# Updated ACIP recommendations for use of hepatitis A vaccine and immune globulin for post-exposure prophylaxis and for international travelers

## Advisory Committee on Immunization Practices
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# Outline

- Postexposure prophylaxis (PEP)
  - Current ACIP recommendations
  - ACIP hepatitis workgroup deliberations
  - Current context
  - Draft updates
- International travel
- Questions/discussion

Advisory Committee on Immunization Practices, Centers for Disease Control & 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 Morb Mortal Wkly Rep 2007;56:1080-1084.

# 2007 ACIP Recommendations for HAV PEP

- **Close personal contact**
  - Previously unvaccinated household and sexual contacts
  - Persons who have shared illicit drugs
  - Considerations: other types of ongoing, close personal contact
- **Child care centers**
  - Previously unvaccinated staff and attendees if hepatitis A recognized in attendees or families
  - In an outbreak setting, household members of attendees in diapers
- **Common-source exposure**
  - Food handlers at establishment where another food handler has hepatitis A
  - Patrons ≤ 2 weeks after exposure if food handler also had poor hygiene
- **Schools, hospitals, and work settings**
  - Only if epidemiologic investigation indicates transmission at facility
  - Not needed for hospital staff, as long as appropriate personal protective equipment used

used

Advisory Committee on Immunization Practices, Centers for Disease Control & 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 Morb Mortal Wkly Rep 2007;56:1080-1084.

# Current ACIP Recommendations for HAV Post-Exposure Prophylaxis

| Group | Recommendation |
|---|---|
| Children < 12 months, immunocompromised, chronic liver disease, vaccine contraindication | IG (0.02 mL/kg) |
| Healthy persons 12 months – 40 years | HepA vaccine |
| Adults > 40 years | IG (0.02 mL/kg) preferred; vaccine if IG cannot be obtained |

MMWR. October 19, 2007: www.cdc.gov/mmwr/preview/mmwrhtml/mm5641a3.htm

# Workgroup deliberations

- Discussion of concerns about use of IG
- Workgroup consensus on the need to update recommendations
- Systematic review of data on hepatitis A vaccine vs. IG
- Draft updated recommendations

# Current Context: Immunoglobulin potency

- Potential decreased potency[1,2]
  - Lower prevalence of HAV antibodies in plasma donors
  - Low anti-HAV potencies in recently tested IG lots

[1] Zaaijer HL, et al. Hepatitis A antibody titers after infection and immunization: implications for passive and active immunization. J Med Virol. 1993;40(1):22-27.
[2] Tejada-Strop A, et al. Evaluation of Potencies of Immune Globulin Products Against Hepatitis A. JAMA Intern Med. 2017;177(3):430-432.

# Current Context: Immunoglobulin potency

- Decreased potency[1,2]
  - Lower prevalence of HAV antibodies in plasma donors
  - Low anti-HAV potencies in recently tested IG lots
- Limited availability
  - Multistate outbreak associated with frozen pomegranate arils (2013)[3]
  - Imported frozen scallops in Hawaii (2016)
  - Multistate outbreak associated with frozen strawberries (2016)
  - Hepatitis A cases among food handlers in New York City (2013)[4]

[1] Zaaijer HL, et al. Hepatitis A antibody titers after infection and immunization: implications for passive and active immunization. J Med Virol. 1993;40(1):22-27.
[2] Tejada-Strop A, et al. Evaluation of Potencies of Immune Globulin Products Against Hepatitis A. JAMA Intern Med. 2017;177(3):430-432.
[3] Collier MG, et al. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. Lancet ID. 2014;14(10):976-981.
[4] Ridpath A, Reddy V, Layton M, Misener M, Scaccia A, Starr D, Stavinsky F, et al. Hepatitis A Cases Among Food Handlers: A Local Health Department Response-New York City, 2013. J Public Health Manag Pract 2017.

