Hepatitis A

Provider Summary

Note: This article also contains information on the combination hepatitis A-hepatitis B (HepA-HepB) vaccine.

What's New

See Recommended Child and Adolescent Immunization and Catch-up Schedules and Recommended Adult Immunization Schedule for the 2022 US recommended schedules. No significant changes have occurred since the 2021 schedules.

Introduction

Hepatitis A infection occurs worldwide and is caused by hepatitis A virus (HAV), which is mainly transmitted via the fecal-oral route or via consumption of contaminated food or water and is then replicated in the liver. Although the virus is present in serum, its concentration is much less than in feces. The resulting immune response causes liver inflammation and hepatic dysfunction. Hepatitis A is classified into 6 genotypes, 3 of which circulate among humans; only 1 serotype has been identified globally. Hepatitis A is clinically indistinguishable from other types of acute viral hepatitis but does not cause chronic infection even though prolonged or relapsing hepatitis A may occur.

Epidemiology

Endemicity is inversely related to the age at midpoint of population immunity; as the age increases, endemicity generally decreases. Hepatitis A is highly endemic in developing countries (particularly in Africa, Asia, Central and South America, the Middle East, and the Western Pacific) with inadequate sanitation, limited access to clean water, and poor hygienic conditions. Endemicity rates are intermediate in developing countries with transitional economies and in some regions of industrialized countries where sanitary conditions are variable. Although endemicity rates are low in developed countries with good hygienic practices (e.g., countries in western Europe, Australia, Canada, New Zealand, Japan, and the US), foci of high transmission may occur in certain risk populations or may be due to consumption of imported HAV-contaminated food from global sources.

In the US, the endemicity rate of hepatitis A is low because the estimated age at midpoint of population immunity to hepatitis A is ≥ 40 years. Acute hepatitis A rates vary cyclically every 10 to 15 years. As a result of routine hepatitis A (HepA) vaccination of all children aged 12-23 months, a 95.5% decrease in reported hepatitis A cases was observed between 1996 and 2011; the last peak occurred in 1995. However, beginning in 2016, increased person-to-person transmission resulted in widespread community-wide hepatitis A outbreaks; approximately 6,700 cases occurred in 2017 and approximately 12,500 cases occurred 2018. In 2017, adults aged 30-39 years had the highest hepatitis A rate among all age groups. No hepatitis A outbreaks associated with drinking water have been reported in the US since 2009.

Mode of Transmission

HAV is mainly transmitted via the fecal-oral route, usually from direct person-to-person contact (e.g., household or oral-anal sexual contact) or through the consumption of contaminated foods. Commonly implicated foods include raw or undercooked shellfish (e.g., oysters, clams, scallops, mussels), fresh fruits and vegetables (e.g., lettuce, green onions, strawberries, raspberries, pomegranate arils), inadequately cooked (heat levels insufficient to inactivate HAV) or frozen foods (including fruits and vegetables), and water/ice. Food or water contaminated by acutely infected food handlers after cooking can also transmit HAV. Common-source outbreaks and sporadic cases occur from exposure to contaminated food or water.

Humans are the only natural hosts of the virus; no insect or animal vectors exist. Transmission through blood transfusion and solid-organ transplantation, although uncommon, is possible via contaminated blood, blood products, or organs collected from donors during the viremic phase of their infection.

HAV may be present in blood and feces beginning 10 to 12 days after infection. Persons can shed the virus in stool beginning several weeks before the onset of symptoms (including jaundice) and for about 1 to 3 weeks afterward; children may excrete virus much longer (up to 6 months after infection) than adults.

HAV is relatively resistant to heat and freezing; thus, it survives well in the environment outside the human host. The virus can persist on hands for several hours and in room-temperature food for considerably longer.

Risk Factors

Risk is generally influenced by host and environmental factors and varies in different settings. The risk for HAV infection after a household or sexual exposure is often greater than the risk associated with a common source exposure (e.g., exposure to a contaminated food product or restaurant exposure).

Current risk in travelers is estimated to be high (6-30 per 100,000 travelers per month of travel to developing countries) and increases with duration of travel. For individuals from developed countries (i.e., low rates of transmission) going to countries with intermediate or high rates of transmission, risk is highest for long-stay travelers; persons who live in or visit rural areas, trek in remote, undeveloped backcountry areas, eat or drink frequently in high-risk settings with poor sanitation, have close physical contact with local persons (especially young children) in settings with poor sanitation; and for persons who travel outside prearranged, fixed itineraries (including common tourist packages). However, cases can also occur in travelers who have tourist itineraries, accommodations, and eating behaviors considered low risk or who visit settings with good sanitary conditions because of an infected food handler (low risk) or consumption of contaminated food (including undercooked shellfish).

