

The first descriptions of hepatitis (epidemic jaundice) are generally attributed to Hippocrates. Outbreaks of jaundice, probably hepatitis A, were reported in the 17th and 18th centuries, particularly in association with military campaigns. Hepatitis A (formerly called “infectious hepatitis”) was first differentiated epidemiologically from hepatitis B, which has a longer incubation period, in the 1940s. Development of serologic tests allowed definitive diagnosis of hepatitis B. In the 1970s, identification of the virus and development of serologic tests helped differentiate hepatitis A from other types of non-B hepatitis.

In the prevaccine era, the primary methods used for preventing hepatitis A were hygienic measures and passive protection with immune globulin (IG). Hepatitis A (HepA) vaccines were first licensed for use in the United States in 1995. These vaccines provide long-term protection against hepatitis A virus (HAV) infection. The similarities between the epidemiology of hepatitis A and poliomyelitis suggest that widespread vaccination of appropriate susceptible populations with HepA vaccines can substantially lower disease incidence, eliminate virus transmission, and ultimately, eliminate HAV infection. Prior to 2004, hepatitis A was the most frequently reported type of hepatitis in the United States. From 1996, when the HepA vaccine was introduced, through 2011, hepatitis A cases decreased by over 95%, but re-emerged in 2016 in the United States due to widespread outbreaks among persons reporting drug use and homelessness. In response, CDC has been assisting multiple state and local health departments with hepatitis A outbreaks.

Hepatitis A Virus

Hepatitis A is caused by infection with HAV, an RNA virus that is classified as a picornavirus. It was first isolated in 1979. Humans are the only natural host, although several nonhuman primates have been infected in laboratory conditions. Depending on conditions, HAV can be stable in the environment for months. The virus is relatively stable at low pH levels, moderate temperatures, and frozen temperatures, but can be inactivated by high temperature (185°F [85°C] or higher), formalin, and chlorine.

Pathogenesis

HAV is typically acquired through ingestion (through fecal-oral transmission) and replicates in the liver. After 10 to 12 days, virus is present in blood and is excreted via the biliary system into the feces. Peak titers occur during the 2 weeks before onset of illness. Although virus is present in serum, its concentration is several orders of magnitude less than in feces. Virus excretion

Hepatitis A

- Descriptions of epidemic jaundice attributed to Hippocrates
- Differentiated from hepatitis B in 1940s
- Serologic tests developed in 1970s
- Vaccines first licensed in the U.S. in 1995

Hepatitis A Virus

- Picornavirus (RNA)
- Humans are only natural host
- Stable at low pH
- Inactivated by temperature of 185°F or higher, formalin, chlorine

Hepatitis A Pathogenesis

- Fecal-oral transmission
- Viral replication in the liver
- Virus present in blood and feces 10 to 12 days after infection
- Virus excretion may continue for up to 3 weeks after onset of symptoms

Hepatitis A Clinical Features

- Incubation period 28 days (range, 15 to 50 days)
- Symptoms: Abrupt onset of fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, jaundice
- Likelihood of symptomatic illness directly related to age
- Children generally asymptomatic, adults symptomatic

begins to decline at the onset of clinical illness and decreases significantly by 7 to 10 days after onset of symptoms. Most infected persons no longer excrete virus in the feces by the third week of illness.

Clinical Features

The incubation period of hepatitis A is approximately 28 days (range 15 to 50 days). The clinical course of hepatitis A is indistinguishable from that of other types of acute viral hepatitis. The illness typically has an abrupt onset of fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, and jaundice. Clinical illness usually does not last longer than 2 months, although 10% to 15% of persons have prolonged or relapsing signs and symptoms for up to 6 months. Virus may be excreted during a relapse or prolonged illness.

The likelihood of symptomatic illness from HAV infection is directly related to age. In children younger than age 6 years, most (70%) infections are asymptomatic. In older children and adults, infection is usually symptomatic, with jaundice occurring in more than 70% of patients.

