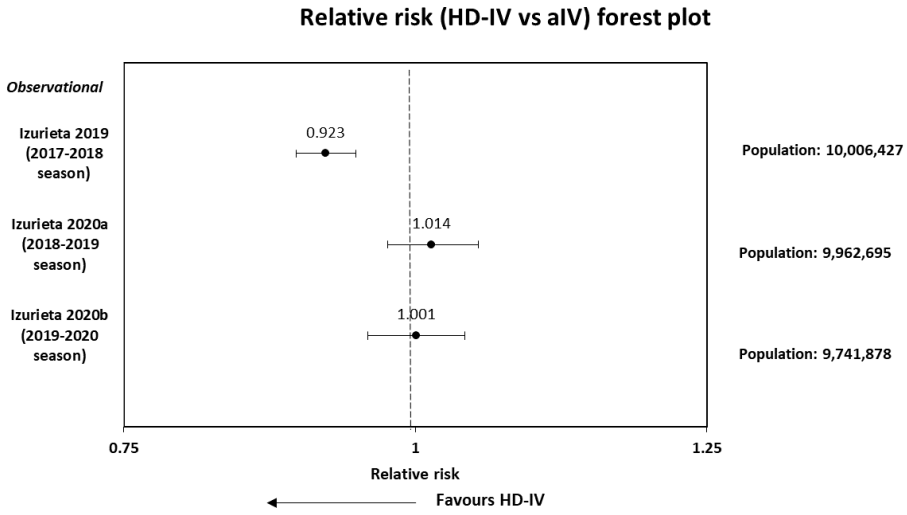
NCIRS is conducting GRADE in support of ATAGI and making pilot results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook Influenza Chapter and the ATAGI Annual Influenza Statement.

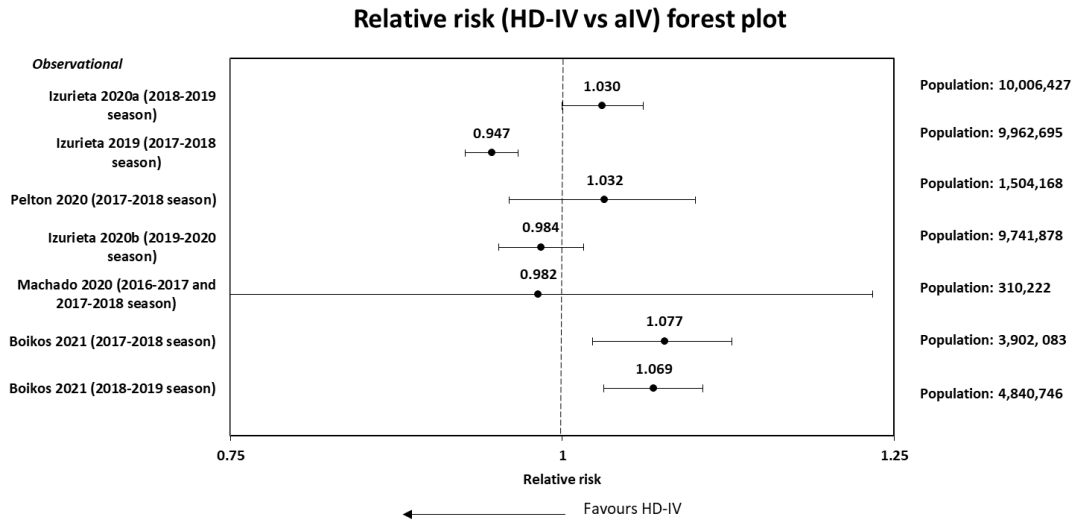
Summary of findings: High-dose influenza vaccine compared with MF-59 adjuvanted influenza vaccine for older adults aged ≥65 years

Patient or population: older adults aged ≥65 years
Intervention: high-dose influenza vaccine (HD-IV)
Comparison: MF-59 adjuvanted influenza vaccine (aIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with adjuvanted influenza vaccine	Risk with high-dose influenza vaccine				
CRITICAL OUTCOME						
Influenza-related hospitalisation assessed with: Identified by ICD-10 and ICD-9 codes: J09.xx, J10.xx, J11.xx, J129 follow up: range 14 days to end of season (up to 12 months)					⨁⨁⨁◯ MODERATE [a]	High-dose influenza vaccine likely results in little to no difference in influenza-related hospitalisation compared with adjuvanted influenza vaccine Ref: 1,2,8

