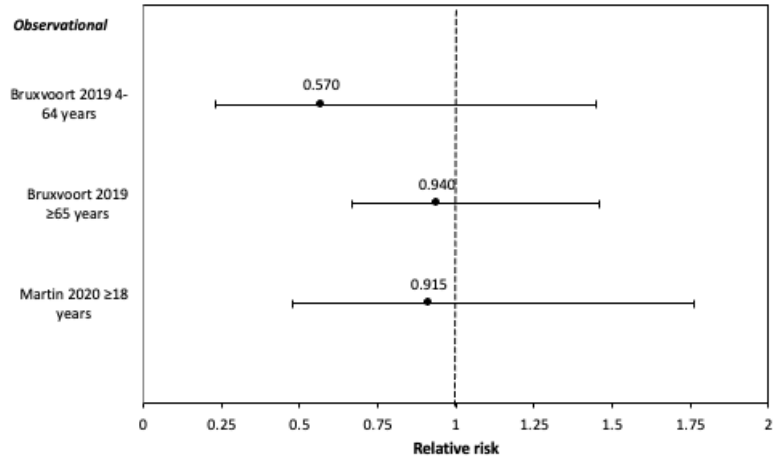
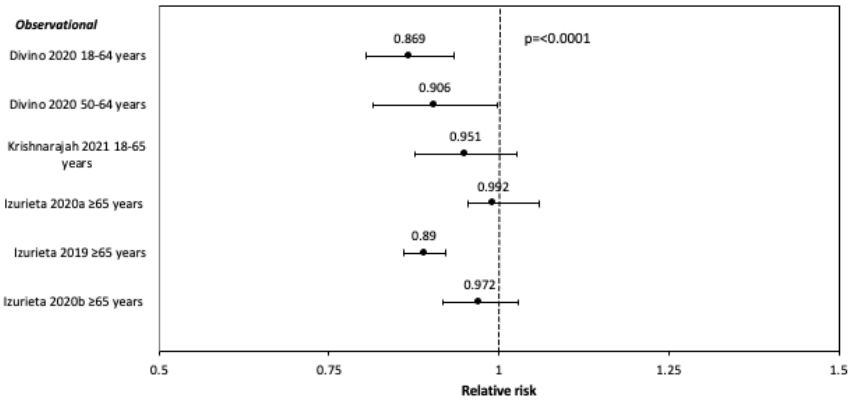
NCIRS is conducting GRADE in support of ATAGI and making results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook Influenza Chapter and the ATAGI Annual Influenza Statement.

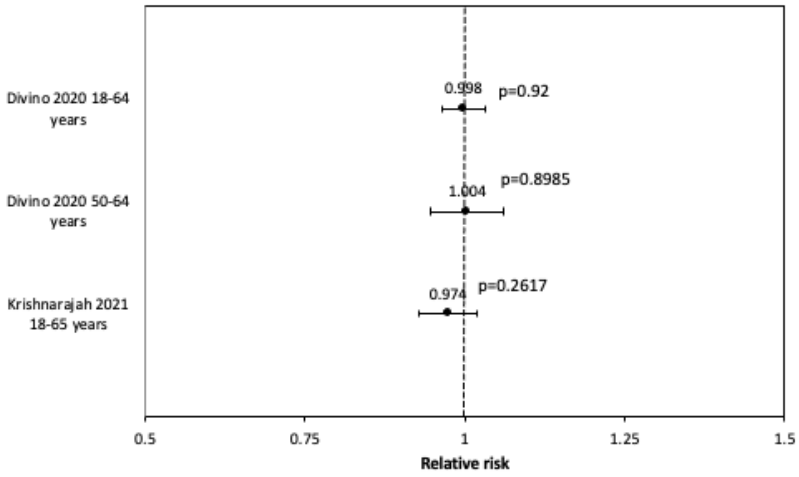
Summary of findings: MDCK cell-derived influenza vaccine compared to standard dose egg-based influenza vaccine in people aged ≥18 years

