

6.16 INFLUENZA VACCINE

Injection (0.5mL) 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 influenza vaccine (Flucelvax® Quad, quadrivalent influenza virus vaccine, surface antigen, inactivated, cell-based, henceforth referred to as QIVc) for the prevention of influenza in individuals aged 6 months and older.
- 1.2 At the September 2022 Intracycle Meeting, the PBAC recommended that QIVc be a designated vaccine for the purposes of the *National Health Act 1953*, for 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 submission proposed extending the population to include children aged 6 months to < 5 years, which is in alignment with the TGA indication.
- 1.3 Listing in the extended population was requested at the same price as was previously recommended by the PBAC for QIVc in the existing NIP-funded population.
- 1.4 The submission also requested advice from the PBAC regarding the claim of superior clinical effectiveness versus quadrivalent egg-based vaccines (QIVe) for the current NIP-funded cohorts. However, the pre-PBAC response withdrew this request. The clinical and economic components included in the submission to support this claim were therefore not considered by the PBAC and are not presented herein.
- 1.5 The key components of the clinical issue addressed by the submission (as stated in the submission) are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population ^a	Children aged ≥6 months to <5 years. Aboriginal and Torres Strait Islander people aged ≥6 months to <65 years. Persons aged ≥6 months to <65 years who have certain medical conditions that increase the risk of influenza disease complications. Pregnant women.
Intervention	QIVc
Comparator	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	In the population aged ≥6 months to <65 years: QIVc is superior to QIVe in effectiveness against clinically relevant influenza-related outcomes ^a QIVc has a comparable safety profile to QIVe.

Source: Table 1.1.1, p26 of the submission

QIVc = cell-based quadrivalent subunit influenza virus vaccine; QIVe = egg-based quadrivalent subunit influenza virus vaccine.

^a The pre-PBAC response updated the requested population to only include children aged 6 months to <5 years.

2 Background

Registration status

- 2.1 QIVc (Flucelvax[®] Quad) received initial registration in the Australian Register of Therapeutic Goods (ARTG) on 1 September 2020 for the prevention of influenza caused by influenza virus, Types A and B for use in adults and children 9 years of age and older. On 11 November 2021, the TGA registration was extended to include use in adults and children 2 years of age and older for the prevention of influenza.
- 2.2 In July 2023, the TGA registration was extended to include use in adults and children 6 months of age and older.
- 2.3 An updated Australian Public Assessment Report (AusPAR) for QIVc was published in November 2023 (AusPAR – Flucelvax Quad – PM-2022-01977-1-2, Final – 1 November 2023). The clinical dossier consisted of the direct Phase III V130_10 immunogenicity and safety trial assessing non-inferiority of QIVc versus QIVe (Afluria[®] Quadrivalent) in healthy children aged 6 months to 47 months (V130_10 was also presented as evidence in the current submission). Immunogenicity endpoints were assessed by the haemagglutination inhibition (HAI) and microneutralisation (MN) assay.
- 2.4 The AusPAR noted the following limitations with the V130_10 data (AusPAR Flucelvax Quad, PM-2022-01977-1-2, November 2023):
 - No clinical efficacy data were available.
 - No data on children with co-morbidities and immune deficiency were available.