Complications

Severe clinical manifestations of hepatitis A infection are rare; however, atypical complications may occur, including immunologic, neurologic, hematologic, pancreatic, and renal manifestations. Relapsing hepatitis, cholestatic hepatitis A, hepatitis A triggering autoimmune hepatitis, subfulminant hepatitis, and fulminant hepatitis have also been reported. Fulminant hepatitis is the most severe rare complication, with mortality estimates up to 80%. Overall case-fatality estimates range from 0.3% to 0.6% for all ages and up to 1.8% among adults age 50 years or older. During outbreaks concentrated in older individuals or higher proportions of individuals with comorbidities, case-fatality rates can be significantly higher. Vaccination of high-risk groups and other public health measures have significantly reduced the overall number of hepatitis A cases and fulminant HAV infections. However, even nonfatal hepatitis A results in substantial morbidity, with associated costs of medical care and work loss.

Laboratory Testing

Hepatitis A cannot be distinguished from other types of viral hepatitis on the basis of clinical or epidemiologic features alone. Serologic testing is required to confirm the diagnosis. Virtually all patients with acute hepatitis A have detectable IgM anti-HAV. Acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of IgM anti-HAV in serum. IgM generally becomes detectable 5 to 10 days before the onset of symptoms and can persist for up to 6 months.

IgG anti-HAV appears in the convalescent phase of infection, remains present in serum for the lifetime of the person, and confers enduring protection against disease. The antibody test for total anti-HAV measures both IgG anti-HAV and IgM anti-HAV. Persons who are total anti-HAV-positive and IgM anti-HAV-negative have serologic markers indicating immunity consistent with either past infection or vaccination.

Molecular virology methods such as polymerase chain reaction (PCR)-based assays can be used to amplify and sequence viral genomes. These assays are helpful to investigate common-source outbreaks of hepatitis A.

Medical Management

There is no specific treatment for hepatitis A virus infection. Treatment and management of HAV infection are supportive.

Epidemiology

Occurrence

Hepatitis A occurs throughout the world. It is highly endemic in some areas, particularly Central and South America, Africa, the Middle East, Asia, and the Western Pacific.

Reservoir

Humans are the only natural reservoir of the virus. There are no insect or animal vectors. A chronic HAV state has not been reported although infections may relapse or be prolonged.

Transmission

HAV infection is acquired primarily by the fecal-oral route by either ingestion of contaminated food or water or direct contact with an infectious person. Since the virus is present in blood during the illness prodrome, HAV has been transmitted on rare occasions by blood transfusion as well as solid organ transplantation. Although HAV may be present in saliva, transmission by saliva has not been demonstrated. Waterborne outbreaks are infrequent in the United States and are usually associated with sewage-contaminated or inadequately treated water.

Temporal Pattern

There is no appreciable seasonal variation in hepatitis A incidence. In the prevaccine era, cyclic increases in reported acute cases were observed every 10 to 15 years and were characterized by large community outbreaks of disease.

Hepatitis A Epidemiology

- Reservoir
 - Human
- Transmission
 - Fecal-oral
- Temporal pattern
 - None
- Communicability
 - Most infectious 1-2 weeks before onset of illness

Communicability

Viral shedding persists for 1 to 3 weeks. Infected persons are most likely to transmit HAV 1 to 2 weeks before the onset of illness, when HAV concentration in stool is highest. The risk then decreases and is minimal the week after the onset of symptoms.

Risk Factors

Groups at increased risk for hepatitis A or its complications include international travelers (particularly those with high-risk itineraries such as travel to rural areas in high-risk regions [Central and South America, Africa, Asia]), recent international adoptees from hepatitis A-endemic countries and their contacts, men who have sex with men, people experiencing homelessness, persons with HIV, and people who use drugs. Outbreaks of hepatitis A have also been reported among persons working with hepatitis A–infected primates.

Persons with chronic liver disease are not at increased risk of infection but are at increased risk of developing fulminant hepatitis A if infected.

