Coversheet on evidence assessment by ATAGI using the GRADE framework for use of Madin-Darby canine kidney (MDCK) cell-derived influenza vaccine (cIIV; Flucelvax Quad)

Summary of key methods and decisions on evidence assessment using GRADE for developing ATAGI recommendations on the use of Madin-Darby canine kidney (MDCK) cell-derived influenza vaccine (cIIV) for the Australian Immunisation Handbook

Background

- Flucelvax Quad (cIIV) was TGA registered in 2020 for children and adults aged ≥9 years.
- Flucelvax Quad underwent first GRADE assessment in 2020.
- There was no preference for cIIV vs standard-dose egg-based influenza vaccines (eIIV) for children and adolescents aged 9–17 years and adults aged ≥18 years (initial assessment in 2020).
- An updated GRADE assessment was required due to extension of age of registration to ≥2 years
- The GRADE assessment was performed in September 2021, incorporating new evidence. There was no change to recommendations.
- Sponsor submission to PBAC in 2022 for the vaccine to be listed on the National Immunisation Program Schedule.
- In 2023, the registered age for Flucelvax Quad was extended to ≥6 months.
- An updated GRADE assessment was performed in 2023 with new PICO structure and additional comparators for those aged over 65 years. There was no change to recommendations.

Research questions

1. Should children aged 6 months to 17 years use Madin-Darby canine kidney (MDCK) cell-derived influenza vaccine (cIIV) in preference to standard dose egg-based influenza vaccine (eIIV)?

Table 1: Population, Intervention, Comparator, Outcomes (PICO-1) – cIIV vs eIIV, aged 6 months to 17 years

Population	Aged 6 months–17 years
Intervention	Cell-derived influenza vaccine (cIIV)
Comparator	Standard-dose influenza vaccines (eIIV)
Outcomes	*Critical* • Laboratory-confirmed influenza hospitalisations • Influenza-related hospitalisations/emergency department (ED) visits • Pneumonia-related hospitalisations/ED visits • Serious adverse events (SAE) and adverse events of special interest (AESI) *Important* • Influenza-related medical encounters (ED visits, hospitalisations, outpatient, primary care) • Test-confirmed influenza (PCR, culture, antigen, antibody [not laboratory confirmed]) • PCR confirmed influenza A/B • All-cause hospitalisation/ED visit • Solicited local adverse events • Solicited systemic adverse events

2. Should adults aged 18–64 years use Madin-Darby canine kidney (MDCK) cell-derived influenza vaccine (cIIV) in preference to standard dose egg-based influenza vaccine (eIIV)?

Table 2: Population, Intervention, Comparator, Outcomes (PICO-2) – cIIV vs eIIV, aged 18 to 64 years

Population	Aged 18–64 years
Intervention	Cell-derived influenza vaccine (cIIV)
Comparator	Standard-dose influenza vaccines (cIIV)
Outcomes	*Critical* • Laboratory-confirmed influenza hospitalisations • Influenza-related hospitalisations/ED visits • Pneumonia-related hospitalisations/ED visits • Serious adverse events (SAE) and adverse events of special interest (AESI) ***Not available:*** • Post-influenza mortality • Influenza or pneumonia-associated mortality • All-cause mortality *Important* • Influenza-related medical encounters (ED visits, hospitalisations, outpatient, primary care) • Test-confirmed influenza (PCR, culture, antigen, antibody [not laboratory confirmed]) • PCR confirmed influenza A/B • All-cause hospitalisation/ED visit • Solicited local adverse events • Solicited systemic adverse events ***Not available:*** • Respiratory-related hospitalisations or ED visits (no laboratory confirmation) • Pneumonia related outpatient or office visits or outpatient or ED visits • Cardiovascular events

3. Should adults aged ≥65 years use Madin-Darby canine kidney (MDCK) cell-derived influenza vaccine (cIIV) in preference to adjuvanted influenza vaccine (aIIV)?

