

CLINICAL PRACTICE

Prevention of Hepatitis A with the Hepatitis A Vaccine

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

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A 34-year-old man presented to the emergency department two weeks after returning from a trip to India, reporting a six-day history of anorexia, vomiting, malaise, fatigue, and dark urine. His alanine aminotransferase level was 7330 U per liter, the bilirubin level was 8 mg per deciliter (137 μ mol per liter), and a test of the serum for hepatitis A IgM antibodies was positive. He was admitted for observation and hydration. Should he have been vaccinated against hepatitis A before his departure, and should his household contacts receive vaccine?

THE CLINICAL AND PUBLIC HEALTH PROBLEMS

The hepatitis A virus occurs throughout the world, and humans are thought to be its principal host.¹ The virus replicates in the liver and is transported through the bile to the stool, where it is shed beginning one to three weeks before the onset of illness and continuing for a week or more after the onset of jaundice. The virus is transmitted from person to person through the fecal–oral route and through the ingestion of contaminated food or drink. Although more than 75 percent of adults with hepatitis A infection have symptoms,² 70 percent of infections in children younger than six years of age are asymptomatic. These biologic characteristics contribute to the stealthy and efficient spread of the virus. The virus is spread easily from asymptomatic young children to other young children and to adult contacts. Young children are thus considered to be a principal reservoir and the dominant source of transmission in the community. The virus may also be transmitted by adults before symptoms occur, given that the virus appears in the stool substantially before the onset of illness. Thus, the source of a patient's infection often remains unknown.

After an average incubation period of 28 days (range, 15 to 50), an illness characterized by nausea, abdominal pain, fever, fatigue, dark urine, and jaundice occurs. Although most patients recover completely and uneventfully, the potential seriousness of hepatitis A in adults is generally underappreciated.³ Coagulopathy, encephalopathy, renal failure, a prolonged duration of disease, and occasional relapses are among its complications. Overall, 13 percent of patients require hospitalization, with a range from 7 percent of children younger than 15 years of age to 27 percent of adults 45 years of age or older.⁴ Each year, approximately 100 deaths in the United States are attributed to fulminant hepatitis A infection.

Enhanced surveillance for hepatitis, conducted since 1981 by the Centers for Disease Control and Prevention (CDC) in four sentinel counties, has demonstrated that the epidemiology of hepatitis A in the United States is heterogeneous.⁴ The CDC surveillance program showed that 52 percent of patients could not identify the source of their infection. Household or sexual contact with a person with hepatitis A (in 12 percent of

patients) and a history of injection-drug use within the six months before the onset of illness (in 14 percent of patients) were the two most commonly recognized risk factors. Whether the latter risk factor reflected actual transmission through the sharing of blood-contaminated needles⁵ or simply close contact could not be ascertained. Other reported risk factors included attendance or employment at a day-care center (in 11 percent of patients), a history of male homosexual activity within the previous six months (in 7 percent), and recent international travel to countries where hepatitis A is endemic (in 4 percent). Contrary to common belief, outbreaks of hepatitis A associated with restaurants are infrequent⁶; their notoriety probably stems from the extensive publicity surrounding these events.

There have been cyclic communitywide outbreaks of hepatitis A every 5 to 10 years in the United States for decades. More than 10,000 cases were reported in this country in 2001.⁷ The actual number of cases of hepatitis A was probably 5 times that reported, and the number of new asymptomatic infections was probably 10 times the number of reported symptomatic cases. The incidence is highest in the western states and among persons 5 to 39 years of age.⁸ One third of the U.S. population has serologic evidence of previous hepatitis A infection, with a prevalence ranging from 9 percent among children 6 to 11 years of age to 75 percent among persons 70 years of age or older.⁶

Periodic community epidemics notwithstanding, the rates of hepatitis A infection in the United States have been decreasing gradually during the past several decades (Fig. 1). This decrease probably reflects advances in hygiene, including improved water supplies, enhanced sewage disposal, reduced crowding, augmented food safety, and other factors. The use of hepatitis A vaccine since 1995 in many communities where the rate of infection had been high has most likely accelerated this downward trend. Rates of hepatitis A infection are similar in Europe and in most developed countries. In developing countries, nearly all people have had hepatitis A infection by early adulthood.⁹

STRATEGIES AND EVIDENCE

Two biologic products, hepatitis A vaccine and immune globulin, have been used successfully to prevent hepatitis A infection.

