Annexes to the 2022 WHO Hepatitis A Vaccine Position Paper

Grading of evidence - Evidence to recommendations tables

World Health Organization

Background

Annexes 1–12 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE). Annexes 13–14 contain the SAGE evidence-to-recommendation framework tables (ETR tables). The ETR tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 11 January 2021).

Contents

Annex 1. GRADE table: Efficacy and safety of hepatitis A vaccines: Two doses of inactivated hepatitis A vaccine (2012 systematic review)

Author(s): Wiersma S, Irving G, Ott J, Holden J

Date of review: 29 June 2011

Population: General population (children and adults)

Intervention: Two doses of inactivated hepatitis A vaccine

Comparison: no intervention, inactive control or placebo

Outcomes: Clinical and laboratory confirmed Hep A disease.
Serious adverse events following immunization

Question: Should inactivated hepatitis A vaccine vs no intervention, inactive control or placebo be used for hepatitis A?

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Inactivated hepatitis A vaccine**	**No intervention, inactive control or placebo**	**Relative (95% CI)**	**Absolute**	**Quality**
Hepatitis A (follow-up 12-18 months; assessed with: clinical and laboratory criteria)											
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[a]	10/19820 (0.05%)	95/19906 (0.48%) 0%	RR 0.12 (0.05 to 0.31)	-	⊕⊕⊕⊕ HIGH
Absence of serious adverse effects (follow-up 12-18 months; assessed with: clinical observation)											
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[b]	0/19820 (0%)	0/19906 (0%) 0%	-	- -	⊕⊕⊕⊕ HIGH

a. A large effect, RR=0.12, was found.

b. b. Innis 1994 reported that no hospitalizations or deaths were attributed to vaccination but did not provide full breakdown of reporting according to ICH GCP 199

Summary of Findings	**Statement on quality of evidence**	Evidence supports a high degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	High scientific evidence that two doses of inactivated hepatitis A vaccine are safe and efficacious to prevent hepatitis A disease.

References

1. Innis B, Snitbhan R, et al. Protection against hepatitis A by an inactivated vaccine. Journal of the American Medical Association 1994;271(17):1328-1334.
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Note: this is the systematic review that has been carried out for the 2012 WHO position paper. The summary of findings table has been added for clarity.

Annex 2. GRADE table: Efficacy and safety of hepatitis A vaccines. Single dose inactivated hepatitis A vaccine. (2012 systematic review).

Author(s): Wiersma S, Irving G, Ott J, Holden J

Date: 29 June 2011

Population: General population (children and adults)

Intervention: One dose of inactivated hepatitis A vaccine

Comparison: no intervention, inactive control or placebo

Outcomes: Clinical and laboratory confirmed Hep A disease.

Serious adverse events following immunization

Question: Should single dose inactivated hepatitis A vaccine versus no intervention, inactive control or placebo be used for hepatitis A?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose inactivated hepatitis A[a]	No intervention, inactive control or placebo	Relative (95% CI)	Absolute	
Hepatitis A (follow-up mean 15 months; assessed with: clinical and laboratory criteria)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	0/136 (0%)	17/136 (12.5%)	RR 0.03 (0 to 0.47)		⊕⊕⊕⊕ HIGH
								0%		-	

a. Virosomal inactivated hepatitis A vaccine.

Summary of Findings	**Statement on quality of evidence**	Evidence supports a high degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	High scientific evidence that single dose inactivated hepatitis A vaccine are safe and efficacious to prevent hepatitis A disease.

References

1. Perez M, Herzog Z. Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. Int J Infect Diseases 2003; 188: 671-7.

Note: this is the systematic review that has been carried out for the 2012 WHO position paper. The summary of findings table has been added for clarity.

Annex 3. GRADE table: Hepatitis A vaccine and post-exposure prophylaxis. Inactivated hepatitis A vaccine versus no intervention. (2012 systematic review).

Author(s): Wiersma S, Irving G, Ott J, Holden J

Date: 29 June 2011

Population: General population (children and adults)

Intervention: One or two dose of inactivated hepatitis A vaccine

Comparison: no intervention, inactive control or placebo

Outcomes: Clinical and laboratory confirmed Hep A disease.
Serious adverse events following immunization

Question: Should use of inactivated hepatitis A vaccine in family contacts of confirmed cases versus no intervention be used for hepatitis A prevention?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Use of inactivated hepatitis A vaccine in family contacts of confirmed cases	No intervention	Relative (95% CI)	Absolute	
Hepatitis A (follow-up mean 45 days; assessed with: clinical and laboratory criteria)											
1	randomized trial	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/197 (1%)	12/207 (5.8%)	RR 0.18 (0.04 to 0.77)	79% efficacious compared to no intervention.	⊕⊕⊕○ MODERATE

a. Sequence generation was unclear, allocation concealment was inadequate, blinding was unclear, and incomplete outcome data was reported.

Summary of Findings	**Statement on quality of evidence**	Evidence supports a moderate degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	Moderate scientific evidence that inactivated hepatitis A vaccine in family contacts of confirmed cases prevent disease.

Reference

1. Sagliocca L, Amoroso P, Stroffolini T, Adamo B, Tosti ME, Lettieri G, Esposito C, Buonocore S, Pierri P, Mele A. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial. Lancet 1999; 353:1136-9.

Note: this is the systematic review that has been carried out for the 2012 WHO position paper. The summary of findings table has been added for clarity.

Annex 4. GRADE table: Hepatitis A vaccine and post-exposure prophylaxis. Inactivated hepatitis A vaccine versus Ig. (2012 systematic review).