Patient or population: people aged ≥18 years
Intervention: MDCK cell-derived influenza vaccine (cIV)
Comparison: standard dose egg-based influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (cIV vs sIV) (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cIV	Risk with sIV				
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 6 months				Population: 1,816 Population: 3,655 Population: 1,741	⊕◯◯◯ VERY LOW [a,b]	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 Ref: 1,13
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 follow up: range 14 days to 6 months				Population: 2,200,846 Population: 1,062,161 Population: 2,812,176 Population: 2,207,867 Population: 2,497,844 Population: 2,387,386	⊕⊕◯◯ LOW [a, b]	Cell-based influenza vaccine may slightly reduce influenza-related hospitalisations or ED visits compared to standard egg-based influenza vaccine Ref: 2-5,14 Note: the 95%CI values are derived from the p-value for studies where the p-value is shown

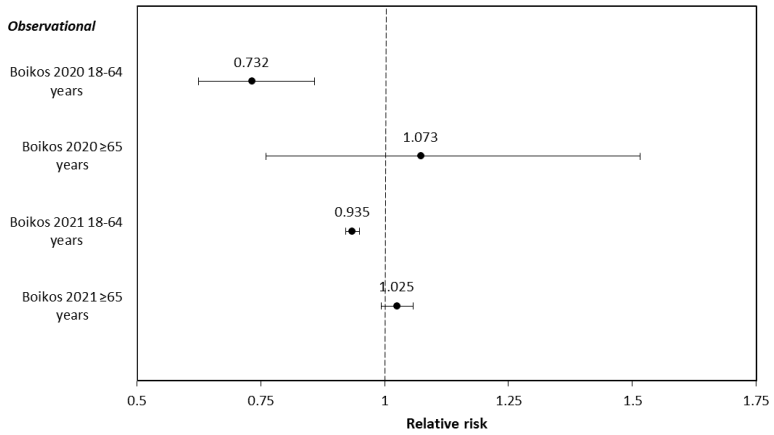
Summary of findings: MDCK cell-derived influenza vaccine compared to standard dose egg-based influenza vaccine in people aged ≥18 years

Patient or population: people aged ≥18 years
Intervention: MDCK cell-derived influenza vaccine (cIV)
Comparison: standard dose egg-based influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (cIV vs sIV) (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cIV	Risk with sIV				
Pneumonia-related hospitalisations or ED visits (no laboratory confirmation) assessed with: diagnosis code in any position for pneumonia follow up: range 14 days to 6 months				Population: 2,200,846 Population: 1,062,161 Population: 2,812,176	⨁⨁◯◯ LOW [a,b]	Cell-based influenza vaccine may result in little to no difference in pneumonia-related hospitalisations or ED visits compared to standard egg-based influenza vaccine Ref: 2,3 Note: the 95%CI values are derived from the p-value for studies where the p-value is shown
Serious adverse events (SAE) assessed with: patient monitoring and active follow up follow up: up to 6 months	**Guillain–Barré syndrome (GBS)** **Adjusted reporting odds ratio (95%CI)** cQIV 15.00 (9.27–24.20)* HD-TIV, SD-TIV, QIV, aTIV = 1.99 (1.28–3.10)			36,227 (1 Observational study)	⨁◯◯◯ VERY LOW	Cell-based influenza vaccines may result in an increase in GBS compared with standard egg-based influenza vaccine but the evidence is very uncertain Ref: 15
	No vaccine-related SAEs were reported in the studies			3825 (2 RCTs)	⨁⨁⨁⨁ HIGH	Cell-based influenza vaccine results in little to no difference in other serious adverse events compared with standard egg-based influenza vaccine Ref: 10,11

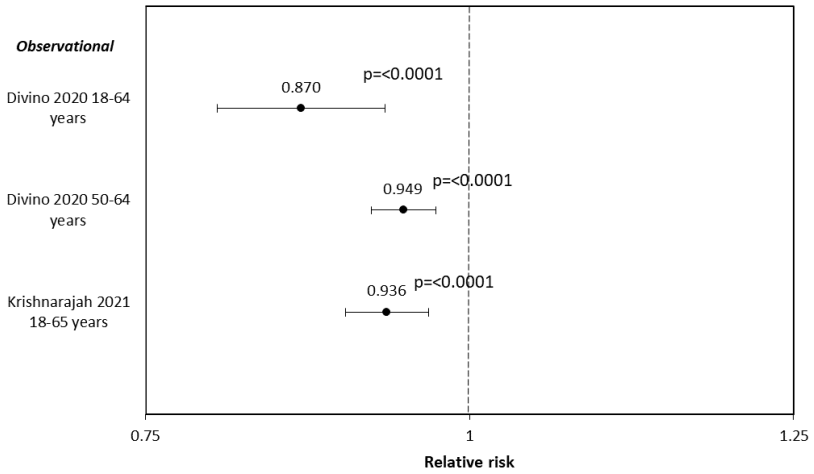
Summary of findings: MDCK cell-derived influenza vaccine compared to standard dose egg-based influenza vaccine in people aged ≥18 years

