

Chapter 3: Hepatitis A

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I. Disease Description

Hepatitis A is caused by infection with hepatitis A virus (HAV), a non-enveloped RNA virus that is classified as a picornavirus. It was first isolated in 1979. Humans are the only natural host, although several nonhuman primates have been infected in laboratory conditions. Depending on conditions, HAV can be stable in the environment for months. The virus is relatively stable at low pH levels and moderate temperatures but can be inactivated by high temperature (185°F [85°C] or higher), formalin, and chlorine.¹

HAV is acquired by mouth (through fecal-oral transmission) and reaches the liver, where it replicates. After 10–12 days, virus is present in blood and is excreted via the biliary system into the feces. The virus is present in stools during the 1-2 weeks before and for 1-3 weeks after onset of illness. Although virus is present in serum, its concentration is several orders of magnitude less than in feces. Children and infants may excrete virus longer than adults.¹

The mean incubation period of hepatitis A is approximately 28 days (range 15–50 days). HAV infection occurs often without overt symptoms. Among persons presenting symptoms, hepatitis A is indistinguishable from other types of acute viral hepatitis, but is usually mild. The illness presentation varies widely: there may be flu-like symptoms, fever, malaise, anorexia, nausea, abdominal discomfort, dark urine and jaundice. Clinical illness usually resolves within 2 months among about 65% of cases and within 6 months for nearly all cases. Virus may be excreted during a relapse. The likelihood of symptomatic illness from HAV infection is directly related to age. In children younger than 6 years of age, most (70%) infections are asymptomatic. In older children and adults, infection is usually symptomatic, with jaundice occurring in more than 70% of patients. There is no specific treatment for hepatitis A virus infection. Disease is usually self-limiting and treatment and management of HAV infection are supportive; HAV infection does not result in chronic infection or chronic liver disease. However, HAV infection can complicate chronic liver disease among persons infected with hepatitis C virus; thus, susceptible persons should be vaccinated.¹

II. Background

Population-based seroprevalence surveys play a critical role in supplementing data systems for disease incidence, vaccination coverage, and vaccine adverse events in the development of vaccination policy. In the United States, seroprevalence is monitored by the National Health and Nutrition Examination Survey (NHANES). NHANES is conducted by the U.S. Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics and obtains nationally representative data on the health and nutritional status of the non-institutionalized, civilian U.S. population. During the 1999–2006 cycles of NHANES, 43,029 people ≥6 years of age were sampled, 34,338 were interviewed and 32,534 had physical examinations. Serum samples were available for anti-HAV testing for 29,858 of the examined individuals.²

Before the availability of vaccine in 1995, seroprevalence of antibody to hepatitis A virus (anti-HAV) in the population solely reflected prior infection. Currently, seroprevalence can reflect immunity due to either previous infection or to vaccination. In the U.S., during 1999–2006, the overall seroprevalence of anti-HAV was 34.9% (95% confidence interval (CI) 33.1–36.7). Seroprevalence among children increased from 8.0% (6.3–10.1) in NHANES 1988–1994 to 20.2% (16.0–24.8) in 1999–2006 ($p < 0.001$). For U.S.-born children aged 6–19 years, the strongest predictor of immunity is residence in a state that implemented vaccination in 1999. During 1999–2006, U.S.-born children living in vaccinating states (33.8%, 26.2–42.4) had a higher seroprevalence of anti-HAV than children in non-vaccinating states (11.0%, 9.4–12.8; $p < 0.001$).²

Among U.S.-born adults aged >19 years, the overall age-adjusted seroprevalence of anti-HAV was 29.9% (28.3, 31.5) during 1999–2006, not significantly different than during 1988–1994

(32.4%, 30.4–34.4). In multivariable models, older age and Mexican-American race/ethnicity are the factors most strongly associated with immunity. Age-adjusted seroprevalence of anti-HAV in 1999–2006 was significantly lower than that in 1988–1994 among adults in lower socioeconomic subgroups including those living below poverty, living in more crowded households, having less than a high school education, and those having no health insurance. The risk of lower prevalence of immunity among adults is the susceptibility of population clusters of at-risk adults leading to outbreaks; examples of these are well documented in the European Union.³ Prevention of secondary transmission of HAV in the United States comes at an enormous public health cost, largely due to the number of persons offered prophylaxis.

