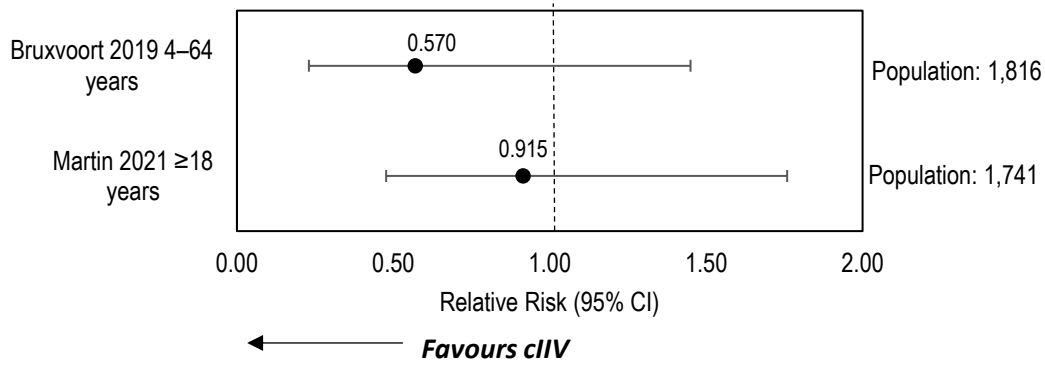
GRADE tables: Comparison of cell-based influenza vaccine with standard egg-based influenza vaccine in adults aged 18–64 years

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.

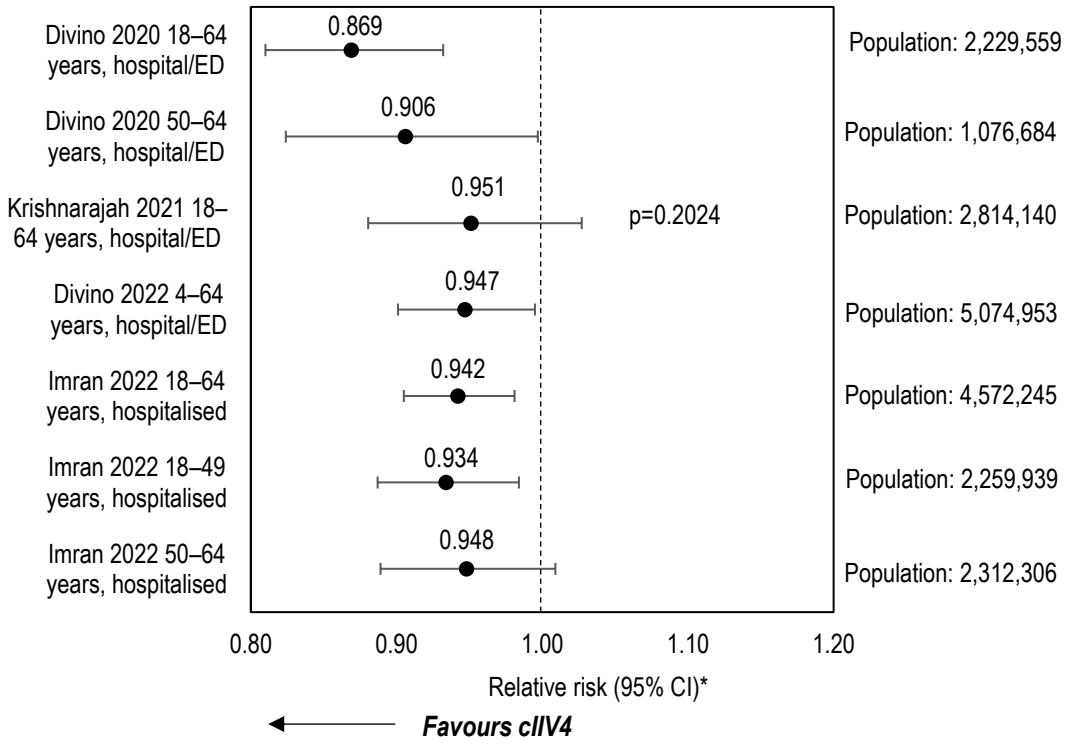
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years

Patient or population: Adults aged 18–64 years
Intervention: Cell-based influenza vaccine (cIIV)
Comparison: Standard 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	**Relative vaccine effectiveness against laboratory-confirmed influenza**  Note: Duration of study follow up not specified for Martin 2021 (indicated only as influenza season). Total participants = 3,557 (2 observational studies)[1,2]		⊕◯◯◯ Very low[a,b,c]	Cell-based influenza vaccine may result in a small reduction in laboratory-confirmed influenza hospitalisation compared with standard egg-based influenza vaccine; however, the evidence is very uncertain.

