Hepatitis A virus infection in adults: Epidemiology, clinical manifestations, and diagnosis

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INTRODUCTION

Hepatitis A infection is caused by the hepatitis A virus (HAV). Humans are the only known reservoir. HAV infection is usually a self-limited illness that does not become chronic. Fulminant hepatic failure occurs in less than 1 percent of cases. Infection confers lifelong immunity and is preventable via vaccination.

HAV is a member of the genus *Hepatovirus* in the family Picornaviridae. Two clinical forms of hepatitis were recognized in 1947 and designated hepatitis A and hepatitis B [1]; subsequently, the virus that causes hepatitis A was identified in 1973 [2]. Other terms previously used for HAV infection include epidemic jaundice, acute catarrhal jaundice, and campaign jaundice.

The epidemiology, clinical manifestations, diagnosis, and treatment of HAV infection in adults are reviewed here. Issues related to HAV vaccination are presented separately, as are issues related to HAV in children and pregnant women. (See "Hepatitis A virus infection: Treatment and prevention" and "Overview of hepatitis A virus infection in children" and "Overview of coincident acute hepatobiliary disease in pregnant women", section on 'Hepatitis A virus'.)

EPIDEMIOLOGY

Transmission and risk factors — HAV is usually transmitted by the fecal-oral route (either via person-to-person contact or consumption of contaminated food or water). Risk factors for HAV transmission are summarized in the table (table 1) [3-7]. Maternal-fetal transmission has not been described.

Fulminant hepatic failure develops in fewer than 1 percent of patients with hepatitis A [8]; important risk factors include age >50 years and underlying liver disease (particularly chronic hepatitis C virus infection) [9-11]. In one study including 163 patients with chronic hepatitis B and 432 patients with chronic hepatitis C followed prospectively, hepatitis A superinfection occurred in 27 patients [11]. Among 17 patients with hepatitis C who acquired hepatitis A, fulminant hepatic failure developed in seven cases, of whom six died. Among 10 patients with hepatitis B who acquired hepatitis A, nine had uncomplicated infection; one patient developed marked cholestasis in the setting of pre-existing cirrhosis.

Distribution and outbreaks — HAV infection occurs worldwide. Globally, an estimated 1.4 million cases occur each year [12]. Hepatitis A can occur sporadically or in an epidemic form [13]. Updated information on outbreaks may be found on websites maintained by the United States Centers for Disease Control and Prevention and the US Food and Drug Administration.

Hepatitis outbreaks have occurred in a variety of settings, including community outbreaks due to contaminated water or food (cooked foods can transmit HAV if the cooking temperature is inadequate to kill the virus or if food is contaminated after cooking) [14-20], outbreaks in health care settings, and outbreaks among homeless individuals [21-24].

After the implementation of vaccination in certain segments of the population in the United States, there was a steady decline in the incidence of HAV until 2014, after which the number of estimated new infections has increased. In 2019, the estimated number of infections had increased to 15 times that of 2014. This increase is due to outbreaks among individuals who report drug use or homelessness, among men who have sex with men, and outbreaks associated with contaminated food [25,26]. In 2017, more than 650 individuals in California were infected with hepatitis A (including 417 hospitalizations and 21 deaths), making this the largest outbreak in the United States in two decades [27].

International outbreaks have occurred via importation of contaminated food from areas where HAV is endemic [17,18,28]. In some circumstances, seemingly sporadic occurrences may reflect cases from geographically distant outbreaks. In one report, for example, 213 cases of hepatitis A were detected from 23 schools in Michigan and 29 cases from 13 schools in Maine; all were related to contaminated frozen strawberries from a common source [29].

Impact of vaccination — The incidence of HAV has declined substantially since implementation of vaccination:

- In the United States, since vaccination was recommended for individuals at increased risk for infection (in 1996), for children living in states with the highest incidence of HAV (in 1999), and for all infants (in 2006), the incidence of acute hepatitis A has declined from 6 to 0.4 cases per 100,000 between 1999 and 2014; an estimated 2500 cases of hepatitis A occurred in 2014 (figure 1 and figure 2) [3,9,14,30-34]. However, increased incidence since 2014 highlights the importance of increasing vaccination rates.