Risk of significant clinical illness or jaundice is practically nonexistent for infants aged < 12 months, even if acutely infected. Individuals residing in settings with good hygiene (e.g., infants who are breastfed or bottle-fed using safe water for formula reconstitution or who eat commercial baby food with no exposure to locally prepared foods) have low risk of infection. Because children generally have asymptomatic or unrecognized illness, they may serve as a source of infection for staff members or attendees of childcare centers (low risk) or unvaccinated household or other close contacts upon return home.

Risk for hepatitis A is increased for persons working with nonhuman primates (NHPs) or with clinical or nonclinical material containing HAV in research laboratories, persons who use drugs, and persons in settings where services to adults are provided. Health-care associated HAV transmission is rare and health care workers (HCWs) are not at substantially increased risk.

Outbreaks among men who have sex with men (MSM) have been reported frequently. Also, homelessness and use of injection and noninjection drugs are risk factors for outbreaks of HAV infection in the US.

Clinical Presentation

HAV infection can be asymptomatic or range in severity from a mild illness lasting 1 to 2 weeks in healthy persons to a severely disabling disease lasting several months and is clinically indistinguishable from other types of viral hepatitis. In young children (aged < 6 years), HAV usually causes either asymptomatic infection or very mild illness without jaundice. Older children and adults are more likely to have symptomatic infection, with jaundice occurring in more than 70% of patients.

Following an asymptomatic incubation period of 15 to 50 days (average: 28 days), an abrupt onset of fever, anorexia, nausea, vomiting, abdominal pain, diarrhea, and malaise may occur, followed within days by jaundice. Dark urine usually occurs before onset of jaundice, and hepatic tenderness may also be present. Peak transmissibility occurs during the 2-week period before the onset of jaundice or elevation of liver enzymes, when the concentration of virus in stool is highest; most persons are no longer infectious 1 week after jaundice onset. Severe hepatic and extrahepatic complications (including fulminant hepatitis and liver failure) are rare, but they commonly occur in older adults and people with underlying liver disease.

Among older children and adults, the illness usually lasts less than 2 months, although approximately 10% to 15% of infected people have prolonged or relapsing symptoms (relapsing hepatitis) lasting from 6 months to a year; such persons should be considered infectious. Recovery from relapse is universal and chronic hepatitis and carrier states do not occur.

A fatal course is rare in previously healthy individuals. The overall case-fatality rate is 0.3% but can reach 1.8% among adults aged > 50 years. Age (> 40 years), immunocompromising conditions, and chronic liver disease increase disease severity and risk of death due to HAV infection.

Immune globulin G (IgG) antibodies to HAV (which appear early in the course of infection) provide lifelong protection against the disease.

Need for Medical Assistance

Persons with symptoms of HAV infection, those who have been exposed to an individual with acute HAV infection, or those possibly exposed during an outbreak situation should seek medical attention. Diagnosis of HAV infection requires detection of either IgM anti-HAV in serum or HAV RNA in serum or stool.

Prevention

Nonvaccine

Travelers should observe food and beverage precautions and hand hygiene (frequent, thorough handwashing), regardless of vaccination status; see ***Food and Beverage Precautions***. Travelers should also observe safer-sex practices.

Vaccine

Hepatitis A (HepA) vaccines are highly immunogenic; a single dose of a single-antigen HepA vaccination any time before travel will provide nearly complete protection for healthy persons. Following 2 doses, nearly 100% of vaccinees (children and adults) will seroconvert within 4 weeks; in persons aged 2-18 years, data showed protective levels of antibody with high geometric mean titers in 97% to 100% of persons 1 month after the first dose and in 100% of persons 1 month after the second dose. Protective antibodies estimated to persist for at least 40 years in more than 90% of adult vaccinees, although the exact duration of protection is unknown. Data from studies of adult vaccinees showed that more than 97% of recipients were seropositive for anti-HAV antibodies 20 years afterward, and mathematical modeling predicted that seropositive anti-HAV levels would persist in ≥ 95% and ≥ 90% of vaccinees 30 and 40 years later, respectively. See ***Literature Watch Review:*** Long-Term Protection against Hepatitis A: Serological and Cellular Studies.

Data indicate that persons vaccinated at an older age might have a lower immune response to HepA vaccination than younger persons. In persons aged ≥ 40 years, immune response was similar to persons aged 20-30 years at 1 month after the first dose (91%–99.7%) and the second dose (95.3%–100%); however, the seroconversion rate was higher at 15 days post vaccination among adults aged 20-30 years (92.3%; 95% CI: 84-97) than among adults ≥ 40 years (79.7%; 95% CI: 68.8-88.2).

Seroconversion is defined as achieving a detectable and quantifiable postvaccination IgG anti-HAV level of ≥ 10 mIU/mL. The absolute lower limit of anti-HAV required to prevent HAV infection has not been determined, although the limit is likely quite low. However, antibody levels of 10 to 22 mIU/mL using different assays have been proposed as the threshold for protection from HAV infection in humans. Due to the robust anamnestic response to the second HepA vaccine dose, it has been suggested that vaccinees who seroconverted will be protected, even if their antibody levels have fallen below protective levels.

