GRADE Hepatitis A vaccine for post-exposure prophylaxis in adults >40 years of age

Noele Nelson, MD, PhD, MPH

CDC Lead, ACIP Hepatitis Vaccines Work Group

Advisory Committee on Immunization Practices

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GRADE Process

- Develop policy questions
- Consider critical outcomes
- Review and summarize evidence of benefits and harms
- Evaluate quality of evidence
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendation and GRADE category

Policy Question: Should hepatitis A vaccine be recommended instead of immune globulin (IG) as post-exposure prophylaxis for prevention of hepatitis A disease in adults >40 years of age?

Population	Healthy adults >40 years of age
Intervention	Hepatitis A vaccine administered within 14 days of exposure
Comparison	Immune globulin administered within 14 days of exposure
Outcomes	• Hepatitis A infection • Deaths • Hospitalizations • Adverse events • Immunogenicity

Outcome measures included in evidence profile

Outcomes	Importance
Benefit	
1. Immunogenicity	Critical
Harms	
1. Hepatitis A infection	Critical
2. Deaths	Critical
3. Hospitalizations	Critical
4. Adverse events	Critical

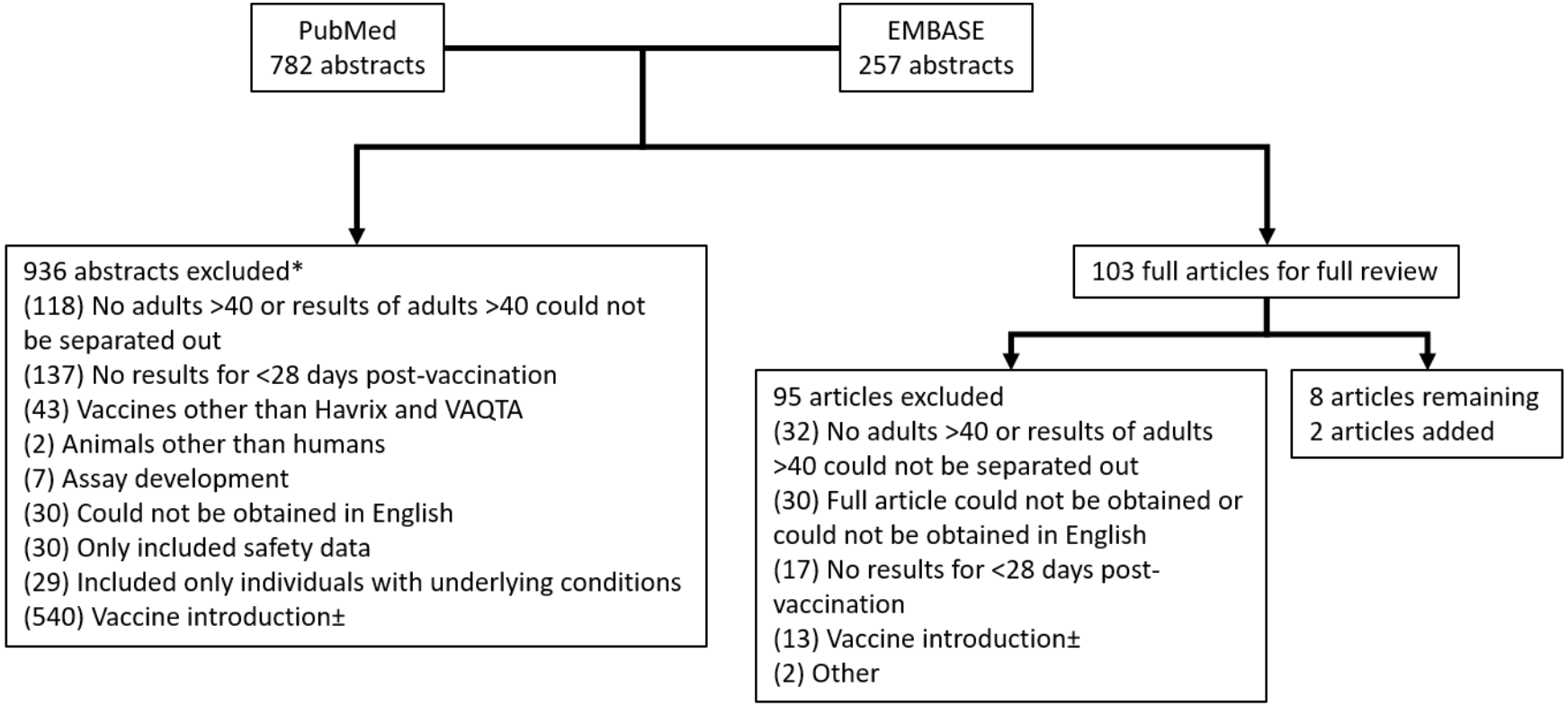
Evidence Retrieval

- Systematic review of data on hepatitis A vaccine in adults aged >40 years, including a search of PubMed and EMBASE from January 1, 1992 through January 7, 2017
- Search terms included: “hepatitis A vaccine*” and “HAV vaccin*”
- Articles in adult humans were included
- No language restrictions on initial searches and included articles from any country

