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

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

## Current ACIP Recommendations for HAV Post-Exposure Prophylaxis

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children &lt; 12 months, immunocompromised, chronic liver disease, vaccine contraindication</td>
<td>IG (0.02 mL/kg)</td>
</tr>
<tr>
<td>Healthy persons 12 months – 40 years</td>
<td>HepA vaccine</td>
</tr>
<tr>
<td>Adults &gt; 40 years</td>
<td>IG (0.02 mL/kg) preferred; vaccine if IG cannot be obtained</td>
</tr>
</tbody>
</table>

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\textsuperscript{1,2}
  - Lower prevalence of HAV antibodies in plasma donors
  - Low anti-HAV potencies in recently tested IG lots

\begin{flushleft}
\footnotesize

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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)\(^4\)

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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)\(^3\)
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- Shorter immunity

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Available research on IG for PEP

- 2007 ACIP recommendations based on Victor et al. study in Kazakhstan¹
  - 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

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
Results: Articles included

<table>
<thead>
<tr>
<th>PubMed</th>
<th>782 abstracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMBASE</td>
<td>257 abstracts</td>
</tr>
</tbody>
</table>

936 abstracts excluded*

- (118) No adults >40 or results of adults >40 could not be separated out
- (137) No results for <28 days post-vaccination
- (43) Vaccines other than HAVRIX and VAQTA
- (2) Animals other than humans
- (7) Assay development
- (30) Could not be obtained in English
- (30) Only included safety data
- (29) Included only individuals with underlying conditions
- (540) Vaccine introduction±

103 full articles for full review

95 articles excluded

8 articles remaining
2 articles added

* 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

Results: Reuman et al. (1997)

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

Results: Nelson et al. (2014)

Seroprotection

<table>
<thead>
<tr>
<th>Time since first dose</th>
<th>40-49 years</th>
<th>50-59 years</th>
<th>≥ 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 days</td>
<td>74%</td>
<td>54%</td>
<td>30%</td>
</tr>
<tr>
<td>30 days</td>
<td>90%</td>
<td>81%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Geometric mean titer (mIU/mL)

<table>
<thead>
<tr>
<th>Time since first dose</th>
<th>40-49 years</th>
<th>50-59 years</th>
<th>≥ 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 days</td>
<td>26.1</td>
<td>12.8</td>
<td>1.6</td>
</tr>
<tr>
<td>30 days</td>
<td>88.0</td>
<td>39.7</td>
<td>4.5</td>
</tr>
</tbody>
</table>

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
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

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\(^3\) 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.

## Recommendations for HAV PEP in Other Countries

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Healthy, &lt; 2 months</td>
<td>IG</td>
<td>IG</td>
<td>Vaccinate caregivers</td>
<td>IG</td>
<td>IG</td>
<td>IG</td>
<td>IG</td>
</tr>
<tr>
<td>Healthy &lt; 2-5 months</td>
<td>IG</td>
<td>IG</td>
<td>Vaccine caregivers OR</td>
<td>IG</td>
<td>IG</td>
<td>IG</td>
<td>IG</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>unlicensed use of vaccine OR</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>exclude from childcare</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Healthy, 6-12 months</td>
<td>IG</td>
<td>Vaccine</td>
<td>Vaccine caregivers OR</td>
<td>IG</td>
<td>IG</td>
<td>IG</td>
<td>IG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>exclude from childcare</td>
<td></td>
<td></td>
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<tr>
<td>Healthy, 1-39 years</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine + IG</td>
<td>Vaccine</td>
<td>Vaccine</td>
</tr>
<tr>
<td>Healthy, 40 years</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine + IG</td>
<td>Vaccine</td>
<td>Vaccine</td>
</tr>
<tr>
<td>Healthy, 41-49 years</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine + IG</td>
<td>IG</td>
<td>IG</td>
</tr>
<tr>
<td>Healthy, 50 years</td>
<td>Vaccine + IG</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Vaccine + IG</td>
<td>IG</td>
<td>IG</td>
</tr>
<tr>
<td>Healthy 51-59 years</td>
<td>Vaccine + IG</td>
<td>Vaccine</td>
<td>Vaccine + IG</td>
<td>Vaccine</td>
<td>Vaccine + IG</td>
<td>IG</td>
<td>IG</td>
</tr>
<tr>
<td>Healthy, ≥ 60 years</td>
<td>Vaccine + IG</td>
<td>May get vaccine + IG</td>
<td>Vaccine + IG</td>
<td>Vaccine</td>
<td>Vaccine + IG</td>
<td>IG</td>
<td>IG</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>Vaccine + IG</td>
<td>Should get vaccine + IG</td>
<td>Vaccine + IG</td>
<td>IG</td>
<td></td>
<td>IG</td>
<td>IG</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>Vaccine + IG</td>
<td>Should get vaccine + IG</td>
<td>Vaccine + IG</td>
<td>IG</td>
<td></td>
<td>IG</td>
<td>IG</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Current</th>
<th>Draft</th>
</tr>
</thead>
<tbody>
<tr>
<td>For healthy persons aged 12 months – 40 years, single antigen hepatitis A vaccine at the age-appropriate dose is preferred.</td>
<td>For healthy unvaccinated persons aged &gt;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.</td>
</tr>
<tr>
<td>For persons aged &gt;40 years, IG is preferred; vaccine can be used if IG cannot be obtained.</td>
<td>Children &lt;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.</td>
</tr>
<tr>
<td>For children aged &lt;12 months, immunocompromised persons, persons who have had chronic liver disease diagnosed, and persons for whom vaccine is contraindicated, IG should be used.</td>
<td>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.</td>
</tr>
</tbody>
</table>
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

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## Prevention of hepatitis A before international travel

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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Vaccine; Protection</th>
<th>Summary</th>
</tr>
</thead>
</table>
| H Briem et al.     | 1994 | Havrix 1440 ELU; ≥ 20 mIU/mL | 15 days: 77% (40-62 years) vs. 90% (20-39 years) protection  
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). 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  
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  
2 weeks: 28% (25 U); 46% (50 U); 67% (100 U) protected  
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\textsuperscript{st} or 2\textsuperscript{nd} dose. Adults (mean 41 years) included  
15 days: 71% protected, GMT 29 mIU/mL (needle); 80% protected , GMT 43 mIU/mL (Biojet)  
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)

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