Chapter 3: Hepatitis A

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I. Disease description

Hepatitis A is caused by infection with the hepatitis A virus (HAV), a non-enveloped RNA agent that is classified as a picornavirus.[1] HAV replicates in the liver, is shed in the feces, and peak concentrations in stool occur during the 2 weeks before and 1 week after onset of illness. Virus is also present in serum during this period, although in concentrations several orders of magnitude less than in feces. Therefore, the most common mode of HAV transmission is fecal-oral with the virus being transmitted from person to person between household contacts or sex partners, or by contaminated food or water. Because virus is present in serum during acute infection, bloodborne HAV transmission can occur, but it has been reported infrequently.

The incubation period of hepatitis A is 15–50 days, with an average of 28 days. The illness caused by HAV infection typically has an abrupt onset of signs and symptoms that include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine and jaundice. Hepatitis A usually does not last longer than 2 months, although some persons may have prolonged or relapsing signs and symptoms for up to 6 months. The likelihood of having symptoms with HAV infection is directly related to age. Among children < 6 years of age, most infections are asymptomatic; among older children and adults, infection is usually symptomatic. HAV infection occasionally produces fulminant hepatitis A. The case-fatality rate among reported cases of all ages is approximately 0.3%, but can be higher among older persons (approximately 2% among persons > 40 years of age).

HAV infection does not result in chronic infection or chronic liver disease.

II. Background

In the United States, large nationwide epidemics have occurred approximately every 10 years, with the last increase in cases in 1995.[2] However, even between these epidemics, disease rates are relatively high and many communities experience periodic epidemics. Until recently, hepatitis A was one of the most frequently reported vaccine-preventable diseases in the U.S. with 20,000–30,000 cases reported to the NNDSS. In 2000, 13,397 hepatitis A cases were reported for a rate of 4.87 cases per 100,000 population. This is the lowest rate of disease ever reported in the U.S. and represents, after correcting for underreporting and asymptomatic infections, an estimated 57,000 cases and 143,000 infections, respectively. This remarkable decline in cases could be the result of vaccination of children, begun in selected areas in 1996.

Based on testing from the Third National Health and Nutrition Examination Survey (NHANES III) survey conducted during 1988–1994, 33% of the general U.S. population has serologic evidence of prior HAV infection. Anti-HAV prevalence is

directly related to age, ranging from 9.4% among children 6–12 years of age to 74.6% among persons ≥ 70 years of age.

Among cases of hepatitis A reported to CDC, the most frequently reported risk factor is household or sexual contact with a person with hepatitis A (25%). An additional 10%–15% of reported cases occur among children and employees of childcare centers and members of their households. International travel (5%–7%) and suspected food- or waterborne outbreaks (2%–5%) each account for a small proportion of cases, and vary little by year. In contrast, the proportions of cases associated with MSM activity or injection drug use vary widely (5%–30% of cases) as a result of periodic outbreaks occurring in these subgroups in some communities. Many persons with hepatitis A do not identify risk factors (45%); their source of infection may be infected persons who are asymptomatic or have unrecognized infection.

Most hepatitis A cases in the United States occur in the context of community-wide epidemics. Communities which experience such epidemics with high and intermediate hepatitis A rates are concentrated in a limited number of states primarily located in the western and southwestern parts of the United States. In these areas, hepatitis A rates are consistently elevated, and cases reported from these areas account for the majority of reported hepatitis A cases nationwide.

Since 1996, routine hepatitis A vaccination of children living in communities with the highest hepatitis A rates has been recommended. These communities often are relatively well-defined either geographically or ethnically and include American Indian, Alaskan Native, and selected Hispanic, migrant, and religious communities. Historically, epidemics typically occurred every 5–10 years, with peak disease rates several fold higher than the national average. Coincident with implementation in recent years of hepatitis A vaccination of children, there have been dramatic reductions in hepatitis A rates in these communities.

In 1999, recommendations for routine vaccination of children were extended to include children living in the 11 states, as well as in counties and communities in other states, with rates that were at least twice the 1987–1997 national average (i.e., ≥ 20 cases per 100,000 population). Routine vaccination should be considered for children living in the six states, as well as in counties and communities in other states, with rates exceeding the 1987–1997 national average (i.e., ≥ 10 and < 20 cases per 100,000 population).[3] Hepatitis surveillance systems, with collection of demographic and risk factor data on cases, are essential to monitor and evaluate the impact of these recommendations.

III. Importance of rapid identification

Rapid identification and prompt reporting of cases of hepatitis A are important because measures can be taken to prevent transmission to other persons.

Post-exposure prophylaxis

Standard immune globulin (IG, formerly called gamma globulin) is a solution of antibodies prepared from human plasma. When administered intramuscularly

before exposure to HAV, or within 2 weeks after exposure, IG is > 85% effective in preventing hepatitis A.