<table>
<tr>
<td>Influenza-related hospitalisations or emergency department (ED) visits (no laboratory confirmation)

Assessed with: ICD-9 487.x, 488.x, ICD-10 J09x-J11x in any diagnosis position

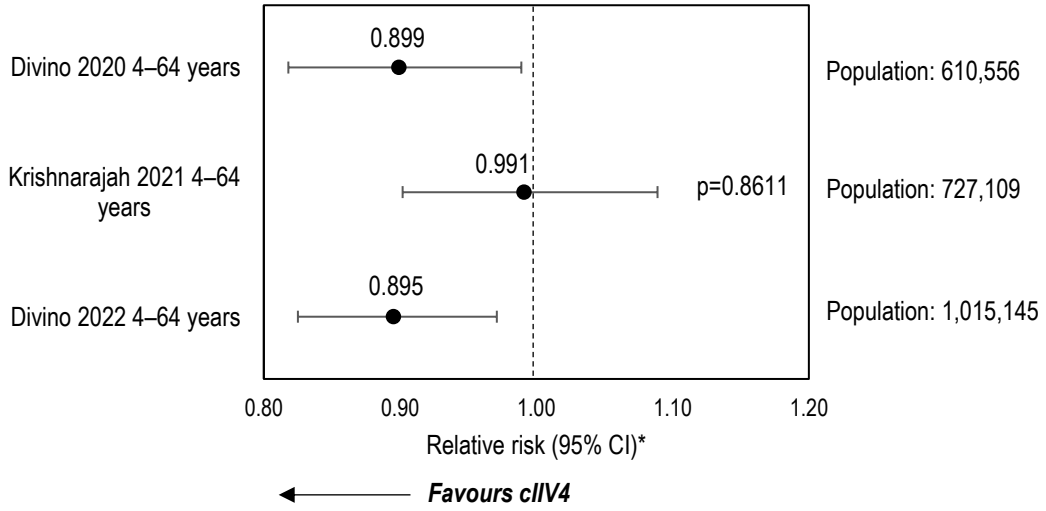
Follow-up: range 14 days to 12 months</td>
<td>Relative vaccine effectiveness of cIIV vs eIIV against ICD-coded hospitalisations/ED visits in the general population
 

Note: Divino 2022 and Imran 2022 follow-up period was truncated to 7 months due to the COVD-19 pandemic.

Total participants = 14,690,897 (4 observational studies)[3-6]</td>
<td>⊕⊕⊕◯
Moderate[a]</td>
<td>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.</td>
</tr>
</table>

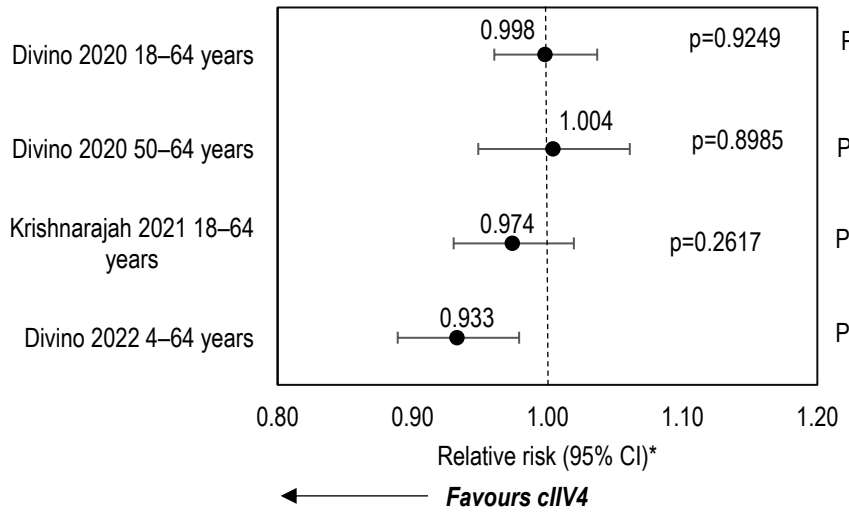
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years

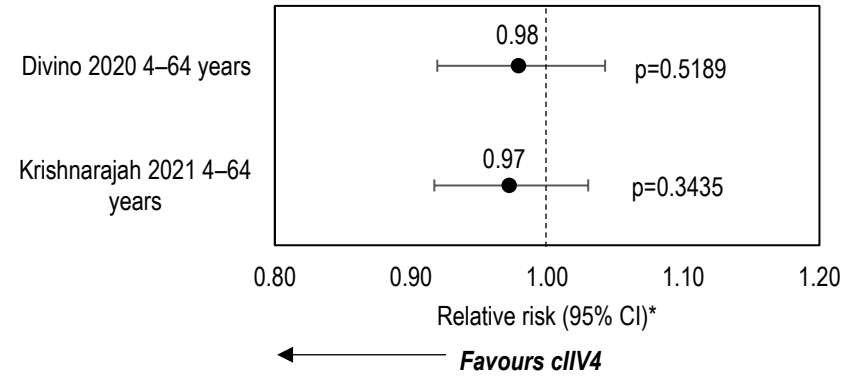
Patient or population: Adults aged 18–64 years
Intervention: Cell-based influenza vaccine (cIIV)
Comparison: Standard egg-based influenza vaccine (eIIV)

