Hepatitis A Vaccine

- Clinical Policy Bulletins
- Medical Clinical Policy Bulletins

Number: 0048

Table Of Contents

Policy

Scope of Policy

This Clinical Policy Bulletin addresses Hepatitis A vaccine.

1. **Medical Necessity**

    1. Aetna considers hepatitis A vaccine a medically necessary preventive service according to the recommendations of the Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) for the following at-risk groups:

        1. All children 12 to 23 months of age;
        2. Children and adolescents aged 2–18 years who have not previously received HepA vaccine;
        3. Hematopoietic cell transplant (HCT) recipients who received vaccines before their HCT may be vaccinated or revaccinated routinely after HCT, regardless of the source of the transplanted stem cells;
        4. Individuals aged 1 year and older who are homeless;
        5. Individuals aged 1 year or older who have human immunodeficiency virus (HIV) infection regardless of their level of immune suppression;
        6. Individuals who anticipate close personal contact (e.g., household contact, caretaker, or regular babysitting) with an international adoptee from a country with high or intermediate endemicity during the first 60 days after arrival of the adoptee in the United States;
        7. Individuals with chronic liver disease, including but not limited to hepatitis B virus (HBV) infection, hepatitis C virus (HCV) 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;
        8. Individuals with occupational risk for exposure (i.e., primate-animal handlers, working with clinical or nonclinical material containing HAV in a research laboratory setting); *
        9. Injection and illicit drug users;
        10. International travelers (e.g., tourists, nonimmune immigrants, military personnel, missionaries) to areas where hepatitis A is endemic; *
        11. Men who have sex with men (MSM);
        12. Pregnant women who are identified to be at risk for hepatitis A virus (HAV) infection during pregnancy (e.g., international travelers, injection or illegal drug users, have occupational risk for infection, anticipate close personal contact with an international adoptee, or experiencing homelessness) or for having a severe outcome from HAV infection (e.g., persons with chronic liver disease or persons with HIV infection);
        13. Unvaccinated adults 19 years of age or older in settings considered to have risk factors for HAV infection (e.g., group homes and nonresidential day care facilities for persons with developmental disabilities, homeless shelters, syringe services programs).

    * **Note:** Most Aetna HMO plans exclude coverage of immunizations required for travel or work. Please check benefit plan descriptions for details.

    2. Aetna considers hepatitis A vaccine medically necessary for prophylaxis when initiated within 2 weeks after hepatitis A exposure.

2. **Policy Limitations and Exclusions**

Note: Disclosure of a risk factor for HAV infection or complication is not necessary for HepA vaccination. Because a person might not disclose a risk factor to the provider, ACIP recommends that any person who has not previously completed the HepA vaccine series may receive HepA vaccine (Nelson et al, 2020).

CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
90632	Hepatitis A vaccine (Hep A), adult dosage, for intramuscular use
90633	Hepatitis A vaccine (Hep A), pediatric/adolescent dosage-2 dose schedule, for intramuscular use
90634	Hepatitis A vaccine (Hep A), pediatric/adolescent dosage-3 dose schedule, for intramuscular use
90636	Hepatitis A and hepatitis B vaccine (HepA-HepB), adult dosage, for intramuscular use

Other CPT codes related to the CPB:

38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
84450	Transferase; aspartate amino (AST) (SGOT)
84466	Transferase; alanine amino (ALT) (SGPT)

Other HCPCS codes related to the CPB:

S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency services, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

ICD-10 codes covered if selection criteria are met:

B15.0-B15.9	Acute hepatitis A
B16.0-B16.9	Acute hepatitis B
B17.0	Acute delta-(super) infection of hepatitis B carrier
B17.10	Acute hepatitis C without hepatic coma
B17.11	Acute hepatitis C with hepatic coma
B18.0	Chronic viral hepatitis B with delta-agent
B18.1	Chronic viral hepatitis B without delta-agent
B18.2	Chronic viral hepatitis C
B19.10 - B19.11	Unspecified viral hepatitis B
B19.20	Unspecified viral hepatitis C without hepatic coma
B19.21	Unspecified viral hepatitis C with hepatic coma
B20	Human immunodeficiency virus [HIV] disease
B97.35	Human immunodeficiency virus, type 2 [HIV 2] as the cause of diseases classified elsewhere
F11.10 - F19.99	Drug dependence and nondependent abuse of drugs
K70.0 - K70.9	Alcoholic liver disease
K73.0 - K74.69	Fibrosis and cirrhosis of liver
K75.4	Autoimmune hepatitis
K75.81	Nonalcoholic steatohepatitis (NASH)
K76.0	Fatty (change of) liver, not elsewhere classified
K76.89 - K76.9	Other specified and unspecified diseases of liver
O98.411 - O98.419	Viral hepatitis complicating pregnancy
O98.711 - O98.719	Human immunodeficiency virus [HIV] disease complicating pregnancy
Z20.828	Contact with and (suspected) exposure to other viral communicable diseases

Code	Code Description
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z23	Encounter for immunization
Z57.0 - Z57.9	Occupational exposure to risk factors
Z59.00 - Z59.02	Homelessness
Z94.0 - Z94.9	Transplanted organ and tissue status

Background

Hepatitis A vaccine is approved for people 12 months of age and older and is given in a 2-dose schedule at least 6 months apart (AAP, 2003). Currently licensed vaccines (Havrix and Vaqta) are given intra-muscularly.