- In China, the incidence among individuals age ≤19 years in one province declined to a historically low rate in 2014, while the highest incidence rate was observed in those aged ≥20 years [35]. In addition, improvement of living conditions in resource-limited settings has been associated with fewer child infections, leading to a larger population of adults who lack protective antibodies and are at risk for outbreaks (figure 3) [35].

PATHOGENESIS

Hepatic injury occurs as a result of the host immune response to HAV. Viral replication occurs in the hepatocyte cytoplasm; hepatocellular damage and destruction of infected hepatocytes is mediated by human leukocyte antigen-restricted, HAV-specific CD8+ T lymphocytes and natural killer cells [36-38]. Interferon-gamma appears to have a central role in promoting clearance of infected hepatocytes [36]. An excessive host response (denoted by a marked reduction of circulation HAV ribonucleic acid (RNA) during acute infection) is associated with severe hepatitis [39].

CLINICAL MANIFESTATIONS

Typical manifestations — Acute HAV infection in adults is usually a self-limited illness; fulminant hepatic failure occurs in fewer than 1 percent of cases. The incubation period of hepatitis A infection averages 28 days (range 15 to 50 days) [40].

Symptomatic illness due to HAV occurs in more than 70 percent of adults. Symptoms are uncommon in children <6 years of age.

Symptoms and signs begin with abrupt onset of nausea, vomiting, anorexia, fever, malaise, and abdominal pain (figure 4) [41]. Within a few days to a week, dark urine (bilirubinuria) appears; pale stools (lacking bilirubin pigment) may also be observed. These are followed by jaundice

and pruritus (40 to 70 percent of cases). The early signs and symptoms usually diminish when jaundice appears, and jaundice typically peaks within two weeks.

Physical findings include jaundice, scleral icterus, hepatomegaly (80 percent of cases), and right upper quadrant tenderness to palpation [13,42]. Less common findings include splenomegaly and extrahepatic manifestations such as skin rash and arthralgias. (See 'Extrahepatic manifestations' below.)

In pregnant women, acute hepatitis A infection has been associated with increased risk of preterm labor and gestational complications [43].

No specific disease manifestations in immunocompromised hosts have been described.

Laboratory abnormalities include elevations of serum aminotransferases (often >1000 international units/dL), serum bilirubin (typically ≤10 mg/dL), and alkaline phosphatase (up to 400 U/L) [42]. The serum aminotransferase elevations precede the bilirubin elevation. Serum alanine aminotransferase is commonly higher than the serum aspartate aminotransferase. Serum aminotransferases peak approximately one month after exposure to the virus and then decline by approximately 75 percent per week [44]. The serum bilirubin concentration usually declines within two weeks of peak levels [13]. Other laboratory abnormalities include elevations of acute-phase reactants and inflammatory markers.

Infected individuals are contagious during the incubation period and remain so for about a week after jaundice appears [45]. HAV replicates in the liver and is shed in the stool in high concentrations from two to three weeks before to one week after onset of clinical illness (figure 4).

Full clinical and biochemical recovery is observed within two to three months in 85 percent of patients, and complete recovery is observed by six months in nearly all patients [44]. HAV infection does not become chronic, and individuals cannot become reinfected after recovering from infection. However, relapse can occur. (See 'Relapsing hepatitis' below.)

Fulminant hepatic failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (international normalized ratio ≥1.5). It occurs most commonly in individuals >50 years of age and individuals with other liver diseases such as hepatitis B or C [8]. Such patients may require liver transplant. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis".)

Extrahepatic manifestations — Several extrahepatic manifestations associated with HAV infection have been described. Extrahepatic manifestations occur most commonly in patients

who have protracted illness such as relapsing or cholestatic hepatitis [46,47]. (See 'Cholestatic hepatitis' below and 'Relapsing hepatitis' below.)

The most common extrahepatic manifestations include evanescent rash and arthralgias (occurring in 10 to 15 percent of patients).

Other conditions related to immune complex disease and vasculitis occur rarely, including [46-51]:

- Leukocytoclastic vasculitis (most often apparent on the legs and buttocks; biopsy demonstrates anti-HAV immunoglobulin (Ig)M and complement in the blood vessel walls)
- Arthritis
- Glomerulonephritis
- Cryoglobulinemia
- Optic neuritis
- Transverse myelitis
- Toxic epidermal necrolysis
- Myocarditis
- Thrombocytopenia
- Aplastic anemia
- Red cell aplasia

Complications — Complications of acute hepatitis A infection include cholestatic hepatitis, relapsing hepatitis, and autoimmune hepatitis [48].