The distribution of risk behaviors and exposures among hepatitis A cases has changed dramatically in the U.S. since implementation of hepatitis vaccination. In sites conducting enhanced hepatitis surveillance during 2005–2007, the most frequent (46%) potential source of infection among persons reported with HAV disease was travel outside the U.S. and Canada. These cases mostly reflected persons who traveled, but also included some exposed to a traveler, but did not travel themselves. Other risk factors reported among cases, during the 2–6 week period before onset of symptoms, included contact with a case (15%), being an employee or child in a daycare center (7%), exposure during a common-source outbreak (7%), using illicit drugs (4%), or men who have sex with men (4%). In 37% of cases, the case denied all the above risk factors.⁴

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. Contacts can be effectively identified and vaccinated post-exposure.

IV. Importance of Surveillance

The main goals of surveillance are to:

1. detect and provide data to control outbreaks;
2. identify contacts of case-patients who require postexposure prophylaxis;
3. characterize changes in the epidemiology of infected populations, and risk factors/ behaviors of their infections; and
4. use surveillance data to guide vaccination policies.

There is evidence that electronic medical records can yield more complete and timely identification of acute, symptomatic hepatitis A infections. These result from a combination of coded clinical and laboratory criteria (aminotransferase levels, jaundice, and positive IgM antibody test result).

Surveillance depends heavily on laboratory-initiated reporting of positive markers of hepatitis A. Persons with positive test results are then investigated using traditional, notifiable diseases methods in most health departments in the U.S. Investigations can be labor intensive; thus, providers should be discouraged from using IgM anti-HAV as a screening tool or as part of testing panels in workups of nonacute liver function abnormalities, because IgM screening of non acute liver function tests may result in high percentage of false-positive IgM results. This will limit the need for health departments to conduct investigations of persons who are unlikely to have acute HAV infection.

Surveillance can supplement case notifications using seroprevalence surveys and administrative data.

V. Disease Reduction Goals

Healthy People 2020 disease reduction goals have been established for achieving the prevention of HAV transmission in the U.S.

IID–23: Reduce hepatitis A.

Target: to reduce the rate of incident hepatitis A disease to 0.3 cases per 100,000 population.

Baseline: 1.0 cases of hepatitis A virus per 100,000 population were reported in 2007.

VI. Case Definition

The following surveillance case definition for hepatitis A was adopted by the Council of State and Territorial Epidemiologists (CSTE) in 2000; plans for updating this definition are ongoing in 2011. This and previous case definitions are available at:

http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/case_definitions.htm

Clinical Criteria

An acute illness with a) discrete onset of symptoms and b) jaundice, elevated serum aminotransferase levels (ALT or AST)

Laboratory criteria:

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

Serologic testing is required to distinguish hepatitis A from other types of viral hepatitis, since clinical or epidemiologic features overlap. Virtually all patients with acute hepatitis A have detectable IgM anti-HAV. Acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of IgM anti-HAV in serum. IgM generally becomes detectable 5–10 days before the onset of symptoms and can persist for up to 6 months. IgG anti-HAV appears in the convalescent phase of infection, remains present in serum for the lifetime of the person, and confers enduring protection against disease.

The antibody test for total anti-HAV measures both IgG anti-HAV and IgM anti-HAV. Persons who are total anti-HAV positive and IgM anti-HAV negative are considered immune, whether from past infection or vaccination history.

CDC laboratory special studies

Molecular epidemiologic methods have been useful in understanding HAV transmission within networks of persons with similar risk factors. When applied in combination with conventional epidemiologic methods, HAV sequencing has also been useful in the investigation and control of outbreaks. However, for routine surveillance purposes, collecting specimens and conducting molecular characterization of HAV strains does not provide actionable information.

Specimens collected as part of enhanced hepatitis surveillance from 2005–2009 were sequenced: 271 (77.4%) of 350 available were PCR positive. Genotypes among the 271 case specimens were: IA (87.8%), IB (11.4%), and IIIA (0.7%). Almost half (131 or 48%) of the PCR positive specimens were from cases reporting travel or exposure to a traveler; 58/131 reported travel to Mexico; and 53/58 grouped within a previously described US-IA1 cluster.⁴

Providers with questions about molecular virology methods should consult with their state health department and the CDC Division of Viral Hepatitis.

