to full life expectancy.
Health related quality of life	Published studies including McCaffrey et al. 2016, Hollmann et al. 2013, Bilcke et al. 2014. Australian norms used to reflect utility of normal health. Disutilities for hospitalised and outpatient influenza were sourced from studies of the Spanish and Belgian populations. Utilities were based on the adult population.
Costs	Direct medical costs, including vaccine administration costs, GP consultation for influenza, averaged AR-DRG costs for influenza hospitalisation episode, influenza test, anti-viral therapy and ambulance for hospitalisations.

Source: Compiled during the evaluation based on Tables 3.1.1, 3.2.3, 3.4.2-3.4.22, 3.5.4, 3.6.3, p126, 140, 156-171, 178, 179 of the submission.

QIVc = cell-based quadrivalent subunit influenza virus vaccine, QIVe = egg-based quadrivalent subunit influenza virus vaccine, CFR = case fatality rate, ATAGI = Australian Technical Advisory Group on Immunisation, GP = general practitioner, AR-DRG = Australian Refined Diagnosis Related Groups, NNDSS = National Notifiable Disease Surveillance System.

- 6.43 The submission applied estimated rVE based on general population effectiveness to each of the specific populations requested for NIP funding. The application of estimated rVEs to the proposed NIP populations was uncertain.
- 6.44 Outcomes from different clinical settings (primary care and hospitalisation) from the observational studies were combined for the meta-analyses used to inform the rVE applied in the economic model. This may not be appropriate (see paragraphs 6.20 and 6.21). The PSCR argued that all outcomes measured in the clinical trials, whether in the primary care or the hospitalisation setting, represented instances of medically attended influenza and therefore it was appropriate to combine them in meta-analysis. The ESC agreed with the evaluation and the ATAGI advice that primary care and hospitalisation represent different severities of influenza, and the reduction in influenza-related hospitalisations or primary health encounters may be due to a change in the virulence of the circulating virus and therefore seasonal severity, as opposed to the risk of infection.
- 6.45 The submission applied the closest match estimated rVE derived from the observational studies to the Australian Influenza seasons from 2015 to 2019. The rVE from the observational studies was matched to the Australian influenza seasons based on circulating virus strain and evidence of egg-adaptation. The approach applied was not justified or referenced.
- 6.46 The issue regarding the uncertain applicability of rVE to incidence of influenza raised by ATAGI remains and it may not be a reasonable approach.
- 6.47 The submission presented combined results weighted by the numbers of vaccinated persons in each population. The method applied was reasonable; however, the structure and presentation of results were difficult to interpret and meant that the evaluation had limited ability to conduct sensitivity analyses. The PSCR provided additional explanation to allow for further sensitivity testing.
- 6.48 The time horizon for the model was one year. The vaccine effectiveness and costs were applied for one year. Those surviving were modelled to full life expectancy with QALY impacts applied. The QALY impact of the 'Outpatient influenza' and 'Hospitalised influenza' health states were short term and the QALYs of the 'Well (no influenza)' state was modelled to full life expectancy. The ESC considered that it was reasonable to extrapolate surviving populations to full life expectancy, with QALY impacts applied. While the life expectancy appeared to be appropriately estimated, the attribution of QALYs did not appear to have been age adjusted. For instance, individuals who were young at time of death gained a larger amount of QALYs throughout their life than would be expected given secular trends in QALY decline with increasing age.
- 6.49 Australian ABS life tables were used to estimate life expectancy and to calculate expected QALYs for both Aboriginal and Torres Strait Islander and non-Indigenous populations. The PSCR acknowledged that this survival was likely overestimated for the Aboriginal and Torres Strait Islander population. An updated economic model was provided in the pre-PBAC response. The pre-PBAC response stated that Aboriginal and

Torres Strait Islander specific life expectancy estimates were applied to the updated model.

- 6.50 Each of the four populations were modelled separately, applying population specific rates to determine incidence, hospitalisation rates and influenza-related mortality. Within the model, data sources were used to estimate the size of three populations: the Aboriginal and Torres Strait Islander population, individuals with high-risk conditions, and women who are pregnant in the modelled year. However, the sizes of these populations appear to be independently assessed. This may result in individuals being 'double counted' due to having two or more of these characteristics. The PSCR acknowledged NIP-populations were double-counted in the static cohort model due to the lack of available data to inform the adjustment but claimed the impact on cost-effectiveness would be negligible.
- 6.51 The submission appeared to have applied a reasonable approach to inflate risk for the higher risk populations (Aboriginal and Torres Strait Islander, high-risk with comorbidities, pregnant women), however the corresponding recalibration of the remaining low-risk (i.e. general population minus high-risk population) population risk data was not undertaken. The combination of inflation of the high-risk population without corresponding adjustment for the low risk had the overall effect of increasing the risk of the total modelled population. This had a flow-on effect to subsequent calculations for hospitalisations and case fatality ratios (CFRs). The pre-PBAC response stated that the hospitalisation rates for the high-risk population in the updated economic model was adjusted, to remove the risk associated with the Aboriginal and Torres Strait Islander population.
- 6.52 Contrary to ATAGI's advice, CFRs in the base case of the economic model were based on modelled age-dependent rates of pooled influenza-associated respiratory and cardiovascular hospitalisations and deaths from Leung et al. (2021). This led to higher CFRs compared to those recommended in the ATAGI's advice that were based on observed data from AIHW for ICD-10 coded deaths from influenza. CFRs based on AIHW data were examined in sensitivity analysis. AIHW observed data for 2015 to 2019 remains the best available evidence to inform influenza hospitalisations and deaths as these outcomes correspond to those presented in the observational studies demonstrating clinical effectiveness and were more recent compared to the 2007 to 2015 data presented in Leung et al. (2021), which do not align with the seasons examined in the economic model. The ICER is highly sensitive to CFRs used, increasing to \$55,000 to < \$75,000 per QALY gained from \$25,000 to < \$35,000 per QALY gained in the high risk population when AIHW observed data was applied instead of modelled respiratory and cardiovascular data. The ESC agreed with the evaluation and considered that that the AIHW observed data remains the most reliable evidence to inform influenza CFRs. The PSCR disagreed with the evaluation and maintained that the modelled excess respiratory and cardiovascular deaths provided the most credible option to estimate CFRs as the observed data may be misclassified and the true burden likely under-represented. The pre-PBAC Response maintained it was appropriate to