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  - Hepatitis A cases among food handlers in New York City (2013)[4]
- Shorter immunity

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[2] Tejada-Strop A, et al. Evaluation of Potencies of Immune Globulin Products Against Hepatitis A. JAMA Intern Med. 2017;177(3):430-432.
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# Available research on IG for PEP

- 2007 ACIP recommendations based on Victor et al. study in Kazakhstan[1]
  - Individuals 2 to 40 years randomized to IG or vaccine
  - Noninferiority criteria were met
    - Assuming 90% IG efficacy, point estimate of vaccine efficacy is 86% (95% CI 73-93%)
    - Assuming 80% IG efficacy, point estimate of vaccine efficacy is 73% (95% CI 47-86%)
  - Risk of hepatitis A among vaccine recipients was never > 1.5% greater than among IG recipients
- No studies have assessed IG vs. vaccine in discrete age groups > 40 years

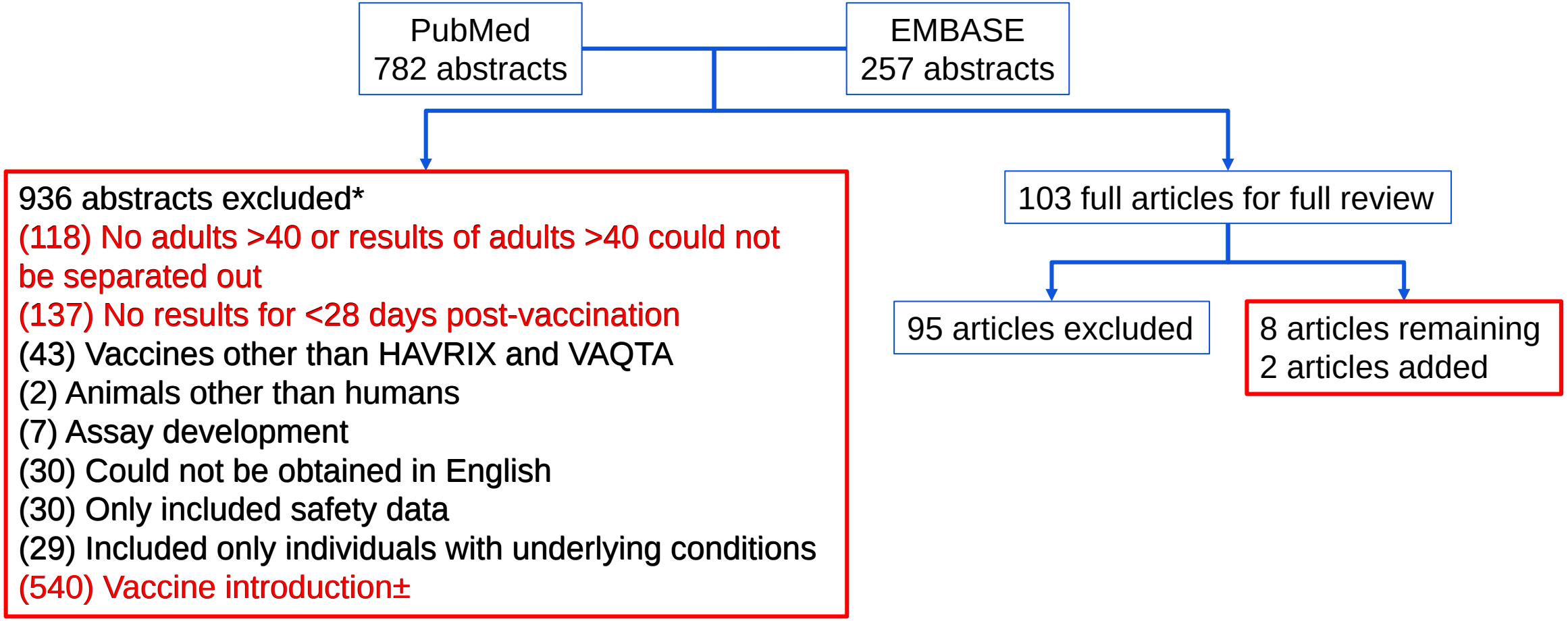
[1] Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, Favorov MO, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med 2007;357:1685-1694.