Data indicate that after a single dose of HepA vaccine, protective anti-HAV antibody levels can persist for almost 11 years and increase or reappear after a 1-dose booster revaccination. Additional data are needed to assess long-term protection after a single dose.

Revaccination (i.e., booster dose, challenge dose, or revaccination with a complete series) is not generally recommended for previously vaccinated persons with a normal immune status.

Since 2008, HepA vaccination has been routine for children aged 1 year in the US; older children may or may not have had catch-up doses. In 2017, HepA vaccination coverage among travelers was approximately 17.7%.

The protective efficacy of HepA vaccination for postexposure prophylaxis (PEP) within 2 weeks after exposure to children and adults aged < 40 years is 86% compared to the 90% efficacy of immune globulin (IG) in this age group. Limited data suggest protection at 2 weeks after vaccination for adults aged 40-49 years and protection at 4 weeks after vaccination for adults aged 50-59 years. IG performs well in all populations. Without PEP, secondary attack rates of 20% to 50% have been reported in households.

A combined HepA-HepB vaccine is also available, and immunogenicity is equivalent to that of the monovalent HepA and HepB vaccines after completion of the recommended schedule; seroconversion for hepatitis A was observed in 93.8% of vaccinees after 1 dose, 98.8% after 2 doses, and 99.9% 1 month after 3 doses.

Indications for Vaccination

Note: Shoreland's vaccine recommendations, which focus primarily on the risk to the individual traveler, reflect a synthesis and reconciliation of available advice from CDC, ACIP, AAP, and WHO, as well as ongoing global surveillance and the published literature. These recommendations may differ from those of individual countries' public health authorities.

Routine

HepA vaccination is routinely recommended for:

- All children in the US at age 1 year (i.e., 12-23 months)
  - Children aged 2-18 years who have not been vaccinated at the recommended time should be vaccinated at any age as catch-up vaccination.
- MSM

- Persons who use illegal drugs, injectable or noninjectable
- Persons working with HAV-infected NHPs or with HAV in a research laboratory setting
- Persons with chronic liver disease (including but not limited to persons with hepatitis B virus or hepatitis C virus infections, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
- Unvaccinated persons who anticipate close personal contact (household or regular babysitting) with an international adoptee from a country with high or intermediate endemicity during the first 60 days after arrival of adoptee. The first dose should be administered as soon as adoption is planned, ideally more than 2 weeks before arrival of the adoptee. The second dose should be given at least 6 months later to provide long-term immunity.
- Any person seeking protection from HAV infection
- Persons aged ≥ 1 year experiencing homelessness
- Persons aged ≥ 1 year with HIV (regardless of CD4 count)

Pregnant women who meet any of the above high-risk criteria for HAV infection should be vaccinated during pregnancy.

Vaccination may be offered to individuals in congregate settings providing services to adults in which a high proportion of persons have risk factors for HAV infection (e.g., health care settings for persons who use injection or noninjection illegal drugs, group homes, and nonresidential day care facilities for developmentally disabled persons).

Vaccination is not routinely recommended for persons handling untreated sewage.

Travel

HepA vaccination is recommended for:

- All susceptible persons aged ≥ 6 months, including pregnant women, traveling to, working in, or living in developing countries and areas of intermediate or high risk for HAV transmission, especially persons who plan frequent trips or have prolonged stays
  - In infants aged 6-11 months, vaccination is noncountable toward the routine schedule and should be followed by routine HepA vaccination (2 additional age-appropriate doses).
  - Vaccination may be considered for travelers aged ≥ 12 months, regardless of destination.
- Susceptible travelers going to some developing countries who engage in risk behaviors (see Risk)
- Risk-averse travelers desiring maximum pretravel protection

Immune globulin intramuscular (IGIM) is recommended for:

- Infants aged < 6 months before travel when protection against HAV is recommended; however, because measles, mumps, rubella (MMR) vaccination should be prioritized for infants aged 6-11 months traveling internationally, IGIM for HAV infection should not be administered within the 6 months prior to MMR vaccination. See Compatibility for more information.
- At-risk travelers who choose not to receive the vaccine or who cannot receive the vaccine due to allergy or if HepA vaccine is unavailable

IGIM may be considered (in addition to the initial dose of HepA vaccine) for:

- Healthy persons aged > 40 years (planning to depart in < 2 weeks), persons aged > 6 months with immunocompromising conditions or chronic liver disease, and pregnant women traveling to intermediate or high-risk areas. The decision to use both HepA vaccine and IGIM depends on the ability of the person to develop a protective antibody level after HepA vaccination, the magnitude of the risk for HAV transmission from the exposure (e.g., endemicity of hepatitis A in the area of travel), and availability of both HepA vaccine and IGIM.