- No immunogenicity and safety data on co-administration with other vaccines in this age group were available, including for those recommended in the childhood immunisation programs.
- 2.5 The Delegate noted that HAI and MN titres are not true surrogate markers as there is no defined cut-off titre correlating with clinical protection, although it has been demonstrated that higher titres tend to correlate with better protection. Although the immunogenicity data are descriptive and without predetermined criteria for success, the QIVc group showed increase in the HAI titres (AusPAR Flucelvax Quad, PM-2022-01977-1-2, November 2023).
- 2.6 The Delegate also noted that the current indication for QIVc is established for those aged ≥ 2 years and that V130_10 provided safety data to support the extension of indication to children aged 6 months to 2 years (AusPAR Flucelvax Quad, PM-2022-01977-1-2, November 2023).
- 2.7 The Advisory Committee on Vaccines (ACV), having considered the evaluations and the Delegate's overview advised the following (AusPAR Flucelvax Quad, PM-2022-01977-1-2, November 2023):
- There is a favourable benefit-risk balance for the use of QIVc in individuals 6 months to 2 years of age.
 - Pre-defined success criteria of non-inferiority for the primary immunogenicity objectives were met, demonstrating that QIVc was non-inferior to the approved comparator vaccine in children 6 to 47 months of age for all 4 influenza strains, which has demonstrated efficacy or effectiveness.
 - While reiterating that people with egg allergy, including a history of anaphylaxis, can be safely vaccinated with any inactivated influenza vaccine (including egg-based vaccines) unless they have reported a serious adverse reaction to influenza vaccines, the ACV noted that the availability of a cell-based vaccine for individuals 6 months to 2 years of age provided choice for parents and prescribers.
 - The safety data appeared to be sufficient and comparable to other inactivated influenza vaccines administered to the age group 6 months to 2 years.

Previous PBAC consideration

- 2.8 At the September 2022 PBAC Intracycle meeting, the PBAC recommended that QIVc 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 Public Summary Document (PSD) for that consideration states:

- “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 QIVe vaccines and the acknowledgment of potential benefits associated with the diversification of vaccine manufacturing” (paragraph 7.1, QIVc, Public Summary Document (PSD), September 2022 PBAC meeting).
- “The PBAC acknowledged there were advantages of cell-based vaccine production technology over the egg-based technology in diversifying vaccine production platforms. The PBAC noted that cell-based technology may allow faster start-up of vaccine production when required (e.g., in the event of a pandemic) and production would not be dependent on egg supply” (paragraph 7.2, QIVc, PSD, September 2022 PBAC meeting).
- “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” (paragraph 7.6, QIVc, PSD, September 2022 PBAC meeting).

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

3 Requested listing

Name, Restriction, Manner of administration and form	Ex-manufacturer price per dose	Proprietary Name and Manufacturer	
CELL-CULTURED QUADRIVALENT INFLUENZA VACCINE (SURFACE ANTIGEN, INACTIVATED) Injection (0.5mL)	\$1	Flucelvax® Quad	Seqirus Australia Pty Ltd

Category/Program:	NIP
NIP indication	All children aged ≥6 months to <5 years
Requested populations:	Aboriginal and Torres Strait Islander people aged ≥6 months to <65 years Persons aged ≥6 months to <65 years who have certain medical conditions that increase the risk of influenza disease complications Pregnant women.

Source: Table 1.4.1, p 42 of the submission

NIP = National Immunisation Program, mL= millilitres

- 3.1 Under the NIP, QIVc is currently funded for pregnant women, Aboriginal and/or Torres Strait Islander Peoples aged ≥5 to <65 years, and people aged ≥5 years to <65 years with certain medical conditions associated with an increased risk of influenza disease complications.
- 3.2 The submission requested extending the NIP listing of QIVc to include all children aged 6 months to <5 years, which would align with the current NIP listing of QIVe.

- 3.3 The submission proposed an ex-manufacturer price per dose of \$[REDACTED], consistent with the price that was previously recommended by the PBAC for QIVc in the existing NIP-funded population.
- 3.4 The submission noted that listing of QIVc was not requested for individuals aged ≥65 years as QIVc was not designed to address immunosenescence from aging, and in Australia, adjuvanted QIVe (aQIVe) is currently funded on the NIP for use in adults aged ≥65 years.

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. Specifically, influenza A and B viruses cause clinically important human disease and seasonal epidemics. Influenza illness is characterised by respiratory/systemic effects which can cause serious illness with complications (pneumonia and exacerbation of many chronic conditions such as asthma, congestive heart failure, and chronic obstructive pulmonary disease). Vulnerable people are at high risk during epidemics and may die of pneumonia or cardiac decompensation¹.
- 4.2 Children are most susceptible to infection by influenza viruses, and young children, particularly those <2 years of age, are at increased risk of severe complications². Moreover, children have been noted to have high influenza transmission potential and an effective vaccine for this age group can have wider public health impacts by preventing the spread to other vulnerable groups, such as older and immunocompromised adults³.
- 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 neutralising the virus. Therefore, protection by vaccination requires annual dosing with updated vaccines.