Persons with clotting factor disorders may be at increased risk of hepatitis A because of administration of solvent/detergent-treated factor VIII and IX concentrates; however, secondary virus reduction steps, common use of recombinant clotting factor concentrates, and screening of plasma for HAV has greatly reduced the risk of HAV transmission from clotting factors to the same as that among the general population.

Persons with occupational risk include only those who work with hepatitis A–infected nonhuman primates or with clinical or nonclinical material containing hepatitis A virus in a research laboratory setting. Food handlers are not at increased risk for hepatitis A because of their occupation, and secondary transmission from food handlers is rare. Health care personnel do not have an increased incidence of HAV infections, and nosocomial HAV transmission is rare. Nonetheless, outbreaks have been observed in neonatal intensive care units and in association with adult fecal incontinence. Other than the occasional transmission within health care settings, no worker-related HAV infections have been reported in the United States. Consistently, serologic studies in the United States have shown no or mildly increased risk of HAV infection in wastewater workers.

Historically, HAV infection was highly endemic in institutions for persons with developmental disabilities. Now, persons with developmental disabilities typically live in group homes or residential facilities. Outbreaks can occur in these settings. Schools are not common sites for HAV transmission. Multiple cases among children at a school require investigation to identify a common source and efforts to improve immunization coverage.

Children generally have asymptomatic or unrecognized illnesses, so they may serve as a source of infection, particularly for household or other close contacts.

In 2018, 5,026 (40%) of the 12,474 hepatitis A cases reported in the United States had a risk factor identified; the other 60% either had no risk factor identified or risk factor data were missing. Of the 40% with a risk factor identified, injection drug use was the most commonly identified risk factor. Other sources of infection identified in the United States in 2018 included men who have sex with men, sexual/household contact with a hepatitis-A-infected person, other contact with a hepatitis A patient, and international travel.

Secular Trends in the United States

Hepatitis A became nationally notifiable as a distinct entity in 1966. During the prevaccine era in the United States, hepatitis A occurred in large, nationwide epidemics. The largest number of cases reported in one year (59,606) was in 1971. Prior to 2000, the incidence of reported hepatitis A was substantially higher in the western United States than in other parts of the country. From 1987 to 1997, 11 mostly western states (Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Idaho, Nevada, California) accounted for 50% of reported cases, but only 22% of the U.S. population. Historically, children age 2 through 18 years had the highest rates of hepatitis A (15 to 20 cases per 100,000 population in the early to mid-1990s).

In 1996, CDC's Advisory Committee on Immunization Practices (ACIP) recommended administration of HepA vaccine to persons at increased risk for the disease, including international travelers, men who have sex with men, people who use non-injection and injection drugs, and children living in communities with high rates of disease. In 1999, ACIP also recommended routine vaccination for children living in 11 Western states with average hepatitis A rates of more than 20 cases per 100,000 population and recommended that vaccination be considered for children in an additional 6 states with rates of 10 to 20 cases per 100,000 population. ACIP expanded these recommendations in 2006 to include routine vaccination of children beginning at age 12 months in all 50 states. In 2019, the ACIP recommended vaccination of all persons experiencing homelessness age 1 year or older. In 2020, ACIP recommended vaccination of all children and adolescents age 2 through 18 years who have not previously received HepA vaccine and routine vaccination of all persons with HIV age 1 year or older.

Hepatitis A rates have been declining since vaccination initiation in 1996 and were less than 1 case per 100,000 until increases occurred due to widespread outbreaks among persons reporting drug use and homelessness. The number

Hepatitis A Secular Trends in the United States

- Large, nationwide epidemic during prevaccine era
- Historically, children 2–18 had highest rates of hepatitis A (15 to 20 cases per 100,000)
- Prior to 2000, incidence higher in Western states
- Rates declined 95.5% since vaccination initiation in 1996 to 2011
- From 2016–2021, over 37,000 outbreak-associated cases reported from 35 states

of reported acute hepatitis A cases decreased 95.5% overall from 1996 to 2011. Many of the high-incidence states began routine hepatitis A vaccination programs for children in the late 1990s, and since 2002, rates have been similar in all parts of the country, ranging from 0.1 case per 100,000 population to 5.1 cases per 100,000 population. Since 2002, rates among children have declined. The wider use of vaccine is largely responsible for the marked decrease in hepatitis A rates in the United States, for the elimination of regional disparities in rates of infection, and for decreased infection rates in children. Beginning in the late 1990s, national age-specific rates declined more rapidly among children than adults; rates were similar among all age groups until the widespread person-to-person outbreaks occurred in 2017, primarily impacting adults and increasing rates among individuals age 20 years or older. Historic differences in rates among racial/ethnic populations have narrowed in the vaccine era.