Table 3: Population, Intervention, Comparator, Outcomes (PICO-3) – cIIV vs aIIV, aged 65 years and over

Population	Aged ≥65 years
Intervention	Cell-derived influenza vaccine (cIIV)
Comparator	Adjuvanted influenza vaccines (aIIV)
Outcomes	*Critical* • Influenza-related hospitalisations/ED visits ***Not available:*** • Laboratory-confirmed influenza hospitalisations • Pneumonia-related hospitalisations/ED visits • Serious adverse events (SAE) and adverse events of special interest (AESI) • Post-influenza mortality • Influenza or pneumonia-associated mortality • All-cause mortality *Important* • Influenza-related primary care/outpatient visits ***Not available:*** • Test-confirmed influenza (PCR, culture, antigen, antibody [not laboratory confirmed]) • PCR confirmed influenza A/B • All-cause hospitalisation/ED visit • Solicited local adverse events • Solicited systemic adverse events • Respiratory-related hospitalisations or ED visits (no laboratory confirmation) • Pneumonia related outpatient or office visits or outpatient or ED visits • Cardiovascular events

4. Should adults aged ≥65 years use Madin-Darby canine kidney (MDCK) cell-derived influenza vaccine (cIIV) in preference to high-dose influenza vaccine (hdIIV)?

Table 4: Population, Intervention, Comparator, Outcomes (PICO-4) – cIIV vs hdIIV, 65 years and over

Population	Aged ≥65 years
Intervention	Cell-derived influenza vaccine (cIIV)
Comparator	High-dose influenza vaccines (hdIIV)
Outcomes	*Critical* • Influenza-related hospitalisations/ED visits ***Not available:*** • Laboratory-confirmed influenza hospitalisations • Pneumonia-related hospitalisations/ED visits • Serious adverse events (SAE) and adverse events of special interest (AESI) • Post-influenza mortality • Influenza or pneumonia-associated mortality • All-cause mortality *Important* • Influenza-related primary care/outpatient visits ***Not available:*** • Test-confirmed influenza (PCR, culture, antigen, antibody [not laboratory confirmed]) • PCR confirmed influenza A/B • All-cause hospitalisation/ED visit • Solicited local adverse events • Solicited systemic adverse events • Respiratory-related hospitalisations or ED visits (no laboratory confirmation) • Pneumonia related outpatient or office visits or outpatient or ED visits • Cardiovascular events

Literature search

For research questions 1 and 2, a literature search was undertaken on 9 March 2023 using the Medline and Embase databases to identify studies assessing vaccine effectiveness/efficacy and/or safety outcomes of the cell-based influenza vaccine compared with standard egg-based influenza vaccine in two age cohorts (age 6 months–17 years and age 18–64 years). The search is an update of a previous literature search conducted on 13 September 2021. Details of the search methods are presented in Appendix A-1. The citations were selected for review if they met the following criteria:

- *Study design:* Randomised controlled trial (RCT), observational study, meta-analysis
- *Population:* (1) Age cohorts 6 months–17 years old and (2) 18–64 years old
- *Intervention:* MDCK cell-derived influenza vaccine (cIIV)
- *Comparator:* Standard-dose egg-based influenza vaccines (eIIV)
- *Outcomes:* Effectiveness, efficacy, safety

A total of 10 citations met the above pre-defined inclusion criteria. Of these, six eligible studies were included (five observational and one RCT). An additional observational study provided by Seqirus, not published at the time of literature search, was included in this review. New studies included in this GRADE are listed under ‘References’.

For research questions 3 and 4, a literature search was undertaken on 4 April 2023 using the Medline and Embase databases to identify studies assessing vaccine effectiveness/efficacy and/or safety outcomes of the cell-based influenza vaccine compared with both 'enhanced' egg-based influenza vaccines – adjuvanted influenza vaccine and high-dose influenza vaccine – in adults aged over 65 years.

As no studies assessing safety outcomes that directly compared these vaccines were identified, on 28 June 2023 a subsequent and broader search was conducted from Medline, Embase and Cochrane CENTRAL. Details of the search methods are presented in Appendix A-2. The citations were selected for review if they met the following criteria:

- *Study design:* RCT, observational study, meta-analysis
- *Population:* Adults aged ≥65 years
- *Intervention:* MDCK cell-derived inactivated influenza vaccine (cIIV)
- *Comparator:* (3) Adjuvanted egg-based and (4) high-dose egg-based influenza vaccines
- *Outcomes:* Effectiveness, efficacy, safety

A total of 10 citations met the above pre-defined inclusion criteria. Of these, three eligible studies were included (all observational studies). There were no studies that could be included to assess safety outcomes. Studies included in this GRADE are listed under 'References'.