base CFRs on rates of pooled influenza-associated respiratory and cardiovascular hospitalisations from Leung et al. (2021) noting the following:

- Mortality due to influenza is under ascertained and misclassified in official mortality statistics, with influenza deaths often attributed to other comorbid conditions or secondary infections.
- In recognition of the under ascertainment, statistical methods have been developed to estimate excess mortality and hospitalisations attributable to influenza. The base case CFRs in the submission are informed by the most comprehensive report to date in Australia, using multiple streams of data to estimate the influenza burden in terms of mortality and hospitalisation.
- Estimates of excess hospitalisations and deaths attributable to influenza are routinely applied in influenza models and have been previously accepted by the PBAC (Adjuvanted TIV and QIV PSD, July and August 2019; and High Dose TIV PSD, November 2019).
- Use of excess respiratory and cardiovascular deaths in the base case is supported by findings that non-respiratory deaths account for substantial proportions (>50% in some instances) of all influenza-associated deaths (Iuliano et al. 2018).

6.53 The values applied to the economic model for the 'Outpatient influenza' and 'Hospitalised influenza' health states were QALYs (-0.009 and -0.0139 QALYs, respectively) and not utility values. Thus, the submission assumed a fixed duration of the impact of influenza in each of these health states, and the assumption of the duration of impact and utility values could not be varied and tested separately during the evaluation. Based on the sensitivity analyses presented in the submission for the static cohort model, the utilities were not identified to be an important driver in the model and had a small impact on the base case ICER. It was not possible to verify this assumption, however the choice of current utilities (relatively high for well state and relatively low for outpatient and hospitalised states) may favour the intervention. The ESC agreed with the evaluation that the methodology adopted to calculate the utility associated with transition to the hospitalised and outpatient influenza health states was not appropriate. Utility values specific to these states and time spent in these states would have been more appropriate.

6.54 Table 13 presents a summary of the key drivers of the static cohort model.

Table 13: Key drivers of the static model

Description	Method/Value	Impact
Seasonal variation in influenza incidence and circulating strain	Based on laboratory confirmed notification rates for influenza from the National Notifiable Disease Surveillance System (NNDSS) for years 2015 to 2019. This is correlated with rVE.	High, favours QIVc. In the 2018 season (low burden, rVE=0%), the cost-effectiveness result was dominated (i.e. QIVc more expensive with less/same effectiveness) whereas in the 2019 season (high burden, rVE=15.6%) the ICER was \$5,000 to < \$15,000 per QALY gained in the high risk population.
rVE	Season-specific based on closest match on circulating virus strain and evidence of egg-adaptation to Australian seasons. Estimated from pooled rVE from meta-analyses. 2015: 14.0% (low 8.8, high 18.65) 2016: 15.6% (10.8, 20.1) 2017: 15.6% (10.8, 20.1) 2018: 0% (0, 0) 2019: 15.6% (10.8, 20.1) 2015-2019: 12.2% (8.2, 18.3)	High, favours QIVc. Sensitivity analysis performed on the high-risk population (averaged 2015-2019) showed that the ICER increased from \$25,000 to < \$35,000 per QALY gained (base case) to \$45,000 to < \$55,000 per QALY gained when the overall rVE estimate reduced from 12.2% to 8.2%.
Case fatality ratio	Calculated from modelled influenza associated respiratory and cardiovascular hospitalisations and deaths from Leung et al (2021). Pooled data for respiratory and cardiovascular hospitalisations and deaths were applied instead of AIHW observed influenza-related mortality rates.	High, favours QIVc. Base case ICER for high risk population (2015-2019) increased to \$55,000 to < \$75,000 per QALY gained from \$25,000 to < \$35,000 per QALY gained when AIHW observed data was applied instead of modelled respiratory and cardiovascular data.

Source: Tables 3.8.17-3.8.21, p205-207 of the submission

AIHW = Australian Institute of Health and Welfare; QIVc = cell-based quadrivalent subunit influenza virus vaccine, QIVe = egg-based quadrivalent subunit influenza virus vaccine, ICER= incremental cost effectiveness ratio, QALY = quality adjusted life year, rVE = relative vaccine effectiveness.