Evidence Retrieval

- *Exclusion criteria*
  - Articles focused solely on children or articles that did not provide information on ages of included individuals
  - Articles that did not include data on HAVRIX or VAQTA (the two single antigen hepatitis A (HepA) vaccines currently licensed in the United States)
  - Articles that only included safety data or discussed vaccine introduction without providing new data
  - Articles which only reported data on individuals with underlying conditions
  - Articles that only provided data ≥28 days after the first dose of HepA vaccine as these data would not be applicable in an outbreak setting

Evidence Retrieval



* Articles may have had multiple reasons for exclusion. Only the primary reason, in the order listed above, was counted.
± Includes articles aimed at assessing the need for vaccine but which do not provide data useful for the current analysis: serosurveys before/after vaccine introduction, outbreak investigations without vaccines, opinion pieces about introducing vaccines, vaccine coverage studies, cost effectiveness of introducing routine vaccination, vaccine recommendations are outdated and/or do not address outbreak settings for adults >40

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 in persons age >40 years: Benefits

Outcome #1: Immunogenicity*

Author, year	Study Design	No. of subjects	Population	Immunogenicity results
Briem et al., 1994	3	60	40 to 62 years, Iceland	Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: **77%** GMT at 15 days: 262 mIU/mL (range: 65-995 mIU/mL)
Reuman et al., 1997[a]	3	23	≥ 40 years, U.S.	Seroconversion (≥10 mIU/mL anti-HAV) at 2 weeks: **31%** GMT at 2 weeks: 6.1 mIU/mL
Van Der Meeren et al., 2015	3	80	≥ 40 years, Belgium, Finland, Iceland	Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: **79.7%** (68.8-88.2%) GMT at 15 days: 126.5 mIU/mL (88.6-180.7 mIU/mL)
Goilav et al., 1995	3	306	Mean age 24 years (range 18-63), UK, Belgium, Germany, France	Seroconversion (≥20 mIU/mL anti-HAV) at 2 weeks: **76.1%** (95% CI: 71.2-81.1%) GMT at 2 weeks: 30.8 mIU/mL (95% CI: 28.1-33.7)
Bertino et al., 1998[b]	3	153	≥ 30 years (median age 42 years), U.S.	Seroconversion (≥10 mIU/mL anti-HAV) at 2 weeks: **46%** GMT at 2 weeks: 10.0 mIU/mL
Williams et al., 2000[c]	1	149	Mean age 42, Alaska Natives	See results for Nelson et al., 2014[a]
Nelson et al., 2014[c]	3	172	40-49 years; 50-59 years; ≥ 60 years, Alaska Natives	Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: 40-49 years: **74%** (n=125); 50-59 years: **54%** (n=37); ≥ 60 years: **30%** (n=10) GMTs at 15 days: 40-49 years: 26.09 mIU/mL (n=125); 50-59 years: 12.80 mIU/mL (n=37); ≥ 60 years: 1.62 mIU/mL (n=10)

*No immune globulin comparator studies were identified in the systematic review

[a]VAQTA 25U

[b]VAQTA 50U results shown

[c]Nelson et al. 2014 is a reanalysis of Williams et al., 2000 with defined age groups.

GRADE of Evidence for Hepatitis A vaccines in persons age >40 years: Harms

Outcome #1-4

Author, year	Study Design	No. of subjects	Population	Outcome
Briem et al., 1994	3	60	40 to 62 years, Iceland	Adverse events
Reuman et al., 1997	3	23	≥ 40 years, U.S.	Adverse events
Van Der Meeren et al., 2015	3	80	≥ 40 years, Belgium, Finland, Iceland	Adverse events
Goilav et al., 1995	3	306	Mean age 24 years (range 18-63), UK, Belgium, Germany, France	Adverse events
Bertino et al., 1998	3	153	≥ 30 years (median age 42 years)	Adverse events
Nelson et al., 2014 (Williams et al., 2000)	3	172	40-49 years; 50-59 years; ≥ 60 years, Alaska Native	Adverse events
Parrón et al., 2017	3	80	>40 years, Catalonia	Hepatitis A infection, deaths, hospitalizations, adverse events
Freeman et al. 2014	3	40 (90)	≥40, Australia	Hepatitis A infection, deaths, hospitalizations, adverse events
Whelan et al., 2013	3	10	≥41 years, Netherlands	Hepatitis A infection, deaths, hospitalizations, adverse events

