



Considerations for use of Hepatitis A Vaccines for Post-exposure prophylaxis and International Travel

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Proposed Updates to the Hepatitis A Vaccine Recommendations for Post-exposure prophylaxis and International travel

- **Recommendations for post-exposure prophylaxis with immune globulin (IG) or hepatitis A (HepA) vaccine**
 - *Children aged <12 months and persons for whom vaccine is contraindicated*
 - *Healthy persons*
 - *Immunocompromised persons, and persons with chronic liver disease*
 - *Pregnant women*

- **Provider Guidance on Risk Assessment and Clinical Decision Making for Post-Exposure Prophylaxis**
 - Close personal contact
 - Child care centers
 - Common-Source food exposure
 - Settings providing services to children and adults
 - Natural disaster settings with flooding

Proposed Updates to the Hepatitis A Vaccine Recommendations for Post-exposure prophylaxis and International travel

- Recommendations for preexposure protection against hepatitis A for travelers
 - *Infants aged <6 months*
 - *Infants aged 6-11 months*
 - *Healthy persons aged >12 months*
 - *Immunocompromised persons, and persons with chronic liver disease*

Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). 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. 2007 Oct 19;56(41):1080-4.

Hepatitis A Vaccines: Policy Questions

■ Post-exposure Prophylaxis

- Q1a. Should hepatitis A vaccines be recommended for post-exposure prophylaxis for all persons age ≥ 12 months?
- Q1b. Should IG be recommended at age >50 years in addition to vaccine?

■ International Travel

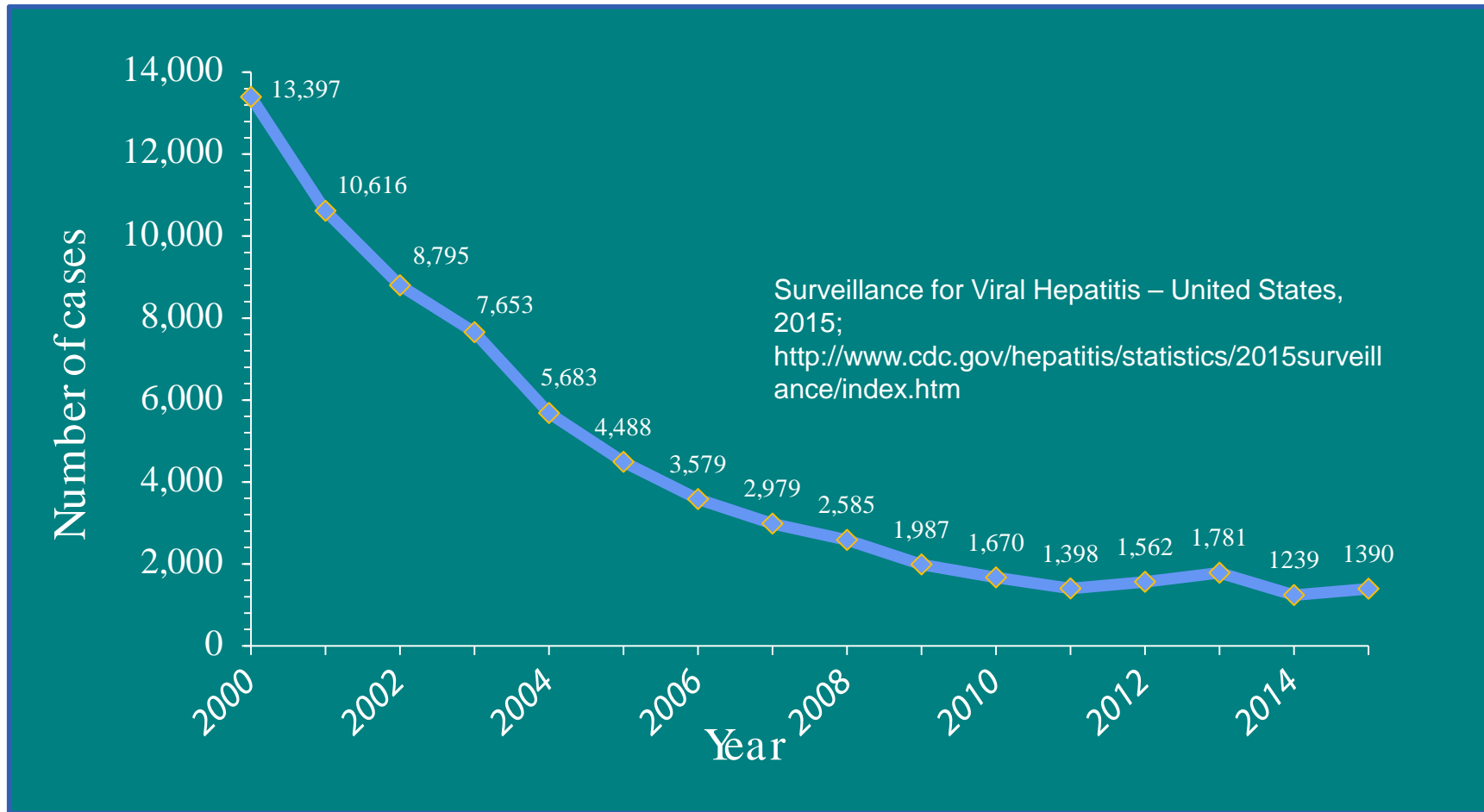
- Q2. Should hepatitis A vaccines be administered to infants age $\geq 6-11$ months of age pre-travel (unless the infant is traveling to an area with no endemic measles transmission)?