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
continued **Influenza-related hospitalisations ED visits (no laboratory confirmation)** Assessed with: ICD-9 487.x, 488.x, ICD-10 J09x-J11x 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 high-risk population**  Note: Divino 2022 follow-up period was truncated to 7 months due to the COVD-19 pandemic. Total participants = 2,352,810 (3 observational studies)[3-5]		⊕⊕◯◯ Low[a,c,d]	Cell-based influenza vaccine may reduce influenza-related hospitalisations or ED visits slightly compared with standard egg-based influenza vaccine in the high-risk population.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years

Patient or population: Adults aged 18–64 years
Intervention: Cell-based influenza vaccine (cIIV)
Comparison: Standard 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-code for pneumonia in any diagnosis position 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 (2022) follow-up period was truncated to approximately 7 months due to the COVD-19 pandemic. Total participants = 2,352,810 (3 observational studies)[3-5]	Population: 2,229,559 Population: 1,076,684 Population: 2,814,140 Population: 5,074,953	⊕⊕⊕◯ Moderate[a,d]	Cell-based influenza vaccine likely results in little to no difference in pneumonia-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 adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard 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-code for pneumonia in any diagnosis position Follow-up: range 14 days to 12 months	**Relative vaccine effectiveness of cIIV vs eIIV against ICD-coded pneumonia hospitalisations/ED visits in the high risk population**  Total participants = 1,337,665 (2 observational studies)[3,4]	Population: 610,556 Population: 727,109	⊕⊕◯◯ Low[a,c,d]	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.

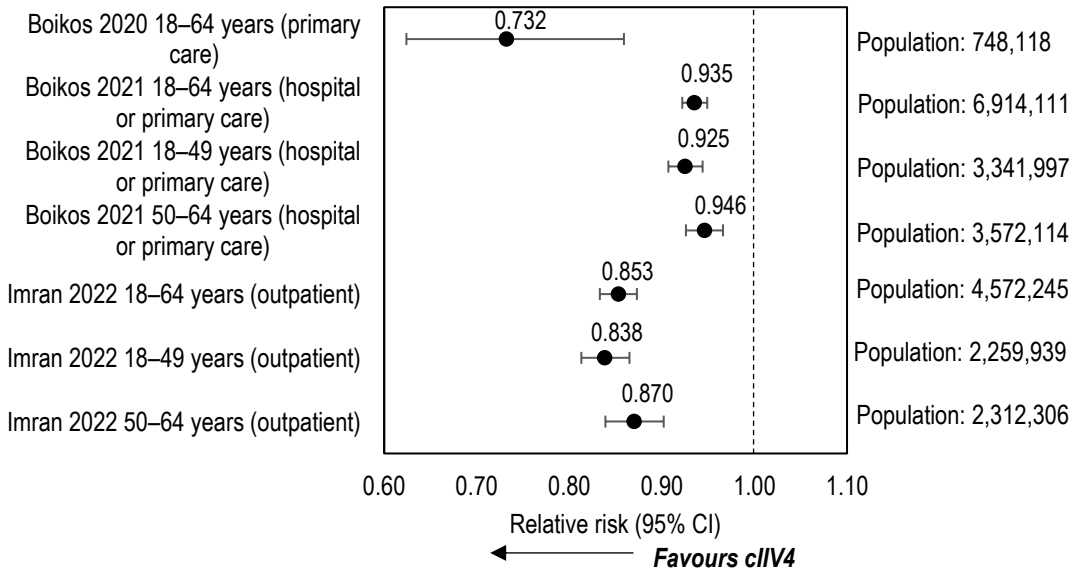
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Serious adverse events (SAEs) Assessed with: patient report, medically attended AE or withdrawal from study due to AE Follow-up: range 1 days to 6 months	Ambrozaitis 2009, 18–60 years; Szymczakiewicz-Multanowska 2009, 18–60 years: No vaccine related SAEs were reported in any of the studies.	3825 (2 randomised controlled trials [RCTs])[7,8]	⨁⨁⨁⨁ 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 adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
SAE – Guillain-Barrè 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 2021, aged ≥6 months: **Guillain-Barrè syndrome (GBS)** Adjusted reporting odds ratio (ROR; 95% CI) cQIV 15.00 (9.27–24.20) egg-culture 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]	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)[9]	⊕◯◯◯ Very low[b,e]	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 months, it is unclear if/how many children aged <18 years were included in final analysis. The results are likely primarily derived from the adult population.**