Summary of findings: High-dose influenza vaccine compared with MF-59 adjuvanted influenza vaccine for older adults aged ≥65 years

Patient or population: older adults aged ≥65 years
Intervention: high-dose influenza vaccine (HD-IV)
Comparison: MF-59 adjuvanted influenza vaccine (aIV)

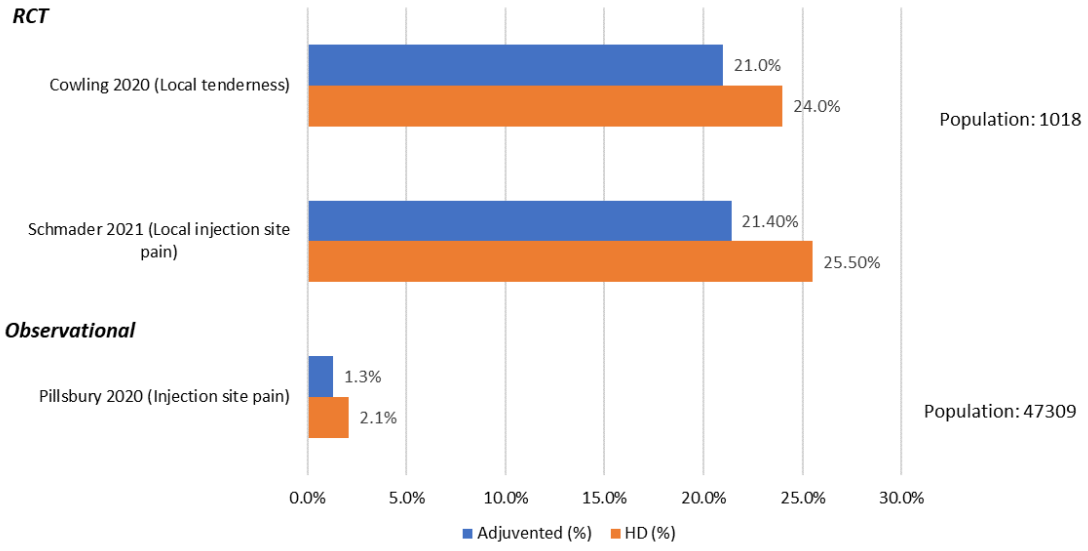
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with adjuvanted influenza vaccine	**Risk with high-dose influenza vaccine**				
Influenza-related hospital encounters (ED visits and hospitalisations) assessed with: ICD-10 code: J09.xx, J10.xx, J11.xx, J12.9 follow up: range 14 days to end of season (up to 12 months)					⊕⊕⊕◯ MODERATE [a]	High-dose influenza vaccine likely results in little to no difference in influenza-related hospital encounters compared with adjuvanted influenza vaccine Ref: 1,2,3,8,9,10

Note: In Pelton 2020, the 95% CI not clearly reported but it does cross 1(~ -4%–10%)

IMPORTANT OUTCOME						
Respiratory-related hospitalisations assessed with: ICD-10 code: all Jxx codes follow up: range 14 days to end of season (up to 12 months)	16 per 100,000	**14 per 100,000** (12 to 15)	**RR 0.880** (0.800 to 0.967)	2124713 (1 observational study)	⊕⊕◯◯ LOW [a, c]	High-dose influenza vaccine may slightly decrease respiratory-related hospitalisations compared with adjuvanted influenza vaccine Ref: 4