6.55 The weighted average rates and estimated numbers of influenza outcomes prevented in the overall vaccinated NIP population are shown in Table 14.

Table 14: Weighted average rates and estimated numbers of influenza outcomes prevented in the overall vaccinated NIP population¹

Season	Influenza-related outcome	Health state	Prevented per 100,000	Prevented per year
2015	Cases	Influenza	58.97	2,005
	GP visits	Outpatient Influenza	42.85	1,457
	Hospitalisations	Hospitalised Influenza	16.12	548
	Deaths	Influenza Death	0.54	18
2016	Cases	Influenza	58.17	1,978
	GP visits	Outpatient Influenza	39.73	1,351
	Hospitalisations	Hospitalised Influenza	18.44	627
	Deaths	Influenza Death	0.65	22
2017	Cases	Influenza	157.89	5,370
	GP visits	Outpatient Influenza	118.49	4,030
	Hospitalisations	Hospitalised Influenza	39.40	1,340
	Deaths	Influenza Death	1.45	49
2018	Cases	Influenza	0.00	0
	GP visits	Outpatient Influenza	0.00	0
	Hospitalisations	Hospitalised Influenza	0.00	0
	Deaths	Influenza Death	0.00	0
2019	Cases	Influenza	199.37	6,780
	GP visits	Outpatient Influenza	152.50	5,186
	Hospitalisations	Hospitalised Influenza	46.87	1,594
	Deaths	Influenza Death	1.64	56
2015-2019	Cases	Influenza	81.63	2,776
	GP visits	Outpatient Influenza	59.78	2,033
	Hospitalisations	Hospitalised Influenza	21.86	743
	Deaths	Influenza Death	0.77	26

Source: Table 3.8.16, p204 of the submission

1. Estimated as a yearly average of 3,400,907 persons for the 2023-2028 period.

6.56 Table 15 presents the results of the stepped economic evaluation for each of the proposed populations and for the overall proposed NIP population using the cost per dose proposed in the submission. The stepped approaches were:

- Step 1: Incremental cost per influenza case avoided within the 1-year time horizon.
- Step 2: Incremental cost per life year gained (LYG), extrapolating influenza deaths to age-dependent loss of life expectancy expressed in years.
- Step 3 (base case analysis): Incremental cost per QALY gained, extrapolating influenza deaths to age-dependent loss of life expectancy expressed in QALYs.

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Table 15: Results of the stepped economic evaluation by population and averaged 2015-2019 seasons

Step and component	QIVc	QIVe	Increment
Children 2-4 years			
Costs	\$	\$	\$
Influenza cases	0.009923	0.011302	-0.001379
Step 1: Incremental cost/influenza case avoided			
LYG	21.03954	21.03950	0.000036
Step 2: Incremental cost/LYG			
QALYs	20.14596	20.14592	0.000048
Step 3: Incremental cost/QALY gained			
Aboriginal and Torres Strait Islander population			
Costs	\$	\$	\$
Influenza cases	0.006350	0.007233	-0.000882
Step 1: Incremental cost/influenza case avoided			
LYG	18.502412	18.502329	0.000083
Step 2: Incremental cost/LYG			
QALYs	16.922490	16.922408	0.000082
Step 3: Incremental cost/QALY gained			
High-risk			
Costs	\$	\$	\$
Influenza cases	0.004615	0.005256	-0.000641
Step 1: Incremental cost/influenza case avoided			
LYG	17.052028	17.051881	0.000147
Step 2: Incremental cost/LYG			
QALYs	15.231421	15.231284	0.000137
Step 3: Incremental cost/QALY gained			
Pregnant and newborns			
Step 1			
Costs	\$	\$	\$
Influenza cases	0.0103	0.0118	-0.00144
Step 1: Incremental cost/influenza case avoided			
LYG	29.5508	29.5508	0.00006
Step 2: Incremental cost/LYG			
QALYs	27.4460	27.4459	0.00008
Step 3: Incremental cost/QALY gained ^a			
NIP population ^b			
Costs	\$	\$	\$
Influenza cases	0.00587	0.00669	-0.00082
Step 1: Incremental cost/influenza case avoided			
LYG	18.42	18.42	0.000121
Step 2: Incremental cost/LYG			
QALYs	16.75	16.75	0.000116
Step 3: Incremental cost/QALY gained			

Source: Table 3.8.2, p192 of the submission

LYG = life years gained, NIP = National Immunisation Program; QALY = quality-adjusted life year, QIVc = cell-based quadrivalent subunit influenza virus vaccine, QIVe = egg-based quadrivalent subunit influenza virus vaccine.

^a ICERs for pregnant women only population for step 3 was \$155,000 to < \$255,000 per QALY gained compared to that presented in combination (\$35,000 to < \$45,000 per QALY gained).

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^b Includes costs and outcomes from pregnant and newborns combined. However, the pregnant women population comprised of only 5% of the overall NIP population, therefore, impact was small. Revised NIP population ICER was \$35,000 to < \$45,000 per QALY gained instead.

