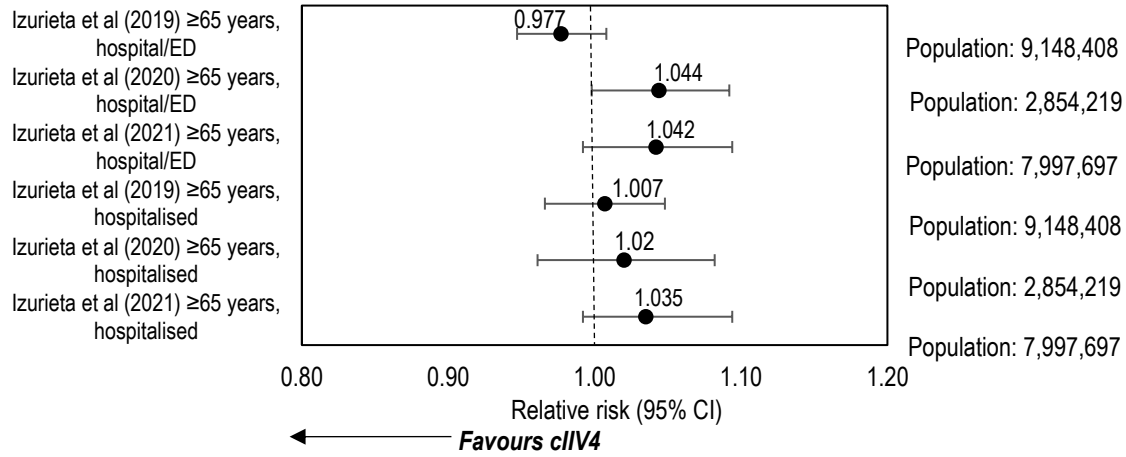
GRADE tables: Comparison of cell-based influenza vaccine with high-dose egg-based influenza vaccine in adults aged ≥65 years

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 high-dose egg-based influenza vaccine in adults aged ≥65 years

Patient or population: Adults aged ≥65 years
Intervention: Cell-based inactivated influenza vaccine (cIIV)
Comparison: High-dose egg-based inactivated influenza vaccine (hdIIV)

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
CRITICAL OUTCOMES				
Influenza-related hospitalisation/emergency department (ED) visits Assessed with: ICD coded J09.xx, J10.xx, J11.xx, and J129 Follow-up: 12 months	**Relative vaccine effectiveness of influenza-related hospitalisation/ED visits for cIIV vs hd-IIV**  Note: In all studies, cIIV4 is compared with hd-IIV3 Total participants = 20,000,324 (3 observational studies)[1-3]		⊕⊕⊕◯ Moderate[a,b]	Cell-based influenza vaccine likely results in no difference in influenza-related hospitalisations/ED visits compared with high-dose egg-based influenza vaccine.

Cell-based influenza vaccine compared with high-dose egg-based influenza vaccine in adults aged ≥65 years				
Patient or population: Adults aged ≥65 years **Intervention:** Cell-based inactivated influenza vaccine (cIIV) **Comparison:** High-dose egg-based inactivated influenza vaccine (hdIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
IMPORTANT OUTCOMES				
Influenza-related primary care/outpatient visits Assessed with: rapid influenza diagnostic test followed by a therapeutic course of oseltamivir prescribed within 2 days of test Follow-up: 12 months	Relative vaccine effectiveness cIIV4 vs hd-IIV3 Izurieta 2019, ages ≥65 years: rVE 11.5% (95% CI: 7.9, 15.0)	N = 9,148,408 (1 observational study)[1]	⨁◯◯◯ Very low[a,c]	The evidence suggests that cell-based influenza vaccine may result in a slight reduction in influenza-related primary care/outpatient visits compared with high-dose egg-based influenza vaccine.

Cell-based influenza vaccine compared with high-dose egg-based influenza vaccine in adults aged ≥65 years				
Patient or population: Adults aged ≥65 years **Intervention:** Cell-based inactivated influenza vaccine (cIIV) **Comparison:** High-dose egg-based inactivated influenza vaccine (hdIIV)				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Explanations a. Downgraded due to potential confounding. b. Downgraded due to wrong comparator. c. Downgraded due to lack of data from other studies. *Abbreviation:* CI=confidence interval; ED=emergency department				
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.				