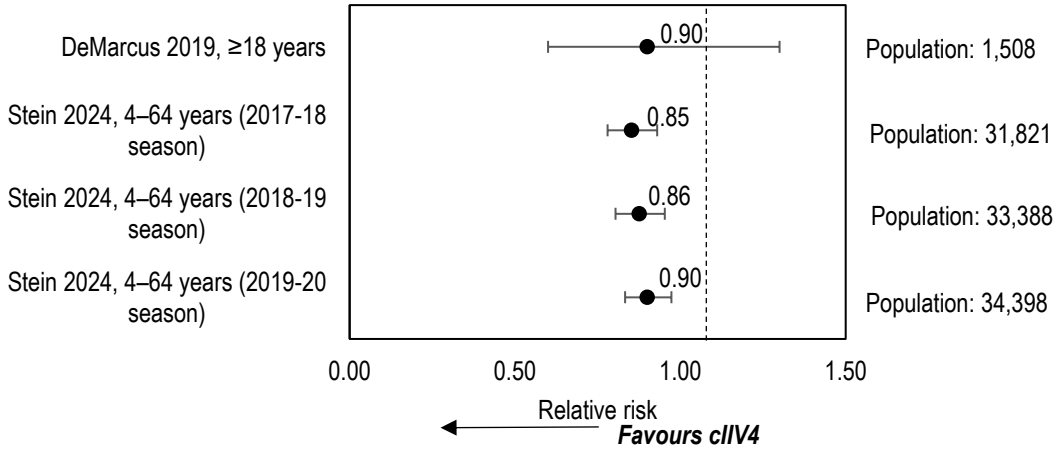
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
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 vaccines Follow-up: 130 days	Fujimori 2022, aged >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)[10]	⨁◯◯◯ Very low[b,e]	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: 49% of the population included for analysis in the VAERS dataset were adults aged 18–64 years. However, this single study presents results based on very small case event (ADEM) 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 adults aged 18–64 years

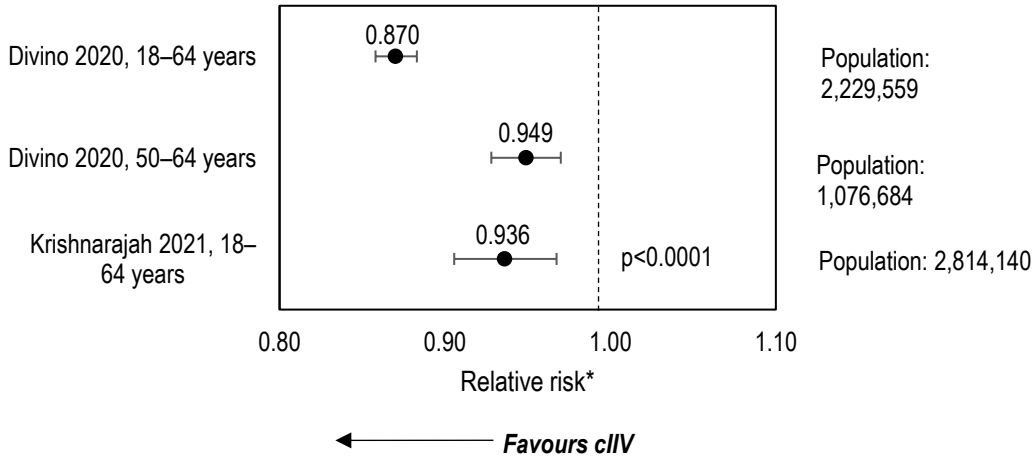
Patient or population: Adults aged 18–64 years
Intervention: Cell-based influenza vaccine (cIIV)
Comparison: Standard egg-based influenza vaccine (eIIV)