# Methods: Systematic review of data on vaccine vs. IG in adults >40 years of age

- Search PubMed and EMBASE from 1992 – 2017
- Included articles with data on HAVRIX, VAQTA, or IG in adults >40 years
- Immunogenicity and disease endpoints, surveillance data, case studies
- Included only results within 2 weeks of vaccination/IG administration
- 2 reviewers for each abstract
- GRADE will be conducted

Link-Gelles, Hofmeister, Nelson, *Vaccine* (in preparation)

# Results: Articles included



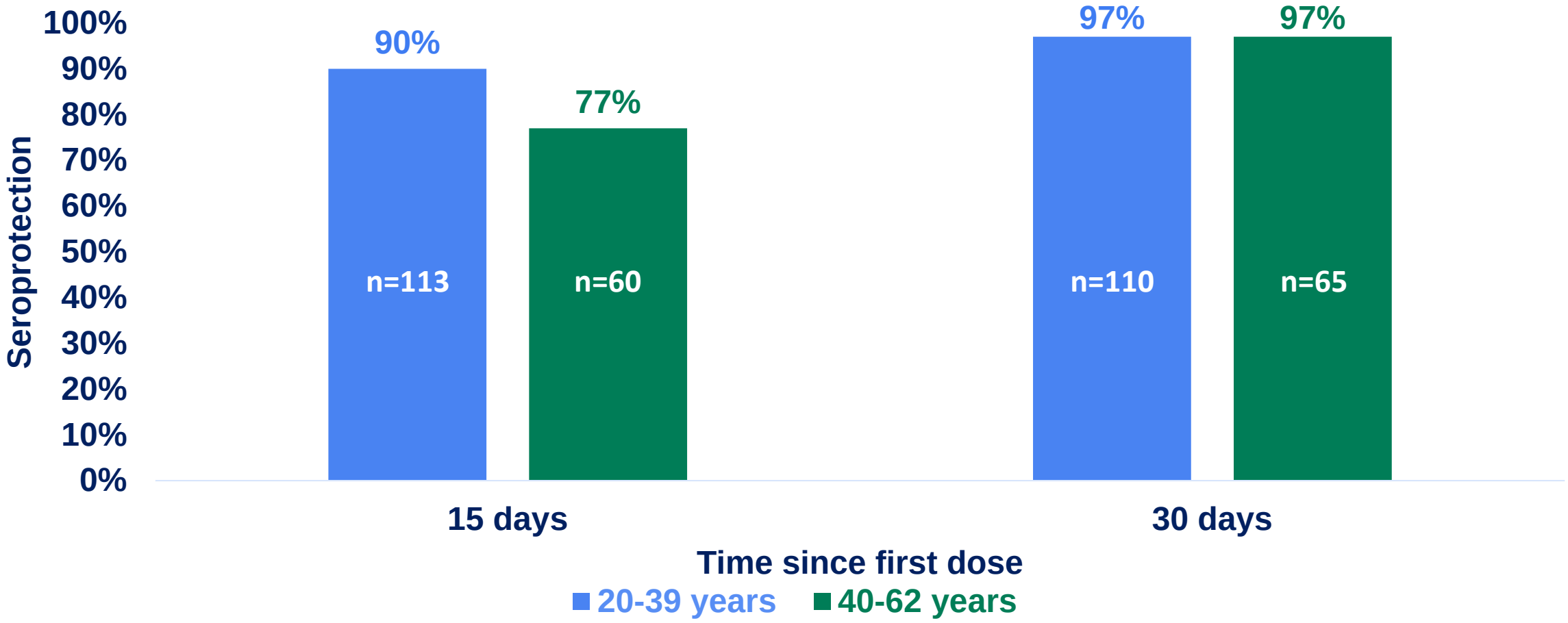

* Articles may have had multiple reasons for exclusion. Only the primary reason, in the order listed above, was counted.

± 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

# Results: Variability by study

- Different vaccines
  - HAVRIX 1440 EL.U.
  - VAQTA 25, 50, 100 U
- Seroprotection cutoff
  - Anti-HAV ≥ 10 mIU/mL or anti-HAV ≥ 20 mIU/mL