Inclusion criteria and rationale

Table 1: Rationale for PICO and inclusion criteria

Inclusion criteria	Rationale
Study type: Observational or RCTs	Study designs most suitable to reporting efficacy/effectiveness and safety between: • PICO 1-2: cIIV vs eIIV. • PICO 3: cIIV vs aIIV • PICO 4: cIIV vs hdIIV Observational studies and RCTs widely available for the PICO questions.
Population: 6 months–17 years, 18–64 years and 65 years and over	PICOs 1–4 assess vaccines in age groups recommended for immunisation in Australia. Restructured PICOs to reflect population groups likely differences in effectiveness/safety, population stratifications in the included studies and populations with different influenza vaccination programs in Australia.
Intervention: Cell-based influenza vaccine (cIIV, Flucelvax)	Note that when MDCK cell-derived influenza vaccine was first developed not all strains included in the vaccine were developed using the cell method. In more recent studies all 4 strains were cell derived. To be more inclusive of early data, early studies were included.
Comparator: Standard-dose egg-based influenza vaccine; adjuvanted egg-based and high-dose egg-based influenza vaccines (both QIV and TIV)	Egg-based vaccines are the main type of vaccine in use with some brands funded on the immunisation program for certain population groups. RCTs using non-influenza comparators were not included as that does not fit the PICO. Further, for PICOs 3 and 4, adjuvanted egg-based and high-dose egg-based influenza vaccines were considered appropriate comparators as they are the preferred influenza vaccine recommended in adults 65 years and over.

Outcomes: Efficacy/effectiveness and safety	Efficacy in RCTs is already well established so effectiveness studies are necessary to assess any benefit of cell-based vaccine over egg-based vaccines.
	Safety of all vaccines being recommended should continually be assessed to weigh any benefit over risk of vaccination.
	Included outcome as stated above in Tables 1 to 4. Included iteratively according to outcomes found in the studies.
	Ranking of importance discussed in many iterations with portfolio leads and/ ATAGI full panel.
	General framework (depending on outcomes measured in studies available): *Critical* • Mortality due to influenza • Laboratory-confirmed influenza hospitalisation • Non-laboratory confirmed influenza hospitalisation with pneumonia or influenza. • Non-laboratory confirmed influenza hospitalisation encounters (i.e. including ED presentations) with pneumonia or influenza. • Non-respiratory influenza-related serious events *Important* • Influenza-related 'office visits' or outpatient visits • Other-respiratory related hospitalisations • Solicited AEs (Systemic and Local) • Laboratory-confirmed influenza Note: some outcomes may be missing in GRADE projects due to no data from available studies. Extra outcomes added due to relevance.

Risk of bias assessment

Risk of bias (RoB) was assessed for all selected studies using the standard GRADE criteria. Two assessors independently undertook this using the ROB 2.0 tool for randomised controlled trials (Appendix B).

References

New Studies - March 2023 (PICOs 1-4)

1. Boikos C, Imran M, Nguyen VH, 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. *Open Forum Infectious Diseases* 2021;8(7) (no pagination).*

2. Divino V, Ruthwik Anupindi V, DeKoven M, et al. A real-world clinical and economic analysis of cell-derived quadrivalent influenza vaccine compared to standard egg-derived quadrivalent influenza vaccines during the 2019-2020 influenza season in the United States. *Open Forum Infectious Diseases* 2022;9(1):ofab604.

3. Boikos C, McGovern I, Molrine D, et al. Review of analyses estimating relative vaccine effectiveness of cell-based quadrivalent influenza vaccine in three consecutive US influenza seasons. *Vaccines* 2022;10(6):03.

4. Imran M, Ortiz JR, McLean HQ, et al. Relative Effectiveness of cell-based versus egg-based quadrivalent influenza vaccines in adults during the 2019-2020 influenza season in the United States. *Open Forum Infectious Diseases* 2022;9(10):ofac532.

5. Imran M, Ortiz JR, McLean HQ, et al. Relative Effectiveness of Cell-based Versus egg-based quadrivalent influenza vaccines in children and adolescents in the United States during the 2019-2020 influenza season. *Pediatric Infectious Disease Journal* 2022;41(9):769-74.

6. Essink BJ, Heeringa M, Jeanfreau RJ, et al. Safety and immunogenicity of cell-based quadrivalent influenza vaccine: a randomized trial. *Pediatrics* 2022;150(5):01.

