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 with standard dose egg-based influenza vaccine in children aged 2–17 years

Patient or population: children aged 2–17 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 cIV				
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	rVE cIV4 vs sIV4 **4-65 years** 43% (95% CI: -45% to 77%)			1896 of which only 237 (8 cIV & 229 sIV) were 4-18 years-old (1 observational study)	⨁◯◯◯ VERY LOW [a,b,c]	Cell-based influenza vaccine may result in a reduction in laboratory-confirmed influenza hospitalisation compared to standard egg-based influenza vaccine but the evidence is very uncertain Ref:1

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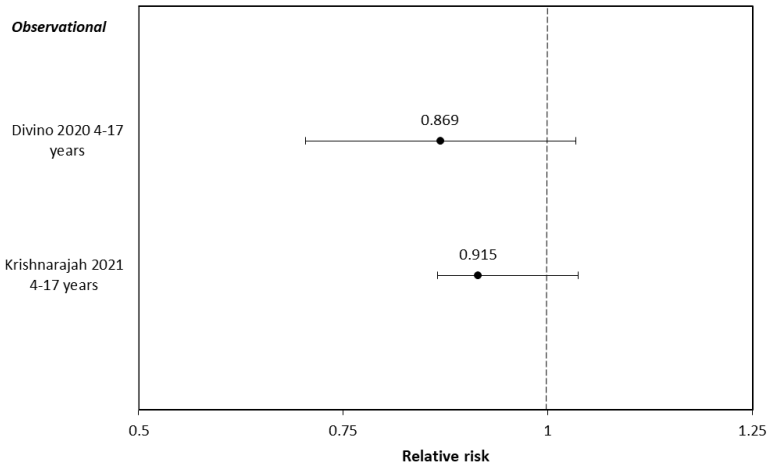
	Risk with cIV	Risk with cIV				
Influenza-related hospitalisations or ED visits (no laboratory confirmation) assessed with: ICD-9 487.x, 488.x, ICD-10 J09.x, J10.x, J11.x follow up: range 14 days to 6 months				Population: 839,664 Population: 919,650	⨁◯◯◯ VERY LOW c,d	Cell-based influenza vaccine may result in a slight reduction in influenza-related hospitalisations or ED visits compared with standard egg-based influenza vaccine; however, the evidence is very uncertain Ref: 2,3

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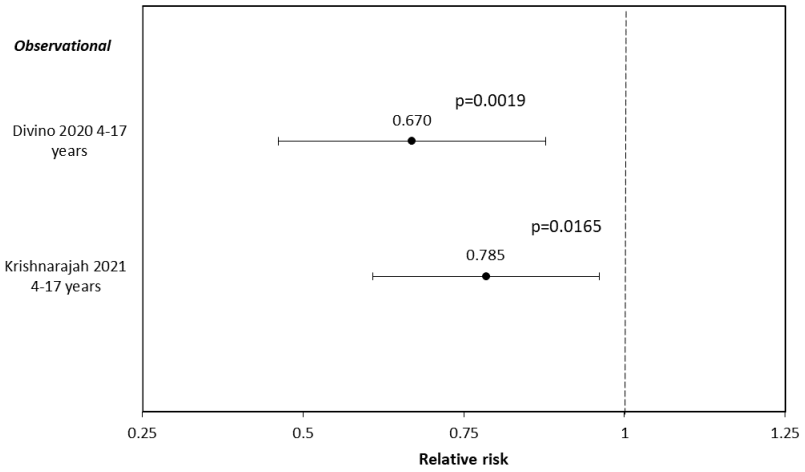
	Risk with cIV	Risk with cIV				
Pneumonia-related hospitalisations or ED visits (no laboratory confirmation) assessed with: diagnosis code in any position for pneumonia follow up: range 14 days to 6 months				Population: 839,664 Population: 919,650	⨁⨁◯◯ LOW[c,d]	Cell-based influenza vaccine may reduce pneumonia-related hospitalisations or ED visits 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
Serious adverse events (SAE) assessed with: patient monitoring and active follow up follow up: up to 6 months	No vaccine related SAEs were reported in the studies			2473 (3 RCTs))	⨁⨁⨁⨁ HIGH	Cell-based influenza vaccine results in little to no difference in serious adverse events compared with standard egg-based influenza vaccine Ref: 8,9,10