The redacted values correspond to the following ranges:

¹\$0 to < \$5,000

²\$135,000 to < \$155,000

³\$95,000 to < \$115,000

⁴\$45,000 to < \$55,000

⁵\$5,000 to < \$15,000

⁶\$25,000 to < \$35,000

⁷\$35,000 to < \$45,000

6.57 The economic evaluation above is based on the price per dose proposed in the original submission (\$~~1~~). These results should be interpreted with caution for the following reasons:

- The results averaged over seasons may understate the uncertainty as it does not capture the distribution around the mean value.
- Seasonal variations in influenza incidence and strain circulation were uncertain as were vaccine coverage rates.
- The use of a less conservative CFR (modelled pooled respiratory and cardiovascular hospitalisation and deaths) as opposed to AIHW observed data (ICD-10 coded deaths from influenza) available for the corresponding seasons evaluated.
- The applicability of rVE to incidence of influenza is uncertain and may not be a reasonable approach.
- Primary care and hospitalisation outcomes have been combined, which may obscure differences in rVE in these settings in some seasons.

6.58 The main cost which contributes to the ICER is the cost of QIVc vaccination. Cost savings from reduced outpatient and hospitalised influenza were observed, mainly from hospitalised influenza. The extent varied by populations and seasons.

6.59 Season specific base case results and key sensitivity analyses are summarised below.

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Table 16: Season specific base case results and key sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change from base case ^a
Base case (Proposed NIP pop. (2015-2019))		0.000116	\$1	
Season 2015		0.000083	\$2	55%
Season 2016		0.000096	\$3	29%
Season 2017		0.000214	\$4	-64%
Season 2018		-	Dominated	-
Season 2019		0.000250	\$4	-76%
Children 2-4 years				
Base case (2015-2019)		0.000048	\$5	184%
Season 2015		0.000043	\$6	230%
Season 2016		0.000040	\$6	252%
Season 2017		0.000083	\$1	24%
Season 2018		0.000000	Dominated ^b	
Season 2019		0.000106	\$7	-19%
Low rVE		0.000033	\$8	369%
High rVE		0.000072	\$2	56%
Observed CFR		0.000021	\$8	547%
Low rVE + Observed CFR		0.000014	\$9	969%
Aboriginal and Torres Strait Islander population				
Base case (2015-2019)		0.000082	\$3	36%
Season 2015		0.000040	\$6	235%
Season 2016		0.000060	\$10	107%
Season 2017		0.000150	\$11	-49%
Season 2018		0.000000	Dominated ^b	
Season 2019		0.000193	\$4	-77%
Low rVE (age20) ^c		0.000017	\$12	749%
High rVE (age20) ^c		0.000038	\$6	239%
Low rVE + Observed CFR (age20) ^c		0.000005	\$13	2928%
Observed CFR (age20) ^c		0.000007	\$14	1853%
Observed CFR (age64) ^c		0.000079	\$11	-38%
Low rVE + Observed CFR (age64) ^c		0.000053	\$2	59%
High risk population				
Base case (2015-2019)		0.000137	\$7	-17%
Season 2015		0.000098	\$3	30%
Season 2016		0.000114	\$1	6%
Season 2017		0.000256	\$4	-71%
Season 2018		0.000000	Dominated ^b	
Season 2019		0.000293	\$4	-78%
Low rVE (age20) ^c		0.000061	\$10	129%
High rVE (age20) ^c		0.000134	\$7	-15%
Low rVE + Observed CFR (age20) ^c		0.000061	\$10	129%
Observed CFR (age20) ^c		0.000024	\$8	439%
Observed CFR (age64) ^c		0.000072	\$3	42%
Low rVE + Observed CFR (age64) ^c		0.000048	\$10	149%

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Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change from base case ^a
Pregnant women only population				
Base case (2015-2019)		0.000021	\$⁸	391%
Season 2015		0.000016	\$ ¹²	647%
Season 2016		0.000016	\$ ¹²	628%
Season 2017		0.000034	\$ ²	102%
Season 2018		0.000000	Dominated ^b	
Season 2019		0.000053	\$ ⁴	-59%
Low rVE		0.000014	\$ ¹²	756%
High rVE		0.000031	\$ ¹⁰	138%
Low rVE + Observed CFR		0.000009	\$ ¹⁵	1295%
Observed CFR		0.000013	\$ ¹²	700%

Source: Compiled during the evaluation based on results presented in the submission

CFR = case fatality ratio; ICER = incremental cost-effectiveness ratio; NIP = National Immunisation Program; QALYs = quality-adjusted life years; rVE = relative vaccine effectiveness; QIVc = cell-based quadrivalent subunit influenza virus vaccine; QIVe = egg-based quadrivalent subunit influenza virus vaccine.