Patient or population: people aged ≥18 years
Intervention: MDCK cell-derived influenza vaccine (cIV)
Comparison: standard dose egg-based influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (cIV vs sIV) (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cIV	Risk with sIV				
IMPORTANT OUTCOMES						
Influenza-like illness (ILI) assessed with: diagnostic codes in subject primary care EMR database (ICD-10 codes: J09*–J11*) follow up: range 14 days to 6 months				Population: 748,118 Population: 193,769 Population: 6,914,111 Population: 1,505,582	⨁◯◯◯ VERY LOW [b, e]	Cell-based influenza vaccine may reduce Influenza-like illness (ILI) slightly compared with standard egg-based influenza vaccine in 18–64 year olds, and may provide little to no difference compared with sIV in adults aged >65 years. However, the evidence is very uncertain. Ref: 6,7
RT-PCR or culture-confirmed influenza assessed with: positive RT-PCR or viral culture from specimens from people with ILI follow up: range 14 days to 6 months	rVE odds ratio cIV4 vs sIV4 **≥18 years** 0.9 (95% CI 0.6-1.3)			1508 (1 observational study)	⨁◯◯◯ VERY LOW [b,e]	Cell-based influenza vaccine may result in little to no difference in RT-PCR or culture-confirmed influenza compared with standard egg-based influenza vaccine but the evidence is very uncertain Ref: 8
PCR-confirmed influenza A assessed with: positive PCR test result for influenza A (GeneXpert PCR assay) follow up: range 7 days to 6 months	rVE cIV4 vs sIV3/4 **18–64 years** -5.8% (-36.1%-17.7%)			941585 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	Cell-based influenza vaccine may result in little to no difference in PCR-confirmed influenza A compared with standard egg-based influenza vaccine; however, the evidence is very uncertain Ref: 9

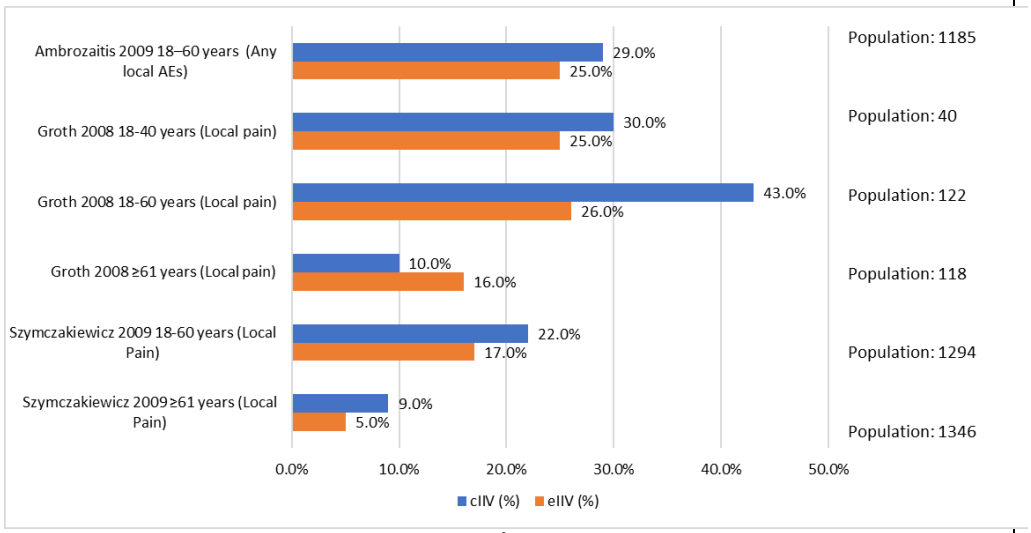
Summary of findings: MDCK cell-derived influenza vaccine compared to standard dose egg-based influenza vaccine in people aged ≥18 years

