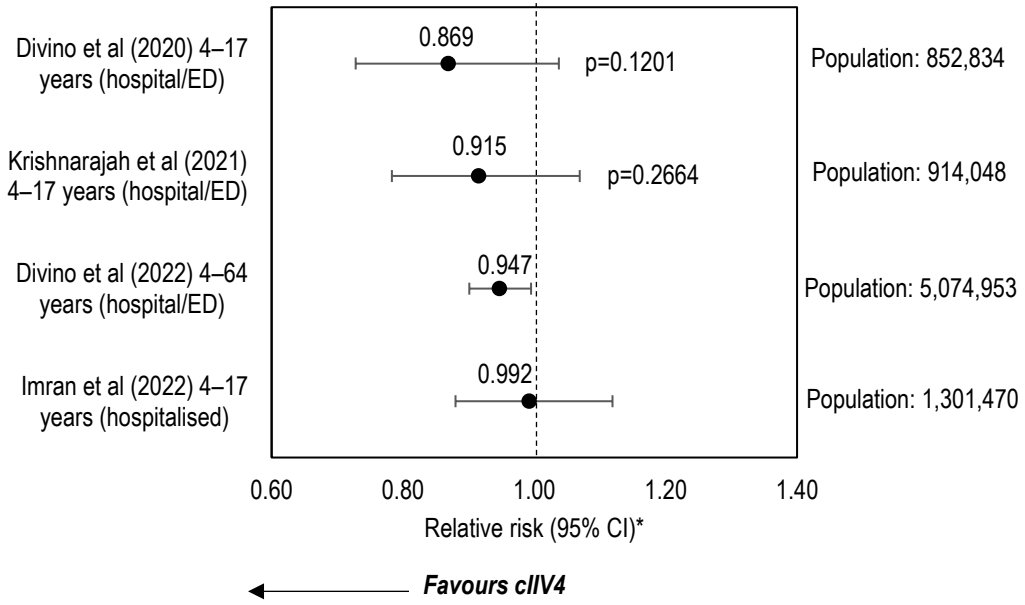
GRADE tables: Comparison of cell-based influenza vaccine with standard egg-based influenza vaccine in children aged 6 months–17 years

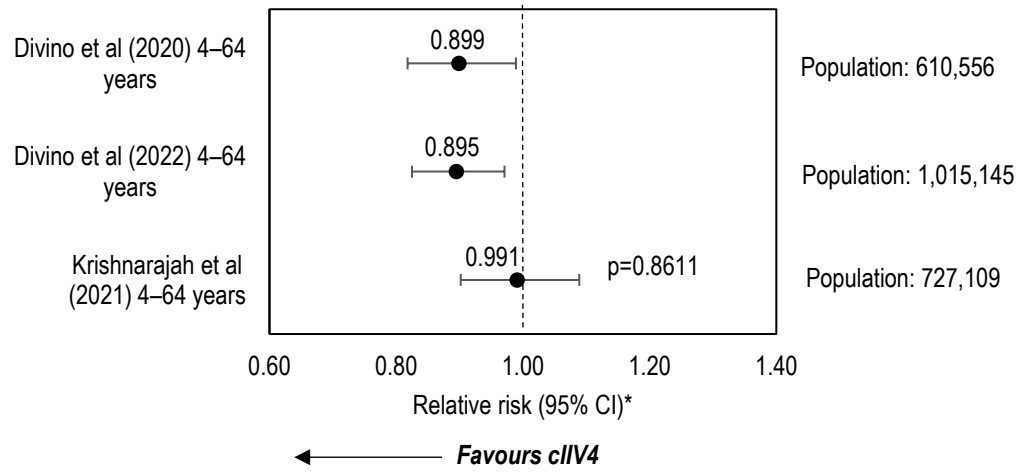
NCIRS is conducting GRADE assessments in support of the Australian Technical Advisory Group on Immunisation (ATAGI) and making results available on the Centre's website. Please read this material as a supplement to the Australian Immunisation Handbook influenza chapter.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
CRITICAL OUTCOMES				
Laboratory-confirmed influenza hospitalisation Assessed with: PCR test from a specimen taken anytime between 14 days prior to 3 days after the admission date Follow-up: range 21 days to 8 months	Bruxvoort et al (2019) 4–64 years rVE cIIV3/cIIV4 vs eIIV3/eIIV4 **4–64 years** 43% (95% CI: −45%–77%)	1,816 of which only 237 (8 cIIV & 229 eIIV) were 4–18 years-old (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c]	Cell-based influenza vaccine may result in a reduction in laboratory-confirmed influenza hospitalisation compared with standard egg-based influenza vaccine; however, the evidence is very uncertain.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years

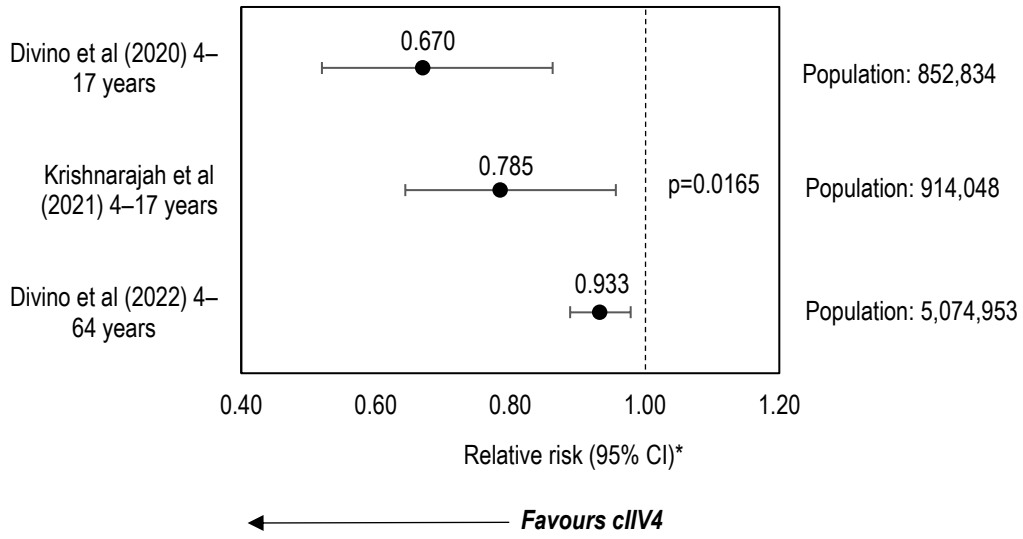
Patient or population: children aged 6 months–17 years
Intervention: MDCK cell-derived influenza vaccine (cIIV)
Comparison: Standard dose egg-based influenza vaccine (eIIV)