A combination hepatitis A/hepatitis B vaccine (Twinrix, GlaxoSmithKline Biologicals, Rixensart, Belgium) is approved for people 18 years of age and older and is given in a 3-dose schedule (0, 1, and 6 months) or an accelerated 4-dose schedule (0, 7, and 21 to 30 days, and a 4th dose at 1 year). The first 3 doses of the 4-dose schedule are intended to provide protection equivalent to the first 2 doses of the original schedule. The new schedule is useful if travel or potential exposure is expected before the 2nd dose (at 1 month) on the original schedule.

The annual recommended childhood and adolescent immunization schedule for approved by the American Academy of Pediatrics (AAP), the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), and the American Academy of Family Physicians (Fiore et al, 2006) recommends universal administration to all children at 1 year (12 to 23 months) of age. Furthermore, the 2 doses in the series should be separated by at least 6 months. Children who are not vaccinated by age 2 years can be vaccinated at subsequent visits to their pediatricians.

Either vaccine can be used for either dose, but use of the same vaccine for both doses is preferable. The recommended dose interval is 6 to 18 months for Vaqta and 6 to 12 months for Havrix.

Havrix, Twinrix, and Vaqta are formulated without a preservative. These vaccines are administered intramuscularly.

Vaqta is licensed in two formulations. Persons aged 12 months through 18 years should receive 25 units of HAV antigen per dose in a 2-dose schedule; persons aged ≥19 years should receive 50 units per dose in a 2-dose schedule.

Havrix also is licensed in two formulations. Persons aged 12 months through 18 years should receive 720 ELISA units per dose in a 2-dose schedule; persons aged ≥19 years should receive 1,440 ELISA units per dose in a 2-dose schedule.

Twinrix is licensed for use in adults aged ≥18 years. Twinrix contains 720 ELISA units of HAV antigen (half of the Havrix adult dose) and 20 µg of recombinant HBV surface antigen protein (the same as the Engerix-B adult dose). Primary vaccination with Twinrix consists of 3 doses, administered on a 0-, 1-, and 6-month schedule, the same schedule as is commonly used for single-antigen HepB vaccine. After 3 doses of Twinrix, antibody responses to both HAV antigen and HBV surface antigens are equivalent to responses seen after the single-antigen vaccines are administered separately on standard schedules; additional information is available in the Twinrix package insert. Twinrix may be administered before travel or any other potential exposure on an accelerated schedule of 3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months that provides long-term protection.

The AAP recommends that regions with immunization programs for 2- to 18-year old children should continue them and expand them to include 12- to 23-month old children. In areas without existing hepatitis A immunization programs, catch-up immunization of unvaccinated 2- to 18-year old children should be considered. In addition, previously unvaccinated children who will be living in, or traveling to, areas with intermediate or high hepatitis A endemicity should be immunized before departure.

The AAP recommends vaccinating children with immunocompromising conditions, as the vaccines do not contain living organisms. Hypersensitivity to vaccine components such as aluminum hydroxide and phenoxyethanol are contraindications to use of hepatitis A vaccines. Hepatitis A vaccine may be co-administered with other vaccines in the childhood immunization series.

The ACIP of the CDC recommends post-exposure prophylaxis with hepatitis A vaccine for healthy individuals between the ages of 1 and 40 years (CDC, 2007). Persons who have recently been exposed to hepatitis A virus and who have not been vaccinated previously should be administered a single dose of single-antigen hepatitis A vaccine or immune globulin (0.02 ml/kg) as soon as possible, within 2 weeks after exposure. All others should receive immune globulin, if possible.

The guidelines vary by age and health status (CDC, 2007). For healthy persons aged 12 months to 40 years, single-antigen hepatitis A vaccine at the age-appropriate dose is preferred to immune globulin because of vaccine's advantages, including long-term protection and ease of administration, as well as the equivalent efficacy of vaccine to immune globulin. For persons aged

more than 40 years, immune globulin is preferred because of the absence of information regarding vaccine performance in this age group and because of the more severe manifestations of hepatitis A in older adults. Vaccine can be used if immune globulin can not be obtained. The magnitude of the risk of hepatitis A virus transmission from the exposure should be considered in decisions to use vaccine or immune globulin in this age group. For children aged less than 12 months, immunocompromised persons, persons with chronic liver disease, and persons who are allergic to the vaccine or a vaccine component, immune globulin should be used.

The ACIP recommendation is based upon evidence that hepatitis A vaccine is as effective as immune globulin in preventing transmission. Researchers randomized 1,090 susceptible household or day-care contacts of patients in Kazakhstan to prophylaxis with either hepatitis A vaccine or immune globulin within 2 weeks of exposure (Victor et al, 2007). The investigators found that the effect of the vaccine would be similar to immune globulin. Between 2 and 8 weeks after exposure, vaccine recipients showed a 1.35 relative risk (95 % confidence interval: 0.70 to 2.67) for developing symptomatic infection as compared with those receiving immune globulin.

The ACIP annually reviews the recommended adult immunization schedule to ensure that the schedule reflects current recommendations for the licensed vaccines.