Population: General population (children and adults)

Intervention: One or two dose of inactivated hepatitis A vaccine

Comparison: Immunoglobulins (Ig)

Outcomes: Clinical and laboratory confirmed Hep A disease.

Serious adverse events following immunization

Question: Should use of inactivated hepatitis A vaccine in contacts of confirmed cases versus immunoglobulins (IG) be used for post-exposure prevention of hepatitis A?

Author(s): Wiersma S, Irving G, Ott J, Holden J

Date: 29 June 2011

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Use of inactivated hepatitis A vaccine in contacts of confirmed cases	Immuno-globulins (IG)	Relative (95% CI)	Absolute	Quality
Hepatitis A (follow-up 4-8 weeks; assessed with: clinical and laboratory criteria)											
1	randomized trial	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[a]	none	25/568 (4.4%)	17/522 (3.3%)	RR 1.35 (0.7 to 2.67)	NOTE[b]	⊕⊕⊕⊕ HIGH

RR= Relative Risk (95% CI)

a. Criterion of noninferiority met; no significant differences between IG and inactivated hepatitis A vaccine in clinical or subclinical hepatitis A. Risk of hepatitis in vaccine group never >1.5% than in IG group.

b. Absolute vaccine efficacy not assessed.

Summary of Findings	**Statement on quality of evidence**	Evidence supports a high degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	High scientific evidence that inactivated hepatitis A vaccine in family contacts of confirmed cases are as efficacious as immunoglobulins to prevent hepatitis A disease.

References

1. Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, Favorov MO, Margolis HS, Bell BP. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med 2007; 357:1685-94.

Note: this is the systematic review that has been carried out for the 2012 WHO position paper. The summary of findings table has been added for clarity

Annex 5. GRADE table: Hepatitis A vaccine long term protection: Inactivated 2 or more doses vs no vaccination (2012 systematic review)

Author(s): Ott J, Wiersma S

Date: 28 September 2011

Population: Children and adults

Intervention: Two or three doses of inactivated Hep A vaccine

Comparison: No HAV vaccination

Outcome: Seroprotection rate, Anti HAV Ab geometric median concentration at 5-14 years of vaccination

Question: Should inactivated hepatitis A vaccine be used for long-term protection against hepatitis A?

Note: this systematic review has been published in a peer review journal: Ott JJ, Irving G, Wiersma ST. Long-term protective effects of hepatitis A vaccines. A systematic review. Vaccine. 2012 Dec 17;31(1):3-11. doi: 10.1016/j.vaccine.2012.04.104.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inactivated hepatitis A vaccine	Control	Relative (95% CI)	Absolute [c]	
Anti-HAV antibodies >5 years after immunization (follow-up 5-14 years; measured with: GMC, GMT, or % seroprotection post vaccination)											
8	observational studies	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	720	-	-	GMT range from 62-1587[2]	⊕○○○ VERY LOW
Anti-HAV antibodies 14 years after immunization (children, 3-dose, Havrix) (follow-up mean 14 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	-	-	GMT range from 131-227[e]	⊕⊕○○ LOW

a. Loss to follow-up reported to be up to 50% and increased with duration of follow-up. There is also a risk of confounding because other factors potentially associated with antibody response are not considered.
b. Results had wide ranges and wide confidence intervals and often only reported GMC/GMT and not ranges of data.

c. Results listed as mean geometric titer or concentration.
d. Three different schedules were used (0, 1, 2 mo; 0, 1, 6 mo; 0, 1, 12 mo) in this study.
e. Seroprotection rate ranged from 86-100% depending on schedule.

Summary of Findings	**Statement on quality of evidence**	Evidence supports a very low degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	Very low scientific evidence that multiple dose schedules of inactivated hepatitis A vaccine provide long term seroprotection against Hepatitis A.

References:

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6. Lopez EL, Contrini MM, Mistchenko A, Debbag R. Long-term immunity after two doses of inactivated hepatitis A vaccine, in Argentinean children. Pediatr Infect Dis J 2010; 29: 568-70
7. Van Herck K, Van Damme P. Inactivated hepatitis A vaccine-induced antibodies: follow-up and estimates of long-term persistence. J Med Virol 2001;**63**:1-7.

Note: this is the systematic review that has been carried out for the 2012 WHO position paper. The summary of findings table has been added for clarity

Annex 6. GRADE table: Efficacy and safety of hepatitis A vaccines. Live attenuated hepatitis A vaccine. 2012 (2012 systematic review).

Author(s): Wiersma S, Irving G, Ott J, Holden J
Date: 29 June 2011

Population: General population (children and adults)

Intervention: One dose of live attenuated hepatitis A vaccine

Comparison: no intervention, inactive control or placebo

Outcomes: Clinical and laboratory confirmed Hep A disease.
Serious adverse events following immunization

Question: Should single dose live attenuated hepatitis A vaccine vs no intervention, inactive control or placebo be used for hepatitis A?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose live attenuated hepatitis A vaccine	No intervention, inactive control or placebo	Relative (95% CI)	Absolute	
Hepatitis A (follow-up 1-60 months; assessed with: clinical and laboratory criteria)											
13	randomised trials	Serious[a]	Serious[b]	no serious indirectness	no serious imprecision	None[c]	63/864813 (0.007%)	723/799585 (0.09%)	RR 0.09 (0.04 to 0.17)		⊕⊕◯◯ LOW
								0%		-	

a. None of the studies had a low risk of bias when considering adequate sequence generation, allocation concealment, blinding, incomplete accounting of patients and outcome events. All studies reported on expected outcomes.
b. I squared equals 80%.
c. RR was 0.09 with over 1.6 million participants.