¹ Rajaram S et al (2020). Influenza vaccines: the potential benefits of cell-culture isolation and manufacturing. Therapeutic advances in vaccines and immunotherapy.

² Center for Disease Control and Prevention (CDC). People at Higher Risk of Flu Complications. Available online <https://www.cdc.gov/flu/highrisk/infantcare.htm> (accessed on 28 November 2023)

³ Mould-Quevedo, JF et al (2023). Vaccine Effectiveness of Cell-Based Quadrivalent Influenza Vaccine in Children: A Narrative Review. Vaccines 11 (10): 1954.

- 4.4 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 (SH). The AIVC meets after the annual World Health Organisation (WHO) strain composition meeting and its advice generally aligns with the WHO recommendations, unless there are scientific or practical reasons for variations. Antigenic drift, and mismatch in vaccine and circulating viruses, means vaccine effectiveness can vary across (and within) seasons.
- 4.5 The traditional manufacturing process for influenza vaccines utilises fertilised chicken eggs. During this process mutations can occur in the receptor binding region of HA, which can lead to antigenic mismatch to circulating viruses, and reduced vaccine effectiveness known as egg adaptation. This is a particular problem for influenza A/H3N2 and B viruses. Manufacturing influenza vaccines in cell-culture, from cell-derived candidate vaccine viruses, was designed to avoid this issue.

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

5 Comparator

- 5.1 The submission nominated QIVe as the main comparator which is currently funded by the NIP for the proposed population. The evaluation considered the comparator appropriate.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from 1 organisation via the Consumer Comments facility on the PBS website.
- 6.3 Lung Foundation Australia expressed its support for the NIP listing of QIVc for people aged 6 months and older. The organisation emphasised the potential benefits of reducing the burden of illness associated with influenza, particularly among children. Lung Foundation Australia noted that availability of QIVc for people aged 6 months and older through the NIP would provide Australians with an alternate supply of influenza vaccine, ensuring continued access when needed. Lung Foundation Australia also noted the benefits of reducing the risk of disease associated with influenza outbreaks and minimising the economic and social burden associated with illness.

Clinical studies

6.4 The submission was based on:

- a retrospective test-negative design (TND) study (V130_67) comparing QIVc versus QIVe in preventing outpatient test-confirmed influenza in people aged 4 to 64 years in the Northern Hemisphere (United States) over three influenza seasons (2017-18, 2018-19, 2019-20). The submission noted that the V130_67 study represents additional evidence to that previously considered by the PBAC in the September 2022 Intracycle meeting to support the claim that QIVc is superior in effectiveness to QIVe. As the request for the PBAC to consider this claim was withdrawn in the pre-PBAC response, the V130_67 study was not considered by the PBAC and is not presented below.
- a direct randomised controlled trial (V130_10) (Essink 2022) assessing the non-inferiority of QIVc compared to QIVe in terms of immunogenicity (as measured by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for A/H3N2 strain using cell-derived target viruses) and safety in healthy children aged 6 months to 47 months during the 2019-2020 influenza season in the United States (US). The submission used this study to demonstrate that QIVc has a non-inferior immune response and a comparable safety profile versus QIVe. Safety data from this study have been previously considered by the PBAC in the September 2022 PBAC Intracycle Meeting.
- a supportive randomised controlled trial (V130_12) comparing QIVc with a non-influenza vaccine comparator (Menveo[®], Meningococcal ACWY vaccine) in children 2 to <18 years of age. The submission noted that V130_12 was excluded from the main body of the previous submission and 'does not take a central place' in current evidence base, as it did not include QIVe as the comparator arm. The submission used this study to demonstrate that the absolute efficacy of QIVc was consistent across different age groups (≥ 2 to <4 years, ≥ 4 to <18 years; ≥ 2 to <9 years and ≥ 9 to <18 years).