Rowe et al (2012) stated that hepatitis A virus (HAV) super-infection in persons with hepatitis C virus (HCV) infection has been associated with a high mortality rate, and vaccination is recommended. The incidence of HAV is low, and the aim of this study was to determine the mortality risk of HAV super-infection and the consequences of routine vaccination in persons with HCV infection. To determine the mortality risk of HAV super-infection, a meta-analysis including studies reporting mortality in HCV-infected persons was performed. Data were extracted independently by 2 investigators and recorded on a standardized spread-sheet. The pooled mortality estimate was used to determine the number needed to vaccinate (NNV) to prevent mortality from HAV super-infection. The total vaccine cost was also calculated. A total of 239 studies were identified using a defined search strategy. Of these, 11 appeared to be relevant, and of these, 10 were suitable for inclusion in the meta-analysis. The pooled odds ratio (OR) for mortality risk in HAV super-infection of HCV-infected persons was 7.23 (95 % confidence interval: 1.24 to 42.12) with significant heterogeneity (I(2) = 56 %; p = 0.03) between studies. Using the pooled OR for mortality, this translates to 1.4 deaths per 1,000,000 susceptible persons with HCV per year. The NNV to prevent 1 death per year is therefore 814,849, assuming 90 % vaccine uptake and 94.3 % vaccine efficiency. The vaccine cost for this totals $162 million, or $80.1 million per death prevented per year. The authors concluded that these data challenge the use of routine HAV vaccination in HCV-infected persons and its incorporation into clinical practice guidelines. HAV vaccination of all HCV-infected persons is costly and likely to expose many individuals to an intervention that is of no direct benefit.

Gutierrez Domingo et al (2012) noted that in the absence of immunity, vaccination against HAV and hepatitis B virus (HBV) is recommended for patients with chronic liver disease and those evaluated for liver transplantation (OLT). HAV and HBV infections after OLT, which are frequent in this setting, are associated with a worse prognosis. These researchers estimated the need for vaccination against HBV and HAV among cirrhotic patients who were candidates for OLT and associations with gender, age, and etiologic factors. HBV and HAV serological markers HBsAg, anti-HBc, antiHBs, immunoglobulin G (IgG)-anti-HAV were investigated among 568 patients, including 75 % men. The overall mean age was 53.6 ± 8.9 years (range of 17 to 69) and 20 % were diabetic. The etiologies were alcohol (68 %), hepatitis C virus (35 %) or other causes (10.4 %). Child-Pugh classes were: A (26 %), B (44 %), and C (30 %). In contrast with 359 patients (63.2 %) who had negative HBV markers, 209 (36.8 %) were positive: HBsAg (+), 43 (7.6 %), isolated anti-HBc (+), 57 (10 %), isolated anti-HBs (+), 19 (3.3 %), anti-HBc (+)/anti-HBs (+), 90 (15.8 %). HBV vaccine indication was performed in 416 patients (73.2 %) who either had negative HBV markers or isolated anti-HBc (+). It was more frequently performed in women (82.3 % versus 70.3 %, p = 0.005), albeit with no differences according to age or etiology. There were only 8.2 % (44/538) IgG-anti-HAV-negative, an indication for vaccination against HAV, which was more frequent affecting patients who were younger [less than or equal to 45 years (27.6 %), 46 to 55 (7.2 %), greater than 55 (2.6 %); p < 0.0001)]; non-diabetic (9.5 % versus 2.8 %, p = 0.023); non-alcoholic (11.4 % versus 6.6 %, p = 0.056); and displayed negative HBV markers (10.2 % versus 4.6 %, p = 0.023). Only t3 patients with IgG-anti- HAV (-) were over 60 years. The authors concluded that there is a frequent indication for HBV vaccination among cirrhotic and especially HAV vaccine for under 45-year old patients undergoing evaluation for OLT.

Andersson et al (2013) stated that liver transplant recipients are at an increased risk for liver failure when infected with HAV and HBV. Therefore, it is important to vaccinate these individuals. These investigators evaluated how well liver transplanted patients in their unit were protected against HAV and HBV infection. Furthermore, they investigated the vaccination rate and the antibody response to vaccination in these liver transplanted patients. Patients liver transplanted from January 2007 until August 2010 with a post-transplant check-up during the period March to November 2010 were included (n = 51). Information considering diagnosis, date of transplantation, Child-Pugh score, and vaccination were collected from the patient records. Anti-HAV IgG and anti-HBs titers in serum samples were analyzed and protective levels were registered. Of the patients, 45% were protected against hepatitis A infection and 29 % against hepatitis B infection after transplantation. Only 26 % were vaccinated according to a complete vaccination schedule and these patients had a vaccine response for HAV and HBV of 50 % and 31 %, respectively. An additional 31 % received greater than or equal to 1 doses of vaccine, but not a complete vaccination and the vaccine response was much lower among these patients, stressing the importance of completing the vaccination schedule. The authors concluded that even when patients were fully vaccinated, they did not respond to the same degree as healthy individuals. They stated that patients seemed to be more likely to respond to a vaccination if they had a lower Child-Pugh score, suggesting that patients should be vaccinated as early as possible in the course of their liver disease.

Young (2018) noted that earlier in 2018, the CDC reported hepatitis A outbreaks among high-risk people, including the homeless, in California, Indiana, Kentucky, Michigan, Missouri, Utah, and West Virginia. Homeless people have 2 to 3 times the risk for hepatitis A infection and 2 to 4 times the risk for severe outcomes if infected, according to an unpublished study cited by CNN. On February 14, 2019, the CDC recommended hepatitis A vaccination for people aged 1 year and older who are homeless. Routine vaccination consists of a 2-dose schedule or a 3-dose schedule when combined hepatitis A and B vaccine is administered. The CDC stated that "Persons experiencing homelessness might have difficulty implementing recommended non-vaccine strategies to protect themselves from exposure (e.g., access to clean toilet facilities, regular hand-washing, and avoidance of crowded living conditions). For this reason, vaccination is the most reliable protection from HAV infection for persons experiencing homelessness. HepA vaccination of persons experiencing homelessness will provide individual protection and increase herd immunity over time, reducing the risk of large-scale, person-to-person outbreaks in this population. The recommendation facilitates routine HepA vaccination of persons experiencing homelessness through facilities that already provide health care services for the homeless population".