■ Post-exposure Prophylaxis and International Travel

- Q3. Should vaccine (or vaccine with addition of IG) for post-exposure prophylaxis and vaccine for International travel be administered to pregnant women due to the risk of adverse fetal outcomes if the woman is infected with hepatitis A virus during pregnancy?

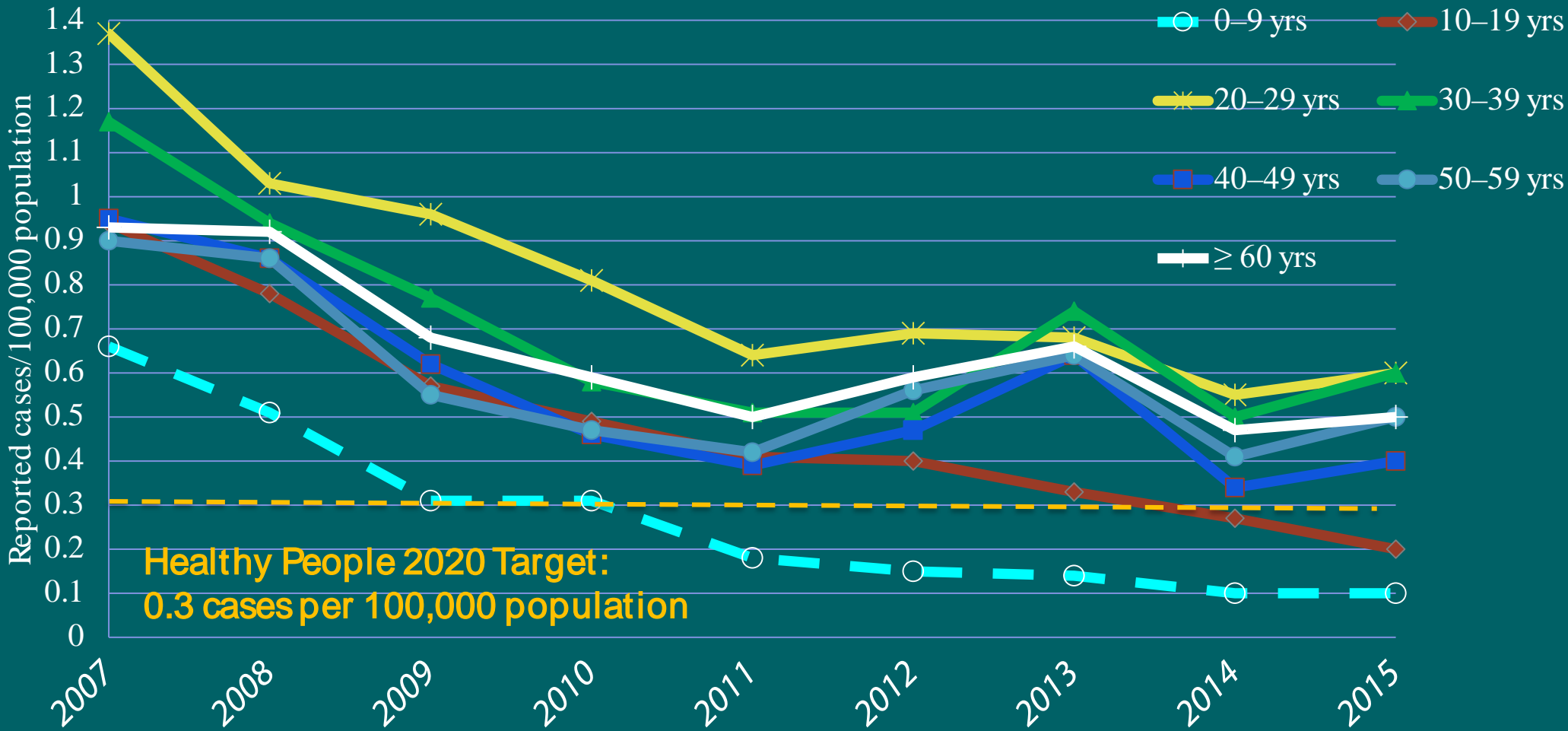
Background

Reported Number of Acute Hepatitis A Cases, United States, 2000-2015



Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

Rates of Reported Acute Hepatitis A United States, 2007-2015



Healthy People 2020 Target:
0.3 cases per 100,000 population

Hepatitis A Vaccine Coverage, United States, 2016

■ Children¹

- 60.6% for children age 19-35 months, ≥ 2 doses
- 86.1% for children age 19-35 months, ≥ 1 dose

■ Adolescents²

- 64.4% for adolescents age 13-17 years, ≥ 2 doses
- 73.9% for adolescents age 13-17 years, 1 dose

■ Adults³

- 9.5% for adults ≥ 19 years, ≥ 2 doses
- 13.4% for adults 19-49 years, ≥ 2 doses
- 5.4% for adults ≥ 50 years, ≥ 2 doses

1. Hill HA, et al. Vaccination Coverage Among Children Aged 19-35 Months - United States, 2016. MMWR 2017;66:1171–1177.

2. Nelson NP, et al. Hepatitis A Vaccination Coverage Among Adolescents (13-17 years) in the United States, 2008-2016. Vaccine 2018. (volume/issue pending)

3. Vaccination Coverage Among Adults in the United States, National Health Interview Survey, 2016.

<https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/NHIS-2016.html#hepA>

Hepatitis A Outbreaks

- **Multi-state outbreak associated with frozen pomegranate arils imported from Turkey, 2013**
 - Confirmed cases: 165 cases
 - Complications: 42% hospitalized, 2 cases fulminant hepatitis, 1 case liver transplant