VIII. Reporting

Hepatitis A became nationally reportable as a distinct entity in 1966. Incidence rates of hepatitis A disease were high in the 60's and 70's (>12 cases per 100,000 population). Since vaccine became available in 1995, rates have declined. In 2009, the rate overall was 0.6 per 100,000 population (1,987 cases). In 2009, rates were highest for persons aged 20–29 years (0.96 cases per 100,000 population); the lowest rates were among children <9 years (0.3 cases per 100,000 population). Infant and childhood immunization is thought to be responsible for this marked decrease in hepatitis A rates in the United States.

The CDC/CSTE surveillance case definition requires is a combination of clinical and laboratory characteristics. Thus, asymptomatic cases are not reportable (see case definition above). To estimate all new infections, case reports are adjusted for the proportion of asymptomatic cases and surveillance underreporting. In 2009 there were an estimated 21,000 new infections.

All states notify hepatitis A cases to CDC. However, each state determines who and how hepatitis A should be reported to their state or local jurisdictions. For a national summary of hepatitis A reporting requirements in the U.S., see the CSTE list available at: <http://www.cste.org/dnn/ProgramsandActivities/PublicHealthInformatics/StateReportableConditionsQueryResults/tabid/261/Default.aspx>

State health departments transmit case reports of hepatitis A along with other notifiable diseases weekly to the National Notifiable Diseases Surveillance System. Surveillance monitors basic demographic information (excluding personal identifiers)— age, race/ethnicity, sex, date of onset, date of report, and county of residence of individual cases. At CDC, the Division of Viral Hepatitis develops and disseminates an annual report available at: <http://www.cdc.gov/hepatitis/Statistics/index.htm>

IX. Vaccination

Hepatitis A vaccines were licensed in the United States in 1995. Shortly thereafter the Advisory Committee on Immunization Practices (ACIP) made recommendations for routine vaccination of children aged 2–18 years, living in communities with the highest rates of infection and disease. By 1999, there was epidemiologic evidence that the strategy had a limited impact on national disease incidence; thus in 1999, ACIP recommended routine vaccination for children living in 11, mostly western states, with average incidence rates that were twice or greater than the 1987–1997 national average (i.e. ≥ 20 cases per 100,000 population). In an additional six states, where average incidence rates were greater than the national average, but less than twice that value (i.e., 10–19 cases per 100,000 population), ACIP recommended consideration of routine vaccination of children. This expansion had a dramatic impact: by 2003, acute hepatitis A disease had declined overall by 76% from a rate of 10.7 per 100,000 in 1990–1997 to 2.6 per 100,000 in 2003, and in 2007 was the lowest ever reported (1.0 per 100,000). In 2006, the ACIP recommended integration of hepatitis A virus (HAV) vaccine into the routine childhood vaccination schedule with HAV vaccine for all children at age 12 months.⁵

In August 2005, the youngest age for which hepatitis A vaccine was licensed was lowered from 24 months to 12 months, and in May 2006, the Advisory Committee for Immunization Practices (ACIP) recommended routine vaccination of all children aged 12–23 months, regardless of risk category or location.⁵

Vaccination of children

All children should receive hepatitis A vaccine at age 1 year (i.e., 12–23 months). Vaccination should be completed according to the licensed schedules (Tables 1, 2) and integrated into the routine childhood vaccination schedule. Children who are not vaccinated by age 2 years can be vaccinated at subsequent visits. States, counties, and communities with existing hepatitis A

vaccination programs for children aged 2–18 years are encouraged to maintain these programs. In these areas, new efforts focused on routine vaccination of 12–23-month-old children should enhance, not replace, ongoing programs directed at a broader population of children. In areas without existing hepatitis A vaccination programs, catch-up vaccination of unvaccinated children <19 years of age can be considered. Such programs might especially be warranted in the context of rising incidence or ongoing outbreaks among children or adolescents.