In 2018, 12,474 cases of acute hepatitis A were reported nationwide to CDC. The overall incidence rate for 2018 was 3.8 cases per 100,000 population, an increase from recent years. The rate was similar for males and females but increased for persons older than age 20 years. In the United States, there have been decreases in incidence of hepatitis A due to universal childhood vaccination. However, this has resulted in the average age of hepatitis A-related hospitalizations and deaths increasing, and the proportion of persons hospitalized is more likely to have liver diseases and other comorbid medical conditions. Analysis of anti-HAV positivity prevalence, based on data from the National Health and Nutrition Examination Surveys (NHANES) conducted in 2007–2016, showed a significant increase among children age 6 through 19 years, and significant increases occurred in the proportion of children age 6 to 19 years with immune markers of protection, most likely from vaccination. Minimal change in anti-HAV positivity prevalence occurred among adults age 20 through 39 years, with 74% of adults being susceptible to disease. Significant decreases occurred in the proportion of adults age 40 years or older with protection. During 2007–2016, the prevalence of anti-HAV positivity among U.S.-born residents differed significantly by race/ethnicity. Overall, antibody positivity prevalence was lowest among non-Hispanic whites, intermediate among non-Hispanic blacks, and greatest among Hispanics across all age groups.

During 2017, a total of 1,521 outbreak-associated HAV cases were reported from California, Kentucky, Michigan, and Utah, with 1,073 (71%) hospitalizations and 41 (3%) deaths; most infections were among persons reporting homelessness or injection or non-injection drug use. From August 2016 through January 2021, over 37,000 outbreak-associated cases had been reported from 35 states.

Among children born during 2016–2017, 85.8% had received at least 1 dose of HepA vaccine by age 24 months, an increase of 1.8 percentage points from 2014–2015. By age 35 months, 76.9% had received at least 2 doses of HepA vaccine, a 2.0 percentage point increase from 2014–2015. In 2019, 77.1% of adolescents age 13–17 years had received at least 2 doses of HepA vaccine compared with 73.6% the year prior. For adults age 19 years or older, vaccination coverage in 2017 was reported at 10.9% for at least 2 doses.

Hepatitis A Vaccines

To produce HepA vaccines, cell culture–adapted virus is propagated in human fibroblasts, purified from cell lysates, inactivated with formalin, and adsorbed to an aluminum hydroxide adjuvant. Single-antigen HepA vaccine was licensed for use in the United States in 1995 (Havrix) and 1996 (Vaqta). In 2001, a combination HepA–HepB vaccine (Twinrix) was licensed.

Characteristics

Single-antigen HepA vaccines (Havrix and Vaqta) are available in two formulations: pediatric and adult. The pediatric formulations of Havrix and Vaqta contain 720 ELISA units and 25 HAV units per dose, respectively. The adult formulations of Havrix and Vaqta contain 1,440 ELISA units and 50 HAV units per dose, respectively. Twinrix contains 720 ELISA units of HepA vaccine and 20 micrograms of hepatitis B surface antigen protein per dose. HepA vaccines are administered by the intramuscular route.

Twinrix contains yeast protein. Each dose of HepA vaccine contains aluminum as an adjuvant and neomycin as an antibiotic. HepA vaccines contain no preservative. Presentations of HepA vaccines contain latex rubber.