6.5 Details of the studies included in the submission are provided in Table 2.

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

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised controlled trial (immunogenicity outcomes and safety)		
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
	Essink, B.J., et al. Safety and immunogenicity of cell-based quadrivalent influenza vaccine: a randomized trial."	<i>Pediatrics</i> 2022; 150 (5) e2022057509
Supporting randomised trial comparing QIVc with a meningococcal vaccine		
V130_12 NCT03165617	Report: A phase III/IV, stratified, randomised, observed blind, multicenter clinical study to evaluate the efficacy, safety, and immunogenicity of a cell-based quadrivalent subunit influenza virus vaccine compared to a non-influenza comparator vaccine in subjects ≥2 years to <18 years.	February 2020

Source: Adapted from Table 2.2.1, p48 of the submission

6.6 The key features of the included evidence are summarised in Table 3. The submission did not consider the V130_12 randomised trial as key evidence due to the lack of a QIVe control arm.

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						
V130_10 Age 6–47 months	QIVc: 1,092 QIVe: 575 Season 2019-20	Unadjusted	Low	Randomised controlled non-inferiority trial. Northern Hemisphere (US)	Immunogenicity and safety. Immunogenicity as measured by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for A/H3N2 strain, using cell-derived target viruses. No effectiveness data available.	Not used

Source: Sections 2.2, 2.3, and 2.4.3 of the submission.

QIVc = cell-based quadrivalent subunit influenza virus vaccine, QIVe = egg-based quadrivalent subunit influenza virus vaccine; US = United States.

6.7 For the direct randomised V130_10 non-inferiority trial, the risk of bias was considered low in the submission. This evaluation considered that this was reasonable.

6.8 The primary objective of the V130_10 trial was to demonstrate that vaccination with QIVc elicits an immune response that is non-inferior to that of QIVe containing the recommended strains for the 2019-2020 season, in children 6 months to 47 months of age, as measured by HAI assay for influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria strains, and by MN assay for influenza A/H3N2 strain, using cell-

derived target viruses. Analyses were performed at Day 29 for previously vaccinated people and at Day 57 for people who have not been previously vaccinated with influenza vaccine.

- 6.9 The non-inferiority criteria for geometric mean titre (GMT) ratio four weeks after the last vaccination (Day 29/57) was an upper bound of the 2-sided 95% confidence interval (CI) for the GMT ratio of less than 1.5.
- 6.10 The non-inferiority criteria for the difference in seroconversion rate (SCR) four weeks after the last vaccination (Day 29/57) was an upper bound of the 2-sided 95% CI for the difference between SCRs of less than 10%.
- 6.11 The evaluation considered that the lack of effectiveness data was a major limitation in V130_10. The pre-PBAC response argued that while effectiveness outcomes were not reported in V130_10, immunogenicity is a well-established outcome for comparing influenza vaccines.

Comparative effectiveness

- 6.12 For the direct V130_10 trial, the ESC recalled that the primary immunogenicity objective was met. For all 4 strains, the upper bounds of the 2-sided 95% CIs did not exceed the pre-specified non-inferiority margin of 1.5 for the Day 29 or Day 57 GMT ratio (influenza A/H1N1: 0.836; influenza A/H3N2: 1.160; influenza B/Yamagata: 0.809; influenza B/Victoria: 0.972) or the pre specified non inferiority margin of 10% for the SCR difference (influenza A/H1N1: -6.423%; influenza A/H3N2: 7.812%; influenza B/Yamagata: -9.983%; influenza B/Victoria: -1.440%).
- 6.13 Using cell derived target viruses, immune responses to influenza A/H3N2 and influenza B/Victoria were not different for the QIVc and QIVe vaccines, whereas for influenza A/H1N1 and influenza B/Yamagata, higher post-vaccination GMTs, geometric mean ratios (GMRs), percentage of people with titre above 1:40, and SCRs were observed for QIVc compared with QIVe. There was no pre-specified threshold for superiority. The evaluation and the ESC considered that HI and MN titres are not well-established surrogate markers of protection as there is no defined cut-off titre correlating with clinical protection. Assays are based on biological reagents that are difficult to standardise and can vary substantially by geography, by chance, by intention (i.e., choosing reagents that yield the most favourable results), and several other factors⁴.
- 6.14 Results from Study V130_12, which evaluated the efficacy and immunogenicity of QIVc compared to a non-influenza comparator vaccine (Menveo[®], Meningococcal

⁴ Ward BJ et al (2018). The establishment of surrogates and correlates of protection: Useful tools for the licensure of effective influenza vaccines? Human vaccines & immunotherapeutics; 14(3):647-56

ACWY vaccine) in healthy children ≥ 2 years to < 18 years of age, are summarised by age subgroup in Table 4.