Vaccination of persons at increased risk for HAV infection

Persons at increased risk for hepatitis A should be identified and vaccinated. Hepatitis A vaccine should be strongly considered for persons aged 1 year and older who are traveling to or working in countries where they would have a high or intermediate risk of hepatitis A virus infection. These areas include all areas of the world except Canada, Western Europe and Scandinavia, Japan, New Zealand, and Australia. The first dose of hepatitis A vaccine should be administered as soon as travel is considered. For healthy persons 40 years of age or younger, 1 dose of single antigen vaccine administered at any time before departure can provide adequate protection. Unvaccinated adults older than 40 years of age, immunocompromised persons, and persons with chronic liver disease planning to travel in 2 weeks or sooner should receive the first dose of vaccine and also can receive immune globulin at the same visit with separate syringes and at different anatomic sites. Travelers who choose not to receive vaccine should receive a single dose of IG (0.02 mL/kg), which provides protection against HAV infection for up to 3 months. Persons whose travel period is more than 2 months should be administered IG at 0.06 mL/kg. IG should be repeated in 5 months for prolonged travel. Other groups that should be offered vaccine include men who have sex with men, persons who use or are in treatment for illegal drugs, contacts of newly arriving adoptees from countries with high or intermediate HAV endemicity, persons who have clotting factor disorders, and persons with occupational risk of infection. Persons with occupational risk include only those who work with hepatitis A-infected primates or with hepatitis A virus in a laboratory setting. No other groups have been shown to be at increased risk of hepatitis A infection due to occupational exposure.

Persons with chronic liver disease are not at increased risk for HAV infection because of their liver disease alone. However, these persons, including those with chronic hepatitis C infection, are at increased risk for fulminant hepatitis A should they become infected. Susceptible persons who have chronic liver disease should be vaccinated. Adults with chronic hepatitis C may be good candidates for vaccination with TWINRIX to prevent both hepatitis A and B. Susceptible persons who either are awaiting or have received liver transplants should also be vaccinated.

Prophylaxis

Pre-exposure:

Currently, Advisory Committee on Immunization Practices (ACIP) recommends hepatitis A vaccination of all children at age 12–23 months, catch-up vaccination of older children in selected areas, and vaccination of persons at increased risk for hepatitis A (including travelers to endemic areas, users of illicit drugs, or men who have sex with men and contacts of newly arriving adoptees from countries with high or intermediate HAV endemicity). During 2007, the overall U.S. vaccination coverage, with at least 1 dose of HAV vaccine, among children 24–35 months was 47.4%.⁵

HAVRIX is available in two formulations: pediatric (720 ELISA units [EL.U.] per 0.5-mL dose) and adult (1,440 EL.U. per 1.0-mL dose) (Table 1). Children 1 through 18 years of age should receive a single primary dose of the pediatric formulation followed by a booster dose 6 to 12 months later. Adults 19 years of age and older receive one dose of the adult formulation followed by a booster 6 to 12 months later. The vaccine should be administered intramuscularly into the deltoid muscle. A needle length appropriate for the vaccinee's age and size (minimum of 1 inch) should be used.

VAQTA is quantified in units (U) of antigen and is available in pediatric and adult formulations (Table 2). Children 1 through 18 years of age should receive one dose of pediatric formulation (25 U per dose) with a booster dose 6 to 18 months later. Adults 19 years of age and older should

receive one dose of adult formulation (50 U per dose) with a booster dose 6 to 18 months after the first dose. The vaccine should be administered intramuscularly into the deltoid muscle. A needle length appropriate for the vaccinee's age and size should be used (minimum of 1 inch).

The hepatitis A component of TWINRIX consists of 720 ELISA units in a 1.0 mL dose (Table 3). It is approved for vaccination of persons aged >18 years in 2 schedules: a 3-dose schedule (0, 1, and 6 months) and alternate 4-dose schedule (0, 7, and 21–30 days, followed by a dose at 12 months). The alternative 4-dose schedule can be used where vaccination with TWINRIX or single antigen HAV vaccine has been initiated and travel or other potential exposure is anticipated before the second dose is due. A person 19 years of age or older who receives one dose of TWINRIX may complete the hepatitis A series with two doses of adult formulation hepatitis A vaccine separated by at least 5 months. A person who receives two doses of TWINRIX may complete the hepatitis A series with one dose of adult formulation hepatitis A vaccine or TWINRIX 5 months after the second dose. A person who begins the hepatitis A series with single-antigen hepatitis A vaccine may complete the series with two doses of TWINRIX or one dose of adult formulation hepatitis A vaccine. An 18-year-old should follow the same schedule using the pediatric formulation.