^a Compared to base case of proposed NIP population (2015-2019)

^b Dominated by QIVe (QIVc more expensive with less/same effectiveness)

^c Modelled cohort age

The redacted values correspond to the following ranges:

¹\$35,000 to < \$45,000

²\$55,000 to < \$75,000

³\$45,000 to < \$55,000

⁴\$5,000 to < \$15,000

⁵\$95,000 to < \$115,000

⁶\$115,000 to < \$135,000

⁷\$25,000 to < \$35,000

⁸\$155,000 to < \$255,000

⁹\$355,000 to < \$455,000

¹⁰\$75,000 to < \$95,000

¹¹\$15,000 to < \$25,000

¹²\$255,000 to < \$355,000

¹³> \$1,055,000

¹⁴\$655,000 to < \$755,000

¹⁵\$455,000 to < \$555,000

6.60 Beyond these analyses, there were additional inputs that were uncertain but were not adequately reflected in the submission's economic model and/or could not be easily tested in the model during the evaluation as a result of the structure of the model and presentation of the results (results generated age-by-age from TreeAge and outputs then adjusted in Excel). These inputs included: assumptions on vaccine coverage, calculation of notification rates for the Aboriginal and Torres Strait Islander and high risk populations with no re-adjustment of rates of the general population to remove the risk associated with high-risk/Aboriginal and Torres Strait Islander/pregnant women populations, age-specific rates among those aged 2-4 years and matching of the Australian season predominant strains and rVE of QIVc. It is likely that a re-specified base case reflecting the appropriate and corrected input and data sources is required to better capture the ICER estimates of the proposed NIP population. This may include use of corrected (re-adjusted) transition probabilities (incidence, hospitalisation, and CFRs calculated from observed AIHW influenza-related mortality data), and revisiting use of rVE values based on applicability of rVE.

6.61 An updated economic model was provided with the pre-PBAC Response. The pre-PBAC Response stated that the economic model included the following revisions:

- adjustment of hospitalisation rates for the high-risk population to remove the risk associated with the Aboriginal and Torres Strait Islander population;
- the inclusion of Aboriginal and Torres Strait Islander specific life expectancy;
- exclusion of children aged 2 to 4 years; and
- A reduced price of Flucelvax Quad at \$¹ per dose.

The results of the updated economic model provided in the pre-PBAC response are provided in Table 17. The updated season-specific economic outcomes for the individual and the overall NIP populations are provided in Table 18.

Table 17: Results of updated cost-effectiveness of QIVc compared to QIVe for the 2015 to 2019 scenario

Population	Average vaccinated 2023-2028		Incremental cost	Incremental QALY	ICER (\$/QALY)
	Number	%			
High-risk ^a	¹	84.8		0.000129	²
ATSI ^b	³	9.3		0.000072	⁴
Pregnant women ^c	⁵	5.9		0.000075	²
Groups above combined (NIP)	¹	100		0.000120	²

Source: Pre-PBAC Response (p1)

^a High-risk population aged ≥5 years to <65 years, using Medicine Insight proportions

^b ATSI population aged ≥5 years to <65 years

^c Pregnant women, including impact on newborns.

The redacted values correspond to the following ranges:

¹12,000,000 to < 3,000,000

²\$25,000 to < \$35,000

³200,000 to < 300,000

⁴\$35,000 to < \$45,000

⁵100,000 to < 200,000

Table 18: Updated season and population-specific cost-effectiveness of the proposed QIVc program compared to QIVe

Population	Season	Incremental cost	Incremental QALY	ICER (\$/QALY)
ATSI	2015		0.000036	¹
	2016		0.000053	²
	2017		0.000132	³
	2018		0.000000	Dominated
	2019		0.000171	⁴
	2015 to 2019		0.000072	⁵
High-risk ^a	2015		0.000093	⁵
	2016		0.000108	⁶
	2017		0.000241	³
	2018		0.000000	Dominated
	2019		0.000273	³
	2015 to 2019		0.000129	⁶
Pregnant women (including newborns)	2015		0.000066	⁵
	2016		0.000064	⁵
	2017		0.000127	⁴
	2018		0.000000	Dominated

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	2019		0.000167	Dominant
	2015 to 2019		0.000075	6
NIP	2015		0.000086	5
	2016		0.000100	6
	2017		0.000224	3
	2018		0.000000	Dominated
	2019		0.000257	3
	2015 to 2019		0.000120	6

Source: Pre-PBAC Response (p6)

^a High-risk population using Medicine Insight proportions.

The redacted values correspond to the following ranges:

¹\$95,000 to < \$115,000

²\$55,000 to < \$75,000

³\$5,000 to < \$15,000

⁴\$0 to < \$5,000

⁵\$35,000 to < \$45,000

⁶\$25,000 to < \$35,000

Vaccine cost/patient/year

Table 19: Drug cost per patient for QIVc and QIVe (as proposed in the submission)

	QIVc / QIVe Recommended dose and frequency	QIVc Model	QIVc Financial estimates	QIVe Model	QIVe Financial estimates
Dose	1 dose ¹	1 dose [1.17 for children 2-4 years]	1 dose [1.17 for children 2-4 years]	1 dose [1.17 for children 2-4 years]	1 dose [1.17 for children 2-4 years]
Frequency	Once a year ¹	Once a year	Once a year	Once a year	Once a year
Cost/patient/year	\$█	\$█ [\$█ for children 2-4 years]	\$█ [\$█ for children 2-4 years]	\$█ ² [\$█ for children 2-4 years]	\$█ ² [\$█ for children 2-4 years]

Source: Table 3.6.3, p181 of the submission

The cost of vaccine administration has not been included in the table above. This cost ranges from \$█ to \$█ depending on the vaccinated population.

¹ Dose recommendation from the product information indicate that children less than 9 years of age who have not been previously vaccinated against influenza, should receive a second dose (as funded under NIP).

² Based on current NIP price of Afluria Quad, a Seqirus product. Note that this is Commercial-In-Confidence information.