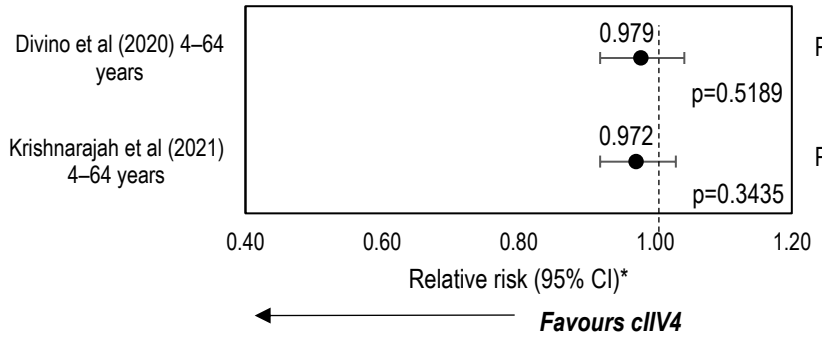
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Influenza-related hospitalisations or emergency department (ED) visits (no laboratory confirmation) Assessed with: ICD-9 487.x, 488.x, ICD-10 J09.x, J10.x, J11.x in any diagnosis position Follow-up: range 14 days to 12 months	**Relative vaccine effectiveness of cIIV vs eIIV against ICD-coded hospitalisations/ED visits in the general population**  Note: Divino et al (2022) and Imran et al (2022) follow up period was truncated to 7 months due to the COVD-19 pandemic. Total participants = 8,143,305 (4 observational studies)[2-5]		⊕⊕⊕◯ Moderate[a,d]	Cell-based influenza vaccine likely results in a slight reduction in influenza-related hospitalisations or ED visits compared with standard egg-based influenza vaccine in the general population.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
continued **Influenza-related hospitalisations or ED visits (no laboratory confirmation)** Assessed with: ICD-9 487.x, 488.x, ICD-10 J09.x, J10.x, J11.x in any diagnosis position Follow-up: range 14 days to 12 months	**Relative vaccine effectiveness of cIIV vs eIIV against ICD-coded hospitalisations/ED visits in high-risk populations**  Note: Divino et al (2022) follow up period was truncated to 7 months due to the COVD-19 pandemic. Total participants = 2,352,810 (3 observational studies)[2-4]		⊕⊕◯◯ Low[a,b]	Cell-based influenza vaccine may result in a slight reduction in influenza-related hospitalisations or ED visits compared with standard egg-based influenza vaccine in the high-risk population.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years

Patient or population: children aged 6 months–17 years
Intervention: MDCK cell-derived influenza vaccine (cIIV)
Comparison: Standard dose egg-based influenza vaccine (eIIV)

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Pneumonia-related hospitalisations or ED visits (no laboratory confirmation) Assessed with: ICD-10 diagnosis code in any position for pneumonia Follow-up: range 14 days to 12 months	**Relative vaccine effectiveness of cIIV vs eIIV against ICD-coded pneumonia hospitalisations/ED visits in the general population**  Note: Divino et al (2022) follow up period was truncated to approximately 7 months due to the COVD-19 pandemic. Total participants = 6,841,835 (3 observational studies)[2-4]		⊕⊕◯◯ Low[a,e]	Cell-based influenza vaccine may reduce pneumonia-related hospitalisations or ED visits compared with standard egg-based influenza vaccine in the general population. Ref: 2,3,4