Summary of Findings	**Statement on quality of evidence**	Evidence supports a low degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	Low scientific evidence that single dose of live attenuated hepatitis A vaccines are safe and efficacious to prevent hepatitis A disease.

References

1. Gong J, Li R, Yang J. Protective efficacy of large scale immunization with a live attenuated hepatitis A vaccine (LA-1 strain. Guangxi Journal of Preventative Medicine 2000;6(5):257-259.
2. Jiang S, Huang J, Chen J. The epidemiological Efficacy Assessment of Attenuated Live Hepatitis A Vaccine in Masses in Liuzhou.. Chinese Journal of Epidemiology 1995;16(3):140-142.
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12. Zhang S, Ma J, Han C. Primary research on Efficacy of Attenuated Live Hepatitis A Vaccine. Chinese Journal of Epidemiology 1994;13(6):341-343.

13. Zhang Y, Liu X, Ma J. A field evaluation of the epidemiological efficacy of an attenuated live hepatitis A vaccine (H2 strain). Chinese Journal of Preventative Medicine 2001;35(6):363-365.

Note: this is the systematic review that has been carried out for the 2012 WHO position paper. The summary of findings table has been added for clarity

Annex 7. GRADE table: Hepatitis A vaccine long term protection: Live attenuated single-dose vs no vaccination (2012 systematic review)

Author(s): Ott J, Wiersma S
Date: 28 September 2011

Population: Children and adults

Intervention: single-dose of Live attenuated Hep A vaccine

Comparison: No HAV vaccination

Outcome: Seroprotection rate, Anti HAV Ab geometric median concentration at 7-15 years of vaccination

Question: Should single dose live attenuated hepatitis A vaccine be used for long-term protection against hepatitis A?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose live attenuated hepatitis A vaccine	Control	Relative (95% CI)	Absolute	
Anti-HAV antibodies (follow-up 7-15 years; measured with: GMC, GMT, or % seroprotection post vaccination; Better indicated by lower values)											
5	observational studies	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	871	-	-	GMT range from 80-918[b]	⊕○○○ VERY LOW
Anti-HAV antibodies 15 years after immunization (children, 1-dose, H2 strain LA) (follow-up mean 15 years; Better indicated by lower values)											
1	observational studies	Serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	220[c]	-	-	GMT 128[d]	⊕○○○ VERY LOW

a. Loss to follow-up not always reported. There is also a risk of confounding because other factors potentially associated with antibody response are not considered.
b. Confidence intervals not consistently reported and studies often only reported GMC and not ranges of data.
c. Initially enrolled participants, not clear how many were lost to follow-up.
d. GMC 128, no CI reported. 81% seroconversion rate. No hepatitis A cases reported.

Summary of Findings	**Statement on quality of evidence**	Evidence supports a very low degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	Very low scientific evidence that single dose of live attenuated hepatitis A vaccine provide long term seroprotection against hepatitis A.

References

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5. Zhuang FC, Mao ZA, Jiang LM, Wu J, Chen YQ, Jiang Q, Chen NL, Chai SA, Mao JS. [Long-term immunogencity and effectiveness of live attenuated hepatitis A vaccine (H2-strain)-a study on the result of 15 years' follow up.] Zhonghua Liu Xing Bing Xue Za Zhi. 2010;31:1332-35.

Note: this is the systematic review that has been carried out for the 2012 WHO position paper. The summary of findings table has been added for clarity

Annex 8. GRADE table: Hepatitis A vaccine long term protection: Inactivated 1 vs 2/multiple doses. (3-7 years of follow up) (2021 systematic review)

Authors: N Walsh, J Torres

Date of publication: 29 March 2022

Population: Children 0 - 17 years at the time of vaccination

Intervention: Single dose of inactivated Hep A vaccine

Comparison: Two doses of inactivated Hep A vaccine

Outcome: Hep A disease incidence, seroprotection rate, Anti HAV Ab geometric median concentration at 3-7 years of vaccination

Question: Can single- dose inactivated hepatitis A vaccines be used to confer long–term protection (3-7 years follow up)?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose HAV vaccine (inactivated)**	**two-dose HAV vaccine (inactivated)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Hepatitis A disease incidence (follow up: range 3 years to 7 years; assessed with: Cases of HAV clinical disease)											
1	observational studies	very serious [a,b]	not serious	not serious	not serious	publication bias strongly suspected [b]	0/204 (0.0%)	0/53 (0.0%)	not estimable	**0 fewer per 1 000** (from 30 fewer to 30 more)	⊕◯◯◯ VERY LOW [1]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose HAV vaccine (inactivated)**	**two-dose HAV vaccine (inactivated)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Hepatitis A seroprotection (follow up: range 3 years to 7 years; assessed with: Anti HAV Ab titre > study cut-off)											
5	observational studies	very serious [a]	not serious	not serious	not serious	publication bias strongly suspected [c]	390/403 (96.8%)	827/831 (99.5%)	**RR 1.00** (0.98 to 1.02)	**0 fewer per 1 000** (from 20 fewer to 20 more)	⨁◯◯◯ VERY LOW [1,2,3,4,5]
Geometric mean concentration (follow up: range 3 years to 7 years; assessed with: Anti HAV Ab titre IU/mL)											
4	observational studies	very serious [a]	serious [d]	not serious	not serious	publication bias strongly suspected strong association dose response gradient [c]	289	639	-	MD **188 IU/mL lower** (196.8 lower to 179.2 lower) GMC in comparison group: 289 IU/ml	⨁⨁◯◯ LOW [1,2,3,4]

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environment.

b. Only one study identified.

c. Limited publications. Manufacturers recommend two doses.

d. Heterogeneity difficult to assess. Only one study had 2 arms

Summary of Findings	**Statement on quality of evidence**	Evidence supports a very low degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	Very low scientific evidence that single-dose inactivated hepatitis A vaccines provide long term protection (3-7 years) against hepatitis A disease.