Outcome #1-4

Outcome	No. of subjects (# studies)	Incidence in comparison group	Incidence in vaccinated	Vaccine efficacy	Absolute risk	Number needed to vaccinate
Hepatitis A infection	130 (3 observational)	N/A	4 cases (3.1%)	N/A	N/A	N/A
Deaths	130 (3 observational)	N/A	None reported	N/A	N/A	N/A
Hospitalizations	130 (3 observational)	N/A	None reported	N/A	N/A	N/A
Serious adverse events	974 (9 observational)	N/A	None reported	N/A	N/A	N/A

GRADE Summary

Evidence Types

- ⨁⨁⨁⨁/A/High/**Evidence Type 1**: We are very confident that the true effect lies close to that of the estimate of the effect.
- ⨁⨁⨁◯ /B/Moderate/**Evidence Type 2:** 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.
- ⨁⨁◯◯ /C/Low/**Evidence Type 3**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- ⨁◯◯◯/D/Very low/**Evidence Type 4**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Limitations

- No randomized controlled trials were identified comparing hepatitis A vaccine and immune globulin in healthy adults >40 years of age
- Only one study (sub-analysis) contained immunogenicity data on discrete age ranges over age 40 years
- No articles provided explicit estimates of the efficacy of HepA vaccine in adults >40 year of age against disease endpoints
- Most studies included persons from outside of the U.S. (Europe, UK, Australia), though they may be similar populations to the U.S.

GRADE SUMMARY

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type	Overall evidence type
BENEFIT							
Immunogenicity	6 observational	No serious	Serious (-1)[b]	Serious (-1)[c]	Serious (-1)[d]	4	4
HARMS							
Hepatitis A incidence	3 observational	Serious (-1)[a]	No serious	No serious	No serious	4	4
Deaths	3 observational	Serious (-1)[a]	No serious	No serious	No serious	4	
Hospitalizations	3 observational	Serious (-1)[a]	No serious	No serious	No serious	4	
Serious adverse events	9 observational	No serious	No serious	No serious	No serious	3	

[a]Two of three studies were surveillance, with little information provided about the potential for missed follow-up.
[b]Immunogenicity results in older adults showed high variability by study, with orders of magnitude differences in GMT results.
[c]Four of six studies did not provide results broken down by age group, included younger individuals, or did not provide details on age ranges.
[d]Studies included very few adults in the oldest age groups. Only one study provided results for adults >60 years and this included only 10 subjects.

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References

[1]Wiseman R, Weil LM, Lozano C, Johnson TJ, Jr., Jin S, Moorman AC, et al. Notes from the Field: Health Care-Associated Hepatitis A Outbreak - Texas, 2015. MMWR Morbidity and mortality weekly report 2016 Apr 29;65(16):425-6.

[2]Collier MG, Khudyakov YE, Selvage D, Adams-Cameron M, Epson E, Cronquist A, et al. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. Lancet Infect Dis 2014 Oct;14(10):976-81.

[3]Bohm SR, Berger KW, Hackert PB, Renas R, Brunette S, Parker N, et al. Hepatitis A outbreak among adults with developmental disabilities in group homes--Michigan, 2013. MMWR Morbidity and mortality weekly report 2015 Feb 20;64(6):148-52.

[4]Advisory Committee on Immunization P, Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports 2006 May 19;55(RR-7):1-23.

[5]Advisory Committee on Immunization Practices Centers for Disease C, Prevention. Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morbidity and mortality weekly report 2007 Oct 19;56(41):1080-4.

[6]Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med 2007 Oct 25;357(17):1685-94.

[7]Srivastava A, Aggarwal R. Hepatitis A vaccine versus immunoglobulin for post-exposure prophylaxis. The National medical journal of India 2007 Nov-Dec;20(6):302-3.

[8]Ridpath A, Reddy V, Layton M, Misener M, Scaccia A, Starr D, et al. Hepatitis A Cases Among Food Handlers: A Local Health Department Response-New York City, 2013. J Public Health Manag Pract 2017 Feb 03.