7. Fujimori M, Nakamura M. Association between seasonal influenza vaccines and the increased risk of acute disseminated encephalomyelitis, estimated using the Vaccine Adverse Event Reporting System. *Pharmazie* 2022;77(7):262-269.

8. Stein AN, Mills CW, McGovern I, et al. Relative vaccine effectiveness of cell- vs egg-based quadrivalent influenza vaccine against test-confirmed influenza over 3 seasons between 2017 and 2020 in the United States. *Open Forum Infectious Diseases* 2024;11:ofae175.

9. Izurieta HS, Chillarige Y, Kelman J, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among elderly persons in the United States, 2017-2018. *Journal of Infectious Diseases* 2019;220(8):1255-1264.*

10. Izurieta HS, Chillarige Y, Kelman J, et al. Relative effectiveness of influenza vaccines among the United States elderly, 2018-2019. *Journal of Infectious Diseases* 2020;222(2):278-87.*

11. Izurieta HS, Lu M, Kelman J, et al. Comparative effectiveness of influenza vaccines among US Medicare beneficiaries ages 65 years and older during the 2019-2020 season. *Clinical Infectious Diseases* 2021;73(11):E4251-E4259.*

*Studies assessed for ROB in previous GRADE.

Appendix A: Literature Search Strategy

PICOs 1 and 2	
EMBASE: Flucelvax vs Standard – FINAL (as at 09.03.23) **Notes: Update of search previously conducted on 13.09.21.** (Which superseded search conducted on 03.09.20) Database: Embase <1974 to 2023 March 07> Search Strategy: --- 1 exp immunization/ (361899) 2 exp vaccine/ (404459) 3 1 or 2 (558375) 4 exp influenza/ (105872) 5 3 and 4 (40413) 6 exp influenza vaccine/ (44074) 7 ((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (33145) 8 6 or 7 (52748) 9 5 or 8 (61918) 10 (cell adj1 (base$ or culture$ or deriv$)).tw. (282692) 11 (cell-base$ or cell-culture$ or cell-deriv$).tw. (258663) 12 exp MDCK cell line/ (4417) 13 ((madin adj1 darby) and cell$).tw. (5388) 14 mdck.tw. (9676) 15 10 or 11 or 12 or 13 or 14 (295371) 16 9 and 15 (1445) 17 flucelvax.tw. (145) 18 16 or 17 (1546) 19 quadrivalen$.tw. (3778) 20 (4-valen$ or 4 valen$ or 4valen$).tw. (130) 21 (four-valen$ or four valen$ or fourvalen$).tw. (63) 22 QIV.tw. (296) 23 trivalen$.tw. (10853) 24 (3-valen$ or 3 valen$ or 3valen$).tw. (82) 25 (three-valen$ or three valen$ or threevalen$).tw. (83) 26 TIV.tw. (1350) 27 (IIV3 or IIV4).tw. (242) 28 (standard or standard-dose$ or convention$ or traditional$).tw. (2876591) 29 (egg adj1 (base$ or culture$ or deriv$)).tw. (1094) 30 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (2891204) 31 9 and 30 (6920) 32 18 and 31 (507) 33 limit 32 to dd=20210910-20230307 (19) 34 limit 32 to dc=20210910-20230307 (84) 35 33 or 34 (84)	**MEDLINE: Flucelvax vs Standard – FINAL (as at 09.03.23)** **Notes: Update of search previously conducted on 13.09.21.** (Which superseded search conducted on 03.09.20) Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current> Search Strategy: --- 1 exp Immunization/ (206225) 2 exp Immunization Programs/ (15970) 3 exp Vaccines/ (272940) 4 1 or 2 or 3 (379173) 5 exp Influenza, Human/ (57106) 6 4 and 5 (19525) 7 exp Influenza Vaccines/ (26535) 8 ((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (26122) 9 7 or 8 (34572) 10 6 or 9 (36164) 11 (cell adj1 (base$ or culture$ or deriv$)).tw. (219167) 12 (cell-base$ or cell-culture$ or cell-deriv$).tw. (200954) 13 exp Madin Darby Canine Kidney Cells/ (4445) 14 ((madin adj1 darby) and cell$).tw. (4942) 15 mdck.tw. (7951) 16 11 or 12 or 13 or 14 or 15 (230703) 17 10 and 16 (1053) 18 flucelvax.tw. (27) 19 17 or 18 (1061) 20 quadrivalen$.tw. (2848) 21 (4-valen$ or 4 valen$ or 4valen$).tw. (103) 22 (four-valen$ or four valen$ or fourvalen$).tw. (69) 23 QIV.tw. (191) 24 trivalen$.tw. (10308) 25 (3-valen$ or 3 valen$ or 3valen$).tw. (68) 26 (three-valen$ or three valen$ or threevalen$).tw. (87) 27 TIV.tw. (913) 28 (IIV3 or IIV4).tw. (192) 29 (standard or standard-dose$ or convention$ or traditional$).tw. (2059569) 30 (egg adj1 (base$ or culture$ or deriv$)).tw. (902) 31 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (2072638) 32 10 and 31 (4511) 33 19 and 32 (367) 34 limit 33 to ed=20210913-20230309 (42) 35 limit 33 to ez=20210913-20230309 (48) 36 34 or 35 (60)