References

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Annex 9. GRADE table: Hepatitis A vaccine long term protection: Inactivated 1 vs 2/multiple doses. (above 7 years of follow up) (2021 systematic review).

Authors: N Walsh, J Torres

Date of publication: 29 March 2022

Population: Children 0 - 17 years at the time of vaccination

Intervention: Single dose of inactivated Hep A vaccine

Comparison: Two doses of inactivated Hep A vaccine

Outcome: Hep A disease incidence, seroprotection rate, Anti HAV Ab geometric median concentration at beyond 7 years of vaccination

Question: Can single- dose inactivated hepatitis A vaccines be used to confer long–term protection (above 7-year follow up)?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose HAV vaccine (inactivated)**	**two-dose HAV vaccine (inactivated)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Hepatitis A disease incidence (follow up: range 7 years to 25 years; assessed with: Cases of HAV clinical disease)											
2	observational studies	very serious [a]	not serious	not serious	serious [b]	none	0/352 (0.0%)	0/51 (0.0%)	**RR 1** (1 to 1)	**0 fewer per 1 000** (from 30 fewer to 30 more)	⨁◯◯◯ VERY LOW [1,2]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose HAV vaccine (inactivated)**	**two-dose HAV vaccine (inactivated)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Hepatitis A seroprotection (follow up: range 7 years to 25 years; assessed with: Anti HAV Ab titre > study cut-off)											
7	observational studies	very serious [a]	serious [c]	not serious	serious [d]	none	342/343 (99.7%)	939/976 (96.2%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1 000** (from 29 fewer to 29 more)	⨁◯◯◯ VERY LOW [1,2,3,4,5,6,7]
Geometric mean concentration (follow up: range 7 years to 25 years; assessed with: IU/mL)											
7	observational studies	very serious [a]	serious [c]	not serious	not serious	publication bias strongly suspected [e]	348	911	-	MD **66.5 IU/mL lower** (68.7 lower to 64.3 lower). GMC in comparison group: 145 IU/mL	⨁◯◯◯ VERY LOW [1,2,3,5,6,7,8]

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environment.

b. The outcome of incidence is not clearly defined and there is infrequent follow-up during the study.

c. Heterogeneity difficult to assess as only one study had two arms.

d. There is variability in the threshold of seroprotection.

e. There are limited publications, and the vaccine manufacturers recommend two doses.

Summary of Findings	**Statement on quality of evidence**	Evidence supports a very low degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	Very low scientific evidence that single-dose inactivated hepatitis A vaccines provide long term protection (above 7 years) against hepatitis A disease.

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Annex 10. GRADE table: Hepatitis A vaccine long term protection: Live attenuated single-dose vs 2/multiple doses of inactivated vaccine (3-7 years of follow up) (2021 systematic review).

Authors: N Walsh, J Torres

Date of publication: 29 March 2022

Population: Children 0 - 17 years at the time of vaccination

Intervention: Single dose of live attenuated Hep A vaccine

Comparison: Two doses of inactivated Hep A vaccine

Outcome: Hep A disease incidence, seroprotection rate, Anti HAV Ab geometric median concentration at 3-7 years of vaccination

Question: Can live attenuated hepatitis A vaccines be used to confer long–term protection (3-7 years follow up)?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose HAV vaccine (live attenuated)**	**two-dose HAV vaccine (inactivated)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Hepatitis A disease incidence (follow up: range 3 years to 7 years)											
2	observational studies	very serious [a,b]	serious [b]	not serious	not serious	publication bias strongly suspected [b]	0/111 (0.0%)	0/53 (0.0%)	**RR 1** (1 to 1)	**0 fewer per 1 000** (from 30 fewer to 30 more)	⨁◯◯◯ VERY LOW [1,2]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose HAV vaccine (live attenuated)**	**two-dose HAV vaccine (inactivated)**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Hepatitis A seroprotection (at study cut-off) (follow up: range 3 years to 7 years)											
6	observational studies	very serious [a,c]	not serious	not serious	not serious	publication bias strongly suspected [b]	1158/1173 (98.7%)	795/799 (99.5%)	**RR 1.00** (0.99 to 1.01)	**0 fewer per 1 000** (from 10 fewer to 10 more)	⨁◯◯◯ VERY LOW [1,2,3,4,5,6]
Hepatitis A GMC (anti-HAV ab titre) (follow up: range 3 years to 7 years)											
5	observational studies	very serious [a,c]	serious [d]	not serious	serious [e]	publication bias strongly suspected strong association dose response gradient [c]	703	639	-	MD **147.6 IU/mL lower** (156.7 lower to 138.5 lower) The GMC in comparison group : 288.9 IU/mL	⨁◯◯◯ VERY LOW [1,2,3,4,6]

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environment.

b. There are no two-dose live attenuated studies in children published.

c. The two-dose group is always inactive vaccine.

d. There is heterogeneity in effect size, including no direction of effect in one study.

e. Wide confidence intervals are reported.

Summary of Findings	**Statement on quality of evidence**	Evidence supports a very low degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	Very low scientific evidence that live attenuated hepatitis A vaccines provide long term protection (3-7 years) against hepatitis A disease.