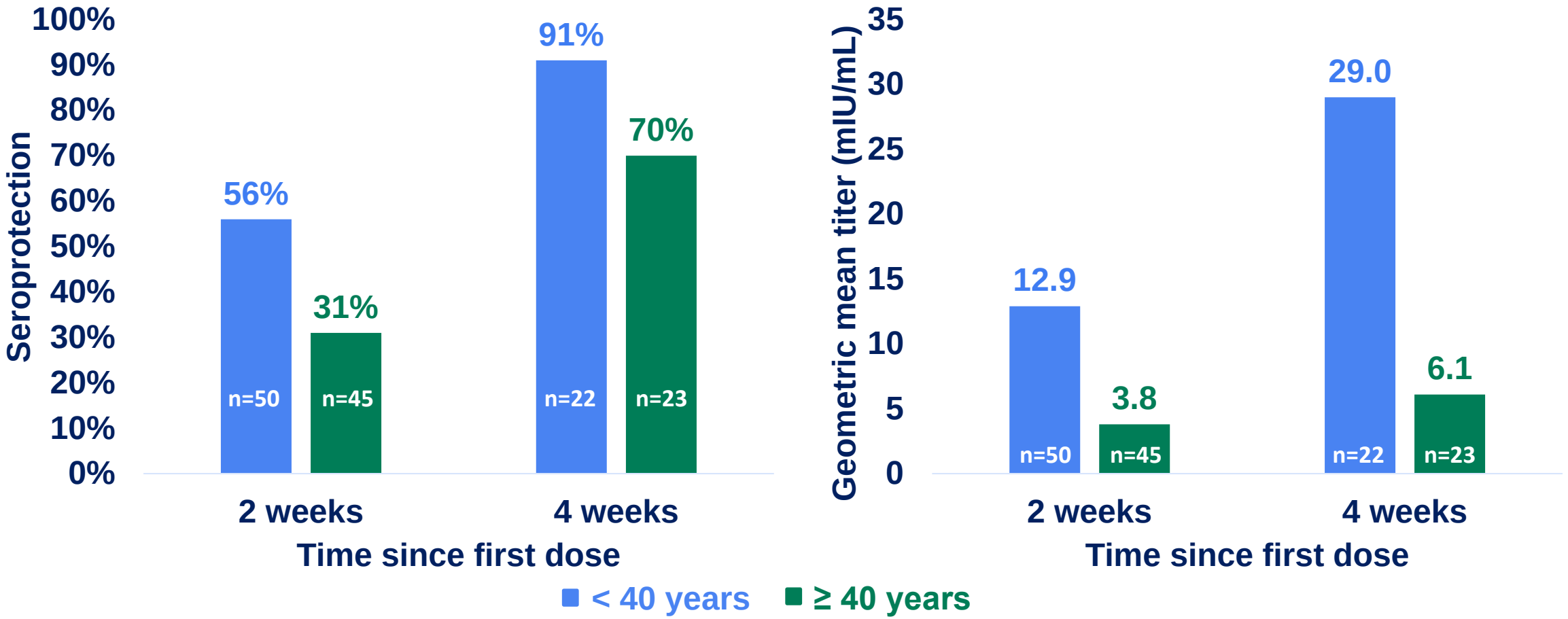
# Results: Briem et al. (1994)




Vaccine: Havrix 1440 EL.U.; Protection: anti-HAV ≥ 20 mIU/mL

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;44:443-445.

