GRADE Hepatitis A vaccine for persons experiencing homelessness

Hepatitis A (HepA) vaccine is a highly effective and a well-understood vaccine over the years. A two-dose inactivated HepA vaccine can induce protective efficacy of >90% and prevent hepatitis A infection. HepA vaccines have been effective in ending and controlling outbreaks in the homeless. During February 2018– October 2018, the ACIP Hepatitis Work Group held monthly conference calls to review and discuss relevant scientific evidence, including homelessness as an indication for HepA vaccine. The ACIP Hepatitis Work Group evaluated the quality of evidence related to the benefits and harms of administering HepA vaccine to persons experiencing homelessness using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.

The evidence assessing benefits and harms of administering a HepA vaccine to prevent HAV infection in persons experiencing homelessness was determined to be GRADE evidence type 4 (i.e., evidence from clinical experience and observations, observational studies with important limitations, or clinical trials with several major limitations).

Policy Question: Should routine inactivated two-dose hepatitis A vaccination be recommended for protection against hepatitis A among persons experiencing homelessness?

Population	Homeless (all ages)
Intervention	Inactivated hepatitis A vaccine administered
Control	Unvaccinated homeless individuals
Outcomes	**Benefits**: • Reduction in disease burden (hepatitis A virus [HAV]-related disease and fulminant hepatitis A) • Protection against HAV related disease (efficacy, immunogenicity) **Harms:** • Local reactions: injection site pain/tenderness, erythema, fever, malaise, headache, loss of appetite drowsiness, irritability • Systemic adverse events: anaphylaxis, transient purpura, interference with other vaccines

Outcome measures included in evidence profile

Outcomes	Importance
Benefit 1. Reduction in disease burden	Critical
Harms 1. Serious adverse events	Critical

Evidence types

Initial Evidence Type	Study Design
1	Randomized controlled trials (RCTs) or overwhelming evidence from observational studies
2	RCTs with important limitations, or exceptionally strong evidence from observational studies
3	Observational studies, or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

GRADE of Evidence for Hepatitis A vaccines among homeless: Benefits
Outcome #1

Author, year	Study Design	No. of subjects	Population	Outcome
Poulos et al., 2010	Clinical trial (4)	201	Mean age 42 years, Sydney, Australia	Outbreak was controlled No mention of the reduction of cases or percent of hepatitis A cases after vaccination

One study was included in the final review. The study was published in 2010 in Sydney, Australia. It was a clinical trial in which 201 homeless individuals (mean age 42 years) were immunized. A single dose of HAVRIX 1440 ELU (ELISA units of inactivated HAV) was given at a federally funded clinic. There was no comparison group, and the main outcome demonstrated the outbreak was controlled with no information presented on the reduction of cases or the percent of hepatitis A cases seen after vaccination.

References:
1.   Poulos, R. G., Ferson, M. J., Orr, K. J., McCarthy, M. A., Botham, S. J., Stern, J. M. and Lucey, A. (2010), Vaccination against hepatitis A and B in persons subject to homelessness in inner Sydney: vaccine acceptance, completion rates and immunogenicity. Australian and New Zealand Journal of Public Health, 34: 130-135. doi:10.1111/j.1753-6405.2010.00496.x

GRADE of Evidence for Hepatitis A vaccines among homeless: Harms
Outcome #1

Author, year	Study Design	No. of subjects	Population	Outcome
Poulos et al, 2010	Clinical trial	201	Homeless Mean age 42 years, Sydney, Australia	No information on adverse events
James et al, 2009	Observational	122	Homeless, substance users and incarcerated persons Age > 21 years Boston, United States	Reported no adverse reactions/events
Tjon et al, 2005	Observational	1,515	Homeless Mean age 42 years Rotterdam, Netherlands	Reported 4 jaundice cases after vaccination. Probably due to vaccine failure where person was already infected at time of vaccination
Weatherill et al, 2004	Observational	3,542	Vulnerable population Median age 46 years Vancouver, Canada	Early 2000 – Reported no adverse reactions or events Fall 2000 – Multiple vaccines (influenza, pneumococcal, and hepatitis A) administered together. Reported 3 cases of anaphylaxis and 8 cases occulo-respiratory syndrome

Of the four studies that were reviewed, two studies reported no adverse reactions or events after vaccination. One study reported four jaundice cases after vaccination, among adults mean aged 42 years. The author indicated it probably was due to vaccine failure where the study participants may have been already infected at the time of vaccination. Another study where adverse events were reported (3 cases of anaphylaxis and 8 cases of oculo-respiratory syndrome) occurred after multiple vaccines were administered together (influenza, pneumococcal, and hepatitis A vaccine) among vulnerable adults with mean age 46 years.