Table 4: V130_12 - Participants with first-occurrence RT-PCR laboratory confirmed influenza (any strain) and absolute vaccine efficacy (95% CI) by age sub-groups – FAS

Age group	RT-PCR or Culture confirmed influenza Number of cases [attack rate]				Absolute vaccine efficacy (95% CI) ^a
	QIVc		Non-influenza comparator		
	N	n (%)	N	n (%)	
≥ 2 to < 4 years	212	21 (9.9)	220	54 (24.5)	62.66 (38.06, 77.49)
≥ 4 to < 18 years	2,045	154 (7.5)	2,032	310 (15.3)	53.33 (43.38, 61.54)
≥ 2 to < 9 years	1,146	123 (10.7)	1,142	234 (20.5)	50.51 (38.43, 60.22)
≥ 9 to < 18 years	1,111	52 (4.7)	1,110	130 (11.7)	61.85 (47.37, 72.34)

Source: Table 2.6.1, p76 of the submission.

CI = confidence interval; FAS = Full Analysis Set (FAS); QIVc = Cell-based quadrivalent subunit influenza virus vaccine; RT-PCR = reverse transcription polymerase chain reaction.

Efficacy: All participants in the All Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination.

^aAdjusted absolute vaccine efficacy

6.15 There were no statistically significant differences in absolute vaccine efficacy between the age groups (between ≥ 2 years to < 4 years and ≥ 4 years to < 18 years, and between ≥ 2 years to < 9 years and ≥ 9 years to < 18 years), with overlapping 95% CIs around the point estimates. The ESC noted that the absolute vaccine efficacy (aVE) results support the consistent efficacy of QIVc across individuals aged ≥ 2 years to < 4 years and other age groups. However, the ESC also noted that the comparator in study V130_12 is a non-influenza vaccine and thus the results do not inform the relative effectiveness of QIVc compared with QIVe.

Comparative harms

6.16 Safety data from V130_10 was used to demonstrate the safety profile of QIVc compared to QIVe. The evaluation considered that this was reasonable as the direct trial population enrolled children six months to 47 months of age. These data have been considered by the PBAC at the September 2022 Intracycle meeting.

6.17 The key safety results for solicited and unsolicited adverse events (AEs) are summarised in Table 5 and Table 6, respectively.

Table 5: V130_10 - Number (%) of participants with at least one solicited adverse event^a postvaccination (Day 1 through Day 7) – solicited safety set^b

Solicited adverse event n (%)	Duration after vaccination			
	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 ^c	8 (0.5)	2 (0.3)	240 (15.3)	136 (17.3)

Source: Table 2.5.5, p73 of the submission and paragraph 6.23, QIVc, Public Summary Document, September 2022 PBAC meeting.

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

Blue shading indicates information previously seen by the PBAC

^aSolicited 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.

^bSolicited 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.

^cAnalgesic/antipyretic use was for prevention or treatment of pain/fever.

Table 6: V130_10 - Number (%) of participants with unsolicited adverse events after vaccination^a – unsolicited safety set^b

	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 – possibly related, n (%)	0	0

Source: Adapted from Table 2.5.7, p 74 of the submission and paragraph 6.23, QIVc, Public Summary Document, September 2022 PBAC meeting

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.

Blue shading indicates information previously seen by the PBAC

^aV130_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.

^bUnsolicited 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.