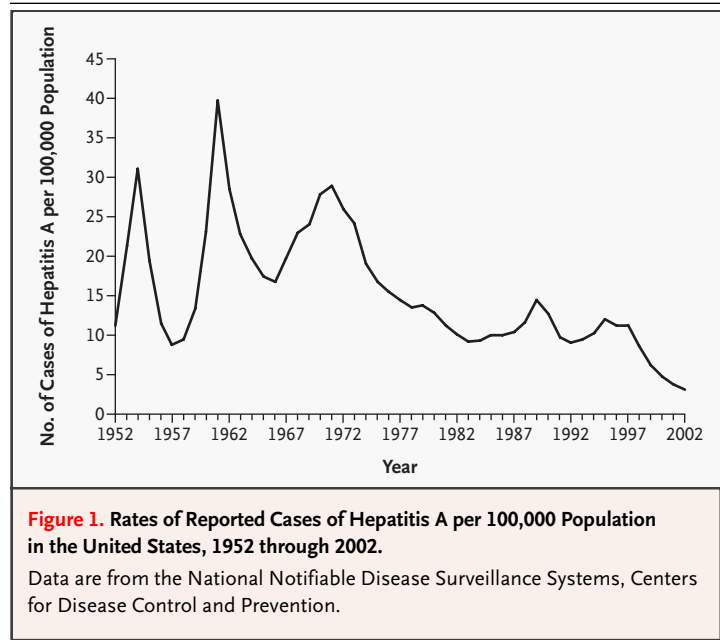


Figure 1. Rates of Reported Cases of Hepatitis A per 100,000 Population in the United States, 1952 through 2002.

Data are from the National Notifiable Disease Surveillance Systems, Centers for Disease Control and Prevention.

HEPATITIS A VACCINE

In the mid-1990s two formalin-inactivated hepatitis A virus vaccines were licensed by the Food and Drug Administration (FDA) for use in preventing disease in persons two years of age or older. Both vaccines are highly immunogenic; neutralizing antibodies are present in more than 94 percent of vaccinees one month after the first dose has been given, and essentially all recipients have a response after the second dose.¹⁰⁻¹² Two large efficacy trials were conducted, one in Thai villages and the other in a religious community in New York, all of which had sustained high rates of transmission of hepatitis A. Vaccination efficacy rates of 94 to 100 percent were recorded in these challenging circumstances.^{13,14} The available data suggest that the vaccine is less immunogenic in patients with chronic liver disease (seroconversion rate, 93 percent),^{15,16} immunocompromised persons (88 percent),¹⁷ and transplant recipients (26 percent).¹⁸ The immunogenicity also appears to be lower in the elderly (65 percent).¹⁹

Hepatitis A vaccine is not approved for use in children younger than two years of age because of concern that children who have passively acquired maternal antibody will have a diminished response to the vaccine.^{20,21} In spite of a lower antibody response, an anamnestic response occurred in chil-

dren who were vaccinated at two, four, and six months of age and then revaccinated several years later.²⁰

The vaccine is considered to be very safe. Reported adverse events have included soreness at the injection site in 18 to 39 percent of persons, headache (in 15 percent), and fever (in less than 10 percent).^{10-14,22} By 1999, more than 65 million doses of hepatitis A vaccine had been administered worldwide; investigators who reviewed data from multiple sources could not identify any serious adverse events that could be attributed to the vaccines with certainty.^{6,23} The only contraindication to vaccination is a previous allergic reaction to either of the vaccines or sensitivity to any vaccine component. Although the vaccines have not been studied in pregnant women, it is likely that they would be safe during pregnancy, given their inactivated formulation. Both vaccines are classified in pregnancy category C (studies in animals and humans have not been conducted). Pregnant women who are at risk for hepatitis A, such as those traveling to developing countries, should be vaccinated only if there is a clear indication; immune globulin (discussed below) is a reasonable alternative for such women.

A two-dose schedule is recommended for both vaccines, with the second dose given 6 to 18 months after the first (Table 1). If the second dose is delayed, it can still be given without the need to repeat the primary dose.²⁴ Because of the high rate of seroconversion, testing for antibodies after vaccination is not required. Pediatric and adult formulations are available for both vaccines. The vaccines are given in the deltoid muscle and can be administered

concurrently with other vaccines. They can also be given with immune globulin, at different anatomical sites, if immediate protection is required. The two brands of vaccine are considered to be interchangeable; if necessary, the two doses of vaccine can be of two different brands.⁶ Serologic testing for hepatitis A before vaccination is likely to be cost effective only among persons who have a high likelihood of previous infection. Three additional hepatitis A vaccines have been licensed for use in Europe, Latin America, and other parts of the world. Routine vaccination programs are in place in Israel²⁵ and in regions of Italy and Spain.