Vaccination Schedule and Use

The pediatric formulations of Havrix and Vaqta vaccines are approved for persons age 12 months through 18 years. The adult formulations are approved for persons age 19 years or older. Both vaccines are approved as a 2-dose series. The second dose of Vaqta is administered 6 through 18 months after the first dose, and the second dose of Havrix is administered 6 through 12 months after the first dose.

HepA–HepB (Twinrix) is licensed for persons age 18 years or older and administered as a 3-dose series at 0, 1, and 6 months. The first and second doses should be separated by at least 4 weeks, and the second and third doses should be separated by at least 5 months. Twinrix is approved for persons age 18 years or older and can be used in persons in this age group

Hepatitis A Vaccines

- HepA (Havrix, Vaqta)
- HepA–HepB (Twinrix)

Hepatitis A Vaccine Characteristics

- Administered by intramuscular injection
- Contains aluminum adjuvant and neomycin
- Twinrix contains yeast protein
- Some presentations contain latex rubber

Hepatitis A Vaccination Schedule

- All children age 12 through 23 months and all children and adolescents age 2 through 18 years who have not previously received HepA vaccine
 - 2-dose series at 0, 6–18 months (Vaqta)
 - 2-dose series at 0, 6–12 months (Havrix)
- Adults age 19 years or older with risk factors
 - 2-dose series at 0, 6–18 months (Vaqta)
 - 2-dose series at 0, 6–12 months (Havrix)
 - 3-dose series at 0, 1, 6 months (Twinrix)
 - 3-dose series with doses at 0, 7, 21–30 days, and booster 12 months after dose 1 (Twinrix, accelerated)

with indications for both hepatitis A and hepatitis B vaccines. Twinrix is also approved using an alternative schedule with doses at 0, 7, and 21–30 days and a booster dose 12 months after the first dose.

All children should receive hepatitis A vaccine at age 1 year (i.e., 12 through 23 months). Vaccination should be completed according to the licensed schedules. All children and adolescents age 2 through 18 years who have not previously received HepA vaccine should be vaccinated (i.e., children and adolescents are recommended for catch-up vaccination).

Adults age 19 years or older with risk factors should receive the adult formulation of HepA vaccine. Persons at increased risk for HAV infection, or who are at increased risk for severe disease from HAV infection, should be routinely vaccinated.

Immune Globulin

Immune globulin (IG) provides protection against hepatitis A through passive transfer of antibody. GamaSTAN is a sterile, preservative-free solution of IG for intramuscular administration and is used for prophylaxis against diseases caused by HAV, measles, varicella, and rubella viruses. GamaSTAN is the only IG product approved by FDA for hepatitis A prophylaxis. In 2017, the dosing of IG was changed to reflect decreased IgG anti-HAV potency, likely resulting from decreasing prevalence of previous HAV infection among plasma donors. GamaSTAN can be administered simultaneously with inactivated vaccines or toxoids in a different anatomic site (e.g., separate limbs) or at any time interval between doses. When MMR and varicella vaccines are recommended, they should be administered at least 2 weeks before or at least 6 months after the administration of IG.

Travelers

Persons at increased risk for hepatitis A should be identified and vaccinated. HepA vaccine is recommended for persons age 6 months or older traveling to or working in countries where they would have a high or intermediate endemicity of HAV infection. These persons should be vaccinated, or receive IG if too young or contraindicated for vaccine, before departure. For travelers who are partially vaccinated already (i.e., did not receive a full vaccine series), a dose should be administered before travel, if needed, according to the vaccine schedule. If the first dose was given within the past 6 months, a second dose is not needed before travel.

HepA vaccine should be administered to infants age 6 through 11 months traveling outside the United States when protection against HAV is recommended. The travel-related dose for infants age 6 through 11 months does not count toward the routine 2-dose series. Therefore, the 2-dose HepA vaccination series should be initiated at age 12 months with the appropriate dosage and schedule.

Healthy persons age 12 months through 40 years who are planning on traveling to an area with high or intermediate hepatitis A endemicity and who have not received HepA vaccine should receive a single dose of HepA vaccine as soon as travel is considered and should complete the HepA vaccine series with the appropriate dosage and schedule.