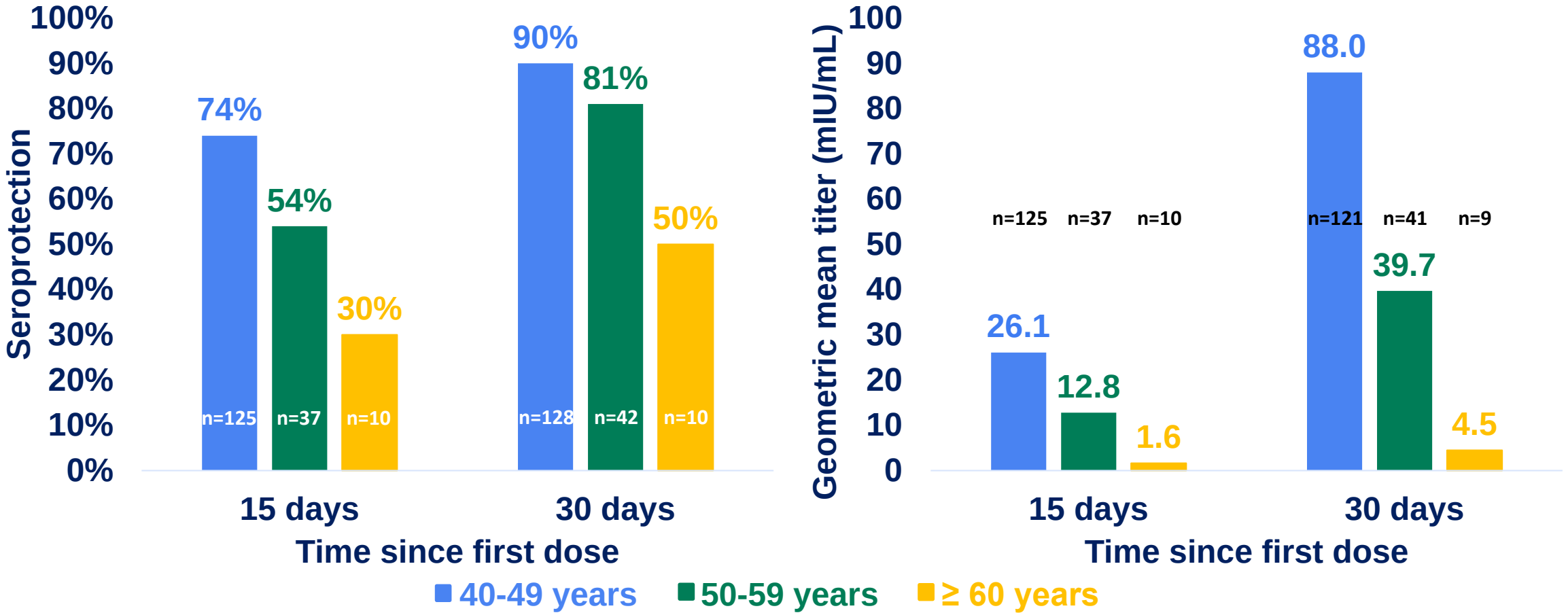
# Results: Reuman et al. (1997)




Vaccine: VAQTA 25 U; Protection: anti-HAV ≥ 10 mIU/mL

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;15:1157-1161. NOTE: 4 week seroprotection percentages and all GMTs include only individuals who were not revaccinated at 2 weeks.

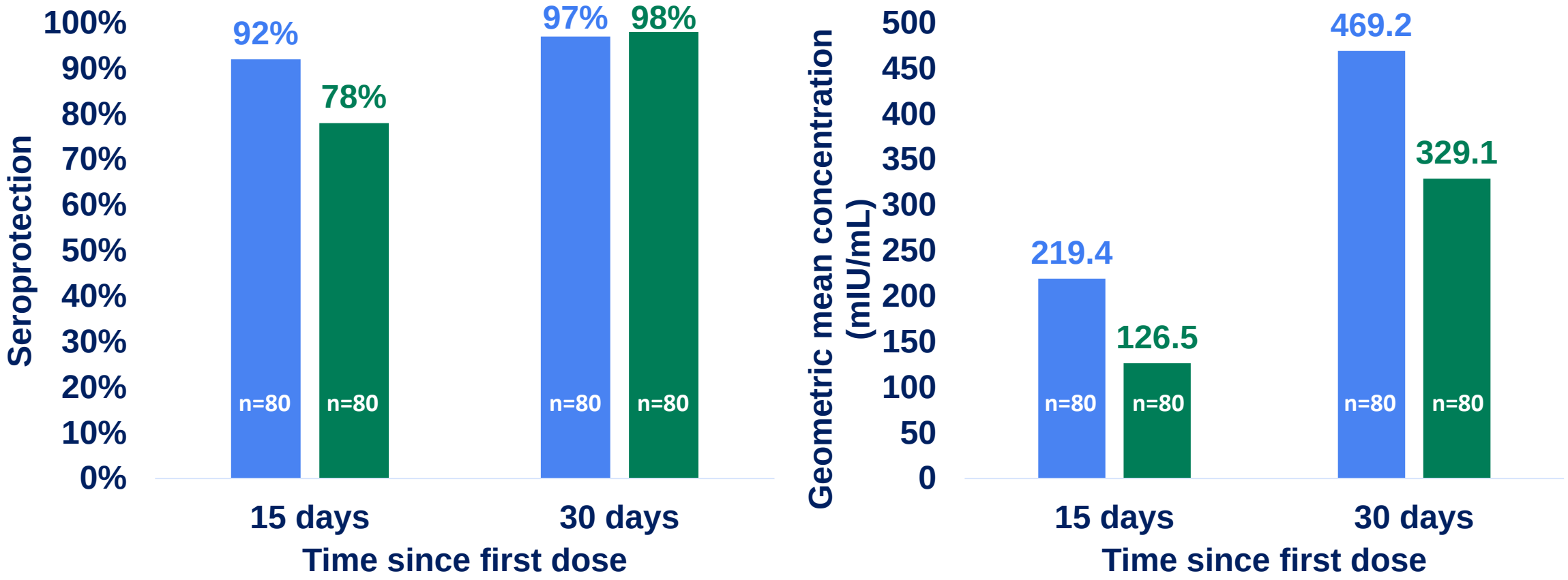
# Results: Nelson et al. (2014)




