Hepatitis A

Medical Summary

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

What's New

Hepatitis A (HepA) vaccination is now recommended by U.S. Advisory Committee for Immunization Practices (ACIP) for:

- All susceptible persons aged ≥ 6 months traveling to or living in developing countries and areas of intermediate or high risk for hepatitis A virus transmission. Infants aged 6-11 months should be given 1 dose (noncountable) prior to travel. Following this dose, routine vaccination with HepA vaccine (2 additional age-appropriate doses) should occur.
- Postexposure prophylaxis for all persons aged ≥ 12 months. Additionally, immune globulin (if available) may be administered to persons aged > 40 years depending on the provider's risk assessment (e.g., patient's age, immune status and underlying conditions, and risk of exposure).

See Table ROUT-CHILD for the 2018 recommended childhood and catch-up immunization schedules and Table ROUT-ADULT for the 2018 adult immunization schedule. No significant changes have occurred since the 2017 schedules.

Introduction

Hepatitis A infection is caused by hepatitis A virus (HAV), which replicates in the liver. The resulting immune response causes liver inflammation and hepatic dysfunction. Infection with any of the genotypes (4 of 7 affect humans) results in lifelong immunity against all strains of HAV.

Epidemiology

HAV infection is highly endemic in developing countries 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, foci of high transmission may occur in certain risk populations or may be due to consumption of imported HAV-contaminated food from global sources.

Mode of Transmission

Humans are the only natural hosts of the virus; no insect or animal vectors exist. Transmission occurs most often through consumption of contaminated foods (e.g., undercooked shellfish, raw or inadequately cooked or frozen foods [including fruits and vegetables]), water, or ice. The virus is also spread through person-to-person contact via the direct fecal-oral route (e.g., contaminated surfaces or oral-anal sexual acts) or via food contaminated by acutely infected food handlers. Blood-borne transmission, although uncommon, is possible via contaminated blood products.

Persons can shed the virus in stool beginning several weeks before the onset of symptoms and for about 1 to 3 weeks afterward; viral concentration in stool is highest in the prodromal stage.

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

Current risk in travelers is estimated to be high (6-30/100,000 travelers per month of travel to developing countries) and increases with duration of travel. For individuals 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, eat or drink frequently in high-risk situations, or have close physical contact with local persons (especially young children) in settings with poor sanitary conditions; and for persons who travel outside prearranged, fixed itineraries (including common tourist packages). However, cases can also occur in settings with good sanitary conditions because of an infected food handler or consumption of contaminated food.

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 actual infection. Because children generally have asymptomatic or unrecognized illness, they may serve as a source of infection for unvaccinated household or other close contacts upon return home.

In countries with very low HAV infection rates, disease may occur among travelers ingesting undercooked shellfish.

Clinical Presentation

Infection can be asymptomatic or range in severity from a mild illness lasting 1 to 2 weeks to a severely disabling disease lasting several months. In young children, HAV usually causes either asymptomatic infection or very mild illness without jaundice; adults are more likely to have symptomatic infection.

Following an asymptomatic incubation period of 15 to 50 days (average: 28 days), anorexia, nausea, vomiting, abdominal pain, diarrhea, malaise, and fever may occur, followed within days by jaundice. Dark urine usually occurs before onset of jaundice, and hepatic tenderness may also be present. 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. Chronic hepatitis and carrier states do not occur.

A fatal course is rare in previously healthy individuals. The overall case-fatality ratio is 0.3% but can reach 1.8% among adults aged > 50 years.

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.

Prevention

Nonvaccine

Travelers should observe food and beverage precautions, regardless of immunization status. Good hygiene is vital, especially handwashing or use of hand sanitizer after using the bathroom, changing diapers, and before preparing or eating food. Safer sex practices should be observed.

Vaccine

HepA vaccines are highly immunogenic; a single dose of a single antigen HepA vaccine given any time before travel will provide nearly complete protection for healthy persons. Following 2 doses, nearly 100% of vaccinees will seroconvert, with protective antibodies estimated to persist for at least 40 years in more than 90% of adult vaccinees. (See *Literature Watch Review:* Long-Term Protection against Hepatitis A: Serological and Cellular Studies). Due to the robust anamnestic response to the second HepA vaccine dose, it has been suggested that vaccine recipients who seroconverted will be protected, even if their antibody levels have fallen below protective levels.