[9]Tejada-Strop A, Costafreda MI, Dimitrova Z, Kaplan GG, Teo CG. Evaluation of Potencies of Immune Globulin Products Against Hepatitis A. JAMA Intern Med 2017 Mar 01;177(3):430-2.

[10]Briem H, Safary A. Immunogenicity and safety in adults of hepatitis A virus vaccine administered as a single dose with a booster 6 months later. J Med Virol 1994 Dec;44(4):443-5.

[11]Reuman PD, Kubilis P, Hurni W, Brown L, Nalin D. The effect of age and weight on the response to formalin inactivated, alum-adjuvanted hepatitis A vaccine in healthy adults. Vaccine 1997 Jul;15(10):1157-61.

[12]Van Der Meeren O, Crasta P, de Ridder M. A retrospective pooled analysis assessing the effect of age on the immunogenicity of Havrix in healthy adults. Human vaccines & immunotherapeutics 2015;11(7):1729-34.

References

[13]Goilav C, Zuckerman J, Lafrenz M, Vidor E, Lauwers S, Ratheau C, et al. Immunogenicity and safety of a new inactivated hepatitis A vaccine in a comparative study. Journal of medical virology 1995 Jul;46(3):287-92.

[14]Bertino JS, Jr., Thoelen S, VanDamme P, Bryan JP, Becherer PR, Frey S, et al. A dose response study of hepatitis A vaccine in healthy adults who are > or = 30 years old and weigh > or = 77 kg. J Infect Dis 1998 Oct;178(4):1181-4.

[15]Whelan J, Sonder GJ, Bovee L, Speksnijder A, van den Hoek A. Evaluation of hepatitis A vaccine in post-exposure prophylaxis, The Netherlands, 2004-2012. PLoS One 2013;8(10):e78914.

[16]Freeman E, Lawrence G, McAnulty J, Tobin S, MacIntyre CR, Torvaldsen S. Field effectiveness of hepatitis A vaccine and uptake of post exposure prophylaxis following a change to the Australian guidelines. Vaccine 2014 Sep 22;32(42):5509-13.

[17]Parron I, Planas C, Godoy P, Manzanares-Laya S, Martinez A, Sala MR, et al. Effectiveness of hepatitis A vaccination as post-exposure prophylaxis. Human vaccines & immunotherapeutics 2017 Feb;13(2):423-7.

[18]Nelson NP, Murphy TV, McMahon BJ. Hepatitis A vaccination for post-exposure prophylaxis in persons aged 40 years and older. Vaccine 2014 May 23;32(25):2939.

[19]Williams J, Fox-Leyva L, Christensen C, Fisher D, Schlicting E, Snowball M, et al. Hepatitis A vaccine administration: comparison between jet-injector and needle injection. Vaccine 2000 Mar 17;18(18):1939-43.

[20]Australian Goverment Department of Health. National Guidelines for Public Health Units. 2009 [cited 2017 19 June]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/FB28A405CBF6E64ECA257BF0001DAB33/$File/hepa-song.pdf

[21]Vacuna Antihepatitis A. Guia Practica de Enfermedades y Vacunas 2014 [cited 2017 19 June]; Available from: http://www.vacunacion.com.ar/index.php/enfermedades-y-vacunas/hepatitis-a/vacuna-antihepatitis-a

[22]Public Health Ontario. Hepatitis A Post-exposure Prophylaxis. 2013 [cited 2017 19 June]; Available from: http://www.publichealthontario.ca/en/eRepository/Hepatitis_A_Post_exposure_Prophylaxis_2013.pdf

[23]National Advisory Committee on Immunization. Update on the Recommended use of Hepatitis A Vaccine. In: Public Health Agency of Canada, editor., 2016.

[24]Ministry of Health - Israel. Guidelines for Vaccination. In: Department of Epidemiology, editor., 2015.

[25]Lucy Thomas and the Hepatitis A Guidelines Group. Guidance for the Prevention and Control of Hepatitis A Infection. 2014 [cited; Available from: http://webarchive.nationalarchives.gov.uk/20140714084352/http:/www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1259152095231

[26]Grifols Therapeutics Inc. Important change in prescribing information. 2017 7 July 2017 [cited; Available from: https://www.hypermunes.com/documents/24720443/24803488/Healthcare+Provider+Letter+GamaSTAN+SD+Revised+Dosage+July+7+2017_with+LIT+CODE.pdf/b831e517-9d0b-472c-b5b5-719f5bb5e47c

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