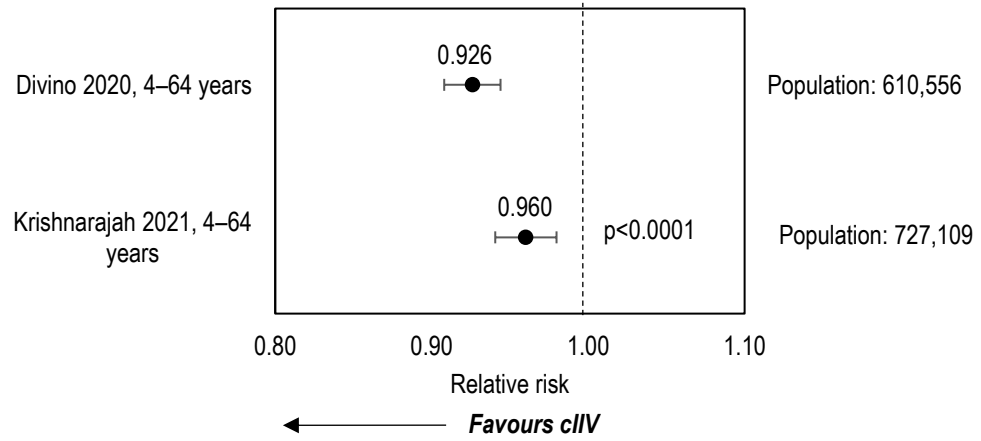
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
IMPORTANT OUTCOMES				
Influenza-related medical encounter (IRME) in hospital, outpatient or primary care setting Assessed with: ICD-10 codes J09x-J11x in any diagnosis position Follow-up: range 14 days to 9.5 months	**Relative vaccine effectiveness of cIIV vs eIIV against IRME in the general population**  Note: Follow up time varied across studies – Boikos 2020, 8 months; Boikos 2021, 9.5 months; Imran 2022, 7 months. Total participants = 12,234,474 (3 observational studies)[6,11,12]		⊕⊕⊕◯ Moderate[a,f]	Cell-based influenza vaccine likely reduces in influenza-related medical encounters (IRMEs) in the hospital, outpatient or primary care setting compared with standard egg-based influenza vaccine.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard 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 codes J09x-J11x in any diagnosis position Follow-up: range 14 days to 9.5 months	**High-risk population:** Boikos (2021) 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)[13]	⨁⨁⨁◯ Moderate[a,d]	Cell-based influenza vaccine likely reduces IRMEs in the hospital or primary care setting compared with standard egg-based influenza vaccine.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard 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 influenza-like illness (ILI) in outpatient setting Follow-up: range 14 days to 7.5 months	**Relative vaccine effectiveness (shown as relative risk) of cIIV vs eIIV against test-confirmed influenza in outpatient setting among adults 18–64 years**  Note 1: Demarcus 2019; influenza confirmed by PCR or viral culture; compared cIIV4 vs eIIV3/eIIV4; follow-up period 7 months. Note 2: Stein 2024; 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 = 101,115 (2 observational studies)[14,15]		⊕⊕◯◯ Low[a,b,f]	Cell-based influenza vaccine may result in a slight reduction in test-confirmed influenza compared with standard egg-based influenza vaccine.

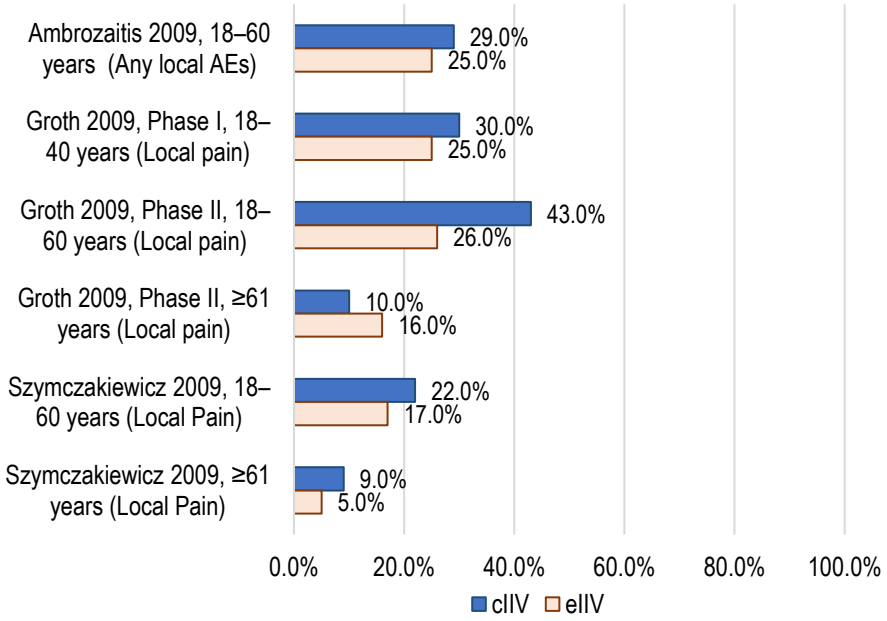
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
PCR-confirmed influenza A Assessed with: positive PCR test result for influenza A (GeneXpert PCR assay) Follow-up: range 7 days to 6 months	Klein (2020), 18–64 years: rVE cIIV4 vs eIIV3/4 18–64 years −5.8% (−36.1%–17.7%)	941585 (1 observational study)[16]	⨁◯◯◯ Very low[a,c]	Cell-based influenza vaccine may result in no 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) Follow-up: range 7 days to 6 months	Klein (2020), 18–64 years: rVE cIIV4 vs eIIV3 18–64 years 21.4% (−7.3%–42.4%)	941585 (1 observational study)[16]	⨁◯◯◯ Very low[a,c]	Cell-based influenza vaccine may result in a reduction in PCR confirmed influenza B compared with standard egg-based influenza vaccine; however, the evidence is very uncertain.