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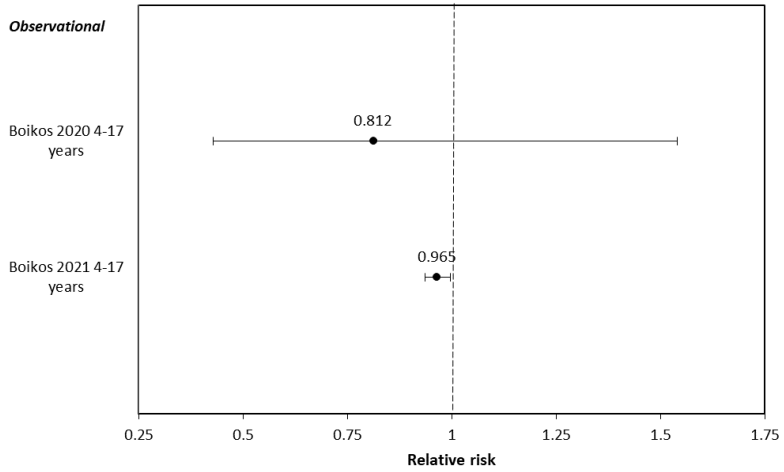
	Risk with cIV	Risk with cIV				
IMPORTANT OUTCOMES						
Influenza-like illness (ILI) assessed with: diagnostic codes in subject primary care EMR database (ICD-10 codes: J09*–J11*) follow up: range 14 days to 6 months				Population: 411,975 Population: 1,706,640	⨁◯◯◯ VERY LOW [a,d]	Cell-based influenza vaccine may result in a slight reduction in Influenza-like illness (ILI) compared with standard egg-based influenza vaccine; however, the evidence is very uncertain Ref: 4,5
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 **6 months-17 years** 1.2 (0.8-1.7)			2273 (1 observational study)	⨁◯◯◯ VERY LOW [c,d]	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; however, the evidence is very uncertain Ref: 6
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 **4 - <18 year old** 17.8% (-6.2%-36.4%)			264154 (1 observational study)	⨁◯◯◯ VERY LOW [a,c]	Cell-based influenza vaccine may result in a slight reduction in PCR confirmed influenza A compared to standard egg-based influenza vaccine; however, the evidence is very uncertain Ref: 7

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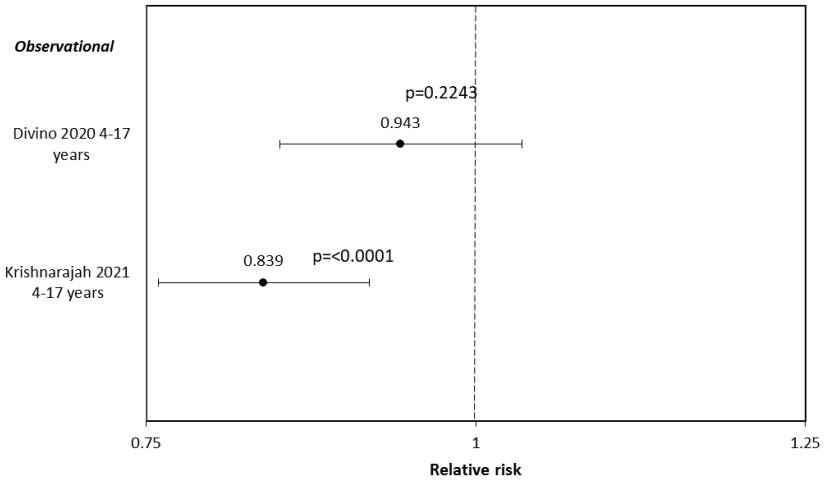
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (cIV vs sIV) (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cIV	Risk with cIV				
PCR-confirmed influenza B assessed with: positive PCR test result for influenza B (GeneXpert PCR assay) follow up: range 7 days to 6 months	rVE cIV4 vs sIV3 **4 - <18 year old** 42.3% (28.4%-53.5%)			264154 (1 observational study)	⊕⊕⊕◯ MODERATE [a]	Cell-based influenza vaccine probably moderately reduces PCR-confirmed influenza B compared with standard egg-based influenza vaccine Ref: 7 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: 839,664 Population: 919,650	⊕◯◯◯ VERY LOW [c,d]	Cell-based influenza vaccine may result in a slight reduction in all cause hospitalisation or ED visit compared with standard egg-based influenza vaccine; however, the evidence is very uncertain Ref: 2,3 Note: the 95% CI values are derived from the p-value for studies where the p-value is shown