Cholestatic hepatitis — Prolonged cholestasis is characterized by a protracted period of jaundice (lasting >3 months); it occurs among fewer than 5 percent of patients with acute hepatitis A infection [52,53].

The course of cholestatic hepatitis is usually characterized by marked jaundice, pruritus, fever, weight loss, diarrhea, and malaise [42,48,52,54]. Laboratory findings include markedly elevated serum bilirubin (often >10 mg/dL) and alkaline phosphatase, modest elevation of serum aminotransferases (5 to 15 times the upper limit of normal), and elevated serum cholesterol. Peak bilirubin levels may be reached in the eighth week or later.

In general, cholestatic hepatitis resolves spontaneously with no sequelae; recognition is important to avoid unnecessary testing. Ultrasonography is appropriate to exclude biliary obstruction; cholangiography or liver biopsy are usually not necessary [52].

Treatment is usually supportive; there is no role for corticosteroids [48,52]. Cholestyramine may be administered if pruritus is bothersome. (See "Pruritus associated with cholestasis".)

Relapsing hepatitis — Up to 10 percent of patients experience a relapse of symptoms during the six months after acute illness [48,55-59]. The duration of clinical relapse is generally less than three weeks, although biochemical relapse may last as long as 12 months [59]. The cause of relapsing hepatitis is unknown, and no predisposing factors for relapse have been identified [55].

The clinical course usually consists of apparent clinical recovery after acute infection with near normalization of the serum aminotransferases, followed by biochemical (and, in some cases, clinical) relapse; clinical manifestations of relapse are often milder than the initial episode [55]. Serum aminotransferases may exceed 1000 international units/dL, and serum anti-HAV IgM antibodies typically persist throughout the course of the disease [55,60]. HAV can be recovered from stool during relapse episodes, so such patients should be considered infectious [59]. (See 'Diagnosis' below.)

Multiple relapses can occur. In one series including 297 adults with acute hepatitis A infection, relapse was observed in 13 percent of patients (of whom 22 percent had more than one relapse); approximately half of patients were asymptomatic during the relapses [56]. Development of extrahepatic manifestations (such as arthritis, vasculitis, nephritis, and cryoglobulinemia) during relapse has been described [46,49]. (See 'Extrahepatic manifestations' above.)

In general, patients with relapsing hepatitis have complete recovery; recognition is important to avoid unnecessary testing. Ultrasonography is appropriate to exclude biliary obstruction in patients with significant jaundice; cholangiography or liver biopsy are usually not necessary.

Autoimmune hepatitis — Rarely, HAV infection may serve as a trigger for development of autoimmune hepatitis in susceptible individuals [61,62]. Autoimmune hepatitis is a chronic hepatitis characterized by hyperglobulinemia, the presence of circulating autoantibodies (such as anti-nuclear, anti-smooth muscle, and/or anti-actin antibodies), and inflammatory changes on liver histology.

Issues related to autoimmune hepatitis are discussed separately. (See "Overview of autoimmune hepatitis".)

DIAGNOSIS

The diagnosis of acute HAV infection should be suspected in patients with abrupt onset of prodromal symptoms (nausea, anorexia, fever, malaise, or abdominal pain) and jaundice or elevated serum aminotransferase levels, particularly in the setting of known risk factors for hepatitis A transmission (table 1) [14].

The diagnosis is established by detection of serum IgM anti-HAV antibodies. Serum IgM antibodies are detectable at the time of symptom onset, peak during the acute or early convalescent phase of the disease, and remain detectable for approximately three to six months (figure 4). Among patients with relapsing hepatitis, serum IgM antibodies persist for the duration of this disease. (See 'Relapsing hepatitis' above.)

Detection of serum IgM antibodies in the absence of clinical symptoms may reflect prior HAV infection with prolonged persistence of IgM, a false-positive result, or asymptomatic infection (which is more common in children <6 years of age than in older children or adults) [63].

Serum IgG antibodies appear early in the convalescent phase of the disease, remain detectable for decades, and are associated with lifelong protective immunity (figure 4). Detection of anti-HAV IgG in the absence of anti-HAV IgM reflects past infection or vaccination rather than acute infection.