Recently, a combination hepatitis A–hepatitis B vaccine was licensed in the United States for use in persons older than 17 years of age. This vaccine appears to be both as safe and as effective as individual vaccines for the two viruses given separately.²⁶ The 1-ml dose is given in a three-dose schedule at 0, 1, and 6 months (Table 1). Studies suggest that the combination vaccine is highly immunogenic in children 1 to 15 years of age.²⁷

STRATEGIES FOR THE USE OF HEPATITIS A VACCINE

One strategy is to immunize people who are recognized to be at high risk for hepatitis A, in order to protect them. Vaccination should be offered to all high-risk persons two years of age or older (Table 2).⁶ Such an approach, however, would be expected to have only a marginal effect on the occurrence of disease nationwide, because most persons who become infected with hepatitis A do not have identifiable risk factors.⁴

In addition to protecting the individual vaccinee, immunization has the public health goal of protecting the entire community. The achievement of this goal requires interruption of the transmission of the hepatitis A virus, which extends protection to immunocompromised persons (who have an insufficient response to the vaccine and who may be at particular risk for severe disease) and to persons who, for whatever reason, have not been immunized. The effectiveness of immunization strategies is also influenced by practical realities, such as the acceptance of the vaccine by the public and providers, competing priorities, and costs.

An initial approach to protecting the community involved the use of hepatitis A vaccine during large community outbreaks. Although small outbreaks in rural communities could be aborted by use of hepatitis A vaccine,²⁸ the strategy was less successful

Table 1. Recommended Doses of Hepatitis A Vaccine and Immune Globulin.*

Agent and Age Group	Dose	Volume <i>ml</i>	Dose Schedule
Havrix			
2–18 Yr	720 ELISA units	0.5	2 doses, 6–12 mo apart
>18 Yr	1440 ELISA units	1.0	2 doses, 6–12 mo apart
Vaqa			
2–18 Yr	25 U	0.5	2 doses, 6–18 mo apart
>18 Yr	50 U	1.0	2 doses, 6–12 mo apart
Twinrix (>17 yr)†	720 ELISA units	1.0	3 doses, at 0, 1, and 6 mo
Immune globulin (any age)	—	0.02 per kg of body weight	1 dose

* ELISA denotes enzyme-linked immunosorbent assay.

† Twinrix is a combination hepatitis A–hepatitis B vaccine.

for epidemics occurring in larger urban centers,²⁹⁻³¹ reflecting the difficulty of attaining high rates of vaccine coverage in the target population. Moreover, by the time mass vaccination campaigns were initiated in urban centers, the outbreaks had begun to wane.

These experiences led to a shift in strategy to classic preexposure prevention: the areas of the country with the highest rates of cases were identified, and routine childhood immunization against hepatitis A was recommended in the identified communities. The intent was to reduce the rates of hepatitis A infection and disease among immunized children and — because children had been the primary sources of the spread of hepatitis A virus in these settings — to curtail the transmission of the virus and the incidence of disease among older children and adults through a herd-immunity effect. The introduction of routine immunization of young children in selected areas with high rates of infection, including a California county,³² a community in New York,³³ and Indian reservations,³⁴ has demonstrated that universal childhood immunization against hepatitis A is feasible and that it can be sustained. Furthermore, after the introduction of hepatitis A vaccine in these communities, the incidence of disease rapidly decreased to rates that were similar to the national average or even lower. As anticipated, the rates of disease were also reduced among older persons who were not targeted for immunization.³⁵ It is likely that a sustained reduction in the national incidence of hepatitis A will require universal routine immunization, just as the elimination of measles and other diseases has been achieved by means of childhood vaccination.

IMMUNE GLOBULIN FOR PASSIVE IMMUNOPROPHYLAXIS

Immune globulin is a preparation of concentrated antibodies derived from pooled human plasma. In 1945, Stokes and Neefe demonstrated that immune globulin provided protection against illness among children at a summer camp who had been exposed to hepatitis A.³⁶ Since then, immune globulin has been used widely for postexposure prophylaxis. The administration of a dose of 0.02 ml per kilogram of body weight intramuscularly in the gluteus within the first two weeks after exposure prevents disease in more than 85 percent of persons.³⁷ Prophylaxis given later during the incubation period may not prevent disease entirely but does result in reductions in the severity of symptoms and the duration of illness.³⁶ There is no need to perform serologic

testing for antibody against hepatitis A before administering immune globulin.