Patient or population: people aged ≥18 years
Intervention: MDCK cell-derived influenza vaccine (cIV)
Comparison: standard dose egg-based influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (cIV vs sIV) (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cIV	Risk with sIV				
PCR-confirmed influenza B assessed with: positive PCR test result for influenza B (GeneXpert PCR assay) follow up: range 7 days to 6 months	rVE cIV4 vs sIV3 **18–64 years** 21.4% (-7.3%-42.4%)			941585 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	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 Ref: 9 Note: This comparison was between a quadrivalent cIV and a trivalent eIV
All cause hospitalisation or ED visit assessed with: database entry for hospitalisation or ED visit follow up: range 14 days to 6 months				Population: 2,200,846 Population: 1,062,161 Population: 2,812,176	⨁⨁⨁◯ MODERATE [a]	Cell-based influenza vaccine likely reduces all cause hospitalisation or ED visit slightly compared with standard egg-based influenza vaccine Ref: 2,3 Note: the 95%CI values are derived from the p-value for studies where the p-value is shown

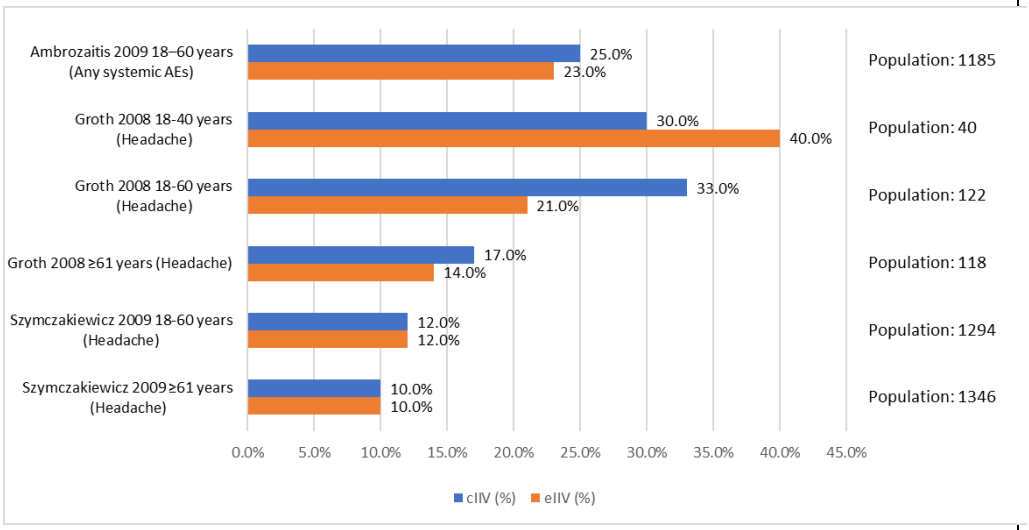
Summary of findings: MDCK cell-derived influenza vaccine compared to standard dose egg-based influenza vaccine in people aged ≥18 years

Patient or population: people aged ≥18 years
Intervention: MDCK cell-derived influenza vaccine (cIV)
Comparison: standard dose egg-based influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (cIV vs sIV) (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cIV	Risk with sIV				
Solicited local adverse events assessed with: diaries follow up: up to 7 days for solicited AEs	 f			⊕⊕⊕⊕ HIGH	Cell-based influenza vaccine increases local adverse events slightly compared with standard egg-based influenza vaccine 3 RCTs [10,11,12]

Summary of findings: MDCK cell-derived influenza vaccine compared to standard dose egg-based influenza vaccine in people aged ≥18 years

Patient or population: people aged ≥18 years
Intervention: MDCK cell-derived influenza vaccine (cIV)
Comparison: standard dose egg-based influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (cIV vs sIV) (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cIV	Risk with sIV				
Solicited Systemic adverse events assessed with: diaries follow up: up to 7 days for solicited AEs	 g			⊕⊕⊕⊕ HIGH	Cell-based influenza vaccine results in little to no difference in systemic adverse events compared to standard egg-based influenza vaccine 3 RCTs [10,11,12]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **rVE:** relative vaccine effectiveness

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

Explanations

a. Risk of bias judgement = moderate - due to confounding
b. Wide confidence intervals
c. Risk of bias judgement = serious - due to potential confounding
d. Not lab confirmed influenza
e. Risk of bias judgement = serious - due to potential confounding
f Estimates shown for “any local AE” or if not available most frequently reported local AE
g Estimates shown for “any systemic AE” or if not available most frequently reported systemic AE

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Evidence profile: Cell-based influenza vaccine compared with standard egg-based influenza vaccine for people aged ≥18 years