Vaccine: Havrix 1440 EL.U.; Protection: anti-HAV ≥ 20 mIU/mL

Nelson NP, Murphy TV, McMahon BJ. Hepatitis A vaccination for post-exposure prophylaxis in persons aged 40 years and older. Vaccine 2014;32:2939.

# Results: Van Der Meeren (2015)




Vaccine: Havrix 1440 EL.U.; Protection: anti-HAV ≥ 20 mIU/mL

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. Hum Vaccin Immunother 2015;11:1729-1734.

# Results: Surveillance Data and Additional Studies

- Surveillance/post-outbreak data[1,2,3]
  - Very few failures in adults > 40[1,2]
  - No additional information provided
- 3 VAQTA formulations in adults ≥ 30 years (median 40-43 years)[4]
  - Seroconversion after single dose of vaccine:
    - 2 weeks: 28% (25 U); 46% (50 U); 67% (100 U) protected
    - 4 weeks: 65% (25 U); 89% (50 U); 93% (100 U) protected
- No studies directly compared vaccine and IG in adults > 40 years for PEP

[1] 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:e78914.
[2] Parron I, Planas C, Godoy P, Manzanares-Laya S, Martinez A, Sala MR, Minguell S, et al. Effectiveness of hepatitis A vaccination as post-exposure prophylaxis. Hum Vaccin Immunother 2016:0.
[3] 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;32:5509-5513.
[4] Bertino JS, Jr., Thoelen S, VanDamme P, Bryan JP, Becherer PR, Frey S, Hayden FG, 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;178:1181-1184.

# Recommendations for HAV PEP in Other Countries

| Contact | Canada, Ontario (2013) | Canada, NACI (2016) | UK (2009) | Australia (2009) | Argentina (2014) | Israel (2015) | US (2007) |
|---|---|---|---|---|---|---|---|
| Healthy, < 2 months | IG | IG | Vaccinate caregivers | IG | IG | IG | IG |
| Healthy < 2-5 months | IG | IG | Vaccine caregivers OR unlicensed use of vaccine OR exclude from childcare | IG | IG | IG | IG |
| Healthy, 6-12 months | IG | Vaccine | Vaccine caregivers OR unlicensed use of vaccine OR exclude from childcare | IG | IG | IG | IG |
| Healthy, 1-39 years | Vaccine | Vaccine | Vaccine | Vaccine | Vaccine + IG | Vaccine | Vaccine |
| Healthy, 40 years | Vaccine | Vaccine | Vaccine | Vaccine | Vaccine + IG | Vaccine | Vaccine |
| Healthy, 41-49 years | Vaccine | Vaccine | Vaccine | Vaccine | Vaccine + IG | IG | IG |
| Healthy, 50 years | Vaccine + IG | Vaccine | Vaccine | Vaccine | Vaccine + IG | IG | IG |
| Healthy 51-59 years | Vaccine + IG | Vaccine | Vaccine + IG | Vaccine | Vaccine + IG | IG | IG |
| Healthy, ≥ 60 years | Vaccine + IG | May get vaccine + IG | Vaccine + IG | Vaccine | Vaccine + IG | IG | IG |
| Immunocompromised | Vaccine + IG | Should get vaccine + IG | Vaccine + IG | IG | | IG | IG |
| Chronic liver disease | Vaccine + IG | Should get vaccine + IG | Vaccine + IG | IG | | IG | IG |