- 6.18 Rates of solicited and unsolicited AEs were similar between the 2 vaccine groups; any solicited AE after any vaccination was reported in 63.7% and 65.9% of children receiving QIVc and QIVe, respectively, and any unsolicited AE was reported during the treatment period in 26.2% and 25.7%, respectively.
- 6.19 The majority of solicited AEs were of mild to moderate severity in both groups. The most common solicited local AEs were tenderness and erythema at the injection site, and most common solicited systemic AEs were irritability and sleepiness. The most frequently reported unsolicited AEs during the treatment period for both vaccine groups were upper respiratory tract infection and pyrexia. Children reporting unsolicited AEs assessed as at least possibly related to study vaccine were similar for QIVc (4.4%) and QIVe (4.5%).
- 6.20 Serious AEs (SAEs) were reported in less than 1% of children in each vaccine group and none were assessed as related to the vaccine.
- 6.21 One limitation of the V130_10 trial is that no safety data on co-administration with other vaccines were available, including for those recommended in the childhood immunisation programs.

- 6.22 Overall, the QIVc and QIVe vaccines were well tolerated in the six to 47 months of age trial population, with both vaccines associated with a clinically acceptable safety profile. There were no notable differences in fever, incidences of anaphylactic reactions and/or hypersensitivity/drug hypersensitivity were reported.
- 6.23 In the pre-submission Australian Technical Advisor Group on Immunisation (ATAGI) advice to the PBAC for the previous submission, 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’ (ATAGI pre-submission advice, September 2021).

Benefits/harms

- 6.24 For the newly requested ≥ 6 months to < 5 years age group, the comparative evidence between QIVc and QIVe was limited to immunogenicity and safety data. Comparative harms have not been presented as the submission did not claim a safety difference.

Clinical claim

- 6.25 For the population aged ≥ 6 months to < 65 years, the submission claimed QIVc was superior to QIVe in effectiveness in terms of clinically relevant influenza-related outcomes, and comparable to QIVe in terms of safety. The pre-PBAC response withdrew this claim.
- 6.26 For the newly requested 6 months to < 5 years age group, the evaluation considered that superior effectiveness was not adequately supported by the evidence presented in the submission because there were no comparative effectiveness data in the included evidence, and:
- the retrospective V130_67 TND study only assessed people 4 years to 64 years of age;
 - the V130_10 direct trial only provided immunogenicity data rather than clinically relevant effectiveness outcomes; and
 - the supporting V130_12 trial consisted of a non-influenza vaccine and thus could only provide absolute vaccine efficacy estimates.

The Pre-Sub-Committee Response acknowledged the lack of comparative effectiveness data in children aged < 4 years but argued that the biological basis for superiority would logically apply to the population aged < 4 years.

- 6.27 The PBAC considered that QIVc was non-inferior in terms of comparative effectiveness in children aged 6 months to < 5 years.
- 6.28 In its previous consideration of QIVc in specific individuals aged ≥ 5 years, the PBAC considered that although the clinical claim of superior efficacy was plausible, the

comparative benefit was difficult to quantify and subject to a moderate level of uncertainty (paragraph 7.6, QIVc PSD, September 2022 PBAC meeting). The ESC considered this advice remained relevant noting the clinical claim was primarily based on immunogenicity outcomes. The ESC also noted that there were minimal clinical data for children between 6 months and < 2 years of age and no comparative clinical efficacy for children aged less than 4 years old. Overall, the PBAC considered this same conclusion was also relevant to the newly requested population of children aged 6 months to <5 years.

- 6.29 The ESC considered the claim of comparable safety versus QIVe appeared reasonable noting the evidence from the direct V130_10 randomised trial suggests that QIVc is well tolerated and has a comparable safety profile to QIVe.
- 6.30 The PBAC considered that the claim of non-inferior comparative safety for children aged ≥6 months to < 5 years old was reasonable.

Economic analysis

- 6.31 The submission presented a cost-utility analysis for a comparison of QIVc vs QIVe based on the V130_67 study. As the request for the PBAC to consider the claim that QIVc is superior in effectiveness to QIVe in the currently funded cohorts on the NIP was withdrawn by the sponsor, the economic model was not considered by the PBAC and is not presented.