Imaging studies are generally not indicated for diagnosis of HAV infection. Ultrasonography may sometimes be appropriate to rule out alternative diagnoses (such as biliary obstruction); cholangiography or liver biopsy are usually not indicated.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of HAV infection includes other viruses that can cause hepatitis, all of which may be distinguished by serology:

- Hepatitis B, C, D, and E – Hepatitis A and E are acute infections transmitted by the fecal-oral route, whereas hepatitis B and C can present acutely or chronically and are transmitted by body fluids. Infection with hepatitis D virus can lead to acute hepatitis in patients with hepatitis B virus infection. (See related topics.)

- Epstein-Barr virus and cytomegalovirus – Both Epstein-Barr virus and cytomegalovirus may present with liver function abnormalities as well as fever, fatigue, and lymphadenopathy. (See "Infectious mononucleosis" and "Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults".)

- Yellow fever virus – Yellow fever virus is transmitted by mosquitoes in endemic regions; initial manifestations consist of malaise and other nonspecific symptoms, followed by acute illness with fever, jaundice, and gastrointestinal manifestations. (See "Yellow fever: Epidemiology, clinical manifestations, and diagnosis".)

- Herpes simplex virus – Hepatitis is a rare complication of herpes simplex virus infection. It may present fulminantly, most commonly in immunocompromised hosts. Occasionally hepatic involvement may develop in the absence of coincident rash. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Hepatitis'.)

- Adenovirus – Adenovirus infection typically involves the respiratory and gastrointestinal tracts; hepatitis may be a complication of adenovirus infection in immunocompromised hosts. (See "Pathogenesis, epidemiology, and clinical manifestations of adenovirus infection", section on 'Gastrointestinal system'.)

- Human immunodeficiency virus (HIV) infection – Patients with acute HIV infection may have nausea, diarrhea, and anorexia. More serious gastrointestinal manifestations such as hepatitis can occur though rarely. (See "Acute and early HIV infection: Clinical manifestations and diagnosis".)

Other infectious causes of fever and jaundice include:

- Malaria – Malaria is a mosquito-borne parasitic infection characterized by fever, anemia, and parasitemia; clinical manifestations include jaundice due to hemolysis. The diagnosis may be established by examination of the peripheral blood smear. (See "Malaria: Clinical manifestations and diagnosis in nonpregnant adults and children".)

- Leptospirosis – Leptospirosis is a bacterial infection characterized by fever, myalgia, headache, and conjunctival suffusion. Modest elevation of hepatic transaminases may be observed. The diagnosis is established by serology. (See "Leptospirosis: Epidemiology, microbiology, clinical manifestations, and diagnosis".)

- Syphilis – Syphilis is a sexually transmitted infection; secondary syphilis consists of several clinical manifestations including elevated serum alkaline phosphatase, often with normal or only slightly abnormal transaminases. The diagnosis is established by serology. (See "Syphilis: Epidemiology, pathophysiology, and clinical manifestations in patients without HIV", section on 'Clinical manifestations'.)

- Q fever – Q fever results from infection with *Coxiella burnetii*; hepatic involvement includes transaminitis, hepatomegaly without jaundice, and granulomas on liver biopsy. The diagnosis is established by serology.

Noninfectious entities with presentations similar to hepatitis A infection include:

- Alcoholic hepatitis – Clinical features of alcoholic hepatitis include jaundice, anorexia, fever, and tender hepatomegaly. Laboratory testing demonstrates moderately elevated transaminases (typically less than 300 international units/mL), with an aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio of two or greater. Patients may also present with right upper quadrant/epigastric pain, hepatic encephalopathy, and signs of malnutrition. (See "Alcoholic hepatitis: Clinical manifestations and diagnosis".)

- Drug-induced liver injury (DILI) – Liver injury can be associated with many drugs. Patients with DILI may be asymptomatic with abnormal liver function tests or have malaise, anorexia, nausea, vomiting, right upper quadrant pain, dark urine, acholic stools, jaundice, and pruritus. The diagnosis may be established via liver biopsy. (See "Drug-induced liver injury".)

- Budd-Chiari syndrome – Budd-Chiari syndrome is defined as hepatic venous outflow tract obstruction. Patients with Budd-Chiari syndrome may present with acute or subacute liver disease or acute liver failure. The diagnosis is established via ultrasonography. (See "Budd-Chiari syndrome: Epidemiology, clinical manifestations, and diagnosis".)