PICOs 3 and 4	
Original search:	
EMBASE: Cell based vs adjuvanted influenza vaccines in those aged 65+ years – FINAL (as at 04.04.23) Database: Embase <1974 to 2023 March 31> Search Strategy: --- 1 exp immunization/ (364475) 2 exp vaccine/ (406658) 3 (immuni$ or vaccin$).tw. (786048) 4 1 or 2 or 3 (930139) 5 exp influenza/ (106282) 6 4 and 5 (45974) 7 exp influenza vaccine/ (44268) 8 ((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (33231) 9 7 or 8 (52966) 10 6 or 9 (66715) 11 (cell adj1 (base$ or culture$ or deriv$)).tw. (283512) 12 (cell-base$ or cell-culture$ or cell-deriv$).tw. (259427) 13 exp MDCK cell line/ (4485) 14 ((madin adj1 darby) and cell$).tw. (5402) 15 mdck.tw. (9695) 16 11 or 12 or 13 or 14 or 15 (296258) 17 10 and 16 (1663) 18 flucelvax.tw. (145) 19 17 or 18 (1764) 20 exp immunological adjuvant/ (32866) 21 exp squalene/ (3815) 22 squalene$.tw. (5102) 23 adjuvant$.tw. (267407) 24 mf59.tw. (840) 25 20 or 21 or 22 or 23 or 24 (288775) 26 10 and 25 (4839) 27 fluad$.tw. (399) 28 (aIIV3 or aIIV4 or a-IIV3 or a-IIV4).tw. (33) 29 27 or 28 (421) 30 26 or 29 (4989) 31 19 and 30 (277) 32 limit 31 to aged <65+ years> (33) 33 aged/ (3550112) 34 (elder$ or senior$ or geriatr$).tw. (551896) 35 (old$ adj adult$).tw. (150574) 36 33 or 34 or 35 (3760883) 37 31 and 36 (47) 38 32 or 37 (47)	**MEDLINE: Cell based vs adjuvanted influenza vaccines in those aged 65+ years – FINAL (as at 04.04.23)** Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current> Search Strategy: --- 1 exp Immunization/ (206968) 2 exp Immunization Programs/ (15984) 3 exp Vaccines/ (274010) 4 1 or 2 or 3 (380462) 5 exp Influenza, Human/ (57261) 6 4 and 5 (19602) 7 exp Influenza Vaccines/ (26608) 8 ((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (26231) 9 7 or 8 (34702) 10 6 or 9 (36299) 11 (cell adj1 (base$ or culture$ or deriv$)).tw. (219985) 12 (cell-base$ or cell-culture$ or cell-deriv$).tw. (201705) 13 exp Madin Darby Canine Kidney Cells/ (4453) 14 ((madin adj1 darby) and cell$).tw. (4952) 15 mdck.tw. (7958) 16 11 or 12 or 13 or 14 or 15 (231531) 17 10 and 16 (1056) 18 flucelvax.tw. (27) 19 17 or 18 (1064) 20 exp Adjuvants, Immunologic/ (180543) 21 exp Squalene/ (2555) 22 squalene$.tw. (4376) 23 adjuvant$.tw. (177212) 24 mf59.tw. (659) 25 20 or 21 or 22 or 23 or 24 (339457) 26 10 and 25 (3470) 27 fluad$.tw. (81) 28 (aIIV3 or aIIV4 or a-IIV3 or a-IIV4).tw. (26) 29 27 or 28 (102) 30 26 or 29 (3486) 31 19 and 30 (177) 32 limit 31 to ("all aged (65 and over)" or "aged (80 and over)") (23) 33 exp Aged/ (3442221) 34 (elder$ or senior$ or geriatr$).tw. (384066) 35 (old$ adj adult$).tw. (117497) 36 33 or 34 or 35 (3595543) 37 31 and 36 (35) 38 32 or 37 (35)