Combination HepA-HepB vaccine is recommended for:

- Persons aged ≥ 18 years who are at risk for both forms of hepatitis.

Outbreak Situations

Preexposure vaccination is recommended for all unvaccinated persons aged ≥ 1 year at risk for HAV infection (e.g., persons who use illegal drugs, injectable or noninjectable, persons experiencing homelessness, or MSM) or severe disease from HAV (e.g., persons with chronic liver disease or those infected with HIV) during a HAV outbreak.

In community outbreak settings propagated by person-to-person transmission, vaccination may be offered to high-risk persons in the vicinity of the outbreak due to increased risk of HAV infection among persons in congregate settings (correctional facilities, homeless shelters, group homes for persons with developmental disabilities, and syringe service programs).

HepA vaccine or IGIM should be used as indicated below:

- HepA vaccine (1 dose) should be administered for preexposure prophylaxis (PrEP) in all persons aged ≥ 12 months (aged ≥ 6 months in Canada) at risk for HAV infection during an outbreak.
- IG may be administered in addition to HepA vaccine for:
  - Persons aged > 40 years (aged ≥ 60 years in Canada) who are high-risk persons in a congregate setting
  - Persons of any age based on the following considerations: altered immune status, underlying conditions (especially chronic liver disease or infection), provider's risk assessment, and availability of IGIM
- IG should be used as a single agent for children aged < 12 months, for those for whom the vaccine is otherwise contraindicated, and if HepA vaccine is indicated but unavailable.

Postexposure Prophylaxis

Healthy individuals who have completed the HepA vaccination series at any time do not need additional PEP if exposed to HAV.

PEP is recommended as soon as possible (within 2 weeks) to individuals at risk for exposure through close personal contact or after exposure to a clinical case of HAV infection or in these settings:

- Household and sexual contacts or known contaminated food source
- Persons using injection and noninjection drugs with HAV-infected persons
- Daycare center staff, attendees, and household members of attendees if ≥ 1 cases occur among ***children*** or if cases are recognized in ≥ 2 households of attendees
- Schools, hospitals, and work settings, if close contact exists with the index patient

Some experts recommend IG for newborn infants of acutely HAV-infected mothers, if the mother's symptoms began between 2 weeks before and up to 1 week after delivery.

PEP is generally not indicated but may be considered for:

- Patrons of food establishments or coworkers of an infected food handler if the food handler was symptomatic when handling food.
- Staff and attendees at childcare centers if ≥ 1 cases occur among employees. PEP should be considered based on the duties, hygienic practices, and presence of symptoms at work. In settings where care is not provided to children in diapers, PEP can be considered only for contacts of the index patient.
- All unvaccinated residents and employees of settings providing services to children and adults where close personal contact occurs regularly and hygiene standards are difficult to maintain (e.g., correctional facility, homeless shelter, psychiatric facility, group home, or residential facility for persons with developmental disabilities). PEP should be limited only to persons in the area with risk for exposure if the setting contains multiple enclosed units or sections.
- HCWs in the US on a case-by-case basis if the risk for exposure to HAV is considered high. Outbreaks caused by transmission from patients to HCWs are usually associated with fecal incontinence and inadequate hand hygiene.

PEP is not routinely indicated for:

- Patrons of food service establishments with an HAV-infected worker
- Attendees and employees of a school or work setting if a single case (with an outside source of infection) is present in that setting

The decision to use IGIM, vaccine, or both should be based on the ability of the recipient to develop a protective level of antibodies after vaccination, the magnitude of the risk for HAV transmission from the exposure, and the availability of IGIM and vaccine.

HepA vaccine or IGIM should be used as indicated below:

- HepA vaccine (1 dose) should be administered for PEP in all persons aged ≥ 12 months (aged ≥ 6 months in Canada) at risk for HAV infection during an outbreak.
- IGIM may be administered in addition to HepA vaccine for:
  - Persons aged > 40 years (aged ≥ 60 years in Canada) depending on the provider's risk assessment

  - Persons aged ≥ 12 months based on the following considerations: immune compromise, underlying conditions (especially chronic liver disease or infection), provider's risk assessment, and availability of IGIM
- IGIM should be used as a single agent for: children aged < 12 months, persons for whom vaccination is otherwise contraindicated, and persons for whom the vaccine is indicated but unavailable.

If only HepA vaccine or IGIM is available, administer the available product as soon as possible; the individual may receive the other product if it becomes available within 2 weeks of exposure.

Note: Because HAV has a relatively long incubation period, the vaccine may not prevent the disease in individuals who have an unrecognized HAV infection at the time of vaccination.