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other consider-ations	cIV	sIV	Relative (95% CI)	Absolute (95% CI)	
CRITICAL OUTCOMES											
Laboratory-confirmed influenza hospitalisation (follow up: range 21 days to 6 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]	not serious	not serious	very serious [b]	none	Bruxvoort 2019:[1] rVE cIV4 vs sIV4 **ages < 65 years** 43% (95% CI: -45 to 77) **≥ 65 years old** 6% (95% CI: -46 to 39) Martin 2020:[13] rVE cIV4 vs sIV4 **≥ 18 years old** 8.5 (95% CI: −75.9 to 52.3), p=0.79			⨁◯◯◯ VERY LOW
Influenza-related hospitalisations or ED visits (no laboratory confirmation) (follow up: range 14 days to 6 months; assessed with: ICD-9 487.x, 488.x, ICD-10 J09.x, J10.x, J11.x)											
5	observational studies	serious [a]	not serious	not serious	serious [b]	none	Divino 2020:[2] Adjusted rVE cIV4 vs sIV4 **18-64 years** 13.1 % p=<0.0001 **50-64 years** 9.4% p=0.0429 Krishnarajah 2021:[3] Adjusted rVE cIV4 vs sIV4 **18-64 years** 4.94 % p=0.2024 Izurieta 2020a:[5] QIV-SD as reference rVE **≥65 years** 0.8 % (CI -4.6-5.9) **Izurieta 2019:**[4] QIV (egg) as the reference group Adjusted rVE **≥65 years** 11% (95% CI: 7.9-14%) Izurieta 2020b:[14] **≥65 years** QIV (egg) (ref) vs QIV (cell): 2.8 (95% CI: −2.8, 8.2)			⨁⨁◯◯ LOW
Pneumonia-related hospitalisations or ED visits (no laboratory confirmation) (follow up: range 14 days to 6 months; assessed with: diagnosis code in any position for pneumonia)											
2	observational studies	serious [a]	not serious	not serious	serious [c]	none	Divino 2020:[2] Adjusted rVE cIV4 vs sIV4 **18-64 years** 0.2% p=0.92 **50-64 years** -0.4% p=0.8985 Krishnarajah 2021:[3] Adjusted rVE cIV4 vs sIV4 18-64 years 2.61% p=0.2617			⨁⨁◯◯ LOW
Serious adverse events (SAE) (follow up: up to 6 months; assessed with: patient monitoring and follow up)											
2	randomised trials	not serious	not serious	not serious	not serious	none	All studies reported similar SAEs in both arms. Most studies did not report any SAEs in either group.[10,11]				⨁⨁⨁⨁ HIGH