- **Raw scallops served at Chain A restaurants on Oahu and Kauai, Hawaii, 2016**
 - Confirmed cases: 292 (as of January 11, 2017)
 - Hospitalized: 74
- **Multistate outbreak of hepatitis A linked to frozen strawberries, 2016**
 - Confirmed cases: 129 (as of September 26, 2016)
 - Hospitalized: 59

Collier MG, 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.
<http://www.vdh.virginia.gov/blog/2016/09/10/hepatitis-a-investigation>
<http://www.cdc.gov/hepatitis/outbreaks/2016/hav-strawberries.htm>

Hepatitis A Outbreaks, cont.

■ Outbreaks of hepatitis A in multiple states among people who are homeless and people who use drugs, 2017-2018

- California
 - Case count (as of February 9, 2018): 694
 - Hospitalizations: 454
 - Deaths: 21
- Michigan
 - Case count (as of February 14, 2018): 751
 - Hospitalizations: 609 (81.1%)
 - Deaths: 25 (3.3%)
- Utah
 - Case count (as of February 20, 2018): 181
 - Hospitalizations: 90 (50.6%)
- Kentucky (active investigation)
- Missouri (active investigation)

<https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immuni-zation/Hepatitis-A-Outbreak.aspx>

http://www.michigan.gov/mdhhs/0,5885,7-339-71550_2955_2976_82305_82310-447907--,00.html

http://health.utah.gov/epi/diseases/hepatitisA/HAVoutbreak_2017

Current Recommendations (2007) – Post-exposure Prophylaxis

- Persons who recently have been exposed to hepatitis A virus (HAV) and who previously have not received hepatitis A vaccine should be administered a single dose of single-antigen hepatitis A vaccine or immune globulin (IG) (0.02 mL/kg) as soon as possible.
 - For healthy persons aged 12 months–40 years, single antigen hepatitis A vaccine at the age-appropriate dose is preferred.
 - 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.