- Autoimmune hepatitis – Autoimmune hepatitis may be asymptomatic or present with nonspecific symptoms, such as malaise, anorexia, nausea, abdominal pain, itching, and arthralgia. The diagnosis is established via serologic testing and histology. (See "Overview of autoimmune hepatitis".)

- Wilson disease – Wilson disease is a genetic disorder characterized by excess copper; it can present as acute hepatitis, jaundice, abdominal pain, and elevated transaminase levels (typically <2000 international units/dL with an AST/ALT ratio >2). The diagnosis is based on serum ceruloplasmin and copper levels and ocular slit-lamp examination for Kayser-Fleisher rings. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Travel medicine".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hepatitis A (The Basics)")
- Beyond the Basics topic (see "Patient education: Hepatitis A (Beyond the Basics)")

SUMMARY

- **Epidemiology** − Hepatitis A is caused by the hepatitis A virus (HAV) and has a worldwide distribution. HAV is typically transmitted by the fecal-oral route (either via person-to-person contact or consumption of contaminated food or water). Risk factors for HAV transmission include residence in or travel to areas with poor sanitation, household or sexual contact with another person with hepatitis A, exposure to daycare centers, exposure to residential institutions, and intravenous drug use (table 1). (See 'Epidemiology' above.)
- **Clinical manifestations**
  - **Typical manifestations** − The incubation period of HAV averages 28 days (range 15 to 50 days). Most adults with HAV infection have symptomatic illness which begins with abrupt onset of nausea, anorexia, fever, malaise, and abdominal pain. Within a few days to a week, dark urine and acholic stools appear, followed by jaundice and pruritus.

The early clinical manifestations usually diminish when jaundice appears, and jaundice typically peaks within two weeks. Hepatitis A is usually a self-limited illness that does not become chronic (See 'Clinical manifestations' above.)

- **Complications and extrahepatic manifestations** − Complications of acute hepatitis A infection include cholestatic hepatitis, relapsing hepatitis, and autoimmune hepatitis. Extrahepatic manifestations include evanescent rash, arthralgias, and other conditions related to immune complex disease and vasculitis. (See 'Extrahepatic manifestations' above and 'Complications' above.)

- **Fulminant hepatic failure** − Fulminant hepatic failure occurs in fewer than 1 percent of patients with HAV infection. It consists of severe acute liver injury with encephalopathy and impaired synthetic function and occurs most commonly in individuals >50 years of age and individuals with other liver diseases such as hepatitis B or C. Patients with fulminant hepatic failure should be transferred to a center capable of performing liver transplantation. (See 'Clinical manifestations' above and "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis".)

- **Laboratory abnormalities** − Laboratory abnormalities include elevations of serum aminotransferases (often >1000 international units/dL), followed by elevations of serum bilirubin (up to 10 mg/dL). Serum aminotransferases peak approximately one month after exposure to the virus and then decline by approximately 75 percent per week. The serum bilirubin concentration usually declines within two weeks of peak levels. (See 'Clinical manifestations' above.)

- **Diagnosis** − The diagnosis of acute HAV infection should be suspected in patients with abrupt onset of gastrointestinal signs and symptoms and jaundice or elevated serum aminotransferase levels, particularly in the setting of known risk factors for hepatitis A transmission (table 1). The diagnosis is established by detection of serum immunoglobulin (Ig)M anti-HAV antibodies. (See 'Diagnosis' above.)