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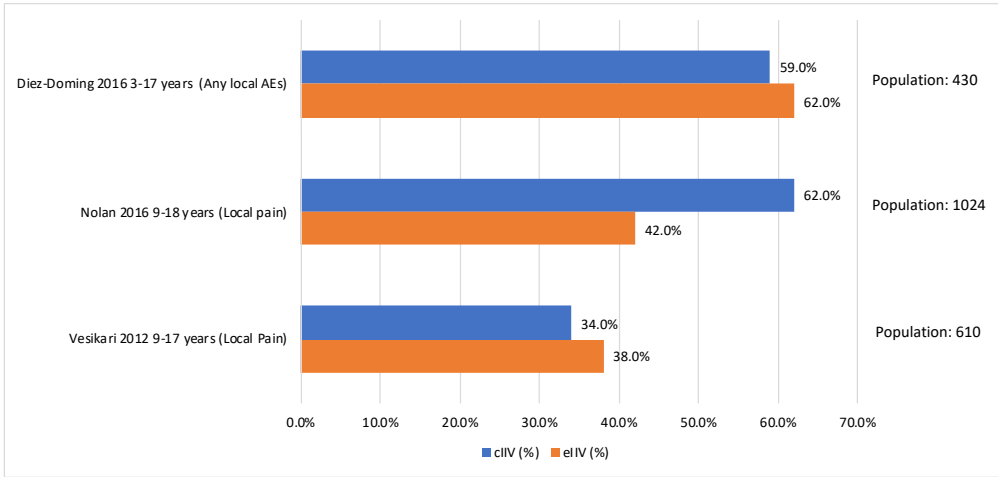
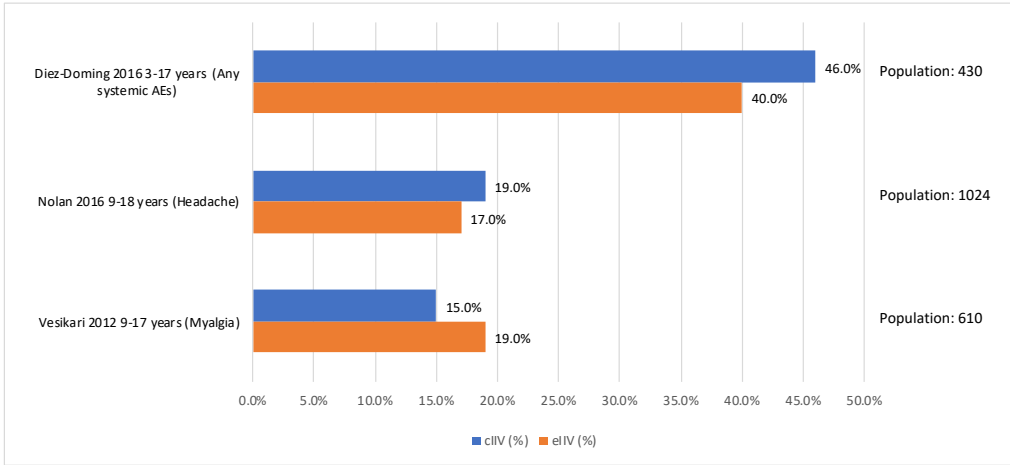
	Risk with cIV	Risk with cIV				
Solicited local adverse events assessed with: diaries follow up: up to 7 days for solicited AEs	 e			⊕⊕⊕⊕ HIGH	Cell-based influenza vaccine increases local adverse events slightly compared with standard egg-based influenza vaccine 3 RCTs [8,9,10]
Solicited systemic adverse events assessed with: diaries follow up: up to 7 days for solicited AEs	 f			⊕⊕⊕⊕ HIGH	Cell-based influenza vaccine results in little to no difference in systemic adverse events compared with standard egg-based influenza vaccine 3 RCTs [8,9,10]

***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. result for 4-64 year-olds; 4-17 year-olds comprised <11% of sample
c. wide confidence interval/ non-statistically significant
d. Risk of bias judgement = Serious- due to confounding
e Estimates shown for "any local AE" or if not available most frequently reported local AE
f Estimates shown for "any systemic AE" or if not available most frequently reported systemic AE