Nelson et al (2018) provided and update to the recommendations of the ACIP for use of Hep A vaccine for post-exposure prophylaxis (PEP) and for pre-exposure prophylaxis for international travel. The authors stated that HepA vaccine is recommended for persons aged ≥ 12 months for PEP. Providers may also administer immune globulin (IG) to adults aged > 40 years, if indicated. In addition, simultaneous administration of MMR and HepA vaccines is recommended for infants aged 6–11 months traveling internationally. Persons who are immunocompromised or have chronic liver disease and who have been exposed to HAV within the past 14 days and have not previously completed the 2-dose HepA vaccination series 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. For long-term immunity, the HepA vaccination series should be completed with a second dose at least 6 months after the first dose; however, the second dose is not necessary for PEP. A second dose should not be administered any sooner than 6 months after the first dose, regardless of HAV exposure risk.

Freedman and colleagues (2020) stated that "In June 2019, ACIP recommended all persons with HIV aged 1 year or older be routinely vaccinated with hepatitis A vaccine. The list of other populations at risk for hepatitis A infection or severe hepatitis A disease has not changed significantly and includes persons with chronic liver disease; travelers in countries with high or intermediate endemic hepatitis A; persons with close, personal contact with an international adoptee in the first 60 days after arrival from a country with high or intermediate endemic hepatitis A; men who have sex with men; persons who use injection or non-injection drugs; persons experiencing homelessness; and persons who work with hepatitis A virus in a laboratory or nonhuman primates infected with the virus. Clotting factor disorders has been removed from the list. The definition of chronic liver disease has been expanded and includes, but is not limited to, persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level greater than twice the upper limit of normal. A 2-dose series HepA (or 3-dose series HepA-HepB) is recommended for pregnant women if they are at risk for infection or severe outcome from infection during pregnancy. Lastly, hepatitis A vaccination is recommended for persons working in settings of exposure (e.g., those working in health care settings for injection or non-injection drug users or group homes and nonresidential day care facilities for developmentally disabled persons). In addition, any person who is not at risk for hepatitis A virus infection but wants protection against it may be vaccinated".

Per ACIP (Nelson et al, 2020), the following includes adults at risk for HAV infection or for severe disease from HAV:

- International travelers. Unvaccinated persons from developed countries who travel to countries that have high or intermediate hepatitis A endemicity have a substantial risk for acquiring hepatitis A. Travelers at risk include tourists, nonimmune immigrants and their children returning to their country of origin to visit friends or relatives, military personnel, missionaries, and others who work or study abroad. Hepatitis A remains one of the most common vaccine-preventable diseases acquired during travel. Risk is highest for those who live in or visit rural areas, trek in backcountry areas, or frequently eat or drink in settings with poor sanitation. However, cases of travel-related hepatitis A can occur in travelers who have tourist itineraries, accommodations, and eating behaviors that are considered low risk. Travelers who acquire hepatitis A during their trips might transmit HAV to others on their return.
- Men who have sex with men.
- Persons who use injection or non-injection drugs.
- Persons with occupational risk for exposure. Outbreaks of hepatitis A have been reported among persons working with nonhuman primates. Primates that were infected had been born in the wild. Persons working with clinical or nonclinical material containing HAV in a research laboratory setting are considered at risk for HAV infection. Health care personnel are not at substantially increased risk for HAV infection through occupational exposure, and health care–associated HAV transmission is rare. Food handlers are also not considered at increased risk for HAV infection.
- Persons who anticipate close personal contact with an international adoptee.
- Persons experiencing homelessness.
- Persons with HIV infection.
- Persons with chronic liver disease (e.g., HBV infection, HCV infection, cirrhosis, fatty liver disease, alcoholic liver disease, and autoimmune hepatitis) has been associated with increased risk for fulminant hepatitis when HAV infection occurs.
- Persons living in group settings for those with developmental disabilities. Persons with developmental disabilities who require assistance with activities of daily living often live in group homes or small residential facilities. Outbreaks have occurred in these settings and are associated with poor hand hygiene, wearing diapers, and living in close quarters.

- Persons who are incarcerated. Offering HepA vaccine in jails and prisons is an effective strategy to reach persons at high risk for HAV infection who are otherwise difficult to access in the community. Corrections-based vaccination programs have played a role in mitigating communitywide outbreaks of hepatitis A in the United States, the United Kingdom, and Australia. These programs also have been successfully implemented to limit HAV transmission inside jails and prisons.
- Older adults (aged greater than 40 years). HAV infections are usually symptomatic among adults. The severity of hepatitis A disease increases with age. Adults aged over 40 years are more likely to be hospitalized after HAV infection.