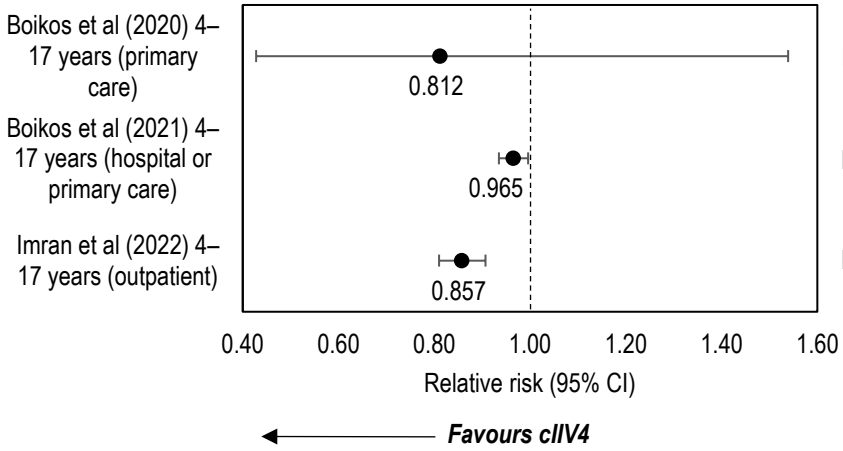
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
continued **Pneumonia-related hospitalisations or ED visits (no laboratory confirmation)** Assessed with: ICD-10 diagnosis code in any position for pneumonia Follow-up: range 14 days to 12 months	**Relative vaccine effectiveness of cIIV vs eIIV against ICD-coded pneumonia hospitalisations/ED visits in high-risk populations**  Total participants = 1,337,665 (2 observational studies)[2,3]		⊕⊕◯◯ Low[a,b]	Cell-based influenza vaccine may result in little or no reduction in pneumonia-related hospitalisations or ED visits compared with standard egg-based influenza vaccine in the high-risk population; however, the evidence is very uncertain
Serious adverse events (SAEs) Assessed with: Patient report Follow-up: range 1 days to 6 months	cIIV3 v eIIV3: Diez-Domingo et al (2016) 3–17 years, Vesikari et al (2012), 9–17 years and Nolan et al (2016), 9–17 years. cIIV4 v eIIV4: Essink et al (2022), 6–47 months. **No vaccine related SAEs were reported in any of the studies.**	8487 (4 RCTs)[6-9]	⊕⊕⊕⊕ High	Cell-based influenza vaccine results in little to no difference in serious adverse events compared with standard egg-based influenza vaccine.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
SAE – Guillain-Barré syndrome (GBS) Assessed with: reports of AEs related to GBS and identified by a preferred-term code in VAERS among recipients of cell-based and egg-based vaccines Follow-up: 42 days	Fujimori et al (2021), Aged over 6 months: **Guillain-Barré syndrome (GBS)** Adjusted reporting odds ratio (ROR) cQIV 15.00 (95% CI: 9.27–24.20) egg-culture based influenza vaccine (HD-TIV, SD-TIV, QIV, aTIV) ROR = 1.99 (95% CI: 1.28–3.10) [The ROR is the ratio of the odds of reporting an AE versus all other events associated with seasonal influenza vaccines compared with the reporting odds for AEs associated with all other vaccines present in VAERS]	36,227 AE reports (GBS cases n=119, non-GBS cases n=36,108; Of GBS cases 64 had a seasonal influenza vaccine and 55 had other vaccines) (1 observational study)[10]	⊕◯◯◯ Very low[b,f]	Cell-based influenza vaccines may result in an increase in GBS compared with standard egg-based influenza vaccine; however, the evidence is very uncertain. Note: While this study includes data enquiry from those aged ≥6, it is unclear if/how many children <18 years were included in final analysis. The results are likely primarily derived from the adult population.**
SAE – Acute disseminated encephalomyelitis (ADEM) Assessed with: reports of ADEM in VAERS identified by a preferred-term code among recipients of cell-based or egg-based influenza	Fujimori & Nakamura (2022), Aged over 6 months: **Acute disseminated encephalomyelitis (ADEM)** Adjusted reporting odds ratio (ROR [95%CI]): cell-based IV = 10.40 (3.74–28.9), egg-based IV = 2.91 (1.63–5.22) [The **ROR**, is defined as the ratio of the odds of reporting an AE versus all other events associated with seasonal influenza vaccines, compared with the odds for AEs associated with all other vaccines present in the database]	591,416 AEs (subset for analysis) (propensity score matched 295,708 flu vaccine to 295,708 non-flu vaccine controls 1:1 (1 observational study)[11]	⊕◯◯◯ Very low[b,f]	Cell-based influenza vaccines may result in an increase in ADEM compared with standard egg-based influenza vaccine; however, the evidence is very uncertain. Note: 20.5% of the population included in the VAERS dataset for analysis were children aged 0.5–17 years. However, this single study presents results based on very small case event (ADEM)

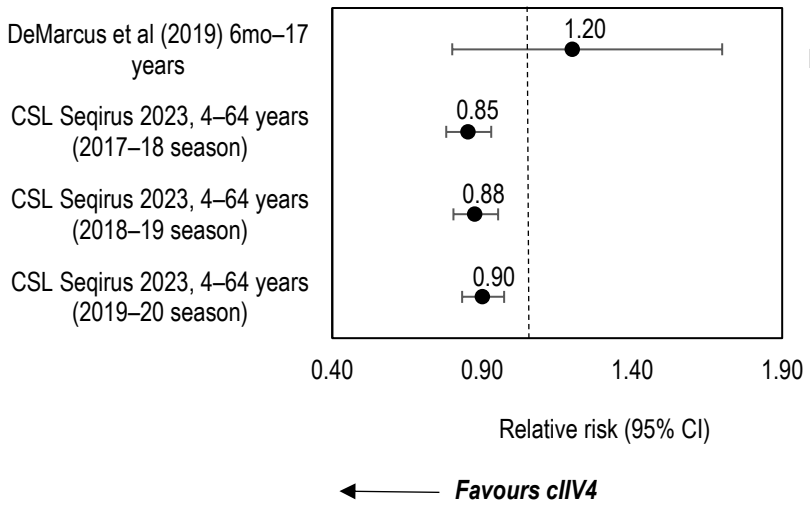
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
vaccines Follow-up: 130 days				numbers (51 ADEM AE reports/343,824 AE reports who received a seasonal influenza vaccine).**

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years

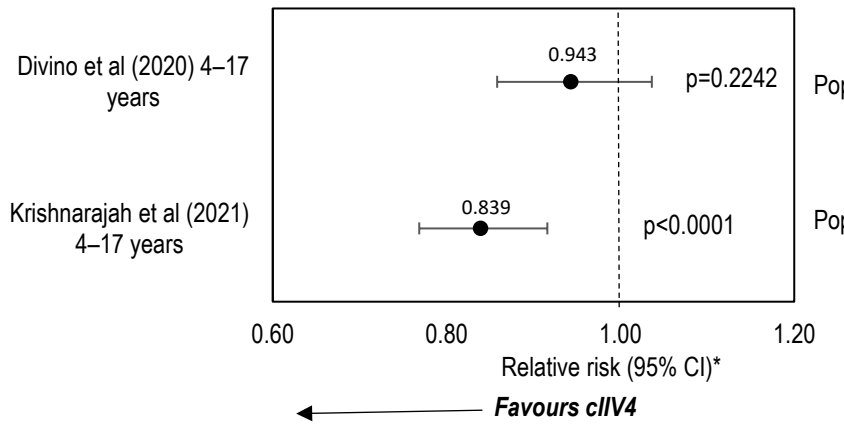
Patient or population: children aged 6 months–17 years
Intervention: MDCK cell-derived influenza vaccine (cIIV)
Comparison: Standard dose egg-based influenza vaccine (eIIV)