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Annex 11. GRADE table: Hepatitis A vaccine long term protection: Live attenuated single-dose vs 2/multiple doses of inactivated vaccine (above 7 years of follow up).

Authors: N Walsh, J Torres

Date of publication: 29 March 2022

Population: Children 0 - 17 years at the time of vaccination

Intervention: Single dose of live attenuated Hep A vaccine

Comparison: Two doses of inactivated Hep A vaccine

Outcome: Hep A disease incidence, seroprotection rate, Anti HAV Ab geometric median concentration at beyond 7 years of vaccination

Question: Can live attenuated hepatitis A vaccines be used to confer long–term protection (above 7-year follow up)?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose HAV vaccine (live-attenuated)**	**2 doses HAV vaccine (inactivated)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Hepatitis A disease incidence (follow up: range >7 years to 25 years; assessed with: Cases of HAV clinical disease)											
2	observational studies	very serious [a,b]	serious[b]	not serious	not serious [c]	publication bias strongly suspected[b,c]	0/98 (0.0%)	0/51 (0.0%)	**RR 1** (1 to 1)	**0 fewer per 1 000** (from 30 fewer to 30 more)	⊕◯◯◯ VERY LOW [1,2]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose HAV vaccine (live-attenuated)**	**2 doses HAV vaccine (inactivated)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Hepatitis A seroprotection (follow up: range >7 years to 25 years; assessed with: Anti HAV Ab titre > study cut-off)											
7	observational studies	very serious [a,b]	serious[b]	not serious	serious[d]	publication bias strongly suspected [c]	123/145 (84.4%)	863/881 (98.0%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1 000** (from 29 fewer to 29 more)	⊕◯◯◯ VERY LOW [1,2,3,4,5,6,7,e]
Geometric mean concentration (follow up: range >7 years to 25 years; assessed with: IU/mL)											
7	observational studies	very serious [a,b]	serious[e]	not serious	serious	publication bias strongly suspected [b,c]	98	676	-	MD **65.4 IU/mL lower** (68 lower to 62 lower) The GMC in comparison group : 145 IU/mL	⊕◯◯◯ VERY LOW [1,2,3,4,5,6,7,e]

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environment.

b. There are no 2 dose live attenuated studies in children published.

c. The vaccine manufacturers recommend two doses.

d. There is variability in the threshold of seroprotection.

e. The heterogeneity in effect size difficult to assess given limited single dose live attenuated studies.

Summary of Findings	**Statement on quality of evidence**	Evidence supports a very low degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion	Very low scientific evidence that live attenuated hepatitis A vaccines provide long term protection (above 7 years) against hepatitis A disease.

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Annex 12. SAGE evidence-to-recommendation framework: Should hepatitis A vaccination two doses inactivated vs no intervention, inactive control or placebo be used to prevent hepatitis A disease?

Question:	Should hepatitis A vaccination two doses inactivated vs no intervention, inactive control or placebo be used to prevent hepatitis A disease ?
Population:	Children 0 - 17 years; adults (vaccinated during childhood)
Intervention:	Two doses of inactivated vaccine
Comparison(s):	No intervention, inactive control or placebo
Outcome:	Efficacy, effectiveness (disease seroprotection, GMC titres), long term protection, safety

Background:

Hepatitis A is caused by the hepatitis A virus (HAV) which is transmitted primarily via the faecal/oral route either through ingestion of contaminated food and water or through direct contact with an infectious person. The incidence of hepatitis A is strongly correlated with socioeconomic indicators; with increasing income and access to clean water and adequate sanitation, the incidence of HAV infection decreases *(1-3)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	An estimated 159 million acute hepatitis A cases and 39 000 deaths occurred in 2019, with 2.3 million disability-adjusted life years related to hepatitis A *(4)*.	The burden of disease in 2019 was not equally distributed worldwide. Overall, 66% of acute hepatitis A cases and 97% of hepatitis A deaths occurred in low-income countries and low-middle-income countries. In absolute numbers, South-East Asia had the greatest number of hepatitis A cases (42 million) and deaths (23 711; 60% of the total number of deaths). In terms of rates, hepatitis A disease incidence was highest in the African
		☐	☐	☐	☒		

								Region (3.8 infections per 100 population per year) and hepatitis A-related mortality was highest in South-East Asia and Eastern Mediterranean Region (12 deaths per million population per year).
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒		*Varies* ☐	Vaccine efficacy in a randomised control trial in Thailand on 40 000 children was 94% *(5)*. Vaccine effectiveness has been shown based on disease reduction across many countries *(6-8)*. The impact on the population level depends on the hepatitis A prevalence in the country, but studies all suggest decreased disease incidence post vaccine introduction *(9-13)*.(see Annex 1). Observational studies with follow-up up to 25 years (with two or three doses) suggest long term seroprotection *(14-20)*. (see Annex 8 and Annex 9).	a
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒		*Varies* ☐	Inactivated vaccines have an excellent and well documented safety profile *(21-26)*.	Note that for a population level perspective in high endemicity populations, the risk of paradoxical increase of the disease exists.
	Balance between	*Favours intervention*	*Favours comparison*	*Favours both*	*Favours neither*	Unclear	Efficacy, effectiveness, and seroprevalence data demonstrate a	