Groups and settings with low risk for hepatitis A (Nelson et al, 2020):

- Persons with blood clotting disorders (e.g., hemophilia). In the United States, more than 80% of persons with clotting disorders receive recombinant clotting factor concentrates, which are sterilized (e.g., pasteurization, heat inactivation, and filtration), eliminating the risk for HAV contamination. The risk for HAV transmission via transfusion of blood products among persons with clotting disorders is now considered the same as that among the general population.
- Food service establishments and food handlers. Foodborne hepatitis A outbreaks occur relatively infrequently in the United States. Contamination of food with HAV can happen at any point: growing, harvesting, processing, handling, or after cooking. Food handlers are not at increased risk for hepatitis A because of their occupation. Transmission of HAV from infected food handlers to susceptible consumers or restaurant patrons in the workplace is rare. Transmission among food handlers has not been common since the adoption of the universal childhood HepA vaccination recommendation in 2006, despite costly and resource-intensive investigations of HAV infections among food handlers.
- Child care centers. Hepatitis A outbreaks in child care centers are now rare.
- Schools. HepA vaccination is recommended for all children. Before universal childhood vaccination, the occurrence of hepatitis A cases in U.S. elementary or secondary schools typically reflected disease acquisition in the community, and HAV transmission in school settings was uncommon (and remains uncommon). If multiple cases occur among children at a school, a common source of infection should be investigated.
- Health care institutions. HepA vaccine is not routinely recommended for health care personnel.
- Workers exposed to sewage. Published reports of three serologic surveys conducted among U.S. wastewater workers and appropriate comparison populations did not identify any substantial or consistent increase in the prevalence of anti-HAV among wastewater workers. In addition, in the United States, floods, which can carry raw sewage, are unlikely to cause outbreaks of communicable diseases, and outbreaks of HAV caused by flooding have not been reported.
- Public water systems. Water treatment processes and dilution within public water systems render HAV noninfectious. No hepatitis A outbreaks associated with drinking water have been reported since 2009 in the United States. Recreational water venues (e.g., spas and swimming pools) that are adequately treated and are not contaminated (e.g., by sewage or children in diapers) are unlikely to pose a risk for hepatitis A outbreaks.

ACIP overview of recommendations for the prevention of hepatitis A virus in the United States (Nelson et al, 2020) :

- Vaccination of all children and adolescents aged 2 to 18 years who have not previously received HepA vaccine (i.e., children and adolescents are recommended for catch-up vaccination);
- Vaccination of all persons aged 1 year or older infected with human immunodeficiency virus (HIV);
- Vaccination of persons with chronic liver disease, including but not limited to persons with hepatitis B virus (HBV) infection, hepatitis C virus (HCV) 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;
- Vaccination of pregnant women who are identified to be at risk for HAV infection during pregnancy (e.g., international travelers, persons who use injection or non-injection drugs [i.e., all those who use illegal drugs], persons who have occupational risk for infection, persons who anticipate close personal contact with an international adoptee, or persons experiencing homelessness) or for having a severe outcome from HAV infection (e.g., persons with chronic liver disease or persons with HIV infection);
- Vaccination during hepatitis A outbreaks of persons aged ≥1 year who are at risk for HAV infection (e.g., persons who use injection or non-injection drugs [i.e., all those who use illegal drugs], persons experiencing homelessness, or MSM) or who are at risk for severe disease from HAV (e.g., persons with chronic liver disease or who are infected with HIV);
- Vaccination in settings providing services to adults in which a high proportion of persons have risk factors for HAV infection (e.g., health care settings with a focus on those who use injection or non-injection drugs [i.e., all those who use illegal drugs], group homes, and nonresidential day care facilities for developmentally disabled persons);
- Vaccination of persons who receive blood products for clotting disorders (e.g., hemophilia) is no longer recommended.

ACIP (2020) recommendations for hepatitis A vaccine:

- ACIP recommends Hep A vaccination for all children aged 12 to 23 months.
- ACIP recommends that all children and adolescents aged 2 to 18 years who have not previously received HepA vaccine be vaccinated (i.e., children and adolescents are recommended for catch-up vaccination).
- Persons traveling to or working in countries with high or intermediate HAV endemicity.
    - HepA vaccine should be administered to infants aged 6–11 months traveling outside the United States when protection against HAV is recommended. The travel-related dose for infants aged 6–11 months does not count toward the routine 2-dose series. Therefore, the 2-dose HepA vaccination series should be initiated at age 1 year with the appropriate dose and schedule.

    - Healthy persons aged 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 dose and schedule.
    - Persons aged >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.

- Men who have sex with men.
- Persons who use injection or non-injection drugs (i.e., illicit drug use).
- Persons who work with HAV-infected nonhuman primates or with clinical or nonclinical material containing HAV in a research laboratory setting should be vaccinated. No other occupational groups (e.g., health care providers or food handlers) have been demonstrated to be at increased risk for HAV infection because of occupational exposure.
- All persons who anticipate close personal contact (e.g., household contact, caretaker, or regular babysitter) with an international adoptee from a country with high or intermediate endemicity during the first 60 days following arrival of the adoptee in the United States should be vaccinated against hepatitis A.
- All persons aged 1 year of age or older experiencing homelessness should be routinely vaccinated against hepatitis A.
- Persons with chronic liver disease (including but not limited to persons with HBV infection, HCV infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, or an ALT or AST level persistently greater than twice the upper limit of normal) should be routinely vaccinated against hepatitis A.
- All persons with HIV infection aged ≥1 year be routinely vaccinated with HepA vaccine.
- Pregnant women who are identified to be at risk for HAV infection during pregnancy (e.g., international travelers, persons who use injection or non-injection drugs, persons who have occupational risk for infection, persons who anticipate close personal contact with an international adoptee, or persons experiencing homelessness) or for having a severe outcome from HAV infection (e.g., persons with chronic liver disease or persons with HIV infection) should be vaccinated during pregnancy if not previously vaccinated.
- Disclosure of a risk factor for HAV infection or complication is not necessary for HepA vaccination. Because a person might not disclose a risk factor to the provider, ACIP recommends that any person who has not previously completed the HepA vaccine series may receive HepA vaccine.