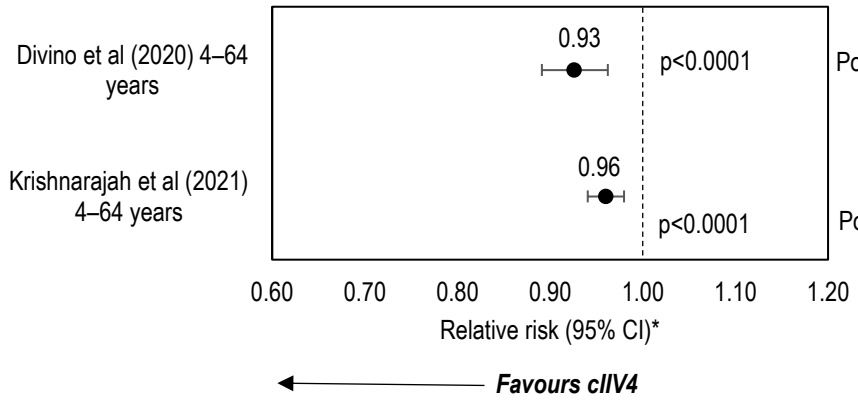
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
IMPORTANT OUTCOMES				
Influenza-related medical encounter (IRME) in hospital, outpatient or primary care setting Assessed with: ICD-10 diagnosis code (J09*–J11*) in any diagnostic position Follow-up: range 14 days to 9.5 months	**Relative vaccine effectiveness of cIIV vs eIIV against influenza related medical encounter in hospital, primary care or outpatient setting, among the general population**  Note: Follow up time varied across studies – Boikos et al (2020), 8 months; Boikos et al (2021), 9.5 months; Imran et al (2022), 7 months. Total participants = 3,420,085 (3 observational studies)[5,12,13]	Population: 411,975 Population: 1,706,640 Population: 1,301,470	⨁⨁◯◯ Low[a,d,g]	Cell-based influenza vaccine may result in a slight reduction in IRMEs in hospital, outpatient or primary care setting, in the general population, compared with standard egg-based influenza vaccine. Refs: 5,12,13

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
continued **IRME in hospital, outpatient or primary care setting** Assessed with: ICD-10 diagnosis code (J09*–J11*) in any diagnostic position Follow-up: range 14 days to 9.5 months	**High-risk population:** Boikos 2021 (2), 4–64 years (hospital or primary care) rVE cIIV4 vs eIIV4 **13.4% (95% CI: 11.4–15.4)**	2,113,216 (1 observational study)[14]	⨁⨁◯◯ Low[a,b]	Cell-based influenza vaccine may result in a slight reduction in IRMEs in the primary-care or outpatient setting compared with standard egg-based influenza vaccine.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Test-confirmed influenza Assessed with: positive RT-PCR, viral culture, rapid antigen or antibody test from specimens from people with ILI in outpatient setting Follow-up: range 14 days to 7.5 months	**Relative vaccine effectiveness of cIIV vs eIIV against test-confirmed influenza from ILI in outpatient setting**  Note 1: Demarcus et al (2019); influenza confirmed by PCR or viral culture; compared cIIV4 v eIIV3/eIIV4; follow up period 7 months. Note 2: CSL Seqirus (2023); influenza confirmed by any test; follow up period was 7.5 months except for 2019/20 which was truncated to 5 months due to the COVID-19 pandemic. Total participants = 101,880 (2 observational studies)[15]		⊕⊕◯◯ Low[a,b,d]	Cell-based influenza vaccine may result in a slight reduction in test-confirmed influenza compared with standard egg-based influenza vaccine. Ref: 15,16

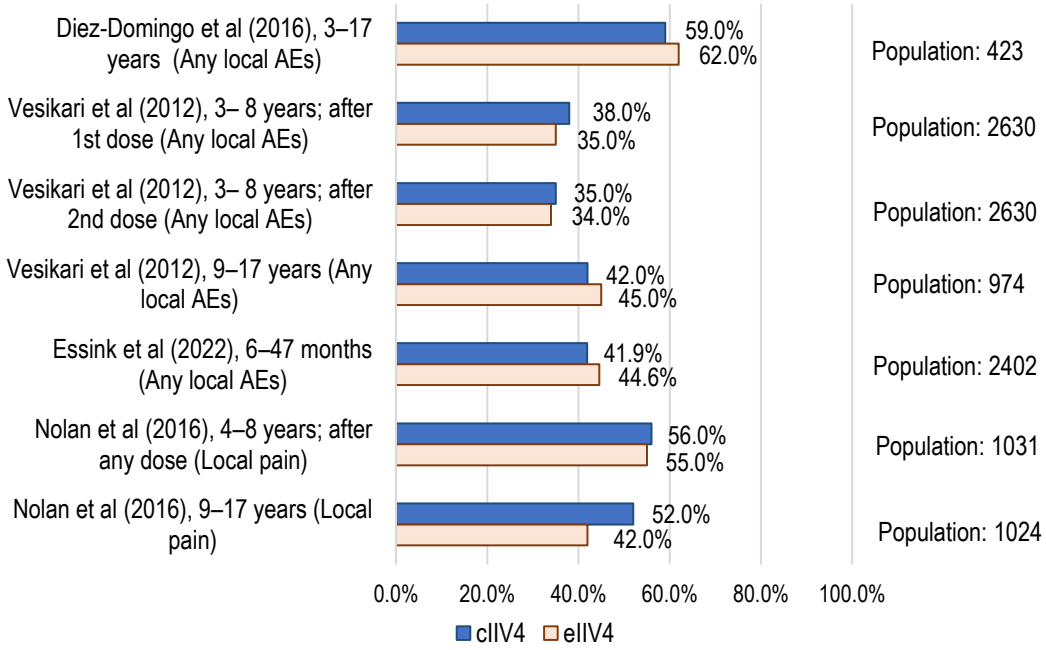
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
PCR-confirmed influenza A Assessed with: positive PCR test result for influenza A (GeneXpert PCR assay) from primary care/hospital setting Follow-up: range 7 days to 6 months	Klein et al (2020) 4–17 years: rVE cIIV4 v eIIV3/4 4–17 years 17.8% (−6.2%–36.4%)	264,154 (1 observational study)[16]	⨁◯◯◯ Very low[a,c]	Cell-based influenza vaccine may result in a slight reduction in PCR confirmed influenza A compared with standard egg-based influenza vaccine; however, the evidence is very uncertain.
PCR-confirmed influenza B Assessed with: positive PCR test result for influenza B (GeneXpert PCR assay) from primary care/hospital setting Follow-up: range 7 days to 6 months	Klein et al (2020) 4–17 years: rVE cIIV4 v eIIV3 4–17 years 42.3% (28.4%–53.5%)	264,154 (1 observational study)[16]	⨁⨁⨁◯ Moderate[a]	Cell-based influenza vaccine likely results in a moderate reduction in PCR-confirmed influenza B compared with standard egg-based influenza vaccine.