IG should be given to exposed persons as soon as possible, but not more than 2 weeks after the exposure. Recipients may include 1) persons with close contact (household, sexual, or needle sharing) to a person with hepatitis A; 2) staff and attendees at childcare centers where a hepatitis A case is recognized; and 3) selected common-source exposure situations (e.g., to patrons at a food establishment with an HAV-infected food handler, if the risk of transmission is determined to be high).[3]

IV. Importance of surveillance

Disease surveillance should be used to do the following:

- Identify contacts of cases who require post-exposure prophylaxis
- Detect outbreaks
- Determine the effectiveness of hepatitis A vaccination
- Monitor disease incidence in all age groups
- Determine the epidemiologic characteristics of infected persons, including the source of their infection
- Assess and reduce missed opportunities for vaccination

Surveillance for hepatitis A depends upon an understanding of the local epidemiology of hepatitis A.

V. Disease reduction goals

The proposed disease reduction goal for hepatitis A calls for reducing the incidence of reported cases from a baseline of 11.3 cases per 100,000 reported in 1997 to no more than 5 cases per 100,000 by the year 2010.

VI. Case definition

The following case definition for hepatitis A has been approved by the Council of State and Territorial Epidemiologists (CSTE), and was published in 1997.[4]

Clinical case definition

An acute illness with

- A discrete onset of symptoms
- Jaundice or elevated serum aminotransferase levels

Laboratory criteria for diagnosis Immunoglobulin M (IgM) antibody to hepatitis A virus (anti-HAV) positive.

Case classification

Confirmed. A case that meets the clinical case definition and is laboratory confirmed or a case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A (i.e., household or sexual contact with an infected person during the 15–50 days before the onset of symptoms).

VII. Laboratory Testing

Serologic Testing

IgM anti-HAV. Virtually all patients with acute hepatitis A have detectable IgM anti-HAV. Therefore, the diagnosis of acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of IgM anti-HAV in serum. IgM anti-HAV generally disappears within 6 months after onset of symptoms.

Total anti-HAV. IgG anti-HAV appears in the convalescent phase of infection, remains 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. The presence of total anti-HAV and absence of IgM anti-HAV indicates immunity consistent with either past infection or vaccination. Commercial diagnostic tests are widely available for the detection of IgM and total (IgM and IgG) anti-HAV in serum.

CDC laboratory special studies

Occasionally, molecular virologic methods such as polymerase chain reaction (PCR)-based assays are used to amplify and sequence viral genomes. These assays may be helpful to investigate common source outbreaks of hepatitis A. Providers with questions about molecular virologic methods should consult with their state health department or the Division of Viral Hepatitis, Laboratory Branch, CDC. For additional information on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 19, "Laboratory Support for the Surveillance of Vaccine-Preventable Diseases."

VIII. Reporting

In the United States, case reports of viral hepatitis are classified as hepatitis A, hepatitis B, or hepatitis C/non-A, non-B hepatitis. Serologic testing is necessary to determine the etiology of viral hepatitis and case reports should be based on laboratory confirmation (see above). Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[5]

These regulations and laws list the diseases and conditions to be reported and describe those responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare facilities, and other institutions. Contact your state health department for reporting requirements in your state.

Reporting to CDC

Case reports of acute hepatitis A and other reportable diseases are transmitted weekly by the state health department to CDC via the National Electronic Telecommunications Surveillance System (NETSS) or National Electronic Disease Surveillance System (NEDSS), once available. The NETSS core record includes basic demographic information (excluding personal identifiers)—age, race or ethnicity, sex, date of onset, date of report, and county of residence. The Division of Viral Hepatitis has developed a hepatitis program area module for use in NEDSS in which symptoms, risk factors and serologic data can be entered. The hepatitis module form can be found in **Appendix 5** and can also be found at the following web address:
http://www.cdc.gov/ncidod/diseases/hepatitis/resource/PDFs/vhsp02.pdf.
This form can be used for data collection and case investigation, and data collected on the form can be directly entered into NEDSS.

IX. Vaccination schedules

Immune globulin (for hepatitis A post-exposure prophylaxis)

For persons with recent exposure (within 2 weeks) to HAV who have not previously received hepatitis A vaccine, a single intramuscular dose of IG (0.02 mL/kg) should be given as soon as possible, but not more than 2 weeks after the exposure. Persons who have received one dose of hepatitis A vaccine at least 1 month before a HAV exposure do not need IG.