Since 2008, HepA vaccine has been given routinely to children in the U.S. at age 1 year; older children may or may not have had catch-up doses.

The protective efficacy of HepA vaccine given for postexposure prophylaxis within 2 weeks after exposure to children and adults aged < 40 years is 86% compared to the 90% efficacy of 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.

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.

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 vaccine is routinely recommended for:

- All children in the U.S. at age 1 year (i.e., 12-23 months)
  - Children aged ≥ 2 years who have not been vaccinated at the recommended time (see above)
- Men who have sex with men
- Persons who use illegal drugs
- Persons working with HAV-infected primates or with HAV in a research laboratory setting
- Persons with chronic liver disease (including persons waiting for or who have received liver transplants). Available data do not indicate a need for routine vaccination of persons with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections without evidence of chronic liver disease.
- Persons who receive clotting factor concentrates
- 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

Travel

HepA vaccine is recommended for:

- All susceptible persons aged ≥ 6 months, traveling to 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 vaccination with HepA vaccine (2 additional age-appropriate doses).
  - Some experts recommend that travelers consider HepA vaccination regardless of destination.
- Susceptible travelers going to some developing countries who engage in risk behaviors (see Risk)
- Risk-averse travelers desiring maximum pretravel protection

IG given intramuscularly (IM) should be considered for:

- At-risk travelers who choose not to receive the vaccine or who cannot receive the vaccine due to allergy
- Older adults, immunocompromised persons, and those with chronic liver disease or other chronic medical conditions who are planning to depart in ≤ 2 weeks should receive IG in addition to the initial dose of HepA vaccine for optimal protection.

Combination HepA-HepB vaccine is recommended for:

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

Postexposure Prophylaxis

Postexposure prophylaxis is recommended after exposure to a clinical case of HAV infection in these settings:

- Household and sexual contacts
- Persons who have shared illegal drugs
- Daycare center staff, attendees, and household members of attendees
- Common-source exposure such as a known infected food handler or an exposure in a known outbreak setting where the specific source is unknown
- 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.

Either HepA vaccine or IG should be used as indicated below:

- HepA vaccine should be administered for postexposure prophylaxis in all persons aged ≥ 12 months (aged ≥ 6 months in Canada).
- IG may be administered in addition to HepA vaccine in persons aged > 40 years (aged ≥ 60 years in Canada), depending on providers' risk assessment (e.g., patient age, immune status and underlying conditions, exposure type/risk of transmission, and availability of IG).
- IG should be used as a single agent for children aged < 12 months and for those for whom the vaccine is otherwise contraindicated.

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

Vaccines - U.S.

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
- 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, trace amounts of neomycin, residual formaldehyde, polysorbate 20, and yeast protein
- Thimerosal- and preservative-free
- The tip caps of the prefilled syringes may contain NRL.

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

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

Vaccines – Available Outside the U.S.

Hepatitis A Virus Vaccines, Inactivated

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

- 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 12 months.
- In Europe, 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 160 antigen units of HAV antigen.
- Contains 2-phenoxyethanol, formaldehyde, aluminum hydroxide, polysorbate 80, trace amounts of neomycin, and may contain bovine serum albumin
- Thimerosal-free

Havrix (GSK): Australia, Canada, and Switzerland

- Pediatric formulation (Havrix Junior) is also available.
- Approved for use in persons aged ≥ 1 year and Havrix Junior for persons aged 1-18 years
- Available in 0.5 mL and 1 mL single-dose vials and prefilled syringes; 1 mL of Havrix adult (≥ 19 years) dose contains 1,440 ELISA units of HAV antigen; 0.5 mL of Havrix Junior contains 720 ELISA units of HAV antigen.
- Contains aluminum hydroxide, trace amounts of neomycin, polysorbate 20, and formaldehyde
- 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 and Canada

- Same as U.S. vaccine

Hepatitis A Live Attenuated Vaccines

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 as 1 dose
- 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 (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.