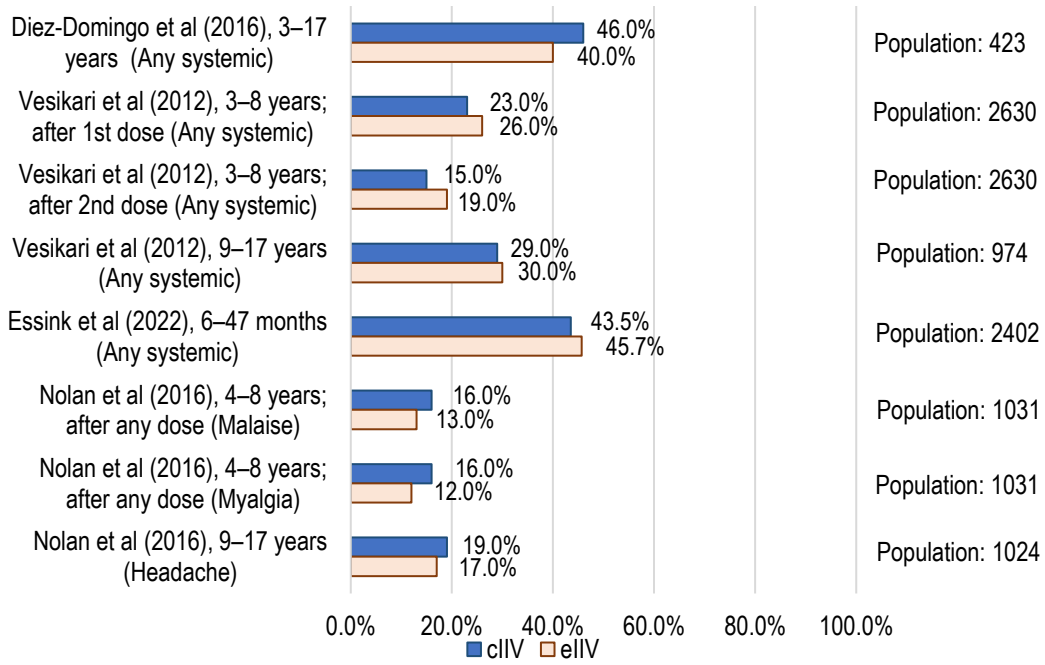
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
All cause hospitalisation or ED visit Assessed with: database entry for hospitalisation or ED visit Follow-up: range 14 days to 12 months	**Relative vaccine effectiveness of cIIV vs eIIV against all-cause hospitalisations/ED, in the general population**  Total participants = 1,766,882 (2 observational studies)[2,3]		⊕⊕◯◯ Low[a,c]	Cell-based influenza vaccine may result in a slight reduction in all cause hospitalisation or ED visit compared with standard egg-based influenza vaccine in the general population.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
continued **All cause hospitalisation or ED visit** Assessed with: database entry for hospitalisation or ED visit Follow-up: range 14 days to 12 months	**Relative vaccine effectiveness of cIIV vs eIIV against all-cause hospitalisations/ED among high risk population**  Total participants = 1,524,604 (2 observational studies)[2,3]	Population: 610,556 Population: 914,048	⊕⊕◯◯ Low[a,b]	Cell-based influenza vaccine may result in a slight reduction in all cause hospitalisation or ED visit compared with standard egg-based influenza vaccine in the high-risk population.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years

Patient or population: children aged 6 months–17 years
Intervention: MDCK cell-derived influenza vaccine (cIIV)
Comparison: Standard dose egg-based influenza vaccine (eIIV)

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited local adverse event (AE) Assessed with: diary Follow-up: range 1 days to 7 days	**Solicited local adverse events of cIIV vs eIIV in children 6 months to 17 years**  Note: Vesikari et al (2012), Diez-Domingo et al (2016) and Nolan et al (2016) compared cIIV3 with eIIV3; Essink et al (2022) compared cIIV4 with eIIV4. Total participants = 8,484 (excluding repeat participants); 4 Randomised controlled trials.[6-9]		⊕⊕⊕⊕ High	Cell-based influenza vaccine results in little to no difference in local AEs compared with standard egg-based influenza vaccine.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years				
Patient or population: children aged 6 months–17 years **Intervention:** MDCK cell-derived influenza vaccine (cIIV) **Comparison:** Standard dose egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Solicited systemic AE Assessed with: Diary Follow-up: range 1–7 days	**Solicited systemic adverse events of cIIV vs eIIV in children 6 months to 17 years**  Note: Vesikari et al (2012), Diez-Domingo et al (2016) and Nolan et al (2016) compared cIIV3 with eIIV3; Essink et al (2022) compared cIIV4 and eIIV4. Total participants = 8,484 (excluding repeat participants); 4 Randomised controlled trials.[6-9]		⊕⊕⊕⊕ High	Cell-based influenza vaccine results in little to no difference in systemic AEs compared with standard egg-based influenza vaccine.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in children aged 6 months–17 years