Immune globulin remains an effective intervention for preventing the transmission of hepatitis A to family members and other close contacts of patients who have recently become ill. Immune globulin has also been used widely for preexposure prophylaxis in persons planning short-term or long-term travel to developing countries, as well as in persons exposed to food prepared by someone who was infected with hepatitis A. The use of immune globulin in travelers has been largely superseded by the use of hepatitis A vaccine, except when the traveler's departure is imminent and immediate protection must be provided or the traveler is younger than two years of age (Table 2), or possibly when the traveler is pregnant. The most common adverse event is pain at the injection site.

AREAS OF UNCERTAINTY

Although experience has been limited, hepatitis A vaccination appears likely to provide long-term pro-

Table 2. Persons Currently Considered to Have an Indication for Hepatitis A Vaccine or Immune Globulin.

Hepatitis A vaccine

Children at least 2 years of age living in a state (Alaska, Arizona, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Utah, or Washington) or a county with a high rate of infection (≥ 20 cases per 100,000 population from 1987 through 1997)*

Travelers at least 2 years of age to countries with high or intermediate rates of disease†

Men who have sex with men

Users of illicit drugs

Persons who have chronic liver disease or who have received or will receive a liver transplant

Persons who use clotting-factor concentrates

Laboratory personnel who work with the hepatitis A virus or with nonhuman primates that are infected with hepatitis A

Immune globulin

Persons who will be traveling to countries with high or intermediate rates of disease within the next 2 weeks

Children younger than 2 years of age who will be traveling to countries with high rates of disease

For postexposure prophylaxis, within 14 days after exposure: persons who have been exposed to food that was handled by someone with acute hepatitis A who had either poor hygiene or diarrhea or persons exposed to a family member with acute hepatitis A

* Further information is available at <http://www.cdc.gov/ncidod/diseases/hepatitis/a/vax/index.htm>.

† Further information is available at <http://www.cdc.gov/ncidod/diseases/hepatitis/a/prevalence.htm>.

tection. Follow-up five to six years after vaccination has demonstrated protective levels of antibody,³³ and clinical efficacy has been maintained for seven to nine years.^{38,39} Models based on the kinetics of antibody against hepatitis A virus suggest that immunity will persist for at least 20 years, without the need for periodic boosters.³⁸⁻⁴²

The question of whether hepatitis A vaccine can be used for postexposure prophylaxis is unresolved. One study suggests that it may be effective when given after exposure,⁴³ but this study was small and did not involve a comparison with immune globulin, and its observations remain unconfirmed.

Fulminant infection may develop in patients with chronic liver disease if they are exposed to hepatitis A virus. There has been some debate about the cost effectiveness of hepatitis A vaccination in this population.⁴⁴⁻⁴⁷ We believe that hepatitis A vaccine should be given to persons who have evidence of chronic liver disease and those who are awaiting or have received a liver transplant; these groups are at high risk for complications from a superimposed insult to the liver.

Although the FDA has approved these vaccines only for use one month or more before international travel, the vaccine is protective in most persons two weeks after the administration of the first dose, and many travel clinics administer it up to two weeks before departure.⁴⁸

GUIDELINES

The Advisory Committee on Immunization Practices of the CDC⁶ recommends the vaccination of

high-risk persons two years of age or older, as outlined in Table 2. The advisory committee also recommends the routine immunization of all children in states or counties with high rates of infection, beginning at two years of age. The cases of hepatitis A reported in the 11 states that have high infection rates, most of which are in the West, accounted for half the total number of cases in the United States between 1987 and 1997, yet these states contained only 22 percent of the U.S. population (Table 2).⁶

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette clearly should have been vaccinated when he was planning his journey to a country that is known to have a high rate of hepatitis A. His family members should now receive immune globulin as postexposure prophylaxis against infection. The new combination hepatitis A–hepatitis B vaccine is an option for adults who are at risk for either infection and have not previously been vaccinated.

Routine vaccination is currently recommended for all young children in states with high rates of hepatitis A infection. Nevertheless, large community-wide outbreaks of hepatitis A continue to occur throughout the United States, with consequent disruption, hospitalizations, and deaths. Although it is not current policy, we propose that the universal vaccination of children for hepatitis A be extended to the entire United States, starting at two years of age, with catch-up immunization for all older children through adolescence.^{49,50}

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CORRECTION

Prevention of Hepatitis A with the Hepatitis A Vaccine

Prevention of Hepatitis A with the Hepatitis A Vaccine . On page 478, lines 6 and 7 of the first full paragraph of the right-hand column should have read, "The 1-ml dose is given in a three-dose schedule at 0, 1, and 6 months," rather than "The 1-ml dose is given in a three-dose schedule at 0, 1, and 6 months of age," as printed. The Web version of the article has been corrected. We regret the error.