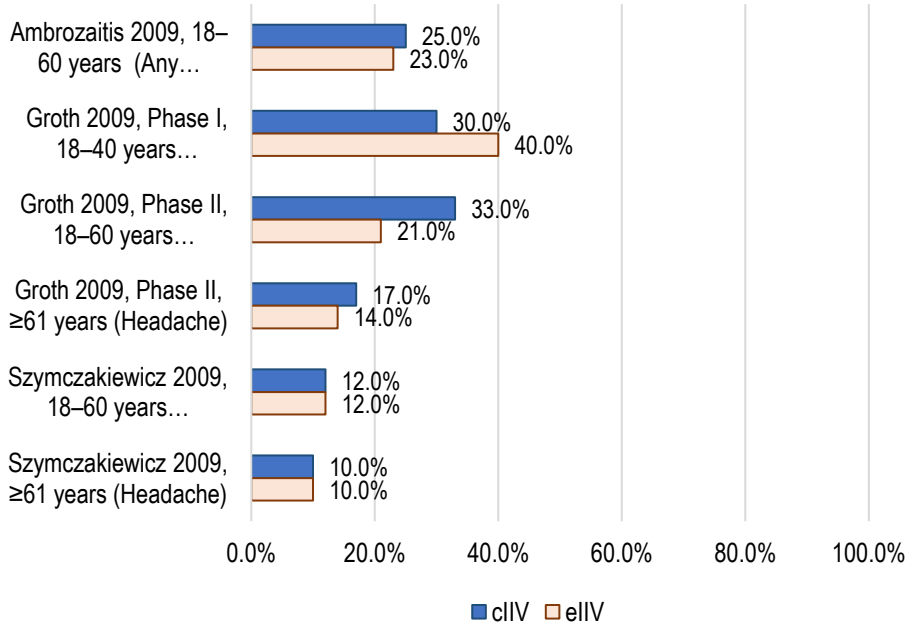
Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard egg-based influenza vaccine (eIIV)				
Outcomes	**Impact**	**№ of 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 (shown as relative risk) of cIIV vs eIIV against all-cause hospitalisations/ED, in the general population, inclusive of adults 18–64 years**  Total participants = 5,043,699 (2 observational studies)[3,4]		⊕⊕⊕◯ Moderate[a]	Cell-based influenza vaccine likely results 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 adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard 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 (shown as relative risk) of cIIV vs eIIV against all-cause hospitalisations/ED, in the high risk population, inclusive of adults 18–64 years**  Total participants = 1,337,665 (2 observational studies)[3,4]		⊕⊕⊕◯ Moderate[a,d]	Cell-based influenza vaccine likely results 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 adults aged 18–64 years

Patient or population: Adults aged 18–64 years
Intervention: Cell-based influenza vaccine (cIIV)
Comparison: Standard egg-based influenza vaccine (eIIV)

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited local AE Assessed with: diary Follow-up: range 1 days to 7 days	**Solicited local adverse events of cIIV vs eIIV in adults 18–64 years**  Note: All studies shown compared cIIV with eIIV for three virus strains Total participants = 4,105 (3 RCTs)[7,8,17]		⊕⊕⊕⊕ High	Cell-based influenza vaccine increases local adverse events slightly compared with standard egg-based influenza vaccine.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years				
Patient or population: Adults aged 18–64 years **Intervention:** Cell-based influenza vaccine (cIIV) **Comparison:** Standard 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 days to 7 days	**Solicited systemic adverse events in adults aged 18–64 years**  Note: All studies shown compared cIIV with eIIV for three virus strains Total participants = 4,105 (3 RCTs)[7,8,17]		⊕⊕⊕⊕ High	Cell-based influenza vaccine results in little to no difference in systemic adverse events compared with standard egg-based influenza vaccine.

Cell-based influenza vaccine compared with standard egg-based influenza vaccine in adults aged 18–64 years

Patient or population: Adults aged 18–64 years
Intervention: Cell-based influenza vaccine (cIIV)
Comparison: Standard 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. Not downgraded for indirectness as adults account for high proportion of overall cohort.
e. Risk of bias judgement = serious – due to confounding and methodologic issues.
f. With the addition of new studies, the effect estimates are more precise. Non-significance of CIs is no longer an issue.