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Topic 2692 Version 48.0

GRAPHICS

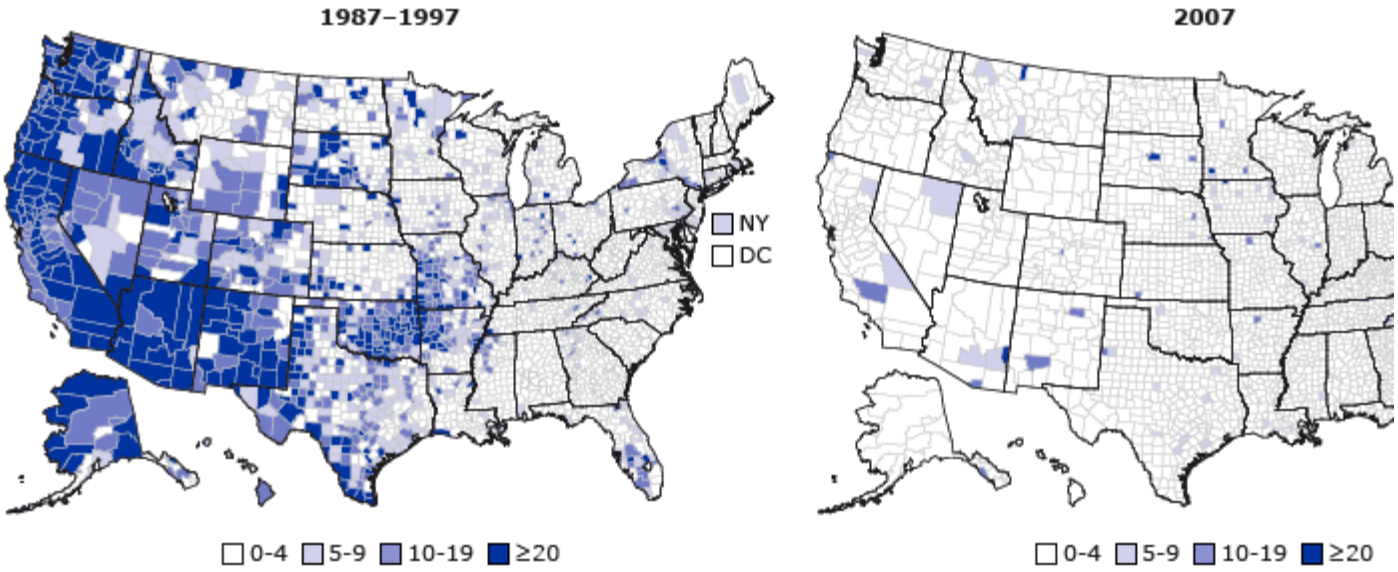
Modes of hepatitis A virus transmission*

Person-to-person contact
Transmission within households
Sexual transmission
Residential institution transmission
Daycare center transmission
Transmission among military personnel
Contact with contaminated food or water
Consumption of raw or undercooked shellfish, vegetables, or other foods
Consumption of foods contaminated by infected food handlers
Blood transfusion
Illicit drug use

* Hepatitis A virus is usually transmitted via the fecal-oral route, either via person-to-person contact or consumption of contaminated food or water.

Graphic 80824 Version 2.0

Incidence* of reported acute hepatitis A cases, by county — National Notifiable Surveillance System, United States, 1987 to 1997¶ (prevaccine) and 2007



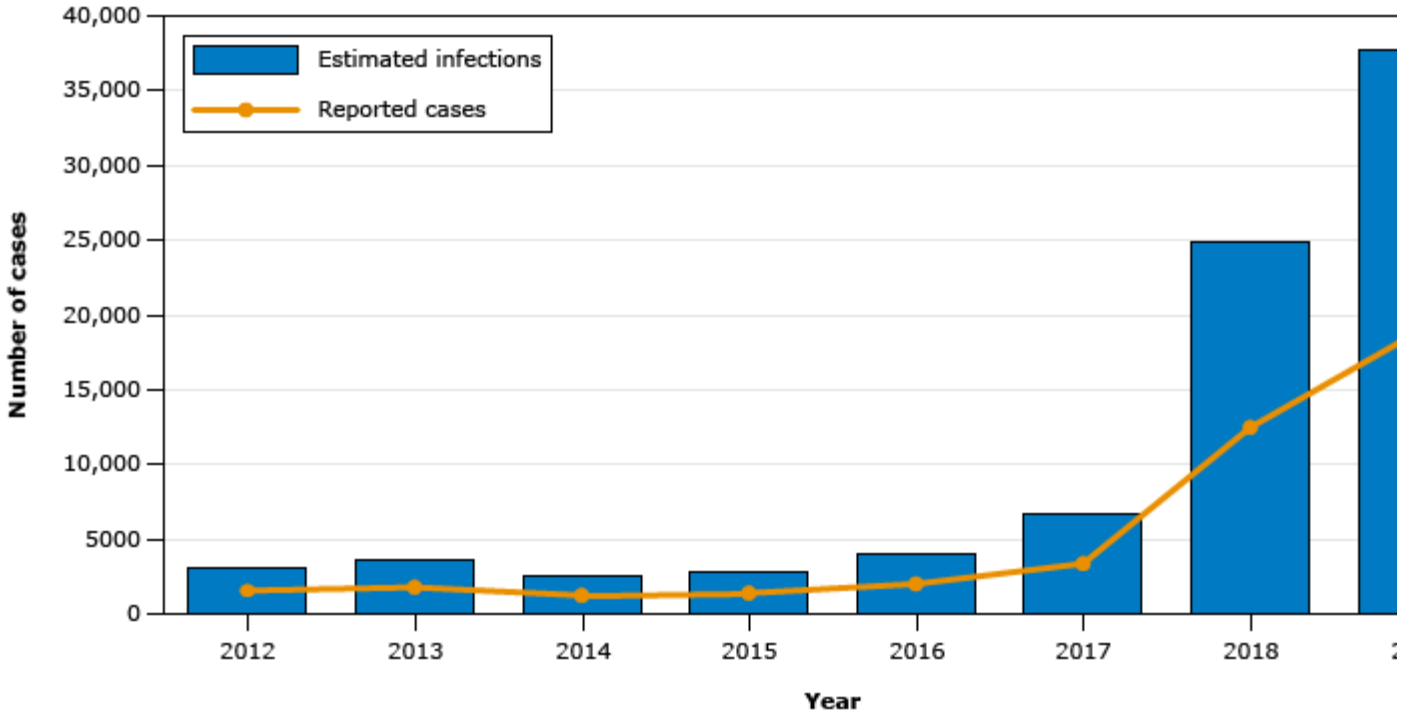
* Rate per 100,000 population.