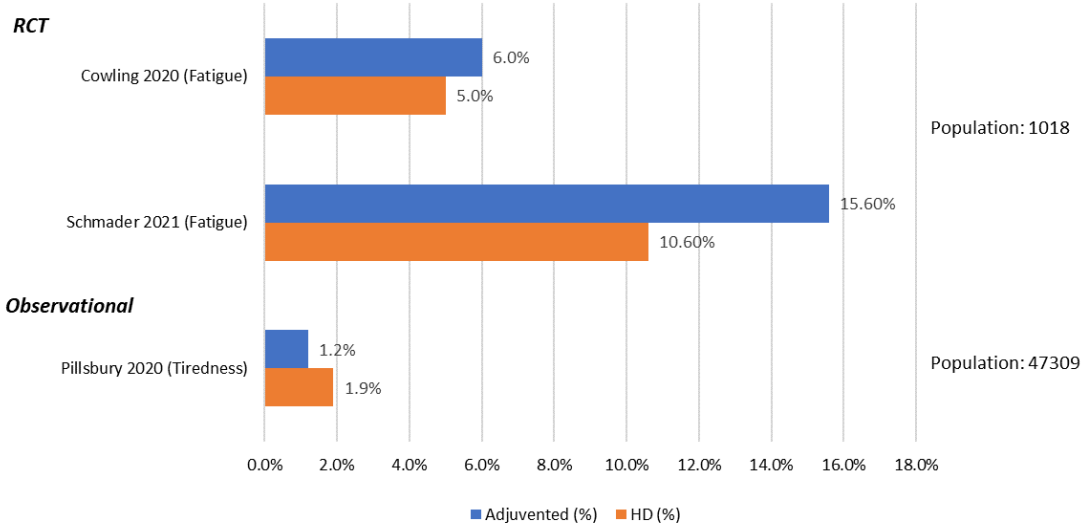
Summary of findings: High-dose influenza vaccine compared with MF-59 adjuvanted influenza vaccine for older adults aged ≥65 years

Patient or population: older adults aged ≥65 years
Intervention: high-dose influenza vaccine (HD-IV)
Comparison: MF-59 adjuvanted influenza vaccine (aIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with adjuvanted influenza vaccine	Risk with high-dose influenza vaccine				
Influenza-related office visits assessed with: community-based physician office visits or hospital outpatient visits with a 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 follow up: range 14 days to end of season (up to 12 months)	557 per 100,000	**519 per 100,000** (507 to 531)	**RR 0.932** (0.911 to 0.954)	9962695 (1 observational study)	⨁⨁◯◯ LOW [a,c]	High-dose influenza vaccine may slightly decrease Influenza-related office visits compared with adjuvanted influenza vaccine Ref: 1
Solicited local adverse events assessed with: diaries follow up: range 1 day to 14 days post-vaccination				⨁⨁⨁⨁ HIGH	High-dose influenza vaccine results in little to no difference in solicited local adverse events compared with adjuvanted influenza vaccine Ref: 5,11,6

Summary of findings: High-dose influenza vaccine compared with MF-59 adjuvanted influenza vaccine for older adults aged ≥65 years

Patient or population: older adults aged ≥65 years
Intervention: high-dose influenza vaccine (HD-IV)
Comparison: MF-59 adjuvanted influenza vaccine (aIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with adjuvanted influenza vaccine	**Risk with high-dose influenza vaccine**				
Solicited systemic adverse events assessed with: diaries follow up: range 1 day to 14 days post vaccination				⨁⨁⨁⨁ HIGH	High-dose influenza vaccine results in little to no difference in solicited systemic adverse events compared with adjuvanted influenza vaccine Ref: 5,11,6
Adverse events of special interest assessed with: various (e.g. administrative data, insurance claims) follow up: range 8 days to 84 days post vaccination	OR of GBS in primary risk window (8–21 days post vaccination) versus control window (i.e. no vaccination) was the period days 43 to 84 post vaccination aTIV: 3.75 (95%CI: 1.01-13.96), p=0.049 TIV-HD: 0.89 (95%CI: 0.48-1.65), p=1.000 Risk for aTIV was not statistically significant after multiplicity adjustment.			9985824 (1 observational study)	⨁⨁◯◯ LOW [b,d]	High-dose influenza vaccine may result in slight lower adverse events of special interest compared with adjuvanted influenza vaccine Ref: 7

***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

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. not laboratory confirmed
b. Risk of bias assessment = moderate (due to confounding + missing data + measurement of outcomes)
c. Risk of bias assessment = moderate (due to confounding + missing data)
d. Comparator groups were each compared to self-controlled placebo (pre/post study) not to each other