EMBASE: Cell based vs high dose influenza vaccines in those aged 65+ years (as at 03.04.23)

Database: Embase <1974 to 2023 March 31>
Search Strategy:

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1 exp immunization/ (364475)
2 exp vaccine/ (406658)
3 (immuni$ or vaccin$).tw. (786048)
4 1 or 2 or 3 (930139)
5 exp influenza/ (106282)
6 4 and 5 (45974)
7 exp influenza vaccine/ (44268)
8 ((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (33231)
9 7 or 8 (52966)
10 6 or 9 (66715)
11 (cell adj1 (base$ or culture$ or deriv$)).tw. (283512)
12 (cell-base$ or cell-culture$ or cell-deriv$).tw. (259427)
13 exp MDCK cell line/ (4485)
14 ((madin adj1 darby) and cell$).tw. (5402)
15 mdck.tw. (9695)
16 11 or 12 or 13 or 14 or 15 (296258)
17 10 and 16 (1663)
18 flucelvax.tw. (145)
19 17 or 18 (1764)
20 exp dose response/ (424311)
21 (highdos$ or high-dos$ or high dos$).tw. (237213)
22 iiv-hd.tw. (11)
23 20 or 21 or 22 (640724)
24 10 and 23 (1551)
25 fluzone$.tw. (808)
26 24 or 25 (2228)
27 19 and 26 (149)
28 limit 27 to aged <65+ years> (21)
29 aged/ (3550112)
30 (elder$ or senior$ or geriatr$).tw. (551896)
31 (old$ adj adult$).tw. (150574)
32 29 or 30 or 31 (3760883)
33 27 and 32 (29)
34 28 or 33 (29)

MEDLINE: Cell based vs high dose influenza vaccines in those aged 65+ years (as at 28.03.23)

Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current>
Search Strategy:

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1 exp Immunization/ (206706)
2 exp Immunization Programs/ (15976)
3 exp Vaccines/ (273557)
4 1 or 2 or 3 (379939)
5 exp Influenza, Human/ (57174)
6 4 and 5 (19561)
7 exp Influenza Vaccines/ (26570)
8 ((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (26169)
9 7 or 8 (34633)
10 6 or 9 (36228)
11 (cell adj1 (base$ or culture$ or deriv$)).tw. (219605)
12 (cell-base$ or cell-culture$ or cell-deriv$).tw. (201360)
13 exp Madin Darby Canine Kidney Cells/ (4450)
14 ((madin adj1 darby) and cell$).tw. (4948)
15 mdck.tw. (7953)
16 11 or 12 or 13 or 14 or 15 (231145)
17 10 and 16 (1054)
18 flucelvax.tw. (27)
19 17 or 18 (1062)
20 exp Dose-Response Relationship, Immunologic/ (12862)
21 exp Dose-Response Relationship, Drug/ (438189)
22 (highdos$ or high-dos$ or high dos$).tw. (157017)
23 iiv-hd.tw. (9)
24 20 or 21 or 22 or 23 (585604)
25 10 and 24 (959)
26 fluzone$.tw. (109)
27 25 or 26 (1039)
28 19 and 27 (61)
29 limit 28 to ("all aged (65 and over)" or "aged (80 and over)") (12)
30 exp Aged/ (3441056)
31 (elder$ or senior$ or geriatr$).tw. (383458)
32 (old$ adj adult$).tw. (117045)
33 30 or 31 or 32 (3593951)
34 28 and 33 (13)
35 29 or 34 (13)

Revised search for safety studies (PICOs 3 and 4):

Cochrane Library Central Register of Controlled Trials, Issue 7 of 12, July 2023:
Flucelvax in adults – efficacy/effectiveness/safety (as at 20.07.23)