# Conclusions about IG vs. vaccine for PEP

- Benefits of vaccine
  - Long term protection
  - Ease of administration
  - Availability in the U.S. (only one manufacturer of IG – Grifols)
  - Switching to vaccine brings U.S. in line with other countries
- Vaccine and IG are similarly priced
  - IG: $75 for 2 mL single dose vial
  - HAVRIX/VAQTA:
    - VFC: $26/$28
    - Private sector: $64/$67

# Draft proposed recommendations

| Current | Draft |
|---|---|
| For healthy persons aged 12 months – 40 years, single antigen hepatitis A vaccine at the age-appropriate dose is preferred. | For healthy unvaccinated persons aged >12 months possibly exposed to hepatitis A, administer a single dose of hepatitis A vaccine as soon as possible, followed by a second dose at least 6 months later. There is no upper age limit for this recommendation. |
| For persons aged >40 years, IG is preferred; vaccine can be used if IG cannot be obtained. | |
| For children aged <12 months, immunocompromised persons, persons who have had chronic liver disease diagnosed, and persons for whom vaccine is contraindicated, IG should be used. | Children <12 months and persons for whom vaccine is contraindicated should receive IG (0.02 mL/kg) instead of vaccine as soon as possible after exposure. |
| | Immunocompromised persons and persons with chronic liver disease should receive both IG (0.02 mL/kg) and hepatitis A vaccine (if previously unvaccinated) simultaneously in different anatomical sites as soon as possible after exposure |

# Who would continue to receive IG for PEP?

- IG alone: Infants <12 months of age, vaccine contraindication
- Vaccine + IG:
  - Persons with chronic liver disease (e.g., cirrhosis)
  - Immunocompromised persons, including persons:
    - With congenital or acquired immunodeficiency
    - With HIV/AIDS;
    - With chronic renal failure/undergoing hemodialysis;
    - Who have received solid organ, bone marrow or stem cell transplants;
    - Who have iatrogenic immunosuppression*;
    - With a contraindication for hepatitis A vaccine; or
    - Who are otherwise less capable of developing a normal response to immunization

*(Diseases requiring treatment with immunosuppressive drugs (e.g., TNF-alpha inhibitors), including long-term systemic corticosteroids and radiation therapy. Immune status relative to the dose of immunosuppressive drugs should be assessed by the provider

# Hepatitis A PEP in pregnant women

- 2006 ACIP recommendations:
  - No pregnancy-specific recommendations
  - Vaccine safety has not been determined, but theoretical risk is low

- Workgroup deliberations
  - Data show vaccine is safe during pregnancy[1]
  - Review published in November 2015 on hepatitis A during pregnancy[2]
    - Generally, infants born to mothers with HAV are healthy, but rare exceptions
    - Hepatitis A infection during pregnancy associated with gestational complications (preterm labor, placental abruption, premature rupture of membranes)
    - No increased risk of mortality
  - Vaccinating women at high risk
  - Communication/education issues

[1] Moro PL, Museru OI, Niu M, Lewis P, Broder K. Reports to the Vaccine Adverse Event Reporting System after hepatitis A and hepatitis AB vaccines in pregnant women. Am J Obstet Gynecol 2014;210:561 e561-566.
[2] Chaudhry SA, Koren G. Hepatitis A infection during pregnancy. Can Fam Physician 2015;61:963-964.

# Prevention of hepatitis A before international travel

| Current | Draft |
|---|---|
| One dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons | No change, other than clarification of recommendation if the person has previously received 1 or more doses |
| Older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions planning to depart to an area in <2 weeks should receive the initial dose of vaccine and also simultaneously can be administered IG (0.02 mL/kg) at a separate anatomic injection site. | Previously unvaccinated adults > 40 years of age, immunocompromised persons, and persons with chronic liver disease should be vaccinated as soon as possible.<br><br>If departing in <2 weeks, these persons should also receive IG at a separate anatomic injection site. |
| Travelers who elect not to receive vaccine, are aged <12 months, or **are allergic to a vaccine component** should receive a single dose of IG. | Travelers who elect not to receive vaccine, are aged <12 months, or **have a contraindication to vaccine** should receive a single dose of IG. |

# Questions for discussion

- Based on the evidence presented, what are ACIP members' opinions on the recommendation for PEP for healthy individuals > 40 years?
  - Differences in 40-49 vs. 50-59 vs. 60-69 years?