¶ Annual average incidence.

Reproduced from: Murphy TV, Denniston MM, Hill HA, et al. Progress Toward Eliminating Hepatitis A Disease in the United States. MMW 65:29.

Graphic 60763 Version 8.0

Number of reported hepatitis A virus infection cases and estimated infections, States, 2012 to 2019

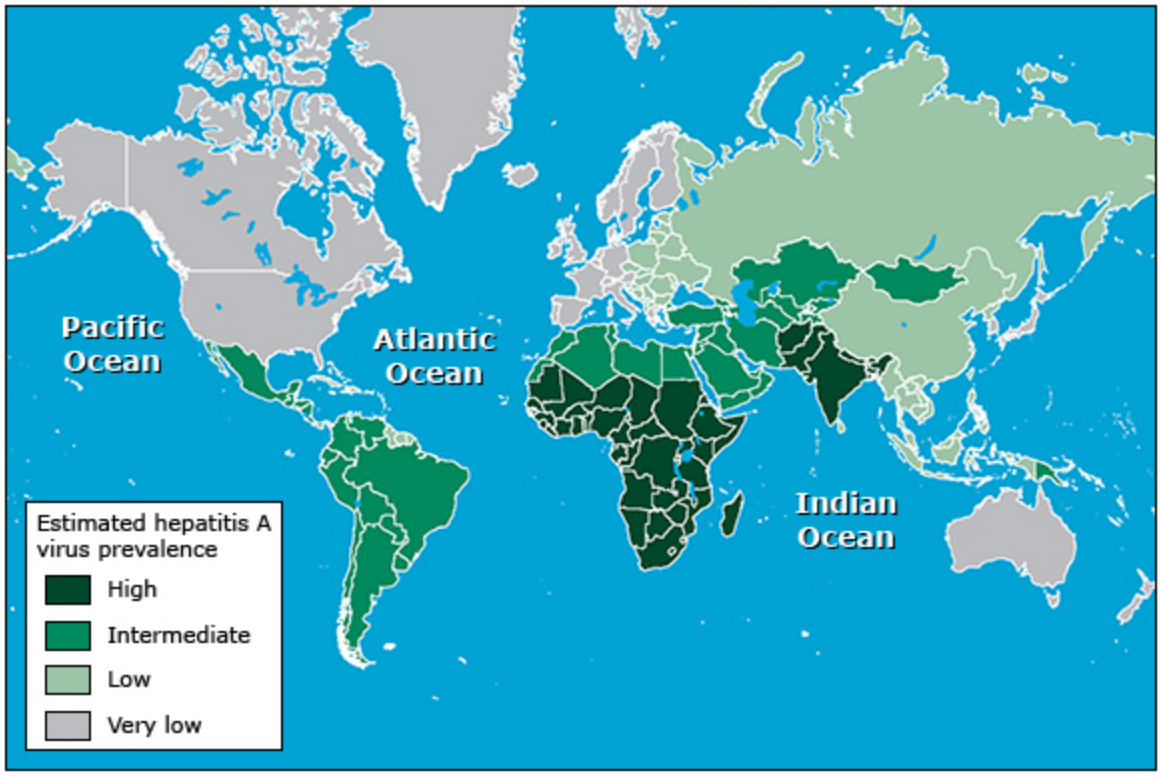


The number of estimated viral hepatitis infections was determined by multiplying the number of reported ca that met the classification criteria for a confirmed case by a factor that adjusted for under-ascertainment an underreporting.

Reproduced from: Centers for Disease Control and Prevention. Viral Hepatitis Surveillance Report 2019. Available at: https://www.cdc.gov/hepatitis/statistics/2019surveillance/Figure1.1.htm (Accessed on February 15, 2022).

Graphic 134984 Version 1.0

Prevalence of antibodies against hepatitis A



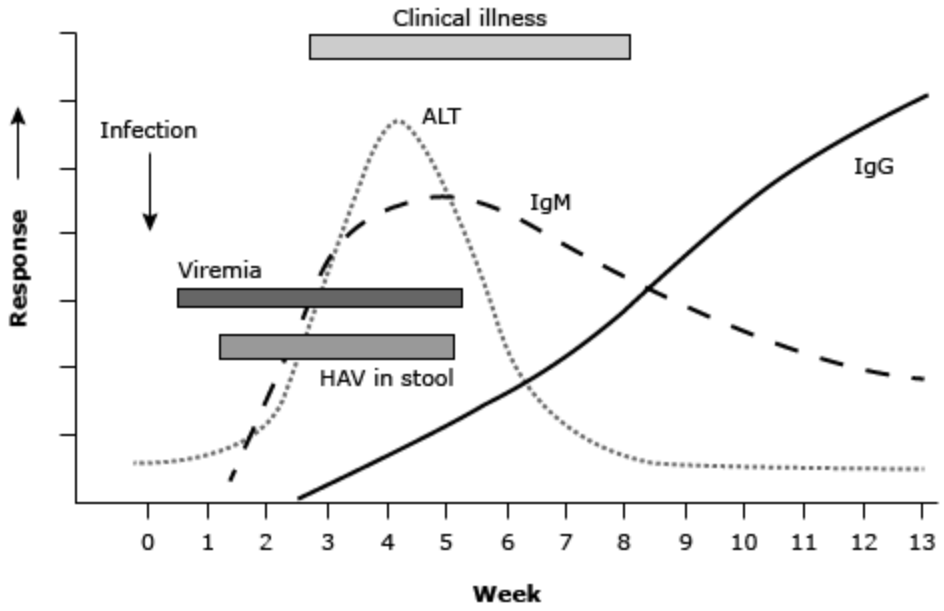
Estimates of prevalence of antibody to hepatitis A virus (anti-HAV IgG), a marker of previous HAV infection, are based on a systematic literature review conducted for the period of 1990 to 2005. In addition, anti-HAV prevalence might vary within countries by subpopulation and locality. As used on this map, the terms "high," "medium," "low," and "very low" endemicity reflect available evidence of how widespread HAV infection is within each country, rather than precise quantitative assessments.

HAV: hepatitis A virus; IgG: immunoglobulin G.

Original figure from: Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine 2010; 28:6653. Reproduced with the permission of Elsevier Inc. All rights reserved. Original figure modified and reproduced from: Centers for Disease Control and Prevention. Yellow Book 2012.

Graphic 69392 Version 6.0

Course of hepatitis A



Timeline for hepatitis A manifestations.

ALT: alanine transaminase; HAV: hepatitis A virus; Ig: immunoglobulin.

Reproduced from: American Medical Association; American Nurses Association-American Nurses Foundation; Centers for Disease Control and Prevention; Center for Food Safety and Applied Nutrition, Food and Drug Administration; Food Safety and Inspection Service, US Department of Agriculture. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. MMWR Recomm Rep 2004; 53(RR-4):1.

Graphic 57931 Version 4.0

Contributor Disclosures

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