Patient or population: children aged 6 months–17 years
Intervention: MDCK cell-derived influenza vaccine (cIIV)
Comparison: Standard dose egg-based influenza vaccine (eIIV)

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation

Explanations

a. Risk of bias judgement = moderate, due to confounding

b. Study results are not specific to the age group being assessed

c. Wide confidence intervals

d. With the addition of new studies, the effect estimates are more precise. Non-significance of CIs is no longer an issue

e. Relative vaccine effectiveness estimates differ markedly between studies

f. Risk of bias judgement = serious, due to confounding and methodologic issues

g. While point estimates are similar, specific outcomes under the umbrella term of 'IRME' vary.

Footnotes

* 95% CI values were derived from the p-value where the p-value is shown

** Regarding studies by Fujimori, data is to be interpreted with caution due to methodological and reporting issues - Cases were not validated; reported characteristics of cases do not seem to reflect GBS/ADEM (unusually short duration of symptoms); duplicates were not excluded; interpretation of reported odds ratio may be ambiguous as comparator was against other adverse events for egg-based vaccines; and large proportions of missing data.

Abbreviations: AE=adverse event; CI=confidence interval; ED=emergency department; IRME=influenza-related medical encounter; RR=Risk Ratio; OR=Odds ratio; rVE=relative vaccine effectiveness; SAE=serious adverse event

GRADE working group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE evidence profile

Cell-based influenza vaccine compared with standard egg-based influenza vaccine for children aged 2–17 years