References

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Evidence profile: Cell-based influenza vaccine compared with standard egg-based influenza vaccine for children aged 2–17 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)											
1	observational studies	serious [a]	not serious	serious [d]	very serious [b]	none	Bruxvoort 2019:[1] rVE cIV4 vs sIV4 **ages 4-< 65 years** 43% (95% CI: -45 to 77)				⨁◯◯◯ 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)											
2	observational studies	serious [a]	not serious	not serious	very serious [b]	none	Divino 2020:[2] Adjusted rVE cIV4 vs sIV4 **4-17 years** 13.1% p=0.12 Krishnarajah 2021:[3] Adjusted rVE cIV4 vs sIV4 **4-17 years** 8.54% p=0.2664				⨁◯◯◯ VERY 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 [b]	none	Divino 2020:[2] Adjusted rVE cIV4 vs sIV4 **4-17 years** 33.0% p=0.0019 Krishnarajah 2021:[3] Adjusted rVE cIV4 vs sIV4 **4-17 years** 21.52% p=0.0165 2				⨁⨁◯◯ LOW
Serious adverse events (SAE) (follow up: up to 366 days; assessed with: patient monitoring and follow up)											
3	randomised trials	not serious	not serious	not serious	not serious	none	No vaccine related SAEs reported [8,9,10]				⨁⨁⨁⨁ 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 EMR database (ICD-10 codes: J09*–J11*))											
2	observational studies	very serious [c]	not serious	not serious	serious [b]	none	Boikos 2020:[4] rVE cIV4 vs sIV4 **Age 4-17** 18.8 % (-53.9-57.2) Boikos 2021:[5] rVE cIV4 vs sIV4 **Age 4-17** 3.5% (0.4-6.5)				⨁◯◯◯ 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 [c]	not serious	not serious	serious [b]	none	DeMarcus 2019:[6] rVE odds ratio cIV4 vs sIV4 **children** 1.2 (0.8-1.7)				⨁◯◯◯ VERY 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:[7] rVE cIV4 vs sIV3/4 **4 - <18 years old** 17.8% (-6.2%-36.4%)				⨁◯◯◯ 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	not serious	none	Klein 2020:[7] rVE cIV4 vs sIV3/4 **4 - <18 years old** 42.3% (28.4%-53.5%) 6				⨁⨁⨁◯ MODERATE

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 [c]	not serious	not serious	very serious [b]	none	Divino 2020:[2] adjusted rVE cIV4 vs sIV4 **4-17 years** 5.7% p=0.2243 Krishnarajah 2021:[3] adjusted rVE cIV4 vs sIV4 **4-17 years** 16.12% p=0.2243				⨁◯◯◯ VERY LOW
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	Diez-Domingo 2016:[8] **Any Local AE at risk** **3 to <18 years** cIV3=59%, sIV3 =62% Nolan 2016:[10] **Local reaction: Pain** **9-18 years** cIV3 =62%, sIV3 =42% Vesikari 2012:[9] **Solicited local reaction: Pain** **9-17 years** cIV3 =34%, sIV3 =38%				⨁⨁⨁⨁ 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	Diez-Domingo 2016:[8] **Any Systemic AE** **At risk children 3 to <18 years** cIV3 =46% sIV3 =40% Nolan 2016:[10] **Systemic reactions: Headache** **9-18 years** cIV3 =19%, sIV3 =17% Vesikari 2012:[9] **Solicited systemic reaction: Myalgia** **9-17 years** cIV3 =15%, sIV3 =19%				⨁⨁⨁⨁ HIGH

a. Risk of bias judgement = moderate - due to confounding
b. Wide confidence intervals/Non-statistically significant results
c. Risk of bias judgement = serious - due to potential confounding
d. Indirect due to age group inclusion

Evidence to Decision Framework: Individual perspective

Patients: 2–17 years old

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 doesn't require eggs. Theoretically this process will be more efficient and mitigates the issue of antigenic drift in egg-based vaccines. The question is whether 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

- While the direction of the effect was generally favourable to cIV compared with sIV, there is currently insufficient evidence to demonstrate cIV is more effective against influenza than sIV.
- Furthermore a clinical trial in children aged 2-<18 years that compared cIV with a non-influenza vaccine found absolute efficacy values around expected values for influenza vaccines in this population (55%; 95%CI 46-62%)[11]

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 cIV and sIV recipients.

Certainty of evidence

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- Overall, the certainty of evidence on the effectiveness of cIV compared with sIV was very low and was downgraded because of the risk of bias due to potential confounding, and low precision with critical outcomes having very low certainty of evidence. Most evidence on influenza outcomes reported results that did not

demonstrate significantly different effectiveness between the intervention or control. 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 with those of 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.						