ACIP best practice guidance states that HCT recipients who received vaccines before their HCT should be vaccinated or revaccinated routinely after HCT, regardless of the source of the transplanted stem cells; revaccination doses of HepA vaccine are recommended after HCT. The Infectious Disease Society of America has guidance for vaccination of the immunocompromised host. The guidance states that solid organ transplant candidates who are unvaccinated, under-vaccinated, or seronegative for hepatitis A, particularly liver transplant candidates, aged 12 to 23 months (strong recommendation, moderate-quality evidence) and 2 years of age or older (strong recommendation, moderate-quality evidence) should receive a HepA vaccine series (Nelson et al, 2020).

Settings in which a high proportion of persons have risk factors for HAV infection include health care settings that focus on persons who use injection or non-injection drugs, as well as group homes and non-residential day care facilities for persons with developmental disabilities. Health care providers may assume that unvaccinated adults aged 19 years or odler in these settings are at risk for HAV infection and offer HepA vaccination to those who have not previously completed vaccination. HepA vaccination may be offered in outreach and other settings in which services are provided to persons at risk for HAV infection (e.g., homeless shelters and syringe services programs). HepA vaccination should be considered for persons (e.g., residents and staff) in facilities where hygiene is difficult to maintain (e.g., group homes for persons with development disabilities, and homeless shelters.) (Nelson et al, 2020).

One or Two Doses of Hepatitis A Vaccine

Andani et al (2022) stated that HAV is a global health concern as outbreaks continue to occur. Since 1999, several countries have introduced universal vaccination (UV) of children against HAV according to approved 2-dose schedules. Other countries have implemented 1-dose UV programs since 2005; the long-term impact of this schedule is unclear. In a systematic review, these investigators examined available evidence in 4 electronic databases for data published between January 2000 and July 2019 to evaluate scientific literature on 1-dose and 2-dose UV of children with non-live HAV vaccines and described their global impact on incidence, mortality, and severity of hepatitis A, vaccine effectiveness, vaccine effectiveness, and antibody persistence. A total of 3,739 records screened, 33 peer-reviewed articles and 1 conference abstract were included. Rapid declines in incidence of hepatitis A and related outcomes were observed in all age groups following introduction of UV programs, which persisted for at least 14 years for 2-dose and 6 years for 1-dose programs according to respective study durations. Vaccine effectiveness was 95 % or more over 3 to 5 years for 2-dose programs. Vaccine effectiveness was 98 % or more over 0.1 to 7.5 years for 1-dose vaccination. Antibody persistence in vaccinated individuals was documented for up to 15 years (90 % or more) and 10 years (74 % or more) for 2-dose and 1-dose schedules, respectively. The authors concluded that experience with 2-dose UV of children against HAV is extensive, demonstrating an impact on the incidence of hepatitis A and antibody persistence for at least 15 years in many countries globally. Because evidence is more limited for 1-dose UV, these investigators were unable to draw conclusions on immune response persistence beyond 10 years or the need for booster doses later in life. These researchers stated that ongoing epidemiological monitoring is essential in countries implementing 1-dose UV against HAV. Based on current evidence, 2 doses of non-live HAV vaccines are needed to ensure long-term protection.

Hepatitis A Vaccine Immunogenicity and Boostability in Adults Receiving Immunosuppressive Therapy and Adults living with HIV

Schnyder et al (2024) HAV is highly immunogenic in healthy individuals; however, there is uncertainty regarding the immunogenicity in immune-compromised populations (ICPs). In a prospective study, people living with HIV (PLWH), patients on immunosuppressive mono- and combination therapy, and controls received 2 HAV doses at months 0 and 6 to 12, or 3 combined hepA/B vaccine doses at months 0, 1, and 6 to 12. Antibody levels were measured before and at different time-points post-vaccination (T2, 6, 8, 12 months). The primary endpoint was the sero-conversion rate (SCR) at T8, defined as hepA antibodies of 20 mIU/ml or higher. To evaluate boostability, an additional vaccine dose was administered 1 to 5 years after T12 in those with antibodies of less than 50 mIU/ml, with antibody measurements before and 7 days after the booster dose. This trial included 150 subjects. At T2 SCRs ranged between 35 % to 58 % in ICPs versus 94 % in controls. Among PLWH, patients on monotherapy, combination therapy and controls SCRs at T8 were 33/34 (97 %), 32/34 (94 %), 25/30 (83 %) and 28/28 (100 %), respectively. The booster dose resulted in 71 % additional sero-conversion (17/24), with only patients using combination therapy not responding. The authors concluded that HAV was highly immunogenic in virologically suppressed PLWH and patients on immunosuppressive monotherapy, with SCRs after the complete HAV schedule similar to controls and adequate booster responses in case of waning immunity. However, patients using immunosuppressive combination therapy as well as all ICPs who did not receive the complete HAV schedule, were at risk of non-response to vaccination and post-vaccination antibody measurements are recommended.

Hepatitis A Vaccine Immunogenicity Among Seronegative Liver Transplanted Children

Sintusek et al (2024) stated that the HAV vaccine is highly immunogenic in general; however, data on its use in liver-transplanted (LT) children is limited. These investigators examined the sero-immunity to HAV in all LT children, and the immunogenicity of an inactivated HAV vaccine in seronegative LT children at King Chulalongkorn Memorial Hospital. Seronegative LT children received the inactivated HAV vaccine at 0 and 6 to 8 months with adverse events (AEs) monitored for 3 days post-immunization. The result reviewed that among 105 LT children, vaccination records were available for 81 %, of which 7.1 % and 16.5 % with 1 and 2 doses of HAV vaccine were immunized before transplantation, respectively. Post-transplantation, 20.1 % were seropositive for HAV, with 9.5 % due to pre-transplant immunization. A total of 83 seronegative LT children (age of 7.25 ± 4.40 years; 48.6 % male) received 2 vaccine doses. The seropositive rate increased following the 1st and 2nd doses and reached to 51.5 %, and 92.9 %, respectively ($p < 0.001$), with no serious AEs reported. Age at vaccination and the interval from transplantation to vaccination were risk factors for non-responsiveness ($p < 0.001$). The authors concluded that the findings of this study highlighted inadequate HAV vaccination coverage, leaving most LT children susceptible to infection. These researchers stated that HAV vaccine proved highly immunogenic and safe, emphasizing the need for improved vaccination strategies before and after liver transplantation.