Vaccines and Immune Globulins

See Administration for Hepatitis A Vaccine

Vaccines: US

Hepatitis A Virus Vaccines, Inactivated

Havrix (HepA; GSK)

- Approved for use in persons aged ≥ 12 months
- Available in 0.5 mL and 1 mL single-dose vials and prefilled syringes.
- Formulations include:
  - Pediatric - each 0.5 mL dose contains 720 ELISA units of HAV antigen.
  - Adult - each 1 mL dose contains 1,440 ELISA units of HAV antigen.
- Contains aluminum, formalin, polysorbate 20, and neomycin sulfate
- Thimerosal- and preservative-free
- The tip caps of the prefilled syringes may contain natural rubber latex (NRL).

Vaqta (HepA; Merck)

- Approved for use in persons aged ≥ 12 months
- Available in 0.5 mL and 1 mL single-dose vials and prefilled syringes
- Formulations include:
  - Pediatric/adolescent - 0.5 mL dose contains 25 units of HAV antigen
  - Adult - 1 mL dose contains 50 units of HAV antigen
- Contains aluminum, trace amounts of formaldehyde, bovine serum albumin, and neomycin
- Thimerosal- and preservative-free
- The vial stoppers, syringe plunger stoppers, and tip caps contain dry NRL.

Hepatitis A and Hepatitis B (Recombinant) Vaccine, Inactivated

Twinrix (HepA-HepB; GSK) is a combination of Havrix and Engerix-B.

- Approved for use in persons aged ≥ 18 years
- Available in 1 mL single-dose vials and prefilled syringes; each 1 mL dose contains 720 ELISA units of HAV antigen and 20 µg of HBV antigen.
- Contains aluminum and trace amounts of neomycin, residual formalin, polysorbate 20, and yeast protein
- Thimerosal- and preservative-free
- The tip caps of the prefilled syringes may contain NRL.

In contrast to IGIM, HepA vaccine (an inactivated, viral antigen vaccine) is not derived from blood products.

See ***Immune Globulin*** for information on IGIM used for prevention of HAV infection.

Immune Globulins: US

Immune Globulin Intramuscular (IGIM)

GamaSTAN (Grifols Therapeutics Inc.)

- Approved for prophylaxis of hepatitis A, measles (in persons exposed < 6 days prior), and for the modification of rubella (in exposed women who will not consider a therapeutic abortion) and varicella.
- Available in 2 mL and 10 mL single-dose vials for IM administration
- Contains human plasma and glycine
- Preservative- and thimerosal-free
- Latex-free

Vaccines: Available Outside the US

Hepatitis A Virus Vaccines, Inactivated

Avaxim (Sanofi Pasteur): Australia, Canada, Europe (except Switzerland), and the UK

- In Canada, Avaxim is available in both adult and pediatric (Avaxim Pediatric) formulations approved for use in persons aged ≥ 12 years and 1-15 years, respectively; either vaccine can be used for persons aged 12-15 years. A booster is given after 6 to 36 months.
- In Europe and the UK, Avaxim is approved for use in persons aged ≥ 16 years.
- In Australia, Avaxim is approved for use persons aged ≥ 2 years.
- In other countries, approved age ranges and booster schedules may vary; check the package insert for the country of use.
- Available in 0.5 mL prefilled syringes; each 0.5 mL dose contains 80 antigen units (pediatric) or 160 antigen units (adult) of HAV antigen.
- Contains 2-phenoxyethanol, formaldehyde, aluminum hydroxide, polysorbate 80, ethanol anhydrous, phenylalanine, trace amounts of neomycin, and may contain bovine serum albumin
- Thimerosal-free

Havrix (GSK): Australia, Canada, and the UK

- In Canada, Havrix is available in both adult (Havrix 1440) and pediatric (Havrix 720 Junior) formulations approved for use in persons aged ≥ 19 years and 1-18 years, respectively.
- In Australia, Havrix is available in both adult (Havrix 1440) and pediatric (Havrix Junior) formulations approved for use in persons aged ≥ 16 years and 2-15 years, respectively.
- In the UK, Havrix is available in both adult (Havrix Monodose) and pediatric (Havrix Junior Monodose) formulations approved for use in persons aged ≥ 16 years and 1-15 years, respectively.
- Available in 0.5 mL and 1 mL single-dose vials and prefilled syringes; 1 mL of Havrix adult dose contains 1,440 ELISA units of HAV antigen; 0.5 mL of Havrix pediatric dose contains 720 ELISA units of HAV antigen.
- Contains aluminum hydroxide, trace amounts of neomycin, polysorbate 20, and formaldehyde (not in UK formulation)
- Thimerosal-free

Note: Different strengths and/or concentrations of Havrix may be available or may be used for different patient populations in some countries. Contact the manufacturer directly for any questions that may arise concerning these other formulations.