6.62 The pre-PBAC response proposed a reduced price of \$█ per dose.

Estimated PBS usage & financial implications

6.63 This submission was not considered by DUSC. The submission employed an epidemiological approach to estimate the financial implication from complete substitution of QIVe with QIVc in each of the proposed populations for NIP funding. Therefore, a substitution rate of 100% was assumed for the estimated number of patients being vaccinated (coverage) in each population group. Complete product substitution is unlikely. QIVc could instead take a market share of the existing QIVe market. ATAGI considered that QIVe will also likely remain available.

6.64 The key inputs for estimating the financial implications are summarised in Table 20.

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Table 20: Key inputs for financial estimates

Parameter	Source	Comments
Population of children 2-4 years	ABS Projected population data series B.	The source of this data is unclear. The numbers are similar but do not match those found at Population Projections, Australia, 2017-2066 [website ¹].
Aboriginal and Torres Strait Islander population 5-14 years	Projected population, Aboriginal and Torres Strait Islander Australians, Australia, state and territories, 2016 to 2031 [website ² - accessed 7/6/21].	The source found in the link is in a different format (age bands with 5 years) than those presented in submission (age bands with 1 year). The numbers are similar but do not match.
Aboriginal and Torres Strait Islander population 15-49 years		
Aboriginal and Torres Strait Islander population 50-64 years		
Population with increased risk aged 5-17 years	Estimated based on ABS numbers by age multiplied by the prevalence of medical conditions associated with increased risk of severe influenza from the National Health Survey 2011-12.	The ABS source is unclear. The formulae used do not reduce the population size by the Aboriginal and Torres Strait Islander population in this age group, nor by the number of mothers aged 15-17.
Population with increased risk aged 18-64 years	Estimated based on ABS numbers by age multiplied by the prevalence of medical conditions associated with increased risk of severe influenza from MedicinesInsight 2014.	The ABS source is unclear. ATAGI had indicated that estimates from the National Health Survey may be an underestimate while those from MedicinesInsight were likely to be an overestimate as it reflected those who were already attending GPs. Prevalence of medical conditions associated with increased risk of severe influenza is higher than National Health Survey estimates by approximately 15-20% depending on the age based on MedicinesInsight data (Table 3.4.16 in the submission). The age bands in Table 3.4.16 (25-49) do not match the bands used in the Section 4 spreadsheet (35-49) and the proportion high risk differs (23.5% in Table 3.4.16 vs 26.4% in Section 4 spreadsheet). The formulae used do not reduce the population size by the Aboriginal and Torres Strait Islander population in this age group, nor by the number of mothers aged 18-64.
Population of pregnant women	Estimated based on the female population aged 15 to 44 years and projected pregnancy rates based on AIHW Australia's mothers and babies data visualisations. AIHW 29-6-2020 [website ³]	The ABS source is unclear. The pregnancy data could be updated to the 2019 data tables. This would reduce the projected pregnancy rates by 0.11-0.16%. The submission used the TREND function in Excel with data from 2008-2018 to project the rates for 2023-2028. Other functional forms could also be tested as this assumption could influence numbers projected. The formulae used do not reduce the population size by the Aboriginal and Torres Strait Islander population in this age group.
Vaccine coverage for all children aged 2-4 years	Beard et al. 2020, 2021/previous ATAGI advice QIV PSD, July 2019 (50%)	According to ATAGI pre-submission advice to PBAC, coverage in newly eligible (healthy) children would be 30% in 2020, increasing to 50% in 2025. This would mean that the submission figures are overestimated for 2023-24. If the trend continues to increase from 2026-28, then 50% might be an underestimate.

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Parameter	Source	Comments
Vaccine coverage for Aboriginal and Torres Strait Islander population aged 5-14 years	An average uptake of 34.5% was used based on the ATAGI advice considering that uptake in this group would likely range between uptake in the 6 month to <5 year olds (40%) and the uptake in 15 to <50 year olds (29%)	This appears to be reasonable.
Vaccine coverage for Aboriginal and Torres Strait Islander population aged 15-49 and 50-64 years	Beard et al. 2020 15-49 (29%) 50-64 (52%)	Minor discrepancy with the value presented in Beard et al for the 15-49 age group, which was 28.9%
Vaccine coverage for children (<16 years) with increased risk conditions	FluCAN annual reports 2018 (42%)	This may be an overestimate. ATAGI stated that: 'Uptake was observed to fluctuate over time in children with medical comorbidities, ranging from 16% to 42%. An estimate of 45% is proposed in the base case analysis, based on FluCAN annual report (2018). ATAGI considered that an estimate of 42% may be more reasonable, though the increase observed in 2018 compared to the previous year (24%) may have been due to the introduction of state-funded vaccinations in children aged 6 months to <5 years'. While ATAGI stated that 42% would be more reasonable than 45%, it is on the high end of the reported range in recent years. The higher rate in recent years may be driven by changes in children aged 6 months to <5 years, and only those aged >2 years are eligible in this proposal.
Vaccine coverage for ages 16-64 years with increased risk conditions	ATAGI advice based on FluCAN annual reports (51%)	The approach of taking the average from 2015-18 is different to the approach taken to determine vaccine coverage for children (<16 years) with increased risk conditions.
Vaccine coverage for pregnant women	Kaufman et al. 2020 (43%)	This estimate appears to be uncertain as uptake could range between 38.9% and 60% based on other sources (including Victorian Perinatal Data Collection, 2015–2017) considered by ATAGI. Alternate estimates were not presented in the submission, nor included in the sensitivity analyses.
Additional doses needed for children 2-4 years	The cohort aged 2 to 4 years will receive an average of 1.17 doses, as described in Section 3.6.1 (based on 1.5 doses for cohort aged 24-35 months and 1 dose for those aged 36 to 59 months, i.e. $(1.5+1+1)/3=1.17$).	While this may be consistent with that applied in the economic model, this may underestimate the number of doses needed for those aged 2. Age-specific ABS data were presented in the submission and could be used for these calculations (e.g. children aged 2 * 1.5 doses + children aged 3-4).