	benefits and harms	☒	☐	☐	☐	☐			highly efficacious vaccine that provides long-term protection. The safety profile is excellent. The balance favours clearly the intervention.	
	What is the overall quality of this evidence for the critical outcomes?	**Effectiveness of the intervention** *No included studies* ☐	*Very low* ☒	*Low* ☐	*Moderate* ☐	*High* ☒			The quality of the evidence for efficacy and safety is high (Annex 1). Quality for effectiveness and long-term protection is very low due to the observational studies, with potential confounding bias and important loss to follow up in long time series. (For details see Annex 8, Annex 9, Annex 10, Annex 11)	
		Safety of the intervention *No included studies* ☐	*Very low* ☐	*Low* ☐	*Moderate* ☐	*High* ☒				
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐	*Possibly important uncertainty or variability* ☐	*Probably no important uncertainty or variability* ☒	*No important uncertainty or variability* ☐	*No known undesirable outcomes* ☒			There doesn't seem to be any substantial item on the undesirable outcome side. Hence it is likely that the uncertainty/variability is not important.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐		While, severe disease and risk of fulminant hepatitis is certainly undesirable, based on our review it is not entirely clear in how important the target population is sensitized to the hepatitis A disease (depends on the epidemiology of the disease in a given setting) and thus to the benefits of the vaccine.	
RESOURCE USE	Are the resources required small?	*No* ☒	*Uncertain* ☐	*Yes* ☐	*Varies* ☐				Hepatitis A is a rather costly vaccine (7-20USD, depending on the country), not covered by the GAVI mechanism. The additional	

						programme costs must also be considered.	
	Cost-effectiveness	*No* ☐	*Uncertain* ☐	*Yes* ☐	*Varies* ☒	The opportunity for initiating universal childhood vaccination programme depends on the endemicity of HAV in the country. Studies indicate that the intervention is cost effective (or even cost saving under certain conditions) in intermediate endemicity settings, where virus circulation is still high, but a growing pool of naïve subjects not exposed in early life are at risk of severe hepatitis A disease. *(27)* In high endemicity settings, where children acquire life-long immunity early in life, vaccination is not cost effective. In low and very low endemicity settings the intervention is most likely not cost effective. The paradoxical increase of the disease in a suboptimal coverage situation would further deteriorate the cost effectiveness.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐	*Uncertain* ☐	*Reduced* ☐	*Varies* ☒	The intervention is triggered in LMIC by certain levels of decreased endemicity which shifts infection to older ages. In those settings the intervention would likely decrease inequities as the people who are underserved or disadvantaged (if they are reached by the intervention) are more exposed to the disease due to their living or working conditions.	
ACCEPTABILITY	Which option is acceptable to key stakeholders	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	This depends on the endemicity, and the disease burden.	

	(e.g. ministries of health, immunization managers)?	☐		☐		☐		☐		☒	
	Which option is acceptable to target group?	*Intervention*	*Comparison*	*Both*		*Neither*		*Un-clear*		The vaccine has an excellent safety profile and provides sustained, and long lasting protection against HAV disease which should contribute to acceptance. Provision of audience-tailored information is likely to improve uptake.*(28)*	Specific high risk groups would benefit from targeted approaches/ counselling to improve willingness to receive vaccine *(29)*.
		☒	☐	☐		☐		☐			
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably* No	*Uncertain*		*Probably* Yes		*Yes*	*Varies*	If existing platforms (at least second year of life immunization platform) are used for the programme, the intervention is feasible	
		☐	☐	☐		☒		☐	☐		
BALANCE OF CONSEQUENCES		Undesirable consequences *clearly outweigh* desirable consequences in most settings		Undesirable consequences *probably outweigh* desirable consequences in most settings		The balance between desirable and undesirable consequences *is closely balanced or uncertain*		Desirable consequences *probably outweigh* undesirable consequences in most settings		Desirable consequences *clearly outweigh* undesirable consequences in most settings	
		☐		☐		☐		☐		☒	
TYPE OF RECOMMENDATION		We recommend the intervention		We suggest considering recommendation of the intervention		We recommend the comparison		We recommend against the intervention and the comparison			
		☐		☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations		☐		☐			

RECOMMENDATION (TEXT)	WHO recommends vaccination against hepatitis A virus (HAV) to be introduced into the national immunization schedules for children aged ≥12 months, if indicated on the basis of (1) an increasing trend over time of acute hepatitis A disease, including severe disease, among older children, adolescents or adults, (2) changes in the endemicity from high to intermediate, and (3) considerations of cost-effectiveness. Inactivated hepatitis A vaccines are safe, highly immunogenic and immunization with them generates long-lasting, possibly life-long, protection against hepatitis A in children, as well as in adults. For childhood immunization, inactivated hepatitis A vaccines can be given as a single or 2-dose schedule. For the 2-dose schedule, the doses should be administered intramuscularly (IM) with the first dose given starting from 1 year of age or older and a flexible interval from 6 months up to 4-5 years between the doses, but is usually 6–18 months. To guide country decisions on choice of vaccination strategy (universal childhood immunization versus vaccination of selected high-risk population groups) countries should collect and review the information needed to estimate their national burden of hepatitis A. In addition to surveys estimating age-specific prevalence of anti-HAV IgG antibodies, this may require examining data on hepatitis A incidence, associated morbidity (hospitalization, fulminant hepatic failure or liver transplantation) and mortality. Economic evaluation, including cost-effectiveness analyses of relevant immunization strategies, is a useful additional element for decision-making. In highly endemic countries, almost all persons are asymptomatically infected with HAV in childhood, which prevents clinical hepatitis A in adolescents and adults. In these countries, large-scale vaccination programmes are not routinely recommended, because they carry a risk of a paradoxical increase in disease incidence in unvaccinated people. If a country nevertheless wishes to consider large-scale vaccination, a thorough prior risk-benefit analysis and ensuring a high vaccine coverage are essential to avoid this risk. Countries with improving socioeconomic status may rapidly move from high to intermediate hepatitis A endemicity, rendering a larger proportion of the adolescent and/or young adult population susceptible to HAV infection. In these countries, large-scale hepatitis A vaccination in early childhood is likely to be cost-effective and is therefore recommended. When introducing the vaccine in such situations, countries should consider the need for catch-up immunization based on age-specific seroprevalence rates or other markers of susceptibility. Targeted vaccination of high-risk groups should be considered in low and very low endemicity settings to provide individual health benefits. See special populations section.
IMPLEMENTATION CONSIDERATIONS	Inactivated vaccines can be administered simultaneously with any of the vaccines routinely used in childhood immunization programmes or for travel prophylaxis. Currently, inactivated HAV vaccines are licensed for intramuscular administration in a two-dose schedule with the first dose given at the age 1 year, or older. The interval between the first (primary) dose and the second (booster) dose is flexible (from 6 months up to 4–5 years), but is usually 6–18 months.