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other consider-ations	cIV	sIV	Relative (95% CI)	Absolute (95% CI)	
IMPORTANT OUTCOMES											
Influenza like illness (ILI) (follow up: range 14 days to 6 months; assessed with: diagnostic codes in subject primary care EMR database (ICD-10 codes: J09*–J11*))											
2	observational studies	very serious [e]	not serious	not serious	serious [b]	none			Boikos 2020:[6] rVE cIV4 vs sIV4 **Age 18-64** 26.8% (14.1% - 37.6%) **Age >=65** -7.3% (-51.6% - 24%) Boikos 2021:[7] rVE cIV4 vs sIV4 **Age 18-64** 6.5% (5.1%-7.8%) **Age >=65** -2.5% (-5.7% - 0.7%)	⨁◯◯◯ VERY LOW
RT-PCR or culture confirmed influenza (follow up: range 14 days to 6 months; assessed with: positive RT-PCR or viral culture from specimens from people with ILI)											
1	observational studies	very serious [e]	not serious	not serious	not serious	none			DeMarcus 2019:[8] rVE odds ratio cIV4 vs sIV4 **Adults** 0.9 (95% CI 0.6-1.3)	⨁⨁◯◯ LOW
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 [b]	none			Klein 2020:[9] rVE cIV4 vs sIV3/4 **18–64 years old** -5.8% (-36.1%-17.7%)	⨁◯◯◯ VERY LOW
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 [b]	none			Klein 2020:[9] rVE cIV4 vs sIV3 **18–64 years old** 21.4% (-7.3%-42.4%)	⨁◯◯◯ VERY LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other consider-ations	cIV	sIV	Relative (95% CI)	Absolute (95% CI)	
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	not serious	not serious	none	Divino 2020:[2] Adjusted rVE cIV4 vs sIV4 **18-64 years** 13.0% p=<0.0001 **50-64 years** 5.1% p=<0.0001 Krishnarajah 2021:[3] Adjusted rVE cIV4 vs sIV4 **18-64 years** 6.37% p=<0.0001			⊕⊕⊕◯ MODERATE
Local adverse events (follow up: up to 7 days for solicited AEs and up to 6 months for unsolicited AEs; assessed with: Diaries)											
3	randomised trials	not serious	not serious	not serious	not serious	none	Ambrozaitis 2009:[10] **Any Local reaction** **18–60 years** cIV3=27-31%, sIV3=25% Groth 2008:[12] **Local reaction: Pain** Phase I **18-40 years** cIV3=30%, sIV3=25% phase II **18-60 years** cIV3=43%, sIV3=26% **>=61 years** cIV3=10%, sIV3=16% Szymczakiewicz 2009:[11] **Local reaction: Pain** **18-60 years** cIV3 =22%, sIV3= 17% **>=61 years** cIV3 =9%, sIV3 =5%			⊕⊕⊕⊕ HIGH
Systemic adverse events (follow up: up to 7 days for solicited AEs and up to 6 months for unsolicited AEs; assessed with: diaries)											
3	randomised trials	not serious	not serious	not serious	not serious	none	Ambrozaitis 2009:[10] **Any Systemic reaction** **18–60 years** cIV3=24-26%. sIV3=23% Groth 2008:[12] **Systemic reaction: Headache** Phase I **18-40 years** cIV3=30%, sIV3=40% phase II **18-60 years** cIV3=33%, sIV3=21% **>=61 years** cIV3=17%, sIV3=14% Szymczakiewicz 2009:[11] **Systemic reactions: Headache** **18-60 years** cIV3 =12%, sIV3= 12% **>=61 years** cIV3 =10%, sIV3 =10%			⊕⊕⊕⊕ HIGH
1	Observational study	Very Serious	Not serious	serious	Not serious	none	Fujimori 2021:[15] Guillain–Barré syndrome **Adjusted reporting odds ratio (95%CI)** 0.5-59 years: cQIV 15.00 (9.27–24.20)* HD-TIV, SD-TIV, QIV, aTIV = 1.99 (1.28–3.10)			⊕◯◯◯ VERY LOW

a. Risk of bias judgement = moderate - due to confounding
b. Wide confidence intervals
c. Non-statistically significant results
d. Not lab confirmed influenza
e. Risk of bias judgement = serious - due to potential confounding

Evidence to Decision Framework: Individual perspective

Patients: 18 years of age and older

Intervention: Cell-based influenza vaccine (cIV)

Comparison: Standard dose egg-based influenza vaccines (sIV)

Main outcomes:

- Laboratory-confirmed influenza hospitalisation
- Influenza-related hospitalisation/emergency department visits
- Pneumonia-related hospitalisation/emergency department visits
- Laboratory-confirmed influenza
- Influenza-like illness (ILI)
- Local adverse events
- Systemic adverse events
- Serious adverse events (SAE)

Setting: Global middle- to high-income settings (e.g. Europe, Canada, the US, Australia)

Perspective: Individual

Background

cIV is produced using a new vaccine production process that does not require eggs. Theoretically this process is more efficient and mitigates the issue of antigenic drift in egg-based vaccines. The question is whether the cIV is more effective than sIV in reducing influenza-related morbidity and mortality.

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	Trivial	Small	Moderate	Large

- There is variability in the evidence. Overall, there is insufficient evidence to demonstrate cIV is more protective against influenza-related outcomes compared with sIV.

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 cIV compared with sIV. However, the frequency of systemic AEFI and SAE appears to be similar between cIV and sIV recipients. While one study reported higher rates of Guillain–Barré syndrome after cIV relative to other influenza vaccine types, the certainty of this finding was very low.

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 of cIV was downgraded because of the risk of bias due to potential confounding, with outcomes having very low to low certainty of evidence. Most evidence on safety outcomes was of high certainty.

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						
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?						
Don't know	Varies	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention
• The overall balance of desirable and undesirable effects of cIV are comparable to sIV.						
Acceptability Is the intervention acceptable to key stakeholders?						
Don't know	Varies	No	Probably no	Probably yes	Yes	
• No difference in the acceptability of cIV compared with sIV is expected.						
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.						