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Laboratory-confirmed influenza hospitalisation; follow-up: range 21 days to 8 months; assessed with: PCR test from a specimen taken anytime between 14 days prior to 3 days after the admission date.									
1	Observational studies	Serious[a]	Not serious	Serious[b]	Serious[c]	None	**Bruxvoort et al (2019) 4–64 years** rVE 43% (95% CI: −45–77)[1]	⨁◯◯◯ Very low	CRITICAL
Influenza related hospitalisations or emergency department (ED) visits (no laboratory confirmation); follow-up: range 14 days to 12 months; assessed with: ICD-9 487.x, 488.x, ICD-10 J09.x, J10.x, J11.x in any diagnostic position.									
4	Observational studies	Serious[a]	Not serious	Not serious	Not serious[d]	None	**General population:** rVE (95% CI) **Divino et al (2020) 4–17 years:** 13.1% (no CI), p=0.1201[2] **Krishnarajah et al (2021) 4–17 years:** 8.5% (no CI), p=0.2664[3] **Divino et al (2022) 4–64 years:** 5.3% (0.5–9.9)[4] **Imran et al (2022) 4–17 years:** 0.8% (−11.9–12.0)[5]	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Influenza-related hospitalisations or ED visits (no laboratory confirmation) (follow-up: range 14 days to 12 months; assessed with: ICD-9 487.x, 488.x, ICD-10 J09.x, J10.x, J11.x in any diagnostic position)									
3	Observational studies	Serious[a]	Not serious	Serious[b]	Not serious	None	**High risk population:** rVE (95% CI) **Divino et al (2020) 4–64 years:** 10.1% (1.1– 18.2)[2] **Divino et al (2022) 4–64 years:** 10.5% (2.9– 17.5)[4] **Krishnarajah et al (2021) 4–64 years:** 0.9% (no CI), p=0.8611[3]	⨁⨁◯◯ Low	CRITICAL
Pneumonia-related hospitalisations or ED visits (no laboratory confirmation) (follow-up: range 14 days to 12 months; assessed with: ICD-10 diagnosis code for pneumonia in any diagnostic position)									
3	Observational studies	Serious[a]	Serious[e]	Not serious	Not serious	None	**General population:** rVE (95% CI) **Divino et al (2020) 4–17 years:** 33.0% (13.7– 48.0)[2] **Krishnarajah et al (2021) 4–17 years:** 21.5% p=0.0165[3] **Divino et al (2022) 4–64 years:** 6.7% (2.1– 11.1)[4]	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Pneumonia-related hospitalisations or ED visits (no laboratory confirmation) (follow-up: range 14 days to 12 months; assessed with: ICD-10 diagnosis code for pneumonia in any diagnostic position)									
2	Observational studies	Serious[a]	Not serious	Serious[b]	Not serious	None	**High risk population:** rVE (95% CI) **Divino et al (2020) 4–64 years:** 2.1% (no CI), p=0.5189[2] **Krishnarajah et al (2021) 4–64 years:** 2.8% (no CI), p=0.3435[3]	⊕⊕◯◯ Low	CRITICAL
Serious adverse events (SAEs) (follow-up: range 1 days to 6 months; assessed with: patient report)									
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	**Diez-Domingo et al (2016) 3–17 years; Vesikari et al (2012) 9–17 years; Nolan et al (2016) 9–17 years; Essink et al (2022) 6–47 months.** No vaccine related SAEs reported in any of the above studies.[6-9]	⊕⊕⊕⊕ High	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
SAE – Guillain-Barré syndrome (follow-up: 42 days; assessed with: reports of AEs related to GBS and identified by a preferred-term code in VAERS among recipients of cell-based and egg-based vaccines)									
1	Observational studies	Very serious[f]	Not serious	Serious[b]	Not serious	None	**Fujimori et al (2021) aged over 6 months:** **Guillain-Barré syndrome (GBS)** Adjusted reporting odds ratio (95% CI) cQIV 15.00 (9.27–24.20) egg-based influenza vaccine (HD-TIV, SD-TIV, QIV, aTIV) = 1.99 (1.28–3.10) [The ROR is the ratio of the odds of reporting an AE versus all other events associated with seasonal influenza vaccines compared with the reporting odds for AEs associated with all other vaccines present in VAERS] N=36,227 AE reports (GBS cases n=119, non-GBS cases n=36,108; of GBS cases 64 had a seasonal influenza vaccine and 55 had other vaccines)[10]	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
SAE – Acute disseminated encephalomyelitis (follow-up: 130 days; assessed with: reports of ADEM in VAERS identified by a preferred-term code among recipients of cell-based or egg-based influenza vaccines)									
1	Observational studies	Very serious[f]	Not serious	Serious[b]	Not serious	None	**Fujimori & Nakamura (2022) aged over 6 months:** **Acute disseminated encephalomyelitis (ADEM)** Adjusted reporting odds ratio (95%CI): cell-based IV = 10.40 (3.74–28.9), egg-based IV = 2.91 (1.63–5.22) [The ROR, is defined as the ratio of the odds of reporting an AE versus all other events associated with seasonal influenza vaccines, compared with the odds for AEs associated with all other vaccines present in the database] N=591,416 AEs (subset for analysis) (propensity score matched 295,708 flu vaccine to 295,708 non-flu vaccine controls 1:1)[11]	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Influenza-related medical encounter (IRME) in hospital, outpatient or primary care setting (follow-up: range 14 days to 9.5 months; assessed with: ICD-10 diagnosis code (J09*–J11*) in any diagnostic position)									
2	Observational studies	Serious[a]	Serious[g]	Not serious	Not serious[d]	None	**General population:** rVE (95% CI) **Boikos et al (2020) 4–17 years:** 18.8% (-53.9–57.2)[12] **Boikos et al (2021) 4–17 years:** 3.5% (0.4– 6.5)[13] **Imran et al (2022) 4–17 years:** 14.3% (9.3–19.0)[5]	⨁⨁◯◯ Low	IMPORTANT
IRME in hospital, outpatient or primary care setting (follow-up: range 14 days to 9.5 months; assessed with: ICD-10 diagnosis code (J09*–J11*) in any diagnostic position)									
1	Observational studies	Serious[a]	Not serious	Serious[b]	Not serious	None	**High-risk population** rVE (95% CI) **Boikos et al (2021) (2) 4–64 years:** 13.4% (11.4–15.4)[14]	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Test-confirmed influenza (follow-up: range 14 days to 7.5 months; assessed with: positive RT-PCR, viral culture, rapid antigen or antibody test specimens from people with ILI in outpatient setting)									
1	Observational studies	Serious[a]	Not serious	Serious[b]	Not serious[d]	None	**Relative risk (95% CI)** **DeMarcus et al (2019) 6 months–17 years (PCR or culture):** (Odds ratio) 1.2 (0.8–1.7)[15] **CSL Seqirus 2023, 4–64 years (2017-18 season; any positive test):** 0.852 (0.78–0.93) **CSL Seqirus 2023, 4–64 years (2018-19 season; any positive test):** 0.875 (0.804–0.953) **CSL Seqirus 2023, 4–64 years (2019-20 season; any positive test):** 0.9 (0.833–0.973)	⨁⨁◯◯ Low	IMPORTANT
PCR-confirmed influenza A (follow-up: range 7 days to 6 months; assessed with: positive PCR test result for influenza A (GeneXpert PCR assay) from primary care/hospital setting)									
1	Observational studies	Serious[a]	Not serious	Not serious	Very serious[c]	None	**Klein et al (2020) 4–17 years:** rVE (95% CI) cIIV4 vs eIIV3/4 17.8% (−6.2%–36.4%)[16]	⨁◯◯◯ Very low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
PCR-confirmed influenza B (follow-up: range 7 days to 6 months; assessed with: positive PCR test result for influenza B (GeneXpert PCR assay) from primary care/hospital setting)									
1	Observational studies	Serious[a]	Not serious	Not serious	Serious[c]	None	**Klein et al (2020) 4–17 years:** rVE (95% CI) cIIV4 vs eIIV3/4 42.3% (28.4%–53.5%)[16]	⨁⨁⨁◯ Moderate	IMPORTANT
All cause hospitalisation or ED visit (follow-up: range 14 days to 12 months; assessed with: database entry for hospitalisation or ED visit)									
2	Observational studies	Serious[a]	Not serious	Not serious	Serious[c]	None	**General population:** rVE (95% CI) **Divino et al (2020) 4–17 years:** 5.7% (no CI), p=0.2242[2] **Krishnarajah et al (2021) 4–17 years:** 16.12% (no CI), p<0.0001[3]	⨁⨁◯◯ Low	IMPORTANT
All cause hospitalisation or ED visit (follow-up: range 14 days to 6 months; assessed with: database entry for hospitalisation or ED visit)									
2	Observational studies	Serious[a]	Not serious	Serious[b]	Not serious	None	**High risk population:** rVE (95% CI) **Divino et al (2020) 4–64 years:** 7.4% (no CI), p<0.0001[2] **Krishnarajah et al (2021) 4–64 years:** 4.0% (no CI), p<0.0001[3]	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Solicited local AE (follow-up: range 1 days to 7 days; assessed with: diary)									
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	cIV vs eIV (% frequency of AE) **Diez-Domingo et al (2016) 3–17 years:** any local AE 59% vs 62%[8] **Vesikari et al (2012) 3–8 years; after 1st dose**: any local AE 38% vs 35%[7] **Vesikari et al (2012) 3–8 years; after 2nd dose**: any local AE 35% vs 34%[7] **Vesikari et al (2012) 9–17 years:** any local AE 42% vs 45%[7] **Essink et al (2022) 6–47 months:** any local AE 41.9% vs 44.6%[9] **Nolan et al (2016) 4–8 years, after any dose:** local reaction: Pain 56% vs 55%[6] **Nolan et al (2016) 9–18 years:** local reaction: Pain 62% vs 42%[6]	⨁⨁⨁⨁ High	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Solicited systemic AE (follow-up: range 1 days to 7 days; assessed with: diary)									
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	cIV vs eIV (% frequency of AE) **Diez-Domingo et al (2016) 3–17 years:** any systemic AE 46% vs 40%[8] **Vesikari et al (2012) 3–8 years; after 1st dose**: any systemic AE 23% vs 26%[7] **Vesikari et al (2012) 3–8 years; after 2nd dose**: any systemic AE 15% vs 19%[7] **Vesikari et al (2012) 9–17 years:** any systemic AE 29% vs 30%[7] **Essink et al (2022) 6–47 months:** any systemic AE 43.5% vs 45.7%[9] **Nolan et al (2016) 4–8 years, after any dose:** systemic AE: Malaise 16% vs 13%[6] **Nolan et al (2016) 4–8 years, after any dose:** systemic AE: Myalgia 16% vs 12%[6] **Nolan et al (2016) 9–18 years:** systemic AE: Headache 19% vs 17%[6]	⊕⊕⊕⊕ High	IMPORTANT