MONITORING, EVALUATION AND RESEARCH PRIORITIES	Long term effectiveness of the vaccine has been shown beyond 7 years and up to 25 years. Following introduction of hepatitis A vaccines, regular assessment of their impact using morbidity and mortality surveillance data as well as monitoring seroprotection is important. Modelling studies to describe the relationship between levels of endemicity over time, mean age at infection and increased risk of symptomatic and severe disease are needed to better guide countries on determining the right timing for childhood vaccination introduction.

Annex 13. SAGE evidence-to-recommendation framework: Should single dose hepatitis A vaccination (inactivated or live-attenuated) vs two doses inactivated be used to prevent hepatitis A disease?

Question:	**Should single dose hepatitis A vaccination (inactivated or live-attenuated) vs two doses inactivated be used to prevent hepatitis A disease?**
Population:	Children 0 - 17 years; adults
Intervention:	Single dose of inactivated or live attenuated vaccine
Comparison(s):	Two doses of inactivated vaccine
Outcome:	Efficacy, effectiveness, long term protection, safety

Background:

While inactivated HAV vaccines are licensed in a two-dose schedule, in the past 15-20 years around 20 countries, in Latin America, Asia, Eastern Mediterranean and Europe have introduced universal childhood programme with a one-dose schedule for cost saving reasons.

Conversely, live attenuated vaccines are licensed as single dose vaccines. While these vaccines are not WHO prequalified, they are widely used in China and India.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	An estimated 159 million acute hepatitis A cases and 39 000 deaths occurred in 2019, with 2.3 million disability-adjusted life years related to hepatitis A *(4)*.	The burden of disease in 2019 was not equally distributed worldwide. Overall, 66% of acute hepatitis A cases and 97% of hepatitis A deaths occurred in low-income countries and low-middle-income countries. In absolute numbers, South-East Asia had the greatest number of hepatitis A cases (42 million) and deaths (23 711; 60% of the total number of deaths). In terms of rates, hepatitis A disease incidence was highest in the African
		☐	☐	☐	☒		

								Region (3.8 infections per 100 population per year) and hepatitis A-related mortality was highest in South-East Asia and Eastern Mediterranean Region (12 deaths per million population per year).
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	**Inactivated one dose** Vaccine efficacy against HAV disease in a randomised control trial in Nicaragua in 500 children with a single dose of inactivated vaccine was 85% *(30)*.(Annex 2) A meta-analysis on effectiveness of the long term seroprotection suggests no difference between HAV single-dose vaccine versus multiple-dose vaccine schedules, in terms of disease incidence and seropositivity for follow up to 12 years. A single dose however showed lower GMC IgG titers in one dose vs two-dose schedules. The clinical significance of this is unknown .(see Grade tables (Annex 8 and Annex 9). (very low level of confidence (level 1, or ⊕). **Live attenuated one dose** Vaccine efficacy in 5 RCTs, as summarized in a large meta-analysis on single dose live attenuated HAV schedules was 91% (Grade table 2). **Long term protection**	The WG considered it more adequate to look at the benefits of the intervention (single dose) in its own right (not compared to its comparator on this question). That is why it considers that the benefits are large (compared with doing no intervention).

							A meta-analysis on effectiveness on long term seroprotection suggests no difference between HAV single-dose live attenuated vaccine versus multiple-dose inactivated vaccine schedules, in terms of disease incidence and seropositivity for follow up to 15 years. It however showed lower GMC IgG titers in one dose live attenuated vs two-dose inactivated schedules. The clinical significance of this is unknown. (see Grade tables (Annexes 10 and 11).	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒		*Varies* ☐	**Inactivated** vaccines have an excellent and well documented safety profile *(21-26)*. For **live-attenuated** vaccines, clinical trials and passive surveillance have not identify any safety concern, but the safety profile is less well documented *(3, 26, 31, 32)*.	
	Balance between benefits and harms	*Favours intervention* ☐	*Favours comparison* ☐	*Favours both* ☒	*Favours neither* ☐	Unclear ☐	With a long term follow up of up to 10 to 15 years, the one dose strategies (inactivated or live attenuated) seem to be equally as effective as the two-dose strategy. With the caveat of a less well documented safety profile for the live attenuated vaccine, one and two-dose strategies seems to be equivalent with regards to the benefits and harms balance. It is yet unclear for both dose schedules whether seroprotection has a lifelong duration.	
		Effectiveness of the intervention						