Current Recommendations (2007) – International Travel

- All susceptible persons traveling to or working in countries that have high or intermediate hepatitis A endemicity should be vaccinated or receive IG before departure. Hepatitis A vaccine at the age-appropriate dose is preferred to IG. The first dose of hepatitis A vaccine should be administered as soon as travel is considered.
 - One dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons.
 - 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.
 - 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 (0.02 mL/kg), which provides effective protection for up to 3 months.

Evidence for Current Post-exposure Prophylaxis Recommendations

Hepatitis A Vaccine Post-exposure trial, Kazakhstan, 2007

- **Enrolled 1090 household or daycare contacts of 920 index cases**
 - 2 to 40 years of age
 - Exposed to index case within 2 weeks after index case symptom onset
 - No history of hepatitis A, hepatitis A vaccine or immune globulin (IG) (< past 6 months)
- **Randomized non-inferiority study**
 - Hepatitis A vaccine (VAQTA) or IG
- **Primary outcome: lab confirmed symptomatic hepatitis A during 15-56 days post-exposure**

Evidence for 2007 Recommendations, cont.

Trial Results

- **Hepatitis A vaccine efficacy was similar to that of IG**

- Assuming 90% IG efficacy, point estimate of vaccine efficacy is 86%; (95% CI, 73 to 93%)
- Assuming 80% IG efficacy, point estimate of vaccine efficacy is 73%; (95% CI, 47 to 86%)

- **Study's pre-specified criterion for non-inferiority was met**

- In the per-protocol analyses, 25 primary end points were reached among vaccine recipients (4.4%) and 17 were reached among immune globulin recipients (3.3%)
 - Relative risk: 1.35 (95% confidence interval [CI], 0.70 to 2.67)

Hepatitis A Vaccine Response in Adults >40 years of Age

- **Few studies have evaluated hepatitis A vaccine response in adults ≥ 40 years of age**
 - No randomized control trials are available
 - Limited studies are available with data broken down in discrete age groups >40 years
- **No direct comparisons between hepatitis A vaccine and IG are available for older adults**
- **It is unlikely that additional post-exposure efficacy data would become available, because of the difficulties of conducting post-exposure efficacy studies of IG and vaccine**

Immune Globulin

- **July 2017, GamaSTAN S/D prescribing information was updated**
 - The dose was increased from 0.02 mL/kg to 0.1 mL/kg
- **Changes were made because of concerns about decreased HAV immunoglobulin G antibody (anti-HAV IgG) potency, likely resulting from decreasing prevalence of previous HAV infection among plasma donors, leading to declining anti-HAV antibody levels in donor plasma**

TABLE. Indications and updated dosage recommendations for GamaSTAN S/D human immune globulin for preexposure and postexposure prophylaxis against hepatitis A infection

Indication	Updated dosage recommendation
Preexposure prophylaxis	
Up to 1 month of travel	0.1 mL/kg
Up to 2 months of travel	0.2 mL/kg
2 months of travel or longer	0.2 mL/kg (repeat every 2 months)
Postexposure prophylaxis	0.1 mL/kg

Challenges with Current Post-exposure Prophylaxis Recommendations

- In recent years there has been an increase in hepatitis A outbreaks requiring post-exposure prophylaxis
- State and local health departments report that timely receipt of intramuscular IG has been difficult since most providers and health departments do not routinely stock it
- There is often a need for multiple injections of IG per dose, particularly for adult patients, due to the increased dosing (0.1mL/kg) and subsequent increase in volume of the IG dose
 - Cost and administration concerns and challenges
- In recent outbreaks state and local health departments have opted to administer hepatitis A vaccine, which confers long-term protection, to persons age >40 years for post-exposure prophylaxis

Policy Considerations

Q1a. Should hepatitis A vaccines be recommended for post-exposure prophylaxis for all persons age ≥ 12 months?

Q1b. Should IG be recommended at age >50 years in addition to vaccine?

■ **Work Group Considerations**

- Advantages of Hepatitis A vaccine compared to Immune Globulin
 - Induction of active immunity and longer protection
 - Greater ease of administration compared to IG
 - Increased need for multiple injections of IG due to the increase in dose (volume) of the IG dose
 - Hepatitis A is routinely available
 - IG is available in the United States from only one manufacturer– Grifols Therapeutics, Inc.
 - IG is not routinely stocked by many providers and health departments* making timely administration of intramuscular IG challenging
 - Hepatitis A vaccine might cost less per dose, particularly when multiple injections of IG are needed

Q1a. Should hepatitis A vaccines be recommended for post-exposure prophylaxis for all persons age ≥ 12 months?