References

1. Izurieta HS, Chillarige Y, Kelman J, Wei Y, Lu Y, Xu W, Lu M, Pratt D, Chu S, Wenecke M, Macurdy T, Forshee R. Relative Effectiveness of Cell-Cultured and Egg-based Influenza Vaccines among Elderly Persons in the United States, 2017–2018. The Journal of Infectious Diseases; 2019.
2. Izurieta HS, Chillarige Y, Kelman J, Wei Y, Lu Y, Xu W, Lu M, Pratt D, Wernecke M, MaCurdy T, Forshee R. Relative Effectiveness of Influenza Vaccines Among the United States Elderly, 2018-2019. The Journal of infectious diseases; 2020a.
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4. van Aalst R, Gravenstein S, Mor V, et al. Comparative effectiveness of high dose versus adjuvanted influenza vaccine: a retrospective cohort study. Vaccine; 2019.
5. Cowling BJ, Thompson MG, Ng TWY, Fang VJ, Perera,Rapm Leung NHL, Chen Y, So HC, Ip DKM, Iuliano AD. Comparative Reactogenicity of Enhanced Influenza Vaccines in Older Adults. Journal of Infectious Diseases; 2020.
6. Pillsbury AJ, Fathima P, Quinn HE, Cashman P, Blyth CC, Leeb A, Macartney K. Comparative Postmarket Safety Profile of Adjuvanted and High-Dose Influenza Vaccines in Individuals 65 Years or Older. JAMA Network Open; 2020.
7. Perez-Vilar S, Wernecke M, Arya D, Lo AC, Lufkin B, Hu, , Chu S, MaCurdy TE, Kelman J, Forshee RA.Surveillance for Guillain-Barre syndrome after influenza vaccination among U.S. Medicare beneficiaries during the 2017-2018 season. 2019. Vaccine.
8. Izurieta H, Lu M, Kelman J, et al. Comparative Effectiveness of Influenza Vaccines Among US Medicare Beneficiaries Ages 65 Years and Older During the 2019–2020 Season. Clinical Infectious Diseases. 2020b;1-9.
9. Machado M, Moura C, Abrahamowicz M, et al. Relative effectiveness of influenza vaccines in elderly persons in the United States, 2012/2013-2017/2018 seasons. NPJ Vaccines. 2021;6:108.
10. Boikos C, Fischer L, O'Brien D, et al. Relative Effectiveness of Adjuvanted Trivalent Inactivated Influenza Vaccine Versus Egg-derived Quadrivalent Inactivated Influenza Vaccines and High-dose Trivalent Influenza Vaccine in Preventing Influenza-related Medical Encounters in US Adults ≥ 65 Years During the 2017–2018 and 2018–2019 Influenza Seasons. Clinical Infectious Diseases. 2021;73.
11. Schmader K, Liu C, Harrington T, et al. Safety, Reactogenicity, and Health-Related Quality of Life After Trivalent Adjuvanted vs Trivalent High-Dose Inactivated Influenza Vaccines in Older Adults A Randomized Clinical Trial. JAMA Network. 2021;4(1):e2031266.

Evidence profile: High-dose influenza vaccine compared with MF-59 adjuvanted influenza vaccine for older adults aged ≥65 years