	What is the overall quality of this evidence for the critical outcomes?	*No included studies* ☐	*Very low* ☒	*Low* ☐	*Moderate* ☐	*High* ☒		The quality for efficacy, effectiveness and safety is high for both one- and two-dose schedules. Quality for long term protection is very low in both one- and two-dose schedules due to the observational nature of these studies, with potential confounding bias and important loss to follow up in long time series. For details see Grade tables.	
		Safety of the intervention							
		No included studies ☐	*Very low* ☐	*Low* ☐	*Moderate* ☐	*High* ☒			
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐	*Possibly important uncertainty or variability* ☒	*Probably no important uncertainty or variability* ☐	*No important uncertainty or variability* ☐	*No known undesirable outcomes* ☐		Overall the desired outcome (HAV disease prevention) clearly outweighs harms for these vaccines. However, internationally published evidence on the safety and tolerability of the live attenuated hepatitis A vaccines is more limited.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☒	This is context dependant. In intermediate endemicity contexts where hepatitis A disease prevalence is high (in particular hepatitis fulminans) the desirable effects will be large. A one dose strategy will likely be preferred to a two-dose schedule.	
RESOURCE USE	Are the resources required small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐			In comparison with the two-dose approach the single-dose approach will result in up to 50% cost savings. (see ETR table Annex 12)	
	Cost-effectiveness	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐			The opportunity for initiating universal childhood vaccination programme depends on the endemicity of HAV in the country. Studies indicate that the intervention is cost effective (or	

							even cost saving under certain conditions) in intermediate endemicity settings, where virus circulation is still high, but a growing pool of naïve subjects not exposed in early life are at risk of severe hepatitis A disease. *(27)* In high endemicity settings, where children acquire life-long immunity early in life, vaccination is not cost effective. In low and very low endemicity settings the intervention is most likely not cost effective. The paradoxical increase of the disease in a suboptimal coverage situation would further deteriorate the cost effectiveness. The intervention (one dose) will likely be cost saving than the comparator (two doses).	
EQUITY	What would be the impact on health inequities?	*Increased* ☐	*Uncertain* ☐	*Reduced* ☒	*Varies* ☐		As one dose is the complete series, the effort to reach the disadvantaged population needs only to be made once, not twice. This may increase the ability to reach the most difficult to reach with this interventions. In addition, more resources will be available to reach all the population and potentially to dedicate to reach the underserved or disadvantaged populations.	
ACCEPTABILITY	Which option is acceptable to key stakeholders	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	This will be dependent on the country context i.e. (epidemiological context, current use of two-dose schedule; mandate of NITAGs to	

	(e.g. ministries of health, immunization managers)?	☐	☐	☒	☐	☐	allow for off label recommendations etc.). In countries that currently do not have a routine programme but consider introduction, with expected equal health benefits, stakeholders would very likely favour the intervention approach, as one dose is easier and cheaper to implement than two doses.	
	Which option is acceptable to target group?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☐	The vaccine has an excellent safety profile and provides solid, and long-lasting protection against HAV disease which should contribute to uptake. The one dose schedule and provision of audience-tailored information is likely to improve uptake.*(28)*	Specific high-risk groups should benefit from targeted approaches/ counselling to improve willingness to vaccinate *(29)*.
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably* No ☐	*Uncertain* ☐	*Probably* Yes ☐	*Yes* ☒	*Varies* ☐	A single dose schedule is easier to implement than two-dose schedule.	

BALANCE OF CONSEQUENCES	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒

TYPE OF RECOMMENDATION	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☒	We recommend against the intervention and the comparison ☐

RECOMMENDATION (TEXT)	WHO recommends vaccination against hepatitis A virus (HAV) to be introduced into the national immunization schedules for children aged ⩾12 months, if indicated on the basis of (1) an increasing trend over time of acute hepatitis A disease, including severe disease, among older children, adolescents or adults, (2) changes in the endemicity from high to intermediate, and (3) considerations of cost-effectiveness. Both inactivated and live attenuated hepatitis A vaccines are safe, highly immunogenic and immunization with them generates long-lasting, possibly life-long, protection against hepatitis A in children, as well as in adults. For childhood immunization, inactivated hepatitis A vaccines can be given as a single or 2-dose schedule, and administered intramuscularly (IM). For the 2-dose schedule, the first dose should be given starting from 12 months of age or older. The interval between doses is flexible, from 6 months up to 4–5 years or more, but is usually 6–18 months. Data on vaccine effectiveness, antibody persistence, and modelling on long-term seroprotection indicate that an off-label, single-dose schedule is equivalent to the two-dose schedule in children, in addition to being less expensive and easier to implement. For vaccination with inactivated vaccines of adults above 40 years, the 2-dose schedule should be preferred, since sufficient evidence on the immunogenicity and long-term protection from a single dose in this age group is not available.
IMPLEMENTATION CONSIDERATIONS	Inactivated hepatitis A vaccines produced by different manufacturers, including combined hepatitis A vaccines, are interchangeable. Inactivated vaccines can be administered simultaneously with any of the vaccines routinely used in childhood immunization programmes or for travel prophylaxis. The live attenuated vaccine is administered as a single subcutaneous dose.
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Long term efficacy of the vaccine has been shown beyond 7 years and seroprotection up to 15 years (Live-attenuated vaccine) and 12 year (inactivated vaccines). Following introduction of hepatitis A vaccines, regular assessment of their impact using morbidity and mortality surveillance data as well as monitoring seroprotection is important. The duration of protection induced by single- and two-dose schedules should be regularly monitored. Modelling studies to describe the relationship between levels of endemicity over time, mean age at infection and increased risk of symptomatic and severe disease are needed to better guide countries on determining the right timing for childhood vaccination introduction. Further data need to be generated on individuals vaccinated by a single dose of inactivated vaccine during adult age, in particular when over 40 years, to confirm long-term protection.

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