TWINRIX should be administered by intramuscular injection in the deltoid muscle. Injections in the gluteus can result in a lower response. When given with other vaccines or IG they should be given with different syringes and in different injection sites.

Post-exposure:

In the absence of post-exposure prophylaxis, secondary attack rates of 15%–30% have been reported in households, with higher rates of transmission occurring from infected young children than from infected adolescents and adults. Attack rates among persons exposed to HAV-infected food handlers are generally lower.

Vaccine (either HAVRIX or VAQTA) is recommended as post-exposure prophylaxis in healthy persons 12 months through 40 years of age as of 2007 because it induces active immunity providing longer protection, has higher acceptability and availability, and is easy to administer.

Immune globulin (IG) is typically used for post-exposure prophylaxis of hepatitis A in susceptible persons who are either older than 40 years of age, children younger than 12 months of age, immunocompromised persons, and persons with chronic liver disease.

Vaccination schedule

See additional details above in immunization section.

Table 1. The dose of HAVRIX is quantified in enzyme-linked immunosorbent assay (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 (12 months through 18 years of age), and 1440 EL.U. per dose (1.0 mL) for adults (older than 18 years of age).

Table 1. Recommended doses of HAVRIX® (hepatitis A vaccine, inactivated)*

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

* GlaxoSmithKline

† Enzyme-linked immunosorbent assay units

§ Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.

Table 2. The dose of VAQTA is quantified in units (U). The dose and schedule for children and adolescents (12 months through 18 years of age) is 25 U per dose in a two-dose schedule, and for adults (older than 18 years of age), 50 U per dose in a two-dose schedule.

Table 2. Recommended doses of VAQTA® (hepatitis A vaccine, inactivated)*

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

* Merck & Co., Inc.

† Units

§ Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.

Table 3. The dose of Twinrix is quantified in ELISA units (EL.U.) and micrograms. Each dose of Twinrix contains at least 720 EL.U. of inactivated hepatitis A virus and 20 µg of recombinant hepatitis B surface antigen (HBsAg) protein. There is a three dose schedule, given at 0, 1, and 6 months (the same schedule as that used for single-antigen hepatitis B vaccine), and a four dose schedule to accommodate travelers with short notice.

Table 3. Recommended doses of TWINRIX®*

(combined hepatitis A and B vaccine for adults ≥18 years of age only)

Group	Age	Dose [†]	Volume	No. doses	Schedule [§]
Adults	≥18 years	720 EL.U. and 20mcg of HBsAg	1.0 mL	3	0, 1, 6
Adults	≥18 years	720 EL.U. and 20mcg of HBsAg	1.0 mL	4	0, 7, 21-30 days, 12 months

* GlaxoSmithKline

† Enzyme-linked immunosorbent assay units

§ Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.

X. Enhancing Surveillance

Provider education and case investigation

Providers should be educated about the importance of reporting all cases of acute hepatitis A. A common risk factor for persons with acute infection is contact with a previously identified case-patient. Aggressive case investigations of persons with acute disease provide the best opportunity to administer post-exposure prophylaxis to contacts of case-patients and have the potential to significantly reduce missed opportunities to prevent disease.

Surveillance and epidemiology staff (often the same person) should routinely investigate suspected cases of viral hepatitis. Each state may have their own protocols for conducting these investigations, and CDC is available to provide support as needed (<http://www.cdc.gov/hepatitis/ContactUs.htm>).

Information necessary includes 1) determining a discrete onset of illness, 2) confirming evidence of acute liver disease (jaundice or elevated aminotransferase levels), 3) obtaining serologic laboratory results, and 4) risk factor information and determining the risk for secondary transmission.

Information to collect

Additional information may also be collected at the direction of the state health department.

A case report form that may be useful is available at:

<http://www.cdc.gov/hepatitis/Statistics/index.htm>

Basic information includes:

- Demographic information
- Clinical details, including
 - Date of onset of illness
 - Symptoms including abdominal pain and jaundice
- Laboratory results
- Vaccination status
- Risk factors
- Occupation, contacts for investigation and prophylaxis

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