Persons older than age 40 years, persons with immunocompromising conditions, and persons with chronic liver disease planning on traveling to an area with high or intermediate HAV endemicity should receive a single dose of HepA vaccine as soon as travel is considered. Persons traveling in less than 2 weeks should receive the initial dose of HepA vaccine and simultaneously may be administered IG in a different anatomic injection site (e.g., separate limbs). The HepA vaccine series should be completed according to the routine schedule.

Travelers for whom vaccine is contraindicated, who choose not to receive HepA vaccine when it is indicated, and persons younger than age 6 months old should receive IG. Persons traveling for up to 1 month should receive a single dose of IG (0.1 mL/kg). Persons traveling for up to 2 months should receive IG at 0.2 mL/kg. Persons traveling for 2 months or longer should receive IG at 0.2 mL/kg repeated every 2 months for the duration of travel. Infants age <6 months traveling for 2 months or longer should receive IG at 0.2 mL/kg repeated every 2 months for the duration of travel or until the infant is administered HepA vaccine (i.e., at age ≥6 months).

International Adoptees and Persons Who Anticipate Close Personal Contact with an International Adoptee

Screening asymptomatic people for hepatitis A is generally not recommended; however, clinicians may decide to test internationally adopted children for anti-HAV IgG and IgM to identify those who may be acutely infected and shedding virus and to make decisions regarding HepA vaccination.

HepA vaccination is recommended for all previously unvaccinated persons who anticipate close personal contact (e.g., household contact or regular babysitting) with an international adoptee from a country of high or intermediate endemicity during the first 60 days following arrival of the adoptee in the United States. The first dose of the 2-dose HepA vaccine series should be administered as soon as adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

Vaccination of Groups at Increased Risk

- Persons age 6 months or older traveling to or working in countries with high or intermediate endemicity of HAV infection
 - <6 months or contraindicated for vaccine: IG
 - 6–11 months: 1 dose of HepA vaccine (does not count toward routine 2-dose series)
 - 12 months–40 years and partially vaccinated or unvaccinated: 1 dose of HepA vaccine
 - >40 years, immunocompromised, or chronic liver disease: 1 dose of HepA vaccine when travel is considered; if traveling in less than 2 weeks, 1 dose of HepA vaccine and may be administered IG in a separate limb
- International adoptees and persons who anticipate close personal contact with an international adoptee
 - Adoptees: Consider testing for anti-HAV IgG and IgM to guide decision-making
 - Contacts: 2-dose series as soon as adoption is planned
- Persons experiencing homelessness, persons with chronic liver disease, persons with HIV: Routine vaccination

Persons Experiencing Homelessness

All persons age 1 year or older experiencing homelessness should be routinely vaccinated against hepatitis A. HepA vaccine should be integrated into routine preventive services for persons experiencing homelessness. A homeless person is defined as an individual: who lacks housing (without regard to whether the individual is a member of a family), including an individual whose primary residence during the night is a supervised public or private facility (e.g., shelter) that provides temporary living accommodations and an individual who is a resident in transitional housing; without permanent housing who may live on the streets; stay in a shelter, mission, single-room occupancy facility, abandoned building or vehicle; or in any other unstable or nonpermanent situation; who is “doubled up,” a term that refers to a situation where individuals are unable to maintain their housing situation and are forced to stay with a series of friends or extended family members.

Persons with Chronic Liver Disease

Persons with chronic liver disease are at increased risk for fulminant hepatitis A should they become infected. Persons who have chronic liver disease, including those who either are awaiting or have received liver transplantation, should be vaccinated. Persons with chronic liver disease (including but not limited to persons with hepatitis B virus infection, hepatitis C virus infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, or an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level persistently greater than twice the upper limit of normal) should be routinely vaccinated against hepatitis A.

Persons with HIV

All persons with HIV infection age 1 year or older should be routinely vaccinated with HepA vaccine. Because the response to the vaccine might be reduced in persons with HIV infection who are immunosuppressed, postvaccination serologic testing should be performed for all persons with HIV infection at least 1 month after completing the HepA vaccine series.