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	High-dose influenza vaccine	Adjuvanted influenza vaccine	Relative (95% CI)	Absolute (95% CI)	
CRITICAL OUTCOME											
Influenza-related hospitalisation (follow up: range 2 weeks to outcome; assessed with: Identified by ICD-10 and ICD-9 codes)											
3	observational studies	not serious	not serious	serious [a]	not serious	none	aTIV (egg) as the reference group TIV-HD Adjusted rVE estimates against influenza-related Hospitalisations: 7.7% (95% CI: 5.1 to 10.2%) Izurieta 2019 aTIV as reference: TIV-HD Flu Inpatient Stays (2018/2019 season) rVE -1.4 % (CI -5.4-2.4) TIV-HD Flu Inpatient stays (2019/2020 season) rVE 0.1 (95% CI: -4.1-2.4) Not statically significant 1,2, 6				⨁⨁⨁◯ MODERATE
Influenza-related hospital encounters (medical office visits, ED visits and hospitalisations) (follow up: range 14 days to outcome of interest/Medicare disenrollment/end of study period/death/admission into a nursing home; assessed with: ICD-10 code)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	High-dose influenza vaccine	Adjuvanted influenza vaccine	Relative (95% CI)	Absolute (95% CI)	
6	observational studies	not serious	not serious	serious [a]	not serious	none	aTIV (egg) as the reference group: TIV-HD Adjusted rVE estimates against influenza-related ED visits and/or hospitalisations: 5.3% (95% CI: 3.3–7.3%) Izurieta 2019[1] rVE (95% CI) aTIV vs. TIV-HD aTIV as reference: Hospital Encounters rVE -3.0 % (CI -6.1–0.0) Izurieta 2020 [2] Hospital Encounters (2019/2020 season) rVE: -1.6 (95% CI: -4.8 to 1.6) Izurieta 2020b[6] rVE (95% CI) aTIV vs. TIV-HD (TIV-HD as reference): Pelton 2020[3] 3.2% Not statically significant Machado 2021[7] (across 2 seasons) -1.8 (35.1-23.4) Boikos 2021[8] (2017/2018 season): 7.7 (2.3-12.8) Boikos 2021[8] (2018/2019 season): 6.9 (3.1-10.6)			⊕⊕⊕◯ MODERATE
IMPORTANT OUTCOME											
Respiratory-related hospitalisations (follow up: range July 1 to June 30; assessed with: ICD-10 code)											
1	observational study	serious [b]	not serious	serious [a]	not serious	none	254.1/223793 (0.1%)	296.45/1900920 (0.0%)	**RR 0.880** (0.800 to 0.967)	**2 fewer per 100,000** (from 3 fewer to 1 fewer)	⊕⊕◯◯ LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	High-dose influenza vaccine	Adjuvanted influenza vaccine	Relative (95% CI)	Absolute (95% CI)	
Influenza-related office visits (follow up: range 14 days to outcome of interest; assessed with: community-based physician office visits or hospital outpatient visits with a 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 [c]	not serious	serious [a]	not serious	none	45941/8489159 (0.5%)	8202/1473536 (0.6%)	**RR 0.932** (0.911 to 0.954)	**38 fewer per 100,000** (from 50 fewer to 26 fewer)	⨁⨁◯◯ LOW
Solicited local adverse events (follow up: range 1 days to 14 days; assessed with: diaries)											
2	randomised trials	not serious	not serious	not serious	not serious	none	Any local tenderness was less prevalent on day 1 for aTIV vs TIV-HD 21% vs 24%. Cowling 2020[3] Any injection site pain: aTIV= 21.4%, TV-HD=25.2% Moderate to severe injection site pain; aTIV=3.2%, TIV-HD=5.8% Schmader 2021[9]			⨁⨁⨁⨁ HIGH
1	observational study	not serious	not serious	not serious	not serious	none	Injection site pain aTIV= 1.3%, HD=2.1% sIV= 1.1% Pillsbury 2020[4]				⨁⨁⨁⨁ HIGH
Solicited systemic adverse events (follow up: range 1 days to 14 days; assessed with: diaries)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	High-dose influenza vaccine	Adjuvanted influenza vaccine	Relative (95% CI)	Absolute (95% CI)	
2	randomised trials	not serious	not serious	not serious	not serious	none	Fatigue on day 1 aTIV 6% TIV-HD 5% Cowling 2020 [3] Tiredness aTIV= 1.2% TIV-HD=1.9% Pillsbury 2020 [4] Any fatigue aTIV=15.6%, TIV-HD=10.6% Moderate to severe fatigue aTIV=7.1%, TIV-HD=4.0% Schmader 2021[9]			⊕⊕⊕⊕ HIGH

Adverse events of special interest (follow up: range 8 days to 84 days; assessed with: various (e.g. administrative data, insurance claims)

1	observational studies	serious [b]	not serious	serious [b,d]	not serious	none	OR of GBS in primary risk window (8-21 days post vaccination) versus control window was the period days 43 to 84 post vaccination aTIV: 3.75 (95%CI: 1.01-13.96), p=0.049 TIV-HD: 0.89 (95%CI: 0.48-1.65), p=1.000 Risk for aTIV was not statistically significant after multiplicity adjustment. Perez-Vilar 2019 [5]			⊕⊕◯◯ LOW

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. not laboratory confirmed
b. Risk of bias assessment = moderate (due to confounding + missing data + measurement of outcomes)
c. Risk of bias assessment = moderate (due to confounding + missing data)
d. Comparator groups were each compared to self-controlled placebo (pre/post study). not to each other

References

1. Izurieta, H. S. Chillarige Y. Kelman J. Wei Y. Lu Y. Xu W. Lu M. Pratt D. Chu S. Wenecke M. Macurdy T. & Forshee R.. Relative Effectiveness of Cell-Cultured and Egg-based Influenza Vaccines among Elderly Persons in the United States, 2017–2018. The Journal of Infectious Diseases; 2019.

2. Izurieta, H. S. Chillarige,Y. Kelman,J. Wei,Y. Lu,Y. Xu,W. Lu,M. Pratt,D. Wernecke,M. MaCurdy,T. Forshee,R.. Relative Effectiveness of Influenza Vaccines Among the United States Elderly, 2018-2019. The Journal of infectious diseases; 2020.