Vaccine cost/person/year

Table 7: Drug cost per child (aged 6 months to 5 years) for proposed and comparator drugs

	QIVc / QIVe recommended dose and frequency	QIVc Financial estimates	QIVe Financial estimates
Dose	One or two doses ^a	1.25 doses	1.25 doses
Frequency	Once or twice a year ^a	Once a year	Once a year
Cost/child/year	QIVc: \$ per dose QIVe: \$ per dose	\$	\$

Source: Table 3.6.1, p116 of the submission and the “Flucelvax Quad Section 4 spreadsheet”.

^aThe TGA consumer medicine information sheets for both QIVe and QIVc notes that children less than 9 years of age who have not been previously vaccinated against influenza should receive a second dose (at least 4 weeks after the first dose).

Estimated PBS usage & financial implications

- 6.32 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the financial implications of a complete substitution of QIVe with QIVc in the ≥6 month to <5 year population. The submission had assumed that the QIVc market share would increase from 30% to 100% (replacing QIVe). However, the pre-PBAC response noted that as the request for the PBAC to consider a claim of superiority had been withdrawn, complete substitution was not likely.

6.33 The submission used Australian Bureau of Statistics data to estimate population numbers.

Table 8: Data sources and values applied in the utilisation and financial estimates

Parameter	Source	Comments
Population of children ≥6 months to <5 years	Table B9, ABS 3222.0 Projected population data.	This source is appropriate.
Vaccine coverage	50%. Beard et al. 2020 ⁵ , 2021/previous ATAGI advice QIV PSD, July 2019	ATAGI advice indicated that vaccine coverage would increase from 30% in 2020 to 50% in 2025 for children aged under 5 years.
Additional doses needed for children >6 months to <5 years	The cohort aged ≥6 months to <5 years will receive an average of 1.25 doses	The TGA consumer medicine information sheets for QIVc that states children less than 9 years of age who have not been previously vaccinated against influenza should receive a second dose (at least 4 weeks after the first dose).
Vaccine substitution	Assumed to be 100%.	ATAGI has stated that complete product substitution is unlikely (ATAGI pre-submission advice, September 2021). The pre-PBAC response also states complete substitution is unlikely, however no alternative market share assumptions were provided
Additional vaccine cost	Price per dose of \$ [REDACTED] for QIVc, compared to the current NIP tender price for QIVe of \$ [REDACTED]	The cost for QIVc is stated to be the current cost on the NIP for the approved populations.

Source: generated during the evaluation from Section 4 of the submission.

ABS = Australian Bureau of Statistics; ATAGI = Australian Technical Advisor Group on Immunisation; NIP = National Immunisation Program; PBAC = Pharmaceutical Benefit Advisory Committee; PSD = public summary document; QIVc = Cell-based quadrivalent subunit influenza virus vaccine; QIVe = Egg-based quadrivalent subunit influenza virus vaccine.

6.34 The estimated financial implications to the NIP of listing QIVc for children ≥6 months to <5 years are presented in Table 9.

⁵ Beard F, Hendry A, Macartney K. Influenza vaccination uptake in our most vulnerable groups: how well are we protecting them in 2019. *Commun Dis Intell.* 2020;2020:44.

Table 9 Estimated scripts and financial implications of listing QIVc on the NIP for children ≥6 months to <5 years

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Children ≥6 months to <5 years	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Vaccine coverage	50%	50%	50%	50%	50%	50%
Vaccine uptake	100%	100%	100%	100%	100%	100%
Scripts per person	1.25	1.25	1.25	1.25	1.25	1.25
Total script numbers	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Cost to the NIP of listing QIVc	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Cost to the NIP of current listing QIVe	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Net cost of listing QIVc on the NIP	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²

Source: Generated during the evaluation from “Flucelvax Quad Section 4 spreadsheet”.

NIP = National Immunisation Program; QIVc = Cell-based quadrivalent subunit influenza virus vaccine; QIVe = Egg-based quadrivalent subunit influenza virus vaccine.