HepA vaccination is not routinely recommended for health care personnel, persons attending or working in child care centers, food service establishments and food handlers, or persons who work in liquid or solid waste management (e.g., sewer workers or plumbers). These persons have not been shown to be at increased risk for HAV infection. In addition, transmission of HAV from infected food handlers to susceptible consumers or restaurant patrons in the workplace is rare. As of 2020, persons who receive blood products for clotting disorders (e.g., hemophilia) are no longer specifically recommended to receive HepA vaccine.

Vaccine Interchangeability

Limited data indicate that vaccines from different manufacturers are interchangeable. Completion of the series with the same product is preferable. However, if the originally used product is not available or not known, vaccination with either product is acceptable.

For both vaccines, the dosage of the second dose should be based on the person's age at the time of the dose, not the age when the first dose was given. The minimum interval between the first and second doses of hepatitis A vaccine is 6 months. There is no maximum interval for either vaccine. A second dose given at 12 months or longer after the first dose need not be repeated.

Single-antigen hepatitis A and hepatitis B vaccines may be used in conjunction with Twinrix to form a complete series of these vaccines. Because the hepatitis B component of Twinrix is equivalent to a standard adult dose of hepatitis B vaccine, the schedule when vaccinating against hepatitis B is the same regardless of which hepatitis B vaccine (i.e., single-antigen or Twinrix) is used for which dose. Because the hepatitis A component of Twinrix is equivalent to a pediatric dose of hepatitis A vaccine, a series mixing the single-antigen hepatitis A vaccine and Twinrix is more complex. A person age 19 years or older who receives 1 dose of Twinrix may complete the hepatitis A series with 2 doses of adult formulation hepatitis A vaccine separated by at least 5 months. A person who receives 2 doses of Twinrix may complete the hepatitis A series with 1 dose of adult formulation hepatitis A vaccine 5 months after the second dose. A person who begins the hepatitis A series with single-antigen hepatitis A vaccine may complete the series with 2 doses of Twinrix or 1 dose of adult formulation hepatitis A vaccine. Persons age 18 years should follow the same schedule using the pediatric formulation.

Hepatitis A

Vaccination series for adult using a combination of single-antigen HepA vaccine and Twinrix

1st Dose	2nd Dose*	3rd Dose [†]
TWINRIX	TWINRIX	TWINRIX
		Single-Antigen
		[Not Needed] [§]
	Single-Antigen	TWINRIX
		Single-Antigen
		[Not Needed] [§]
Single-Antigen	TWINRIX	TWINRIX
		Single-Antigen
		[Not Needed] [§]
	Single-Antigen [¶]	[Not Needed]

Persons age 19 years and older—use adult formulation hepatitis A vaccine. Persons age 18 years old—use pediatric formulation hepatitis A vaccine.

*1 month after first dose (see § for exception)

[†]5 months after second dose

[§]A third dose is not needed if all three conditions are met: 1) person being vaccinated is not yet age 19 years old; 2) 6 months separate the first 2 doses; 3) protection against hepatitis B disease is NOT needed.

[¶]6 months after first dose

Postexposure Prophylaxis (PEP)

HepA vaccine should be administered as soon as possible, within 2 weeks of exposure, to all unvaccinated persons age 12 months or older who have recently been exposed to HAV. In addition to HepA vaccine, coadministration of IG (0.1 mL/kg) is recommended under certain circumstances and for persons age 40 years or older based on the provider's risk assessment. Considerations regarding decision to use IG, vaccine, or both should include the ability of the person to develop a protective level of antibodies after receipt of HepA vaccine, the magnitude of the risk for HAV transmission from the exposure, and the availability of IG and vaccine.

Unvaccinated persons who are immunocompromised or have chronic liver disease and who have been exposed to HAV within the past 14 days should receive both IG (0.1 mL/kg) and HepA vaccine simultaneously in a different anatomic site (e.g., separate limbs) as soon as possible after exposure.