Vaqta (CSL/Merck): Australia, Canada, and the UK

- Same as US vaccine

Healive (Sinovac Biotech Co. Ltd): China

- Approved for use in children aged 1-15 years (pediatric formulation) and in persons aged ≥ 16 years (adult formulation)
- Available as single-dose prefilled-syringes or single-dose vials; 0.5 mL of Healive pediatric dose contains 250 antigen units; 1 mL of Healive adult dose contains 500 antigen units
- Preservative-free

Hepatitis A Virus Vaccines, Live Attenuated

ZhePu (Zhejiang Pukang Biotechnology Co): China; branded as Biovac-A (Wockhardt) in India

- Vaccines (freeze-dried) are based on H2 or LA-1 strains.
- H2 vaccine is also available in Bangladesh, Guatemala, Philippines, and Thailand.
- Approved for use in China in persons aged ≥ 1 year (1 dose) and in India in persons aged 1-18 years (2 doses, 6 months apart).

- Meta-analysis showed protective efficacy of 95% for both vaccines, which was equivalent to international inactivated vaccines.

Hepatitis A and Hepatitis B (Recombinant) Vaccine, Inactivated

Twinrix (HepA-HepB; GSK): Australia and Canada; a pediatric formulation, Twinrix Junior (3-dose pediatric formulation) is also available in these countries. Branded as Twinrix Adult and Twinrix Pediatric in Europe and the UK; and as Twinrix (720/20) and Twinrix Junior (360/10) in Australia.

- Twinrix adult formulation is approved for persons aged ≥ 1 year in Australia and Canada, and for persons aged ≥ 16 years in Europe and the UK.
- Twinrix Junior/Pediatric is approved for persons aged 1-15 years in Australia, Europe, and the UK, and for persons aged 1-18 years in Canada.
- Available in 1 mL and 0.5 mL single-dose, prefilled syringes and vials.
- Each 1 mL dose (Twinrix adult formulation) contains 720 ELISA units HAV and 20 µg HBsAg.
- Each 0.5 mL dose (Twinrix Junior/Pediatric) contains 360 ELISA units HAV and 10 µg HBsAg.
- Contains aluminum and trace amounts of formalin, neomycin, polysorbate 20, and yeast protein

Ambirix (HepA-HepB; GSK): Europe, UK; 2-dose pediatric formulation

- Approved for use in persons aged 1-15 years
- Available in single-dose, prefilled syringes
- Each 1 mL dose contains 720 ELISA units HAV and 20 µg HBsAg.
- Contains aluminum, yeast, and a trace amount of thimerosal

Combination Hepatitis A-Vi Polysaccharide Typhoid Vaccines, Inactivated

Several combined inactivated HepA and Vi polysaccharide typhoid vaccines are available outside the US. Check package inserts carefully for full prescribing information.

Vivaxim (Sanofi Pasteur): Australia, Canada, France, New Zealand, and elsewhere; branded as Viatim in the UK

- Approved for use in persons aged ≥ 16 years
- One dose (1 mL) of the combination vaccine (administered IM) is followed by a booster dose of HepA vaccine 6 to 36 months later.
- Protection against typhoid lasts about 3 years.
- Available in single-dose, prefilled, dual-chambered syringe containing 0.5 mL purified Vi polysaccharide typhoid vaccine and 0.5 mL inactivated HepA vaccine, which are mixed immediately prior to administration to produce a 1 mL dose
- Contains aluminum, 2-phenoxyethanol, formaldehyde, traces of polysorbate 80, neomycin, and bovine serum albumin
- Thimerosal-free
- Latex-free

Immune Globulins: Available Outside the US

Immune Globulin Intramuscular (IGIM)

GamaSTAN S/D (Grifols Therapeutics): Canada

- Approved for prophylaxis of hepatitis A and measles and for the modification of rubella (in exposed women who will not consider a therapeutic abortion) and varicella.
- Available in 2 mL, 5 mL, and 10 mL single-dose vials for IM administration
- Contains human plasma and glycine
- Preservative- and thimerosal-free
- Latex-free

GamaSTAN (Grifols Therapeutics): Canada

- Same as US product

Normal Human Immunoglobulin-VF (CSL Ltd) : Australia, New Zealand

- Approved for prophylaxis of hepatitis A and measles for use in persons aged ≥ 12 months via IM administration
- Available in 2 mL and 5 mL vials

- Contains human plasma and glycine
- Preservative-free
- Latex-free

Side Effects

Side effects of HepA vaccination tend to be mild and transient. The most frequently reported side effects are injection-site reactions (pain, redness, warmth, swelling, and tenderness) and mild systemic reactions (e.g., fever, irritability, loss of appetite, drowsiness, and headache). No serious adverse events have been observed.

Side effects of Twinrix (Havrix + Engerix-B) are similar to those of the individual vaccines given concurrently.

Side effects of IGIM include injection-site reactions as well as thromboembolic events, which may occur in the absence of usual risk factors and despite administration route; underlying risk factors may further increase the risk.