The redacted values correspond to the following ranges:

¹ 1,000,000 to < 2,000,000

² \$0 to < \$10 million

6.35 The submission estimated that the net cost of listing QIVc in children ≥6 months to <5 years would be \$0 to < \$10 million over 6 years. However, this was based on the assumption that QIVc would entirely replace QIVe. The pre-PBAC response noted that complete substitution is unlikely and the financial estimates presented by the submission would likely be lower. The pre-PBAC response further stated that QIVe “is likely to gain a minority share of the tender (currently it has 30% for the 5 to 64 year old cohorts)”.

6.36 The uptake of influenza vaccination in children ≥6 months to <5 years has increased over previous years. The evaluation noted that the financial estimates are sensitive to uptake assumptions, however the PBAC agreed with ATAGI that the submission’s estimate of 50% vaccine coverage in this population was reasonable (ATAGI pre-submission advice, September 2021).

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

7 PBAC Outcome

7.1 The PBAC recommended that influenza vaccine (Flucelvax® Quad, QIVc) be a designated vaccine for the purposes of the *National Health Act 1953*, for the vaccination against influenza in children aged ≥6 months to <5 years. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of QIVc would be acceptable at the same price as was previously recommended for QIVc for the current NIP-funded population.

- 7.2 The PBAC welcomed the input from Lung Foundation Australia outlining that QIVc would provide an alternative supply of NIP-funded influenza vaccines for children aged ≥ 6 months to < 5 years old.
- 7.3 The PBAC considered that the nomination of existing NIP-funded quadrivalent egg-based vaccines (QIVe) as the main comparator was appropriate for the proposed population.
- 7.4 The pivotal evidence to support the extended listing of QIVc to include children aged 6 months to < 5 years was based on a direct randomised controlled trial (V130_10; Essink 2022) assessing the non-inferiority of QIVc compared to QIVe in terms of immunogenicity and safety in individuals aged 6 to 47 months during the 2019–2020 influenza season in the United States. The PBAC noted that the TGA Delegate and the Advisory Committee on Vaccines reported that the predefined success criteria of non-inferiority for the primary immunogenicity objectives were met, demonstrating that QIVc was non-inferior to QIVe in children 6–47 months of age.
- 7.5 Based on the data available for the cohort aged 6 months to < 5 years, the PBAC considered that QIVc was non-inferior in terms of comparative effectiveness in children aged 6 months to < 5 years.
- 7.6 Further, the PBAC recalled that, in its previous consideration of QIVc for eligible people aged ≥ 5 to < 65 years, it had considered that the clinical claim of superior efficacy was “plausible” but “the comparative benefit was difficult to quantify and subject to a moderate level of uncertainty” (paragraph 7.6, QIVc PSD, September 2022 PBAC meeting). The PBAC considered this same conclusion was also relevant to the extended population of children aged 6 months to < 5 years.
- 7.7 The PBAC recalled it had previously considered that the V130_10 clinical trial data supported the claim of non-inferior safety of QIVc compared to QIVe (para 7.7, QIVc, PSD, September 2022 PBAC meeting) and considered these data also supported non-inferior safety for the proposed population aged ≥ 6 months to < 5 years old.
- 7.8 The PBAC noted that the submission proposed listing QIVc in the extended population (children aged 6 months to < 5 years old) at the same price as was previously recommended for QIVc for the current NIP-funded populations. The PBAC considered that the cost-effectiveness of QIVc would also be acceptable at this price for the extended population aged 6 months to < 5 years old.
- 7.9 The PBAC noted that the financial estimates presented in the submission assumed that QIVc would substitute all QIVe doses. The PBAC agreed with the pre-PBAC response that complete substitution of QIVe with QIVc was unlikely and the financial implications of listing QIVc for the proposed population would be lower than estimated in the submission.

7.10 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 at least 6 months 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) a child who is at least 6 months old but less than 5 years old; or
- (b) an Aboriginal or Torres Strait Islander person who is at least 6 months old but less than 65 years old; or
- (c) a person who is at least 6 months 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
- (d) a person who is at least 6 months old but is less than 11 years old and is receiving long-term aspirin therapy; or
- (e) 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.