Evidence to decision framework

PICO Question					
Population	6 months to 17 years old				
Intervention	Cell-based influenza vaccine (cIIV)				
Comparison	Standard dose egg-based influenza vaccine (eIIV)				
Main outcomes	**Main outcomes:** • Laboratory-confirmed influenza hospitalisation • Influenza-related hospitalisation/emergency department visits • Pneumonia-related hospitalisation/emergency department visits • Laboratory-confirmed influenza • Influenza-related medical encounter (IRME) • Local adverse events (AEs) • Systemic AEs • Serious adverse events (SAE)				
Setting	Global middle- to high-income settings (e.g. Europe, Canada, the US, Australia)				
ASSESSMENT					
Problem *Is the problem a priority?*					
Don't know	Varies	No	Probably no	Probably yes	Yes
• Influenza causes substantial morbidity and mortality.					
Desirable effects *How substantial are the desirable anticipated effects?*					
Don't know	Varies	Large	Moderate	Small	Trivial
• There is weak evidence that cIIV is more protective than eIIV for non-critical outcomes, the effect estimate varied between studies and the overall magnitude of benefit was small. • Studies in this GRADE included influenza season data from the Northern Hemisphere 2017/18–2019/20. Notably, separate studies examining antigenic differences between the circulating virus strains and those included in the vaccine have demonstrated that during 2017/18 and 2018/19 seasons respectively, only 48% and 19% of viruses tested were well-inhibited by the egg-based vaccine for influenza A(H3N2).[17-20] This factor may have been related to improved vaccine effectiveness (VE) of cIIV over eIIV in 2017/18 where influenza A(H3N2) was in high circulation in the United States (Northern Hemisphere).[19]					

- The northern hemisphere influenza season of 2017/18 used the same vaccine composition as that used in the southern hemisphere influenza season of 2017 where influenza A(H3N2) predominated and egg-adaptation was also thought to contribute to low overall VE in Australia.[21,22]

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Higher frequency of local AEFI; however, frequency of systemic AEFI and SAE appear similar between cIIV and eIIV recipients.
- Of note, two studies (author: Fujimori) that suggested increased rates of GBS[10] and ADEM[11] had major methodological issues and were assessed as providing a very low certainty of evidence.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Don't Know	Varies	Favours comparison	Probably favours comparison	Does not favour either comparison or intervention	Probably favours intervention	Favours intervention

- There is a small increased benefit with use of cIIV compared to eIIV and undesirable effects of cIIV are at least comparable to eIIV.

Certainty of evidence

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- Overall, there is low strength evidence that cIIV provides better protection against influenza outcomes than eIIV. However, the estimate of the magnitude of relative benefit varied considerably and thus the absolute benefit was small. The impact of egg-adaptation reported during the 2017/18 season may have influenced rVE for some studies.
- This grading was revised up from the previous GRADE due to the addition of new studies with increased precision, though potential confounding remains for all outcomes based solely on observational studies. Most evidence on influenza vaccine effectiveness outcomes was of low certainty.
- Most evidence on safety outcomes was of high certainty with the exception of the two studies by Fujimori[10,11] where results should be interpreted with caution.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Important uncertainty	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

- Unlikely to be important uncertainty in how people value protection against influenza.

Acceptability

Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably no	Probably yes	Yes

- No difference in the acceptability of cIIV compared with eIIV is expected.

Equity

What would be the impact on health inequities?

Don't know	Varies	Increased	Probably increased	Probably no impact	Probably reduced	Reduced

- No difference of impact on health inequities as funded influenza vaccine program already extends to disadvantaged and at-risk populations

Feasibility

Is the intervention feasible to implement?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Minimal barriers in implementation, as vaccine delivery system already in use.

ATAGI recommendation

There is no preferential recommendation between the use of cell-derived influenza vaccine (cIIV) and standard dose egg-based influenza vaccine (eIIV) in children aged 6 months to 17 years.

Justification and considerations

1. The direction of the effect was generally slightly favourable to cIIV than eIIV for a range of influenza-related outcomes with mostly low strength evidence demonstrating cIIV is more effective than eIIV against influenza.
2. Compared with eIIV, cIIV results in a very small increase in local adverse events, but there is little to no difference in systemic adverse events, serious adverse events or adverse events of special interest caused by both vaccines.
3. At this time there is insufficient basis for a preferential recommendation due to (a) small estimate of benefit over egg-based vaccine in absolute terms and (b) inconsistent evidence for benefit, particularly when considering vaccines after 17/18 where egg adaptation may have been an issue.

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