Suspected allergic or adverse effects or medical care required after any vaccination should be reported through the Vaccine Adverse Event Reporting System (VAERS). See also Table: Reportable Events following Vaccination and the VAERS form.

Precautions and Contraindications

Precautions

Consider postponing vaccination in persons with moderate or severe illness (with or without a fever) until recovery, to minimize potential adverse effects.

Contraindications

Anaphylactic reaction to a previous dose or a vaccine constituent contraindicates further vaccination with that vaccine or any vaccine containing that constituent.

Persons who are allergic to a vaccine component or who choose not to receive the vaccine should receive IGIM (0.1-0.2 mL/kg), which provides effective protection for up to 2 months depending on the dose. See ***Immune Globulin Intramuscular (IGIM)*** for more information.

Conditions commonly misperceived as contraindications or precautions

Conditions incorrectly perceived as contraindications or precautions to vaccination (i.e., vaccines may be given under these conditions)

- Mild acute illness, with or without fever
- Lack of previous physical examination in a well-appearing person
- Current antimicrobial therapy
- Convalescent phase of illness
- Preterm birth
- Recent exposure to an infectious disease
- History of penicillin allergy, other nonvaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy
- History of Guillain-Barré syndrome

Bleeding Disorders

All HepA and HepA-containing vaccines are intramuscular injections and may pose a risk for persons with bleeding disorders or those receiving anticoagulation drugs. Consider scheduling vaccination just prior to the next dose of anticoagulant drugs. Morning anticoagulant doses can be deferred until after an early morning vaccine dose, or the vaccine dose can be given late in the afternoon in the case of evening anticoagulant doses. Use a fine-gauge needle (23-gauge or smaller) and apply firm, direct pressure to the site for at least 2 minutes following the injection. Do not rub or massage the injection site. A bruising rate of less than 4% results using this approach. See ***Bleeding Disorders and Vaccination***.

Alternatively, single antigen HepA vaccines may be administered subcutaneously.

Immunocompromising Conditions and HIV

Data indicate that immunocompromised persons being treated with immunosuppressive drugs may have inadequate seroprotection after a single dose of HepA vaccine. Such travelers should make efforts to receive the 2-dose HepA vaccination

series over a 6-month period prior to their trip. However, instead of giving concomitant IGIM with the initial dose of HepA vaccine per US CDC recommendation, many experienced clinicians recommend giving a second dose at least 4 weeks after the first dose for time-constrained travelers. However, if this second dose is administered less than 6 months after the first dose, it is invalid for completion of the routine series. Alternatively, limited data show that a modified dosing regimen which includes doubling the standard antigen dose or administration of additional doses may increase response rates. See Administration Errors.

Among adults with HIV infection, 50% to 95% were seroprotected after vaccination with the complete series, and final antibody concentrations were much lower than in HIV-negative persons. Data indicate that high viremia at the time of vaccination is associated with decreased seroprotection in persons with HIV; however, HepA vaccination should not be delayed until the CD4 count exceeds a particular threshold. Additionally, HepA vaccination may not provide long-term protection and IGIM may be needed after a high risk HAV exposure (e.g., sexual or household contact). Postvaccination serologic testing should be performed ≥ 1 month after completing the HepA vaccination series for all persons with HIV. Revaccination should be considered for persons with HIV infection (including those who later demonstrate an improved immune status) and persons who received HepA vaccine while immunosuppressed from chemotherapy who fail to demonstrate an adequate immune response (i.e., ≥10 mIU/mL) after the initial HepA vaccination series.

Hematopoietic cell transplant (HCT) recipients should be revaccinated routinely after HCT regardless of the source of the transplanted stem cells.

Solid-organ transplant (particularly liver transplant) candidates aged ≥ 1 year who are unvaccinated, incompletely vaccinated, or seronegative for hepatitis A should receive a HepA vaccination series.

When indicated for the prevention of hepatitis A in immunocompromised persons, IGIM should be administered using the same dose and schedule as that used for immunocompetent persons. Household and other close contacts of immunocompromised persons should receive all age- and exposure-appropriate vaccines, with the exception of smallpox vaccine.

See also ***Immunocompromised Travelers*** and ***Travelers with HIV***.

For administration and dosage schedules for those with compromised immunity, see Accelerated, Altered, or Lapsed Schedules.

Pregnancy and Breastfeeding

Pregnancy

According to ACIP's General Best Practice Guidelines for Immunization (2017), no evidence exists of risk to the fetus from vaccinating pregnant women with HepA-containing vaccines.

Consider informing the woman that all pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risks are 2% to 4% for major birth defects and 15% to 20% for miscarriages in clinically recognized pregnancies.