Hepatitis A vaccine

Two monovalent inactivated hepatitis A vaccines are commercially available, HAVRIX® (GlaxoSmithKline) and VAQTA® (Merck & Co., Inc.). Both vaccines are licensed for persons ≥ 2 years of age. A combined hepatitis A and B vaccine, Twinrix® (GlaxoSmithKline), is also available for use in persons aged ≥ 18 years. Twinrix® is made of the antigenic components used in HAVRIX® and Engerix-B® (hepatitis B vaccine). These vaccines should be administered by intramuscular injection in the deltoid muscle, with a needle length appropriate for the person's age and size. Hepatitis A vaccine is recommended for children living in states and communities with consistently elevated rates (**Figure 1**), travelers to areas of high or intermediate hepatitis A endemicity, users of illicit drugs, men who have sex with men, persons with clotting factor disorders who receive therapeutic blood products, and patients with chronic liver disease. Any person ≥ 18 years old having an indication for both hepatitis A and B vaccination can be administered Twinrix® .

The dose of HAVRIX® is quantified in ELISA units (EL.U.). HAVRIX® is currently licensed in a two-dose schedule of 720 EL.U. per dose (0.5 mL) for children and adolescents (2–18 years of age) and 1440 EL.U. per dose (1.0 mL) for adults (> 18 years of age) (see **Table 1**).

The dose of VAQTA® is quantified in units (U). The dose and schedule for children and adolescents (2–18 years of age) is 25 U per dose in a two-dose

schedule, and for adults (> 18 years of age), 50 U per dose in a two-dose schedule (see **Table 2**).

The dose of Twinrix® is quantified in ELISA units (EL.U.) and mcg. Each dose of Twinrix contains at least 720 EL.U. of inactivated hepatitis A virus and 20 mcg of recombinant hepatitis B surface antigen (HBsAg) protein. Primary vaccination consists of three doses, given on a 0-, 1-, and 6-month schedule, the same schedule as that used for single antigen hepatitis B vaccine (see **Table 3**).

X. Enhancing surveillance

A number of activities can improve the detection and reporting of hepatitis A cases and improve the comprehensiveness and quality of reporting. Chapter 16 describes general activities for enhancing surveillance, and some specific recommendations for hepatitis A surveillance are listed here.

Appropriate serologic testing. Surveillance for acute hepatitis is challenging for several reasons. There are five different viruses (A–E) that account for nearly all human viral hepatitis. Because the clinical features of acute hepatitis caused by these viruses are similar, serologic testing is necessary to establish a diagnosis for a person with symptoms of acute hepatitis. Acute infection with several of the hepatitis viruses (HBV, HCV, and HDV) progresses to chronic infection, and review of serologic and clinical information of patients is necessary to make the differentiation between acute and chronic disease. A lack of understanding about the epidemiology of these diseases and underutilization of serologic testing may result in significant misclassification in reporting of acute viral hepatitis. For example, a provider may diagnose a child with jaundice as having hepatitis A and not order serologic testing, when in fact the child may have another illness.

To ensure accurate reporting of viral hepatitis and appropriate prophylaxis of household and sexual contacts, all case reports of viral hepatitis submitted to CDC should be investigated to obtain serologic testing information and risk factor data, and should be entered into the NNDSS via NETSS base and hepatitis extended record, and reported by the state health department to CDC.

Provider education. Providers should be educated about the importance of reporting all cases of acute hepatitis. A common risk factor for persons with acute infection is contact with a previously identified case. An aggressive case investigation of persons with acute disease provides the best opportunity to administer post-exposure prophylaxis to contacts of case-patients and has the potential to significantly reduce “missed opportunities” to prevent disease.

Case investigation. Identifying risk factors among persons with acute disease can help better define the epidemiology of viral hepatitis at the state and local level. For example, recognition of hepatitis A outbreaks in daycare centers, among homosexual men, or among injecting drug users can help target hepatitis A vaccination efforts. Analysis of risk factor data can identify populations where targeted interventions may be needed.

Monitoring surveillance indicators. Regular monitoring of surveillance indicators including date of report, timeliness, and completeness of reporting may identify

specific areas of the surveillance and reporting system that need improvement. Important hepatitis A program indicators that can be monitored through the surveillance, reporting, and case investigation system include:

- Cases of acute hepatitis A in vaccinated persons
- Cases of acute hepatitis A where death has occurred

Laboratory reporting. Laboratories should be encouraged to report all persons with acute hepatitis. All IgM anti-HAV positive results should be reported. To facilitate reporting, these IgM results could be included in the state's list of conditions reportable by laboratories.

Hospital-based reporting. Hospitals and infection control practitioners should be encouraged to report all persons with the ICD diagnosis codes of 070.*, acute hepatitis. These patients may then be investigated to determine if they are indeed cases.

XI. Case investigation

Guidelines for investigating a suspected case of viral hepatitis include:

- Determining a discrete onset of illness
- Confirming evidence of acute liver disease (jaundice or elevated aminotransferase levels)
- Obtaining serologic laboratory results.