Q1b. Should IG be recommended at age >50 years in addition to vaccine?

■ **Work Group Considerations**

- Using vaccine for PEP in persons age >40 years brings U.S. practice in line with other countries that provide post-exposure prophylaxis
- In the US some states suggest using vaccine for PEP in adults age >40 years
 - For Example:
 - California Department of Public Health suggests consideration of HepA vaccine for PEP in persons 41-59 years of age because it confers long-term immunity.
 - Michigan Department of Health and Human Services suggests consideration of HAV vaccine for PEP in persons 41 through 74 years of age if IG is in short supply. When indicated for use, IG should be given within 2 weeks of exposure. (interim guidance)

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	Vaccinate caregivers OR unlicensed use of vaccine OR exclude from childcare	IG	IG	IG	IG
Healthy, 6-12 months	IG	Vaccine	Vaccinate 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

Q1a. Should hepatitis A vaccines be recommended for post-exposure prophylaxis for all persons age ≥ 12 months?

Q1b. Should IG be recommended at age >50 years in addition to vaccine?

Work Group Considerations

- Limited data suggest protection at 15 days post-vaccination for adults 40–49 years of age. Among adults ages 50–59 years, data suggest substantial protection by 30 days post-vaccination.

Age	Number	Seroconversion* , 15 days	Seroconversion* , 30 days
40-49 years	125	74%	90%
50-59 years	37	54%	81%
≥ 60 years	10	30%	50%

Nelson NP, et al. Hepatitis A vaccination for post-exposure prophylaxis in persons aged 40 years and older. *Vaccine*. 2014 May 23;32(25):2939

*Seroconversion to anti-HAV positive, defined as ≥ 20 mIU anti-HAV

Studies with a Comparison Age Group and the Recommended dose of HepA vaccine

Author, year	No. of subjects	Population	Immunogenicity results
Briem et al., 1994	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)
	113	20-29 years, Iceland	Seroconversion (≥ 20 mIU/mL anti-HAV) at 15 days: 90% GMT at 15 days: 282 mIU/mL (range: 41-2589 mIU/mL)
Van Der Meeren et al., 2015	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)
	80	20-30 years,	Seroconversion (≥ 20 mIU/mL anti-HAV) at 15 days: 92.3% (84.0-97.1%) GMT at 15 days: 219.4 mIU/mL (168-286.5 mIU/mL)

Q1a. Should hepatitis A vaccines be recommended for post-exposure prophylaxis for all persons age ≥ 12 months?

Q1b. Should IG be recommended at age >50 years in addition to vaccine?

■ **Work Group Perspective**

- It is unlikely that additional post-exposure efficacy data will become available, because of the difficulties of conducting post-exposure efficacy studies of IG and vaccine
- Administering vaccine provides long-term protection and is beneficial for a substantial number of adult recipients even in older ages (> 60 yrs) be considered at any age
- Limited data and evidence of lower efficacy in older adults age >50 years at 15 days, age >60 years at 30 days
 - HAV infection is more severe in these age groups
 - IG in addition to HAV might be beneficial for persons in these age groups
- Data are limited on vaccine or IG failures, however, reports of failures are rare
- If IG or vaccine is not available, the available product should be administered as soon as possible. The person may return for the second product if available within 14 days of exposure

Summary of Proposed Recommendations for Post-Exposure Prophylaxis*

Age/condition	Post-exposure prophylaxis
<6 months of age	IG
>6-11 months of age	IG
Healthy persons ≥ 12 months	Vaccine
Healthy persons >50 years of age	Vaccine with addition of IG*
Vaccine contraindication	IG
Immunocompromised	Vaccine and IG
Chronic liver disease	Vaccine and IG
Pregnant women	Vaccine with addition of IG*

*Based on provider guidance risk assessment and availability of vaccine or IG

Q2. Should hepatitis A vaccines be administered to infants age $\geq 6-11$ months of age pre-travel (unless the infant is traveling to an area with no endemic measles transmission)?