References:
1. Poulos, R. G., Ferson, M. J., Orr, K. J., McCarthy, M. A., Botham, S. J., Stern, J. M. and Lucey, A. (2010), Vaccination against hepatitis A and B in persons subject to homelessness in inner Sydney: vaccine acceptance, completion rates and immunogenicity. Australian and New Zealand Journal of Public Health, 34: 130-135. doi:10.1111/j.1753-6405.2010.00496.x
2. James, Thea & Aschkenasy, Miriam & J Eliseo, Laura & Olshaker, Jonathan & Mehta, Supriya. (2008). Response to Hepatitis A Epidemic: Emergency Department Collaboration with Public Health Commission. The Journal of emergency medicine. 36. 412-6. 10.1016/j.jemermed.2007.10.001.
3. Tjon G. M., Goetz H., Koek A. G., de Zwart O., Mertens P. L., Coutinho R. A., Bruisten S. M. (2005). An outbreak of hepatitis A among homeless drug users in Rotterdam, The Netherlands. J. Med. Virol. 77, 360–36610.1002/jmv.20464
4. Weatherill S. A., Buxton J. A., Daly P. C. (2004). Immunization programs in non-traditional settings. Can. J. Public Health 95, 133–137

GRADE SUMMARY

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type	Overall evidence type
BENEFIT*							
Reduction in disease burden	1 clinical trial	Serious	Serious	Serious	Serious	4	**
HARMS*							
Serious adverse events	1 clinical trial 3 observational studies	Serious	Serious	Serious	Serious	4	⊕⊖⊖⊖ VERY LOW

*Limitations in determining the estimates of the effect as no study had a comparison group available.

**Unable to determine the overall quality of evidence as only one was study available for GRADE.

For the benefit outcome, there was only one clinical trial, which was not conducted in the United States. The study had a serious risk of bias, inconsistency, indirectness and imprecision and hence was downgraded to an evidence type 4. There was no comparison group; thus, the estimates of the effect could not be determined. The magnitude of the effect remains unexplained, thereby decreasing the quality of evidence. We were unable to determine the overall quality of evidence and to complete the GRADE analysis process for the benefit outcome.

For the harms outcome, there were three observational studies and one clinical trial The studies were weak and had no comparison groups. One study that was included in the review did not report any information on adverse events or reactions. Studies which reported on adverse events had limitations as well. One study had multiple vaccines administered along with hepatitis A vaccine; thus, we were unable to determine which vaccine caused the adverse events. In another study, the author indicated that reported cases of jaundice after vaccination may have occurred due to vaccine failure, and that the person may have already been infected at time of vaccination. Hence, evidence type was downgraded to level 4, and the overall quality of evidence was rated as very low using the judgment criteria. Due to lack of confidence intervals and relative risks among the studies, we were not able to compare the estimates of effects across studies.

Evidence to Recommendation Framework

Purpose of the framework:

The purpose of the framework is to help panels developing guidelines move from evidence to recommendations. It is intended to:
- Inform panel members' judgements about the pros and cons of each option (intervention) that is considered
- Ensure that important factors that determine a recommendation (criteria) are considered
- Provide a concise summary of the best available research evidence to inform judgements about each criterion
- Help structure discussion and identify reasons for disagreements
- Make the basis for recommendations transparent to guideline users

CRITERIA	JUDGEMENTS:
Criteria 1: Is the problem a public health priority?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies
Criteria 2: How substantial are the desirable anticipated effects? (Beneficial effects of vaccination)	☐ Minimal ☐ Small ☐ Moderate ☒ Large ☐ Don't know ☐ Varies
Criteria 3: How substantial are the undesirable anticipated effects? (serious adverse events)	☒ Minimal ☐ Small ☐ Moderate ☐ Large ☐ Don't know ☐ Varies
Criteria 4: Do the desirable effects outweigh the undesirable effects?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies
Criteria 5: What is the overall certainty of the evidence for critical outcomes? GRADE	Evidence type 4 Overall evidence type for harms – Very Low
Criteria 6: Does the target population feel that the desirable effects are large relative to the undesirable effects?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies
Criteria 7: Is there important uncertainty about or variability in how much people value the main outcomes?	☐ No ☐ Probably No ☒ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies
Criteria 8: Is the option acceptable to stakeholders?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies
Criteria 9: Is the option a reasonable and efficient allocation of resources?	☐ No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies
Criteria 10: Is the option feasible to implement?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies

Balance of Consequences:

Desirable consequences clearly outweigh undesirable consequences in most settings

Conclusion:

Based on the Evidence to Recommendation Framework, it was concluded that the benefit achieved by vaccinating homeless individuals is significant, and the cost and risk of vaccinating the homeless individual is much lower versus not vaccinating the homeless individuals.