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: ADEM=acute disseminated encephalomyelitis; AE=adverse event; CI=confidence interval; ED=emergency department; IRME=influenza-related medical encounters; OR=odds ratio; RCT=randomised controlled trial; ROR=reporting odds ratio; RR=risk 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: We have limited confidence in the effect estimate: 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 adults aged 18–64 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)									
2	Observational studies	Serious[a]	Serious	Serious[b]	Very serious[c]	None	rVE (95% CI): **Bruxvoort et al (2019) 4–64 years:** 43% (−45–77) **Martin et al (2021) ≥18 years:** 8.5% (−75.9–52.3) [1,2]	⨁◯◯◯ 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 J09x-J11x in any diagnostic field)									
4	Observational studies	Serious[a]	Not serious	Not serious	Not serious	None	**General population** rVE (95% CI): **Divino et al (2020) 18–64 years:** 13.1% (6.8–19.0) **Divino et al (2020) 50–64 years:** 9.4% (0.3–17.6) **Krishnarajah et al (2021) 18–64 years:** 4.94% p=0.2024 **Divino et al (2022) 4–64 years:** 5.3% (0.5–9.9) **Imran et al (2022) 18–64 years:** 5.8% (1.9–9.5) **Imran et al (2022) 18–49 years:** 6.6% (1.6–11.3) **Imran et al (2022) 50–64 years:** 5.2% (−0.9–11.1)[3-6]	⨁⨁⨁◯ 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 J09x-J11x in any diagnostic field)									
3	Observational studies	Serious[a]	Not serious	Not serious[d]	Serious[c]	None	**<u>High risk population</u>** rVE (95% CI): **Divino et al (2020), 4–64 years:** 10.1% (1.1–18.2) **Krishnarajah et al (2021), 4–64 years:** 0.9% (no CI); p=0.8611 **Divino et al (2022), 4–64 years:** 10.5% (2.9–17.5) [3-5]	⨁⨁◯◯ 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 code for pneumonia in any diagnostic position)									
3	Observational studies	Serious[a]	Not serious	Not serious[d]	Not serious	None	**General population** rVE (95% CI): **Divino et al (2020), 18–64 years:** 0.2% (no CI); p=0.9249 **Divino et al (2020), 50–64 years:** −0.4% (no CI); p=0.8985 **Krishnarajah et al (2021), 18–64 years:** 2.61% (no CI); p=0.2617 **Divino et al (2022), 4–64 years:** 6.7% (2.1–11.1) 3-5	⨁⨁⨁◯ Moderate	CRITICAL
Pneumonia-related hospitalisations or ED visits [no laboratory confirmation] (follow-up: range 14 days to 12 months; assessed with: ICD-10 code for pneumonia in any diagnostic position)									
2	Observational studies	Serious[a]	Not serious	Not serious[d]	Serious[c]	None	**High-risk population** rVE (95% CI): **Divino et al (2020), 4–64 years:** 2.1% (no CI); p=0.5189 **Krishnarajah et al (2021), 4–64 years:** 2.8% (no CI); p=0.3435 3,4	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
SAE (follow-up: range 1 days to 6 months; assessed with: patient report, medically attended AE or withdrawal from study due to AE)									
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	**Ambrozaitis et al (2009), 18–60 years; Szymczakiewicz-Multanowska et al (2009), 18–60 years** No vaccine-related SAE in studies [7,8]	⨁⨁⨁⨁ High	CRITICAL
SAE – Guillain-Barrè 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[e]	Not serious	Serious[b]	Not serious	None	**Fujimori et al (2021), aged >6 months: Guillain-Barrè 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)[9]	⨁◯◯◯ 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: 10 years; assessed with: reports of ADEM in VAERS and identified by a preferred-term code among recipients of cell-based or egg-based influenza vaccines)									
1	Observational studies	Very serious[d]	Not serious	Serious[b]	Not serious	None	**Fujimori & Nakamura (2022), aged >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.[10]	⨁◯◯◯ 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 primary care or outpatient setting (follow-up: range 14 days to 9.5 months; assessed with: ICD-10 codes J09x-J11x in any diagnostic position)									
3	Observational studies	Serious[a]	Not serious	Not serious	Not serious[f]	None	**General population** rVE% (95% CI): **Boikos et al (2020), 18–64 years:** 26.8% (14.1–37.6) **Boikos et al (2021), (1) 18–64 years:** 6.5% (5.1–7.8) **Boikos et al (2021), (1) 18–49 years:** 7.5% (5.6–9.3) **Boikos et al (2021), (1) 50–64 years:** 5.4% (3.4–7.4) **Imran et al (2022), 18–64 years:** 14.7% (12.7–16.7) **Imran et al (2022), 18–49 years:** 16.2% (13.5–18.7) **Imran et al (2022), 50–64 years:** 13.0% (9.8–16.1) 6,11,12	⊕⊕⊕◯ Moderate	IMPORTANT
Influenza-related medical encounter (IRME) in primary care or outpatient setting (follow-up: range 14 days to 9.5 months; assessed with: ICD-10 codes J09x-J11x in any diagnostic position)									
1	Observational studies	Serious[a]	Not serious	Not serious[d]	Not serious	None	**High-risk population** rVE% (95% CI): **Boikos et al (2021) (2), 4–64 years:** 13.4% (11.4–15.4) 13	⊕⊕⊕◯ Moderate	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[f]	None	Relative risk (95% CI): **DeMarcus et al (2019) 6 months – 17 years (PCR or culture)** (Odds ratio) 0.9 (0.6–1.3) **Stein (2024), 4–64 years (2017–18 season; any positive test)** 0.852 (0.78–0.93) **Stein (2024), 4–64 years (2018–19 season; any positive test)** 0.875 (0.804–0.953) **Stein (2024), 4–64 years (2019–20 season; any positive test)** 0.9 (0.833–0.973) [14,15]	⨁◯◯◯ Very 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])									
1	Observational studies	Serious[a]	Not serious	Not serious	Very serious[c]	None	**Klein et al (2020) 18–64 years:** cIIV4 vs eIIV3/4 rVE (95% CI): −5.8% (−36.1%–17.7%) [16]	⨁◯◯◯ Very low	IMPORTANT
PCR confirmed influenza B (follow-up: range 7 days to 6 months; assessed with: positive PCR test result for influenza B (GeneXpert PCR assay))									
1	Observational studies	Serious[a]	Not serious	Not serious	Very serious[c]	None	**Klein et al (2020) 18–64 years:** cIIV4 vs eIIV3 rVE (95% CI): 21.4% (−7.3%–42.4%) [16]	⨁◯◯◯ Very low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
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	Not serious	None	**General population** rVE% (95% CI): **Divino et al (2020) 18–64 years:** 13.0% (11.7–14.2) **Divino et al (2020) 50–64 years:** 5.1% (3.0–7.2) **Krishnarajah et al (2021) 18–64 years:** 6.4% (no CI); p<0.0001 3,4	⨁⨁⨁◯ 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[d]	Not serious	None	**High risk population:** rVE% (95% CI): **Divino et al (2020) 4–64 years:** 7.4% (5.6–9.2) **Krishnarajah et al (2021) 4–64 years:** 4.0% (no CI); p<0.0001 3,4	⨁⨁⨁◯ Moderate	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)									
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	cIIV vs eIIV (% frequency of AE) **Ambrozaitis et al (2009) 18–60 years:** Any local AE: 29% vs 25% **Groth et al (2008) 18–40 years:** Local AE – pain: 30% vs 25% **Groth et al (2008) 18–60 years:** Local AE – pain: 43% vs 26% **Groth et al (2008) ≥61 years:** Local AE - pain: 10% vs 16% **Szymczakiewicz-Multanowska et al (2009) 18–60 years:** Local AE – pain: 22% vs 17% **Szymczakiewicz-Multanowska et al (2009) >=61 years:** Local AE – pain: 9% vs 5% [7,8,17]	⊕⊕⊕⊕ 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)									
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	cIIV vs eIIV (% frequency of AE) **Ambrozaitis et al (2009) 18–60 years:** Any systemic reaction: 25% vs 23% **Groth et al (2008) 18–40 years:** Systemic AE – headache: 30% vs 40% **Groth et al (2008) 18–60 years:** Systemic AE – headache:33% vs 21% **Groth et al (2008) ≥61 years:** Systemic AE – headache: 17% vs 14% **Szymczakiewicz-Multanowska et al (2009) 18–60 years:** Systemic AE – headache: 12% vs 12% **Szymczakiewicz-Multanowska et al (2009) ≥61 years:** Systemic AE – headache: 10% vs 10% [7,8,17]	⊕⊕⊕⊕ High	IMPORTANT