When the dose of HepA vaccine administered for postexposure prophylaxis is the first dose the exposed person has received, a second dose should be administered 6 months after the first for long-term immunity; however, the second dose is not necessary for PEP.

IG (0.1 mL/kg) is recommended for postexposure prophylaxis for children younger than age 12 months and for persons for whom vaccine is contraindicated.

Immunogenicity and Vaccine Efficacy

Both monovalent HepA vaccines are highly immunogenic. More than 95% of adults will develop protective antibody within 4 weeks of a single dose of either vaccine, and nearly 100% will seroconvert after receiving 2 doses. Among children and adolescents, more than 97% will be seropositive within a month of the first dose. In clinical trials, all recipients aged 2–18 years had protective levels of antibody after 2 doses.

Both vaccines are effective in preventing clinical hepatitis A. The efficacy of Havrix in protecting against clinical hepatitis A was 94% among 40,000 children in Thailand age 1 to 16 years who received 2 doses, 1 month apart, while living in villages with high HAV disease rates. The efficacy of Vaqta in protecting against clinical hepatitis A was 100% among 1,000 children in New York age 2 to 16 years who received 1 dose while living in a community with a high HAV disease rate.

The exact duration of protection after vaccination is unknown. Anti-HAV has been shown to persist for at least 25 years in adults administered inactivated vaccine as children with the 3-dose schedule recommended prior to 1999, and anti-HAV persistence of at least 20 years also was demonstrated among persons vaccinated with a 2-dose schedule as adults. Detectable antibodies are estimated to persist for 40 years or longer based on mathematical modeling and anti-HAV kinetic studies.

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Contraindications to Twinrix include the contraindications to HepB vaccine.

Vaccine Safety

The most frequently reported adverse events to the Vaccine Adverse Event Reporting System (VAERS) for single-antigen hepatitis A vaccines were fever, injection site erythema, injection site swelling, and rash. The most frequently reported adverse events for combination hepatitis A vaccine and hepatitis B vaccine were fever, headache, injection site pain, and dizziness.

Hepatitis A Vaccine Efficacy

- Highly immunogenic
- More than 95% of adults develop protective antibody within 4 weeks of a single dose
- More than 97% of children and adolescents will be seropositive within 1 month of the first dose

Hepatitis A Vaccine Contraindications and Precautions

- Contraindication
 - Severe allergic reaction to vaccine component or following a prior dose
- Precaution
 - Moderate or severe acute illness

Hepatitis A Vaccine Safety

- Single-antigen HepA vaccines: Fever, injection site erythema, injection site swelling, rash
- HepA-HepB vaccine: Fever, headache, injection site pain, dizziness

Vaccination in Pregnancy

A review of VAERS did not identify any concerning patterns of adverse events in pregnant women or their infants after vaccination with Havrix, Vaqta, or Twinrix during pregnancy. A multisite study in CDC's Vaccine Safety Datalink (VSD) of maternal HepA vaccination found that HepA vaccine administration during pregnancy was not associated with increased risk for a range of adverse events examined among pregnancies resulting in live births. However, an association was found between maternal HepA vaccination and infants who were small for gestational age. Investigators believe this association was likely due to unmeasured confounding but might warrant additional consideration.

Vaccine Storage and Handling

HepA vaccines should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting for Hepatitis A

The 2019 Council of State and Territorial Epidemiologists surveillance case definition for hepatitis A clinical criteria includes an acute illness with a discrete onset of any sign or symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain), and either a) jaundice or elevated bilirubin levels greater than or equal to 3 mg/dL, or b) elevated serum ALT levels greater than 200 IU/L and the absence of a more likely diagnosis. Since hepatitis A cannot be differentiated from other types of viral hepatitis on clinical or epidemiologic features alone, serologic evidence of HAV infection or detection of HAV through nucleic acid testing is necessary. The laboratory criteria for hepatitis A requires the presence of HAV-specific IgM antibody or a positive nucleic acid amplification test. For additional information on the case definition and guidance on case and contact investigations, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/index.html.