- Twinrix approved for persons aged ≥ 1 year in Australia and Canada; in Europe for persons aged ≥ 16 years
- Twinrix Junior/Pediatric approved for persons aged 1-15 years in Australia, Canada, and Europe
- Available in 1 mL and 0.5 mL single-dose, prefilled syringes in Canada and single-dose, prefilled syringes and vials in Europe and Australia
- Each 1 mL dose 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 formaldehyde, neomycin, polysorbate 20, and yeast proteins.

Combination Hepatitis A-Vi Polysaccharide Typhoid Vaccines, Inactivated

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

Vivaxim (Sanofi Pasteur): Canada, Australia, and elsewhere; branded as Viatim in Europe (except Switzerland)

- 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

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. Headache in some adults, feeding problems in children, and secondary respiratory tract infections have also been reported. No serious adverse events have been observed.

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

Suspected allergic or adverse effects or medical care required after any vaccination should be reported through the Vaccine Adverse Event Reporting System (VAERS). Also see Table ADV-1 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 immunization 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 IG (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:

- Mild acute illness, with or without fever
- Mild to moderate local reaction (e.g., swelling, redness, soreness); low-grade or moderate fever after previous dose
- Lack of previous physical examination in 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 IM 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.

Compromised Immunity 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 2 doses of the HepA vaccine over a 6-month period prior to their trip. Many experienced clinicians recommend giving a second dose at least 4 weeks after the first dose for time-constrained travelers.

No special precautions need to be taken when vaccinating immunocompromised persons. If this vaccine is administered to persons with malignancies, immune disorders, or those on immunosuppressive therapy, the expected immune response may not be obtained.

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 HIV-infected persons.

Household and other close contacts of immunocompromised persons should receive all age- and exposure-appropriate vaccines, with the exception of smallpox vaccine.

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

Also see *Immunocompromised Travelers* and *HIV-Infected Travelers*.

Pregnancy and Breastfeeding

The safety of HepA vaccine during pregnancy has not been determined; however, because HepA vaccine is produced from inactivated HAV, the theoretical risk to the pregnant woman or the developing fetus is expected to be low.

- The risk associated with vaccination should be weighed against the risk for infection in pregnant women who may be at high risk for exposure to HAV.
- IG is a safe and effective means of preventing HAV, but immunization with HepA vaccine gives a more complete and prolonged protection.

Whether Twinrix can cause fetal harm when administered during pregnancy is unknown. Twinrix (HepA-HepB) should be given to pregnant women only if clearly indicated.

See *Pregnant Travelers* for additional information.

Compatibility

HepA vaccine 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.

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.

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

IG and measles, mumps, rubella vaccine should not be administered simultaneously.

Special Considerations

Prevaccination Serological Testing

Prevaccination serologic testing is rarely done in clinical practice, but it may be more cost effective than vaccination (as long as it does not interfere with completion of the vaccine series) in the following travelers who are likely already immune:

- Persons who were born in or lived in areas with high or intermediate prevalence of HAV infection
- Older adolescents and adults in certain population groups (i.e., American Indians, Alaskan natives, and Hispanics)
- Adults in groups that have a high prevalence of infection (e.g., men who have sex with men and injection-drug users)

Elevated anti-HAV IgM indicates acute HAV infection, and antibodies decline over several months. This is an inappropriate test for long-term immunity.

Elevated anti-HAV IgG or total anti-HAV indicates previous HAV infection, and protective antibodies persist for life.

Vaccination of an immune person is not contraindicated and does not increase the risk for adverse effects.

Postvaccination Serological Testing

Postvaccination serologic testing is not indicated because of the high rate of vaccine response among adults and children. Additionally, not all testing methods used for routine diagnosis in the U.S. have the sensitivity to detect low but protective anti-HAV concentrations after vaccination.

- The level of anti-HAV antibody needed to provide protection against infection is unknown.
- Persons tested for anti-HAV after immunization may not have detectable antibody but may still be protected.

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.