Evidence to decision framework: individual perspective

PICO Question	
Population	Adults aged 18–64 years
Intervention	Cell-based inactivated influenza vaccine (cIIV)
Comparison	Standard dose egg-based inactivated influenza vaccines (eIIV)
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 • Systemic adverse events • Serious adverse events (SAE)
Setting	Global middle-high-income settings (e.g. Europe, Canada, 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).[18-21] 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).[20]
- 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.[22,23]

Undesirable Effects
How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- There is a slightly higher frequency of local AEFI following cIIV compared with eIIV. However, the 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[9] and ADEM[10] 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 with eIIV and undesirable effects of cIIV are at least comparable with eIIV.

Certainty of evidence
What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- Certainty of evidence on the effectiveness outcomes of cIIV was downgraded because of the risk of bias due to potential confounding, with outcomes having generally low to moderate certainty of evidence. The impact of egg-adaptation reported during the 2017/18 season may have influenced rVE for some studies.
- Most evidence on safety outcomes was of high certainty with the exception of the two studies by Fujimori[9,10] where results should be interpreted with caution.

Values
I*s 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 adults aged 18–64 years					
Justification and considerations					
1. The panel recognises there is variability in the evidence, with some evidence indicating cIIV may be slightly favourable compared to eIIV in reducing a range of influenza-related outcomes. Overall, there is low-moderate strength evidence to demonstrate that cIIV is more protective than eIIV against some critical endpoints of severe influenza (eg influenza related hospitalisations), and there is moderate strength evidence that cIIV may be more protective than eIIV against non-critical endpoints of milder disease (eg IRME). However, the magnitude of benefit was small and varied between studies. 2. Compared with eIIV, cIIV results in a small increase in local adverse events, but little to no difference in systemic adverse events, serious adverse events or adverse events of special interest. 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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