Pregnant women at risk for HAV infection during pregnancy (including travelers) should be vaccinated during pregnancy if not previously vaccinated and should be vaccinated for the same indications as nonpregnant women. Unvaccinated or partially vaccinated pregnant adolescents should receive HepA catch-up vaccination. Unvaccinated pregnant women at risk for HAV infection who choose not to be vaccinated during pregnancy should be counseled about HAV infection prevention methods. IGIM is a safe and effective alternative for preventing HAV infection in pregnancy, but vaccination with HepA vaccine gives a more complete and prolonged protection.

See ***Pregnant Travelers***.

Breastfeeding

Whether HepA vaccine is excreted in human breast milk is unknown. Receipt of HepA-containing vaccines is not a contraindication to breastfeeding and poses no risk to the mother or infant.

Compatibility

HepA-containing vaccines can be administered simultaneously with (or at any time before or after) other vaccines.

All doses of vaccine in a series should come from the same manufacturer; however, if this is not possible or if the manufacturer of the previously given doses is unknown, providers should not defer vaccination but instead administer the vaccine that they have available.

The efficacy and safety of combination vaccines are comparable to previously licensed monovalent or combination products with similar component antigens from the same manufacturer and may be used interchangeably with these products to continue the vaccination series.

HepA and HepA-containing vaccines can be administered simultaneously with (or at any time before or after) any antibody-containing preparation (e.g., immune globulin, hyperimmune globulin, and intravenous immune globulin) but should be given at a different injection site if administered simultaneously.

Separate vaccines should not be combined into the same syringe to be administered together unless indicated for the patient's age and explicitly specified on the FDA-approved product label inserts. The safety, immunogenicity, and effectiveness of unlicensed combinations are unknown.

IGIM used for HepA prophylaxis and MMR vaccine should not be administered simultaneously. Live vaccines (e.g., MMR and varicella vaccines) should be administered at least 2 weeks before or at least 6 months after IG administration. If IGIM must be administered less than 2 weeks after administration of MMR or varicella vaccine, the patient should be revaccinated with MMR or varicella ≥ 6 months after IGIM administration unless serologic testing is feasible and indicates a response to that vaccine.

Special Considerations

Prevaccination Serological Testing

Prevaccination serologic testing is rarely done in clinical practice but may be considered in specific settings to reduce costs by not vaccinating persons who are likely already immune such as:

- Persons who were born in or lived for extensive periods in areas with high or intermediate prevalence of HAV infection
- Older adolescents and adults in certain population groups (i.e., Native Americans, Alaskan Natives, and Hispanics)
- Adults in groups that have a high prevalence of infection (e.g., MSM and injection-drug users)

The inability to perform prevaccination serologic testing should not be a barrier to vaccination of susceptible persons, especially in populations difficult to access. Testing is not generally indicated in children because of low incidence of HAV infection.

Commercially available tests for total anti-HAV or IgG anti-HAV should be used.

- Elevated anti-HAV IgM indicates acute HAV infection, and antibodies decline over several months. This test is inappropriate for determining long-term immunity.
- Elevated anti-HAV IgG or total anti-HAV indicates previous HAV infection, and protective antibodies persist for life.

Vaccination history should be obtained where practical, prior to testing or vaccination of populations expected to have high rates of previous HAV vaccination. Vaccination should not be deferred if vaccination history cannot be obtained, records are unavailable, or prevaccination testing is not feasible. Providers should only accept dated records as evidence of HepA vaccination. Vaccination of a person who has had natural infection or an immune person is not contraindicated and does not incur increased risk for adverse effects.

Total anti-HAV or IgG anti-HAV testing is used in epidemiologic studies to measure the prevalence of previous infection or clinically to determine whether a person with an indication for PrEP is already immune.

Postvaccination Serological Testing

Postvaccination serologic testing is not generally indicated because of the high rate of vaccine response among adults and children; however, persons whose subsequent clinical management depends on knowledge of their immune status and for whom revaccination might be indicated (e.g., persons with HIV and other immunocompromised persons [e.g., HCT and solid organ transplant recipients and persons receiving chemotherapy]) should be tested. If indicated, testing should be performed with total anti-HAV or IgG anti-HAV assays ≥ 1 month after completing the vaccination series.

Anti-HAV persistence studies do not indicate a need for additional HepA doses (i.e., booster or revaccination) beyond the 2-dose primary HepA series (or 3-dose HepA-HepB series) because protective antibodies are estimated to persist for at least 40 years in more than 90% of immunocompetent adult vaccinees.

Persons who do not respond to vaccination should be considered susceptible to HAV infection and counseled about HAV exposure precautions and the need to obtain IGIM postexposure prophylaxis for known or likely exposures to HAV.

Travax content represents decision-relevant, expert synthesis of real-time data reconciled with new and existing available advice from authoritative national and international bodies. National body recommendations such as ACIP/CDC may differ from the manufacturers' recommendations as found in vaccine package inserts. Travax recommendations may differ from those of individual countries' public health authorities.

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