Evidence profile

Cell-based influenza vaccine compared with high-dose egg-based influenza vaccine in adults aged ≥65 years

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Influenza-related hospitalisation/ED visits (follow-up: 12 months; assessed with: ICD coded J09.xx, J10.xx, J11.xx, and J129)									
3	Observational studies	Serious[a]	Not serious	Not serious[b]	Not serious	None	cIIV vs hd-IIV rVE (95% CI): **Izurieta et al (2019), ≥65 years, hospital/ED:** 2.3% (−0.8–5.3) **Izurieta et al (2020), ≥65 years, hospital/ED:** −4.4% (−9.2–0.2) **Izurieta et al (2021), ≥65 years, hospital/ED:** −4.2% (−9.4–0.8) **Izurieta et al (2019), ≥65 years, hospitalised:** −0.7% (−4.8–3.4) **Izurieta et al (2020), ≥65 years, hospitalised:** −2.0% (−8.2–3.9) **Izurieta et al (2021), ≥65 years, hospitalised:** −3.5% (−9.4–0.8) [1-3]	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Influenza-related primary care/outpatient visits (follow-up: 12 months; assessed with: rapid influenza diagnostic test performed [CPT 87804] followed by a therapeutic course of oseltamivir[75 mg twice daily for 5 days] prescribed within 2 days after the test)									
1	Observational studies	Serious[a]	Very serious[c]	Not serious	Not serious	None	cIIV vs hd-IIV rVE (95% CI): **Izurieta et al (2019), ≥65 years:** 11.5% (7.9–15.0) [1]	⨁◯◯◯ Very low	IMPORTANT

Evidence to decision framework

Cell-based influenza vaccine compared with high-dose egg-based influenza vaccine in adults aged ≥65 years

PICO Question					
Population	Adults 65 years and over				
Intervention	Cell-based influenza vaccine (cIIV)				
Comparison	Adjuvanted egg-based influenza vaccine (hdIIV)				
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- to 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 insufficient evidence to demonstrate that cIIV is more protective than hdIIV for either critical or non-critical influenza outcomes.
- 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).[4-7] This factor may have been related to improved vaccine effectiveness (VE) of cIIV over aIIV in 2017/18 where influenza A(H3N2) was in high circulation in the United States (Northern Hemisphere).[6]
- 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.[8,9]

Undesirable effects
How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- There is no evidence comparing adverse events after cIIV vs hdIIV.

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 insufficient evidence to balance desirable and undesirable effects when comparing cIIV and hdIIV.

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

No included studies	Very low	Low	Moderate	High

- The evidence is very uncertain about the effect of cIIV on influenza outcomes compared with hdIIV.
- There is no direct comparative evidence on safety outcomes between cIIV and hdIIV.

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
• As there is an influenza vaccination program already established for adults over 65 years, the introduction of a new vaccine is unlikely to affect acceptability.					
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					
High-dose egg-based influenza vaccine (hdIIV) is preferentially recommended over cell-based influenza vaccine (cIIV) in adults aged over 65 years. However, cIIV or standard-dose egg-based influenza vaccine (eIIV) may be given if the enhanced influenza vaccines (either hdIIV or adjuvanted influenza vaccine (aIIV)), currently recommended for adults over 65 years of age, are unavailable.					
Justification and considerations					
1. Due to contradictory studies, there is insufficient evidence demonstrating that cIIV performs better on desirable outcomes than hdIIV. 2. There is a vast body of evidence that supports the use of enhanced influenza vaccines in adults aged over 65 years, while there is less evidence on the use of cIIV in the older adult population. Previous GRADE assessments undertaken comparing high-dose influenza vaccines to standard-dose egg-based influenza vaccines have highlighted their improved protection against influenza illness and "enhanced" influenza vaccines are recommended as the preferred vaccines by ATAGI for adults aged over 65 years. 3. In the absence of comparative safety data on cIIV vs hdIIV and variable desirable effects data, enhanced vaccines such as hdIIV or aIIV continue to be the preferred vaccines for this age group. 4. GRADE assessments of cIIV have shown only a small incremental benefit compared with standard-dose egg-based influenza vaccine suggesting that either vaccine platform may be offered if the enhanced vaccines are unavailable.					

References

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4. Blanton L, Dugan VG, Abd Elal AI, et al. Update: Influenza Activity - United States, September 30, 2018-February 2, 2019. *Morbidity & Mortality Weekly Report* 2019;68(6):125-134.
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8. Paules CI, Sullivan SG, Subbarao K, et al. Chasing seasonal influenza — the need for a universal influenza vaccine. *New England Journal of Medicine* 2018;378(1):7-9.
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