Information to collect

The following information is epidemiologically important to collect in a case investigation. Additional information may also be collected at the direction of the state health department.

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race

- Reporting Source
  - County
  - Earliest date reported

- Clinical details including
  - Date onset of illness
  - Symptoms including pain, jaundice

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Information to collect (con't.)

- Laboratory results
  - IgM anti-HAV
  - Total anti-HAV

- Vaccine information
  - Dates of vaccination
  - Number of doses received
  - Manufacturer name
  - Vaccine lot number
  - If not vaccinated, reason

- Epidemiological
  - Risk factors
  - Contact investigation and prophylaxis

Table 1. Recommended doses of HAVRIX® (hepatitis A vaccine, inactivated)[a]

Group	Age	Dose (EL.U.)[b]	Volume	No. doses	Schedule[c]
Children and adolescents	2–18 years	720	0.5 mL	2	0, 6–12
Adults	>18 years	1,440	1.0 mL	2	0, 6–12

[a] GlaxoSmithKline
[b] Enzyme-linked immunosorbent assay units
[c] Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.

Table 2. Recommended doses of VAQTA® (hepatitis A vaccine, inactivated) [a]

Group	Age	Dose (U)[b]	Volume	No. doses	Schedule[c]
Children and adolescents	2–18 years	25	0.5 mL	2	0, 6–18
Adults	>18 years	50	1.0 mL	2	0, 6-12

[a] Merck & Co., Inc.
[b] Units
[c] Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.

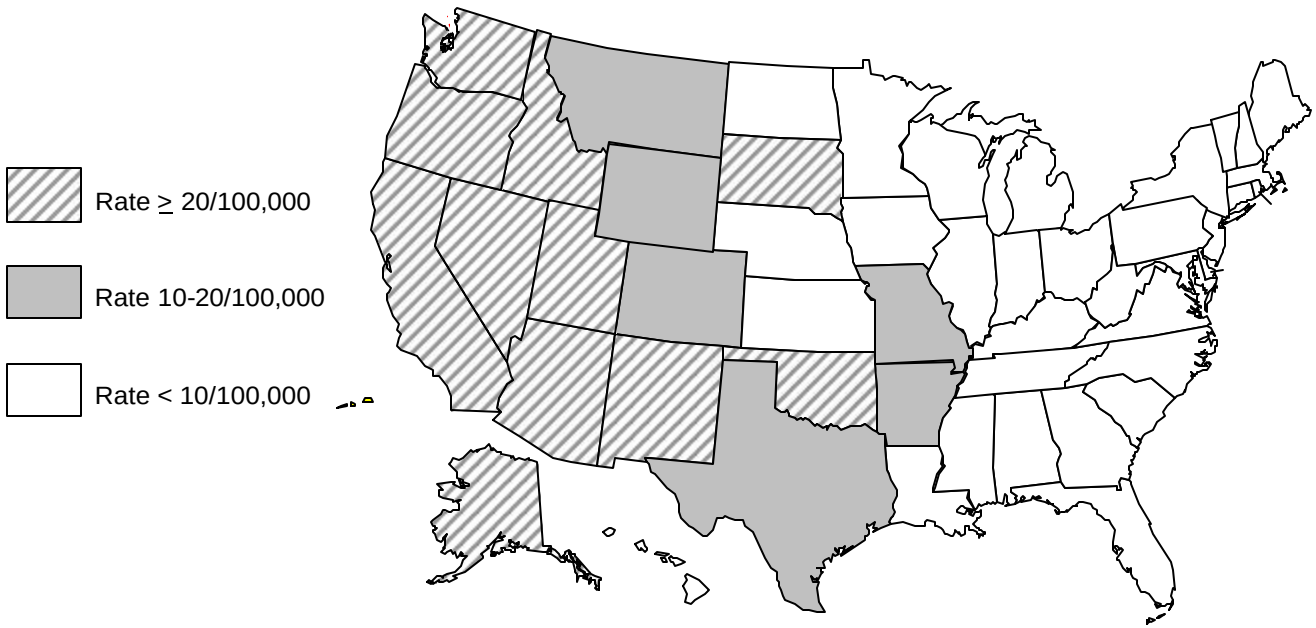
Table 3. Recommended doses of TWINRIX®[a] combined hepatitis A and B vaccine for persons 3 18 years of age)

Group	Age	Dose (EL.U.[b] and mcg)	Volume	No. doses	Schedule[c]
Adults	≥ 18 years	720 EL.U. (Inactivated HAV) 20 mcg (HBsAg protein)	1.0 mL	3	0, 1, 6

[a] GlaxoSmithKline
[b] Enzyme-linked immunosorbent assay units
[c] Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.

Figure 1:

States with Hepatitis A Rates ≥ 10/100,000; 1987-97



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