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4. Pillsbury, Alexis J. Fathima,Parveen Quinn,Helen E. Cashman,Patrick Blyth,Christopher C. Leeb,Alan Macartney,Kristine K.. Comparative Postmarket Safety Profile of Adjuvanted and High-Dose Influenza Vaccines in Individuals 65 Years or Older. JAMA Network Open; 2020.

5. Perez-Vilar, S. Wernecke,M. Arya,D. Lo,A. C. Lufkin,B. Hu,M. Chu,S. MaCurdy,T. E. Kelman,J. Forshee,R. A.. 2019. Vaccine; Surveillance for Guillain-Barre syndrome after influenza vaccination among U.S. Medicare beneficiaries during the 2017-2018 season.

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Evidence to Decision Framework: individual perspective

Patients: 65 years of age and older

Intervention: High-dose influenza vaccine (HD-IV)

Comparison: MF-59 adjuvanted influenza vaccine (aIV)

Main outcomes:

- Influenza-related hospital encounters (medical office visits, ED visits and hospitalisations)
- Influenza related hospitalisation
- Respiratory-related hospitalisations
- Influenza-related office visits
- Solicited local adverse events
- Solicited systemic adverse events
- Adverse events of special interest

Setting: Global high-income settings, mostly North America (Canada and the US)

Perspective: Individual

Background

Among adults aged 65 years and older, standard dose influenza vaccines provide only moderate protection against seasonal influenza. This is likely to be due to immunosenescnce. Two different vaccines, aIV and HD-IV, have been developed to provide greater protection for people aged ≥65 years through enhancing immunogenicity. The aIV works by the inclusion of an adjuvant, the HD-IV by including 4 times the antigen of the standard-dose influenza vaccine. There is evidence that each vaccine is effective over the standard-dose influenza vaccine, but it is unknown whether HD-IV is more effective over aIV in reducing influenza-related morbidity and mortality.

ASSESSMENT

Problem

Is the problem a priority?

Don't know	Varies	No	Probably no	Probably yes	Yes

- High burden of influenza disease in older adults
- Uncertainty regarding most effective vaccine to reduce influenza-related morbidity and mortality among older adults

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Trivial	Small	Moderate	Large

- Overall HD-IV showed little to no difference in reducing influenza and serious influenza outcomes compared with aIV.

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Evidence indicates serious AEFI are rare for both vaccines and solicited local and systemic adverse events occur at similar rates for both vaccines

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

<table>
<tr><td colspan="7">Values
Is there important uncertainty about or variability in how much people value the main outcomes?</td></tr>
<tr><td colspan="2">Important uncertainty</td><td colspan="2">Possibly important uncertainty or variability</td><td colspan="2">Probably no important uncertainty or variability</td><td>No important uncertainty or variability</td></tr>
<tr><td colspan="7">• Unlikely to be important uncertainty in how people value protection against influenza</td></tr>
<tr><td colspan="7">Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?</td></tr>
<tr><td>Don’t know</td><td>Varies</td><td>Favours the comparison</td><td>Probably favours the comparison</td><td>Does not favour either the intervention or the comparison</td><td>Probably favours the intervention</td><td>Favours the intervention</td></tr>
<tr><td colspan="7">• The HD-IV was found to be similar in undesirable effects and desirable effects compared with aIV. While the desirable effects of HD-IV may be slightly higher than those of aIV under certain circumstances, there is not enough evidence at present to indicate this with sufficient certainty.</td></tr>
<tr><td colspan="7">Acceptability
Is the intervention acceptable to key stakeholders?</td></tr>
<tr><td colspan="2">Don’t know</td><td>Varies</td><td>No</td><td>Probably no</td><td>Probably yes</td><td>Yes</td></tr>
<tr><td colspan="7">• Likely to be acceptable to the public as there was a high uptake of HD-IV when it was previously publicly funded.</td></tr>
<tr><td colspan="7">Feasibility
Is the intervention feasible to implement?</td></tr>
<tr><td colspan="2">Don’t know</td><td>Varies</td><td>No</td><td>Probably no</td><td>Probably yes</td><td>Yes</td></tr>
<tr><td colspan="7">• Minimal barriers in implementation, as vaccine delivery system already in use and this vaccine would likely replace the use of another influenza vaccine for the individuals receiving it.</td></tr>
</table>