- Should pregnancy be considered an indication for administration of both IG and hepatitis A vaccine for PEP or is vaccine alone enough?

- Additional thoughts on international travel?

# Back-up slides

# Summary of studies from systematic review (1 of 2)

| Authors | Year | Vaccine; Protection | Summary |
|---|---|---|---|
| H Briem et al. | 1994 | Havrix 1440 ELU; ≥ 20 mIU/mL | 15 days: 77% (40-62 years) vs. 90% (20-39 years) protection<br>30 days: 97% protection in both |
| C Goilav et al. | 1995 | Havrix 720 ELU; ≥ 20 mIU/mL | NOTE: Mean age of study population was 23.7 years (range 18.0-63.0 years).<br>Age had a significant (P < 0.0001) effect on antibody response, but no actual data are provided. |
| PD Reuman et al. | 1997 | VAQTA 25 U; ≥ 10 mIU/mL | 2 weeks: 31% (≥ 40 years) vs. 56% (< 40 years) protection<br>4 weeks: 71% (≥ 40 years) vs. 94% (< 40 years) protection |
| JS Bertino et al. | 1998 | VAQTA 25, 50, 100 U; ≥ 10 mIU/mL | NOTE: adults ≥ 30 years (median 40-43 years, range 30-76) included<br>2 weeks: 28% (25 U); 46% (50 U); 67% (100 U) protected<br>4 weeks: 65% (25 U); 89% (50 U); 93% (100 U) protected |
| Williams et al. | 2000 | Havrix 1440 ELU; ≥ 20 mIU/mL | NOTE: unclear if blood draws were 15/30 days after 1$^{st}$ or 2$^{nd}$ dose. Adults (mean 41 years) included<br>15 days: 71% protected, GMT 29 mIU/mL (needle); 80% protected , GMT 43 mIU/mL (Biojet)<br>30 days: 84% protected, GMT 59 mIU/mL (needle); 92% protected, GMT 142 mIU/mL (Biojet) |

# Summary of studies from systematic review (2 of 2)

| Authors | Year | Vaccine; Protection | Summary |
|---|---|---|---|
| J Whelan et al. | 2013 | Not specified | 7/100 vaccinated contacts became cases: 2/58 ≤15 yrs (3%); 2/32 aged 16-40 yrs (9%); 3/10 >40 yrs (30%);<br>In 72 contacts vaccinated within 8 days of exposure, the RR for >40 years was 12.0 (95% CI: 1.3-106.7) compared to ≤15 yrs |
| E Freeman et al. | 2014 | Havrix, Avaxim, or VAQTA | No contacts >40 years of age who received vaccine were subsequently reported with hepatitis A. No additional data on people age ≥40 years was presented. |
| NP Nelson et al. (reanalysis of Williams et al.) | 2014 | Havrix 1440 ELU; ≥ 20 mIU/mL | 15 days: 74% (40-49 yrs), 54% (50-59 yrs), 30% (≥ 60 yrs) seroconverted<br>30 days: 90% (40-49 yrs), 81% (50-59 yrs), 50% (≥ 60 yrs) seroconverted |
| O Van Der Meeren et al. | 2015 | Havrix 1440 ELU; ≥ 20 mIU/mL | 15 days: 20-30 years: 92.3% seropositive (95% CI: 84.0-97.1%), GMT 219.4 mIU/mL<br>≥ 40 years: 79.7% seropositive (95% CI: 68.8-88.2%), GMC 126.5 mIU/mL<br>30 days: 20-30 years: 97.4% seropositive (95% CI: 91.0-99.7%), GMT 469.2 mIU/mL<br>≥ 40 years: 97.5% seropositive (95% CI: 91.2-99.7%), GMT 329.1 mIU/mL |
| I Parrón et al. | 2016 | | 80 exposed individuals >40 years, 1 secondary case (43 year-old-man). No additional data provided. |