Source: Compiled during the evaluation based on information presented in Section 4.1.1 and 4.1.2 of the submission
ABS = Australian Bureau of Statistics; ATAGI = Australian Technical Advisory Group on Immunisation

6.65 The submission estimated potential cost savings from changes in GP visits and hospitalisations prevented resulting from QIVc. In the context of demand surpassing the supply for these services, any marginal changes in utilisation of these services due to implementation of the proposed listing would be managed by redeploying existing services rather than being realised as financial implications. Moreover, the hospitalisation savings accruing to the Australian Government budget were unclear as these would be expected to largely impact state/territory budgets. GP and hospital savings are not presented in the table below.

Table 21: Estimated use and financial implications (based on price per dose of \$ [redacted] proposed in the submission)

	2023	2024	2025	2026	2027	2028
Estimated extent of use						
Number of patients vaccinated						
Children 2-4 years	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹
Aboriginal and Torres Strait Islander population 5-14 years	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²
Aboriginal and Torres Strait Islander population 15-49 years	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³
Aboriginal and Torres Strait Islander population 50-64 years	[redacted] ⁴	[redacted] ⁴	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²
Increased risk aged 5-17 years	[redacted] ⁴	[redacted] ⁴	[redacted] ⁴	[redacted] ⁴	[redacted] ⁴	[redacted] ⁴
Increased risk aged 18-64 years	[redacted] ⁵	[redacted] ⁵	[redacted] ⁵	[redacted] ⁵	[redacted] ⁵	[redacted] ⁵
Pregnant women	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³
Number of doses ^a	[redacted] ⁶	[redacted] ⁶	[redacted] ⁶	[redacted] ⁶	[redacted] ⁶	[redacted] ⁶
Estimated financial implications of QIVc						
Cost to NIP	\$ [redacted] ⁷	\$ [redacted] ⁷	\$ [redacted] ⁸	\$ [redacted] ⁸	\$ [redacted] ⁸	\$ [redacted] ⁸

Source: Table 4.4.1, p224 of the submission

QIVc=cell-based quadrivalent subunit influenza virus vaccine,

^a Assuming 1 script per year for all populations considered except for children aged 2-4 where 1.17 scripts per year as estimated by the submission.

The redacted values correspond to the following ranges:

¹600,000 to < 700,000

²60,000 to < 70,000

³100,000 to < 200,000

⁴50,000 to < 60,000

⁵2,000,000 to < 3,000,000

⁶3,000,000 to < 4,000,000

⁷\$10 million to < \$20 million

⁸\$20 million to < \$30 million

6.66 The total cost to the NIP of listing QIVc was estimated in the submission to be \$20 million to < \$30 million in Year 6, and a total of \$100 million to < \$200 million in the first 6 years of listing. The cost to the NIP from QIVc was estimated to exceed \$20 million to < \$30 million per year from Year 3 onwards. The pre-PBAC Response did not provide revised financial estimates incorporating the reduced price per dose of \$ [redacted] and the revised population which excludes children between 2-4 years of age.

6.67 Costs may be underestimated based on uncertain coverage and uptake rates (there may also be some minor double counting depending on the overlap between subpopulations).

- 6.68 Vaccine coverage is a key driver of the financial estimates. For example, increasing vaccine coverage for non-elderly adults with medical comorbidities to 58% from 51% increased the net cost to NIP to \$100 million to < \$200 million over 6 years. The submission did not test the impact of vaccine coverage in pregnant women as suggested by ATAGI. Overall, the robustness of the estimates is unknown, in view of the uncertainty associated with the likely substitution rates, population numbers and vaccine coverage.

Quality Use of Medicines

- 6.69 The submission did not provide quality use of medicines information. Given that this is a new vaccine formulation, consideration should be provided to inform public and training health professionals regarding use, storage and waste, and difference age coverage of QIVc compared to other currently available influenza vaccines.