ID	Search	Hits
#1	MeSH descriptor: [Immunization] explode all trees	6911
#2	MeSH descriptor: [Immunization Programs] explode all trees	305
#3	MeSH descriptor: [Vaccines] explode all trees	15942
#4	#1 OR #2 OR #3	17960
#5	MeSH descriptor: [Influenza, Human] explode all trees	3255
#6	#4 AND #5	2247
#7	MeSH descriptor: [Influenza Vaccines] explode all trees	1855
#8	((influenza OR flu) NEAR/2 (immunis* OR immuniz* OR vaccin*)):ti,ab,kw	4708
#9	#7 OR #8	4708
#10	#6 OR #9	4847
#11	(cell NEAR/1 (base* OR culture* OR deriv*)):ti,ab,kw	3604
#12	("cell-base" OR "cell-culture" OR "cell-derived"):ti,ab,kw	2710
#13	MeSH descriptor: [Madin Darby Canine Kidney Cells] explode all trees	11
#14	((madin NEAR/1 darby) AND cell*):ti,ab,kw	28
#15	mdck:ti,ab,kw	33
#16	#11 OR #12 OR #13 OR #14 OR #15	3630
#17	#10 AND #16	199
#18	flucelvax:ti,ab,kw	17
#19	#17 OR #18	204
#20	MeSH descriptor: [Treatment Outcome] explode all trees	181201
#21	MeSH descriptor: [Vaccine Efficacy] explode all trees	45
#22	efficac*:ti,ab,kw	433689
#23	effective*:ti,ab,kw	411374
#24	MeSH descriptor: [Safety] explode all trees	18467
#25	MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees	11
#26	MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees	434
#27	MeSH descriptor: [Drug Evaluation] explode all trees	5967
#28	MeSH descriptor: [Population Surveillance] explode all trees	779
#29	MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees	157
#30	(adverse NEAR/3 (effect* OR event*)):ti,ab,kw	311766
#31	(safe OR safety OR aefi OR aesi):ti,ab,kw	330487
#32	MeSH descriptor: [Mortality] explode all trees	21876

EMBASE: Flucelvax in adults – efficacy/effectiveness/safety (as at 19.07.23)

Database: Embase <1974 to 2023 July 17>
Search Strategy:

1	exp immunization/ (368914)
2	exp vaccine/ (408269)
3	1 or 2 (564341)
4	exp influenza/ (106650)
5	3 and 4 (40844)
6	exp influenza vaccine/ (44597)
7	((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (33064)
8	6 or 7 (53184)
9	5 or 8 (62429)
10	(cell adj1 (base$ or culture$ or deriv$)).tw. (283531)
11	(cell-base$ or cell-culture$ or cell-deriv$).tw. (259328)
12	exp MDCK cell line/ (4662)
13	((madin adj1 darby) and cell$).tw. (5392)
14	mdck.tw. (9711)
15	10 or 11 or 12 or 13 or 14 (296390)
16	9 and 15 (1464)
17	flucelvax.tw. (148)
18	16 or 17 (1567)
19	exp drug efficacy/ (1018249)
20	efficac$.tw. (1591588)
21	effective$.tw. (3276884)
22	exp drug safety/ (553525)
23	exp postmarketing surveillance/ (39141)
24	exp drug surveillance program/ (26816)
25	exp adverse drug reaction/ (631834)
26	(adverse adj3 (effect$ or event$)).tw. (728512)
27	(safe or safety or aefi or aesi).tw. (1548256)
28	exp mortality/ (1359699)
29	exp death/ (813395)
30	(mortalit$ or death$ or fatal$ or case-fatal$ or lethal$ or died).tw. (3090501)
31	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (9048505)
32	18 and 31 (912)
33	limit 32 to (adult <18 to 64 years> or aged <65+ years>) (196)
34	exp adult/ (10625550)
35	(adult$ or elder$ or senior$ or geriatr$).tw. (2532968)
36	34 or 35 (11446836)
37	32 and 36 (244)
38	33 or 37 (244)

#33 MeSH descriptor: [Death] explode all trees 8035 #34 (mortalit* OR death* OR fatal* OR "case-fatality" OR lethal* OR died):ti,ab,kw 180855 #35 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 1033023 #36 #19 AND #35 180 #37 MeSH descriptor: [Adult] explode all trees 585624 #38 (adult* OR elder* OR senior* OR geriatr*):ti,ab,kw 849810 #39 #37 OR #38 949280 #40 #36 AND #39 132	

MEDLINE: Flucelvax in adults – efficacy/effectiveness/safety (as at 28.06.23)

Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current>
Search Strategy:

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1 exp Immunization/ (209006) 2 exp Immunization Programs/ (16042) 3 exp Vaccines/ (276986) 4 1 or 2 or 3 (384252) 5 exp Influenza, Human/ (57706) 6 4 and 5 (19758) 7 exp Influenza Vaccines/ (26794) 8 ((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (26488) 9 7 or 8 (35009) 10 6 or 9 (36616) 11 (cell adj1 (base$ or culture$ or deriv$)).tw. (222505) 12 (cell-base$ or cell-culture$ or cell-deriv$).tw. (204059) 13 exp Madin Darby Canine Kidney Cells/ (4469) 14 ((madin adj1 darby) and cell$).tw. (4968) 15 mdck.tw. (8008) 16 11 or 12 or 13 or 14 or 15 (234099) 17 10 and 16 (1069) 18 flucelvax.tw. (28) 19 17 or 18 (1077) 20 exp Treatment Outcome/ (1243511) 21 exp Vaccine Efficacy/ (763) 22 efficac$.tw. (1087784)	23 effective$.tw. (2512870) 24 exp Safety/ (88742) 25 exp Safety-Based Drug Withdrawals/ (416) 26 exp Product Surveillance, Postmarketing/ (18215) 27 exp Drug Evaluation/ (42061) 28 exp Population Surveillance/ (74473) 29 exp Adverse Drug Reaction Reporting Systems/ (8820) 30 (adverse adj3 (effect$ or event$)).tw. (461656) 31 (safe or safety or aefi or aesi).tw. (1021580) 32 exp Mortality/ (423334) 33 exp Death/ (164283) 34 (mortalit$ or death$ or fatal$ or case-fatal$ or lethal$ or died).tw. (2156321) 35 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (6705207) 36 19 and 35 (598) 37 limit 36 to "all adult (19 plus years)" (104) 38 exp Adult/ (7940154) 39 (adult$ or elder$ or senior$ or geriatr$).tw. (1875310) 40 38 or 39 (8767467) 41 36 and 40 (144) 42 37 or 41 (144)

Appendix B:

Table 1: Risk of Bias assessment for comparative, observational studies using ROBINS-I

Study	Comparison	Outcome	Confounding	Selection	Intervention classification	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
New studies assessed September 2021										
Martin 2021	QIV (cell) vs. QIV (egg)	Hospitalisation (with lab confirmed influenza)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Fujimori 2021	cQIV vs HD-TIV, SD-TIV, QIV, aTIV	GBS (safety)	Moderate	Moderate	Moderate	Low	Serious	Critical	Low	Critical
Izurieta 2021	5 vaccine comparison TIV-HD (egg), aTIV (egg), QIV (egg), QIV (cell), RIV Reference: QIV (cell), aTIV	Influenza related encounters (hospitalisation or ED visits); flu inpatient stays	Low	Low	Low	Low	Low	Low	Low	Low
New studies assessed from March 2023 for PICOs 1–4										
Boikos 2021	cIIV4 vs eIIV4	Influenza-related medical encounter	Low	Low	Low	Low	Low	Low	Low	Low
Divino 2022	cIIV4 vs eIIV4	Influenza-related hospitalisations / ED visits	Low	Low	Low	Low	Low	Low	Low	Low
Imran 2022 (adults)	cIIV4 vs eIIV4	Influenza-related medical encounter (overall, inpatient, outpatient)	Low	Low	Low	Low	Low	Low	Low	Low

Study	Comparison	Outcome	Confounding	Selection	Intervention classification	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
Imran 2022 (children)	cIIV4 vs eIIV4	Influenza-related medical encounter (overall, inpatient, outpatient)	Low	Low	Low	Low	Low	Low	Mod	Low-Mod
CSL Seqirus 2023	cIIV4 vs eIIV4	Test-confirmed influenza (PCR, culture, antigen and antibody)	Low	Low	Low	Low	Low-Mod	Low	Low-Mod	Low-Mod
Fujimori 2022 (ADEM)	Seasonal flu vaccines v other vaccines	Incidence of ADEM	Mod	Mod	Mod	Low	Serious	Critical	Low	Critical

Note: Studies assessed for bias in GRADE prior to 2021 are not shown in the above table.

Table 2: Risk of Bias assessment for randomised controlled trials using ROB 2.0

Study	Outcome	Randomisation process	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
Essink 2022	Safety	Low	Low	Low	Low	Low	Low

Note: Studies assessed for bias in GRADE prior to 2021 are not shown in the above table.