References

The above policy is based on the following references:

1. American Academy of Pediatrics Committee on Infectious Diseases. Recommended childhood and adolescent immunization schedule--United States, 2006. Pediatrics. 2006;117(1):239-240.
2. American Academy of Pediatrics Committee on Infectious Diseases. Hepatitis A vaccine recommendations. Pediatrics. 2007;120(1):189-199.
3. American Academy of Pediatrics. 2003 Red Book. Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003.
4. Andani A, van Damme P, Bunge EM, et al. One or two doses of hepatitis A vaccine in universal vaccination programs in children in 2020: A systematic review. Vaccine. 2022;40(2):196-205.
5. Andersson D, Castedal M, Friman V. Are liver transplant recipients protected against hepatitis A and B? Transplant Proc. 2013;45(3):1193-1197.
6. Askling HH, Rombo L, van Vollenhoven R, et al. Hepatitis A vaccine for immunosuppressed patients with rheumatoid arthritis: A prospective, open-label, multi-centre study. Travel Med Infect Dis. 2014;12(2):134-142.
7. Baker CJ. Another success for hepatitis A vaccine. N Engl J Med. 2007;357(17):1757-1759.
8. Bell BP. Hepatitis A vaccine. Semin Pediatr Infect Dis. 2002;13(3):165-173.
9. Beran J. Ten year's experience with combined hepatitis A and B vaccine. Klin Mikrobiol Infekc Lek. 2008;14(1):13-14, 16-23.
10. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2007;56(41):1080-1084.
11. Centers for Disease Control and Prevention (CDC), Office of Communications. CDC's Advisory Committee on Immunization Practices expands hepatitis A vaccination for children. Press Release. Atlanta, GA: CDC; October 28, 2005.
12. Centers for Disease Control and Prevention (CDC). Notice to readers: FDA approval of an alternate dosing schedule for a combined hepatitis A and B vaccine (Twinrix). MMWR Morbid Mortal Wkly Rep. 2007;56(40):1057.