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

7 PBAC Outcome

- 7.1 The PBAC recommended that quadrivalent influenza virus vaccine, surface antigen, inactivated, cell-based (QIVc, Flucelvax® Quad) be a designated vaccine for the purposes of the *National Health Act 1953*, for the vaccination against influenza in Aboriginal and Torres Strait Islander people aged ≥5 to <65 years, people at increased risk of influenza disease complications aged ≥5 to <65 years and pregnant women. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of QIVc would be acceptable with a price premium compared to egg-based quadrivalent influenza virus vaccines and the acknowledgment of potential benefits associated with the diversification of vaccine manufacturing.
- 7.2 The PBAC acknowledged there were advantages of cell-based vaccine production technology over the egg-based technology and in diversifying vaccine production platforms. The PBAC noted that cell-based technology may allow faster start-up of vaccine production when needed (for example in the event of a pandemic) and production would not be dependent on egg supply.
- 7.3 The PBAC noted that the clinical claim of superior effectiveness was based on 6 retrospective cohort observational studies comparing QIVc to QIVe. The PBAC noted that based on the ROBINS-I tool, the observational studies were scored by the submission as having an overall moderate risk of bias due to a moderate risk of confounding. Although the sponsor presented analyses that attempted to statistically adjust for the potential confounding, the PBAC agreed with the ESC and considered that the size of the comparative effect reported for QIVc in these studies for any particular year was modest, and subject to some uncertainty due to potential residual confounding.

- 7.4 The PBAC noted that different clinical endpoints were used across the 6 retrospective observational studies (primary care presentation and hospital encounters) and that these outcomes reflected varying severities of influenza. The estimated rVE for QIVc was higher overall for primary care encounters compared with hospitalisation. The PBAC considered that combining the outcomes in the meta-analyses was not appropriate as the pooled outcomes may overestimate the efficacy of QIVc to prevent more severe presentations of illness (hospitalisation).
- 7.5 The PBAC considered that the size of any comparative effect of QIVc versus QIVe was dependent on several variables including the degree to which antigenic drift and egg adaptation affects the differential match of vaccine viruses to circulating strains and the severity of the flu season, which varies from year-to-year. The PBAC agreed with the ESC advice that this year-to-year variation makes it difficult to estimate the average benefit that could apply across all years and inform the cost-effectiveness.
- 7.6 Although the PBAC considered that the clinical claim of superior efficacy was plausible, it considered that the comparative benefit was difficult to quantify and subject to a moderate level of uncertainty. However, the PBAC considered that a cell-based influenza vaccine may have certain advantages over the traditional egg-based technology and was supportive of the diversification of vaccine manufacturing.
- 7.7 The PBAC considered that the clinical data provided supported the claim of non-inferior safety of QIVc compared to QIVe.
- 7.8 The PBAC considered that a QIVc vaccination program was not likely to be associated with significant indirect effects and a change in force of infection. For this reason the PBAC considered that the static economic model was more reliable for decision making than the dynamic model.
- 7.9 The PBAC noted the main issues with the economic model that had been raised by the evaluation and the ESC, including:
- Pooling of influenza-like illness outcomes with differing definitions (i.e. primary care presentation and hospital encounters) in the meta-analysis used to obtain the rVE in the economic model.
 - Case fatality rates were based on modelled age-dependent rates of pooled influenza-associated respiratory and cardiovascular hospitalisations and deaths from Leung et al. (2021), and not those recommended in the ATAGI's advice that were based on observed data from AIHW for ICD-10 coded deaths from influenza.
- 7.10 The PBAC noted that in the pre-PBAC Response, the sponsor proposed a reduced price per dose for QIVc of \$1 and provided an updated economic model which excluded the population aged 2 to 4 years old and addressed some of the uncertain inputs (see paragraph 6.62). However, the PBAC noted that the updated model did not address the main issues previously raised by the ESC and the evaluation. Overall, the PBAC did

not consider the economic model to be reliable for informing a cost-effective price of QIVc noting the difficulties associated with quantifying an estimate of the rVE.

- 7.11 The PBAC considered that given the uncertainties around the comparative benefit of QIVc versus QIVe, it could not recommend QIVc at a substantially higher price than QIVe. However, the PBAC considered that a premium of no more than 1% compared to QIVe (equating to maximum price of \$1) for the potential advantages of cell-based vaccine production technology compared to egg-based technology, would be reasonable.
- 7.12 The PBAC noted that this submission is not eligible for an independent review as independent review is only relevant to requests for PBS listing.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item to the Determination:

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Number and timing of doses
Influenza	Flucelvax Quad	Injection (0.5mL)	For children older than 5 years but less than 9 years, 2 doses at least 1 month apart for the first vaccination and 1 dose per calendar year after that. For persons 9 years and less than 65 years, 1 dose per calendar year.

Circumstances

Vaccine may be provided to any of the following:

- (a) an Aboriginal or Torres Strait Islander person who is at least 5 years old but less than 65 years old; or
- (b) a person who is at least 5 years old but less than 65 years old and who:
 - (i) has cardiac disease including cyanotic congenital heart disease, coronary artery disease and congestive heart failure; or
 - (ii) has a chronic respiratory condition including suppurative lung disease, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease, chronic emphysema and severe asthma; or
 - (iii) has another chronic illness requiring regular medical follow-up or hospitalisation in the preceding year, including diabetes mellitus, chronic metabolic diseases, chronic renal failure, haemoglobinopathies and impaired immunity (including drug-induced immune impairment); or
 - (iv) has a chronic neurological condition, including multiple sclerosis, spinal cord injuries, seizure disorders or other neuromuscular disorders; or
 - (v) has impaired immunity, including HIV infection; or
- (c) a person who is at least 5 years old but is less than 11 years old and is receiving long-term aspirin therapy; or
- (d) a woman who is pregnant.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.