■ Work Group Considerations

- IG cannot be administered simultaneously with MMR vaccine, which is recommended for infants age 6-11 months traveling internationally from the US
- Administering hepatitis A vaccine in infants is off-label and doses administered prior to age 12 months are considered invalid
 - Infants receiving HepA vaccine would need to complete the full, 2-dose HepA vaccine series beginning at 12 months of age or 6 months after the invalid dose to gain long-term immunity.
- Infants 6-11 months traveling in countries classified as having no endemic measles transmission (e.g., Western Hemisphere), but where hepatitis A may remain at intermediate or high endemicity, IG may be used
 - Routine administration of MMR vaccine may be delayed because it may be administered no earlier than 3 months after IG administration

Nelson NP. Updated Dosing Instructions for Immune Globulin (Human) GamaSTAN S/D for Hepatitis A Virus Prophylaxis. MMWR. 2017 Sep 15;66(36):959-960.

McLean HQ, et al. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62:1-34.

Q2. Should hepatitis A vaccines be administered to infants age $\geq 6-11$ months of age pre-travel (unless the infant is traveling to an area with no endemic measles transmission)?

■ Work Group Perspective

- Due to the severity of measles in infancy compared to HAV infection in infancy, MMR vaccine should be administered preferentially to immune globulin
- Administration of hepatitis A vaccine (off-label) and MMR vaccine to infants age 6-11 months would provide protection against HAV and measles and allow for simultaneous administration

Nelson NP. Updated Dosing Instructions for Immune Globulin (Human) GamaSTAN S/D for Hepatitis A Virus Prophylaxis. MMWR. 2017 Sep 15;66(36):959-960.

McLean HQ, et al. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62:1-34.

Summary of Proposed Recommendations for International Travel

Age/condition	International travel
<6 months of age	IG
≥6-11 months of age	Vaccine (or IG [^])
Healthy persons ≥12 months	Vaccine
Vaccine contraindication	IG
Immunocompromised	Vaccine with addition of IG [*]
Chronic liver disease	Vaccine
Pregnant women	Vaccine

[^]If measles is not endemic in the region of travel

^{*}Based on provider guidance risk assessment and availability of vaccine or IG

Q3. Should vaccine (or vaccine + IG) be administered for pregnant women due to the risk of adverse fetal outcomes if the woman is infected with HAV during pregnancy?

■ Work Group considerations

- Data show vaccine is safe during pregnancy¹
- Review published data in November 2015 on hepatitis A during pregnancy²
 - Generally, infants born to mothers with HAV infection are healthy, but there are rare exceptions
 - Hepatitis A infection during pregnancy is associated with gestational complications (e.g. preterm labor, placental abruption, premature rupture of membranes)³
 - No increased risk of maternal or infant mortality after HepA vaccination in pregnancy
- Vaccination of pregnant women who have a specific risk or who lack a risk but want protection is included in the CDC Adult Immunization Schedule by “Medical and Other Indications”

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.

³ Elinav E, Ben-Dov IZ, Shapira Y, Daudi N, Adler R, Shouval D, Ackerman Z. Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. *Gastroenterology*. 2006 Apr;130(4):1129-34. PubMed PMID: 16618407.

Q3. Should vaccine (or vaccine + IG) be administered for pregnant women due to the risk of adverse fetal outcomes if the woman is infected with HAV during pregnancy?

■ Work Group perspective

- Administration of HepA vaccine during pregnancy is safe
- Risk of gestational complications exists if a pregnant woman is infected with hepatitis A virus
- Vaccine provides long-term protection
- IG administration in addition to vaccine can be considered based on infection risk

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.

³Elinav E, Ben-Dov IZ, Shapira Y, Daudi N, Adler R, Shouval D, Ackerman Z. Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. *Gastroenterology*. 2006 Apr;130(4):1129-34. PubMed PMID: 16618407.

Summary of Proposed Recommendations for Hepatitis A Post-exposure and International travel?

Age/condition	Postexposure prophylaxis	International travel
<6 months of age	IG	IG
≥6-11 months of age	IG	Vaccine (or IG [^])
Healthy persons ≥12 months	Vaccine	Vaccine
Healthy persons >50 years of age	Vaccine with addition of IG*	Vaccine
Vaccine contraindication	IG	IG
Immunocompromised	Vaccine and IG	Vaccine with addition of IG*
Chronic liver disease	Vaccine and IG	Vaccine
Pregnant women	Vaccine with addition of IG*	Vaccine

*Based on provider guidance risk assessment and availability of vaccine or IG

[^]If measles is not endemic in the region