13. Centers for Disease Control and Prevention (CDC). Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1996;45(RR-15):1-30.
14. Centers for Disease Control and Prevention (CDC). Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1999;48(RR-12):1-37.
15. Centers for Disease Control and Prevention (CDC). Recommended adult immunization schedule – United States, 2010. MMWR Morbid Mortal Wkly Rep. 2010;59(01):1-4.
16. Centers for Disease Control and Prevention (CDC). Recommended childhood and adolescent immunization schedule - United States, 2006. MMWR Morbid Mortal Wkly Rep. 2006;54(52):Q1-Q4.
17. Centers for Disease Control and Prevention. Licensure of inactivated hepatitis A vaccine and recommendations for use among international travelers. MMWR Morb Mortal Wkly Rep. 1995;44(29):559-560.
18. Cheng A, Chang SY, Sun HY, et al. Long-term durability of responses to 2 or 3 doses of hepatitis A vaccination in human immunodeficiency virus-positive adults on antiretroviral therapy. J Infect Dis. 2017;15;215(4):606-613.
19. Committee on Infectious Diseases. Recommendations for administering hepatitis A vaccine to contacts of international adoptees. Pediatrics. 2011;128(4):803-804.
20. Craig AS, Schaffner W. Prevention of hepatitis A with the hepatitis A vaccine. N Engl J Med. 2004;350(5):476-481.
21. Crum-Cianflone NF, Wilkins K, Lee AW, et al; Infectious Disease Clinical Research Program HIV Working Group. Long-term durability of immune responses after hepatitis A vaccination among HIV-infected adults. J Infect Dis. 2011;203(12):1815-1823.
22. DeGroote NP, Mattson CL, Tie Y, et al. Hepatitis A virus immunity and vaccination among at-risk persons receiving HIV medical care. Prev Med Rep. 2018;11:139-144.
23. Doshani M, Weng M, Moore KL, et al. Recommendations of the Advisory Committee on Immunization Practices for use of hepatitis A vaccine for persons experiencing homelessness. MMWR Morb Mortal Wkly Rep 2019;68:153-156.
24. Faridi MM, Shah N, Ghosh TK, et al. Immunogenicity and safety of live attenuated hepatitis A vaccine: A multicentric study. Indian Pediatr. 2009;46(1):29-34.
25. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-7):1-23.
26. Freedman M, Kroger A, Hunter P, Ault KA; Advisory Committee on Immunization Practices. Recommended adult immunization schedule, United States, 2020. Ann Intern Med. 2020;172(5):337-347.
27. Garcia Garrido HM, Veurink AM, Leeflang M, et al. Hepatitis A vaccine immunogenicity in patients using immunosuppressive drugs: A systematic review and meta-analysis. Travel Med Infect Dis. 2019;32:101479.
28. Garcia Garrido HM, Wieten RW, Grobusch MP, Goorhuis A. Response to hepatitis A vaccination in immunocompromised travelers. J Infect Dis. 2015;212(3):378-385.
29. Gutierrez Domingo I, Pascasio Acevedo JM, Alcalde Vargas A, et al. Prevalence of hepatitis B and A virus markers and vaccination indication in cirrhotic patients evaluated for liver transplantation in Spain. Transplant Proc. 2012;44(6):1502-1504.
30. Irving GJ, Holden J, Yang R, Pope D. Hepatitis A immunisation in persons not previously exposed to hepatitis A. Cochrane Database Syst Rev. 2012;7:CD009051.
31. Juliao P, Abadia I, Welby S, et al. Hepatitis A antibody persistence 8 and 10 years after 1-dose and 2-dose vaccination in children from Panama. Vaccine. 2021;39(1):26-34.
32. Link-Gelles R, Hofmeister MG, Nelson NP. Use of hepatitis A vaccine for post-exposure prophylaxis in individuals over 40 years of age: A systematic review of published studies and recommendations for vaccine use. Vaccine. 2018;36(20):2745-2750.
33. Longworth DL. Update on infectious disease prevention: Human papillomavirus, hepatitis A. Cleve Clin J Med. 2008;75(6):402-403, 409-410.
34. Marshall H, Nolan T, Díez Domingo J, et al. Long-term (5-year) antibody persistence following two- and three-dose regimens of a combined hepatitis A and B vaccine in children aged 1-11 years. Vaccine. 2010;28(27):4411-4415.
35. Mawhorter SD. Who should receive hepatitis A vaccine? Cleve Clin J Med. 2001;68(10):825-827.
36. Miller KE, Ruiz DE, Graves JC. Update on the prevention and treatment of sexually transmitted diseases. Am Fam Physician. 2003;67(9):1915-1922.
37. National Advisory Committee on Immunisation (NACI). An Advisory Committee Statement (ACS). Update on hepatitis A vaccine (Avaxim, Aventis Pasteur). Can Commun Dis Rep. 2001;27:1-2.
38. Nelson NP, Link-Gelles R, Hofmeister MG, et al. Update: Recommendations of the Advisory Committee on Immunization Practices for use of heaptitis A vaccine for postexposure prophylaxis and for preexposure prophylaxis for international travel. Centers for Disease Control and Prevention (CDC), Mobridity and Mortality Weekly Report (MMWR). 2018;67(43):1216-1220.
39. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. Centers for Disease Control and Prevention (CDC), Morbidity and Mortality Weekly Report (MMWR). 2020;69(5):1-38.
40. No authors listed. Hepatitis A vaccine. Med Lett Drugs Ther. 1995;37(950):51-52.
41. Reiss G, Keeffe EB. Review article: Hepatitis vaccination in patients with chronic liver disease. Aliment Pharmacol Ther. 2004;19(7):715-727.
42. Rosenthal P. Cost-effectiveness of hepatitis A vaccination in children, adolescents, and adults. Hepatology. 2003;37(1):44-51.

43. Rowe IA, Parker R, Armstrong MJ, et al. Hepatitis A virus vaccination in persons with hepatitis C virus infection: Consequences of quality measure implementation. Hepatology. 2012;56(2):501-506.
44. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):e44-e100.
45. Schnyder JL, Garcia Garrido HM, Tanck MW, et al. Hepatitis a vaccine immunogenicity and boostability in adults receiving immunosuppressive therapy and adults living with HIV: A prospective single-centre cohort study. J Travel Med. 2024 Sep 11 [Online ahead of print].
46. Sintusek P, Khunsri S, Vichaiwattana P, et al. Hepatitis A vaccine immunogenicity among seronegative liver transplanted children. Sci Rep. 2024;14(1):22202.
47. Tung J, Carlisle E, Smieja M, et al. A randomized clinical trial of immunization with combined hepatitis A and B versus hepatitis B alone for hepatitis B seroprotection in hemodialysis patients. Am J Kidney Dis. 2010;56(4):713-719.
48. Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. Expert Rev Vaccines. 2004;3(3):249-267.
49. van Doorslaer E, Torman G, van Damme P, et al. Cost effectiveness of alternative hepatitis A immunisation strategies. Pharmacoeconomics. 1995;8(1):5-8.
50. Victor JC, Monto AS, Surdina TY, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med. 2007;357(17):1685-1694.
51. Whelan J, Sonder GJ, Bovee L, et al. Evaluation of hepatitis a vaccine in post-exposure prophylaxis, the Netherlands, 2004-2012. PLoS One. 2013;8(10):e78914.
52. Wigg AJ, Wundke R, McCormick R, et al. Efficacy of high-dose, rapid, hepatitis A and B vaccination schedules in patients with cirrhosis. Clin Gastroenterol Hepatol. 2019;17(6):1210-1212.
53. Wolters B, Müller T, Ross RS, et al. Comparative evaluation of the immunogenicity of combined hepatitis A and B vaccine by a prospective and retrospective trial. Hum Vaccin. 2009;5(4):248-253.
54. Young K. CDC advisory group recommends vaccinating homeless against hepatitis A. NEJM JournalWatch, October 26, 2018. Available at: https://www.jwatch.org/fw114709/2018/10/26/cdc-advisory-group-recommends-vaccinating-homeless. Accessed February 18, 2019.
55. Zhang L. Hepatitis A vaccination. Hum Vaccin Immunother. 2020;16(7):1565-1573.

Policy History

- Last Review 02/19/2025

  Effective: 08/03/1995

  Next Review: 01/08/2026

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes