



# Hepatitis A Vaccine Recommendations

Committee on Infectious Diseases

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

## ABSTRACT

Since licensure in 1995 of a hepatitis A vaccine, the Centers for Disease Control and Prevention and the American Academy of Pediatrics have been implementing an incremental hepatitis A immunization strategy for children. In 1996, children living in populations with the highest rates of disease were targeted for immunization, and in 1999 the program was expanded to immunization of children 2 years and older living in states and counties with rates of hepatitis A that historically have been higher than the national average. The 1999 program has been successful; the current rate of hepatitis A is the lowest ever reported in the United States. Regional, ethnic, and racial differences in the incidence of hepatitis A have been eliminated. The incidence of hepatitis A in adults in immunizing states has decreased significantly, suggesting a strong herd-immunity effect associated with immunization. In 2005, the US Food and Drug Administration changed the youngest approved age of administration of hepatitis A vaccine from 24 to 12 months of age, which facilitated incorporation of the vaccine into the recommended childhood immunization schedule. As the next step in the implementation of the incremental vaccine immunization strategy, the American Academy of Pediatrics now recommends routine administration of a Food and Drug Administration–licensed hepatitis A vaccine to all children 12 to 23 months of age in all states according to a Centers for Disease Control and Prevention–approved immunization schedule. Available data suggest that hepatitis A vaccine can be coadministered with other childhood vaccines without decreasing immunogenicity. Hepatitis A vaccines have proven to be extremely safe. In prelicensure clinical trials of both Havrix (GlaxoSmithKline, Rixensart, Belgium) and Vaqta (Merck & Co Inc, Whitehouse Station, NJ), adverse events were uncommon and mild when they occurred, with resolution typically in less than 1 day. Hepatitis A vaccine is contraindicated in people with a history of severe allergic reaction to a previous dose of hepatitis A vaccine or to a vaccine component. Because the hepatitis A vaccine is an inactivated product, no special precautions are needed for administration to people who are immunocompromised. No data exist about administration of the hepatitis A vaccine to pregnant women, but because it is not a live vaccine, the risk to mother and fetus should be extremely low to nonexistent.

## BACKGROUND AND RATIONALE FOR RECOMMENDATIONS

The purpose of this statement is to provide the rationale and recommendations for universal administration of hepatitis A vaccine to children living in the United States. The rationale for implementation of universal immunization is based on several considerations. For the 15 years before availability of hepatitis A vaccines

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### Key Words

hepatitis A, immunization, prevention, epidemiology, child

### Abbreviations

FDA—Food and Drug Administration  
CDC—Centers for Disease Control and Prevention  
ELU—enzyme-linked immunosorbent assay units  
VAERS—Vaccine Adverse Event Reporting System  
QALY—quality-adjusted life-year  
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(1980–1995), approximately 30 000 cases of symptomatic hepatitis A infections (disease) were reported annually in the United States.<sup>1</sup> Because of underreporting and the large number of asymptomatic infections in young children, the actual number of cases was projected to be nearly 300 000 per year in the United States.<sup>1</sup> The US Food and Drug Administration (FDA) licensed the first inactivated hepatitis A vaccine (Havrix [GlaxoSmith-Kline, Rixensart, Belgium]) in 1995 and a second product (Vaqta [Merck & Co Inc, Whitehouse Station, NJ]) in 1996. Initial licensure limited use to people 2 years and older. With the availability of a hepatitis A vaccine, the infection became one of the most common vaccine-preventable infections in the United States.

In 1996, the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics provided guidance for the use of hepatitis A vaccine.<sup>2,3</sup> As part of an incremental strategy, the vaccine was recommended for use in people in specific high-risk groups, including children 2 years and older who live in defined and circumscribed communities with high endemic rates or periodic outbreaks, people with chronic liver disease, men who have sex with men, illicit drug abusers, and people with occupational hazards that put them at increased risk of acquiring hepatitis A.<sup>2</sup> Despite implementation of the initial part of the strategy, hepatitis A remained one of the most frequently reported vaccine-preventable diseases, with more than 23 000 cases reported in 1996 (Fig 1). In 1999, the CDC expanded the hepatitis A immunization program to include immunization of children who live in states, counties, and communities with rates of hepatitis A consistently above the national average between 1987 and 1997.<sup>4</sup> Eleven states with rates at least twice the national average ( $\geq 20$  cases per 100 000) were advised to “recommend” immunization of children at 2 years of age, and an additional 6 states (with 10–20 cases per 100 000) were advised to “consider” immunization of children.<sup>4</sup>

Coincident with implementation of the 1999 recommendation, hepatitis A rates dropped to the lowest rates ever recorded in the United States and in 2003 were 76% lower than the rates before immunization was initiated in 1996 (Fig 1).<sup>5</sup> Before hepatitis A immunization, incidence was highest in younger children and in the American Indian/Alaska Native and Hispanic communities (Figs 2 and 3).<sup>5</sup> However, since 1999, these age, ethnic, and regional differences in incidence have nearly been eliminated (Figs 2 and 3). By 2003–2004, rates of hepatitis A were highest among men 18 to 39 years of age who were residing in the states that were not advised in 1999 to immunize against hepatitis A virus (nonimmunizing states).

An additional finding associated with the implementation of immunization of children against hepatitis A was a significant decrease in the incidence of disease in adults, suggesting a strong herd-immunity effect of the immunization program.<sup>6</sup> Similar findings have been reported from Israel, where within 2 years of initiation of routine immunization of children 18 to 24 months of age against hepatitis A, there was a 90% reduction in hepatitis A disease in adults throughout the country.<sup>7</sup> These data suggest that focusing on routine administration of hepatitis A vaccine in young children will have a significant effect on disease incidence in the rest of the population.

The success of the interim 1999 strategy has created an opportunity to consider universal immunization of infants in the United States against hepatitis A virus. As of 2005, the FDA approved use of the hepatitis A vaccine in children as young as 12 months of age, allowing for its incorporation into the recommended early childhood immunization schedule. This approval was followed by the recent CDC recommendation for routine use of hepatitis A vaccine in all children 12 months of age and older regardless of their state of residence.<sup>8</sup> Incorporation of the vaccine into the routine childhood immuni-

FIGURE 1  
Incidence of hepatitis A: United States, 1980–2004. ACIP indicates Advisory Committee on Immunization Practices (of the CDC).

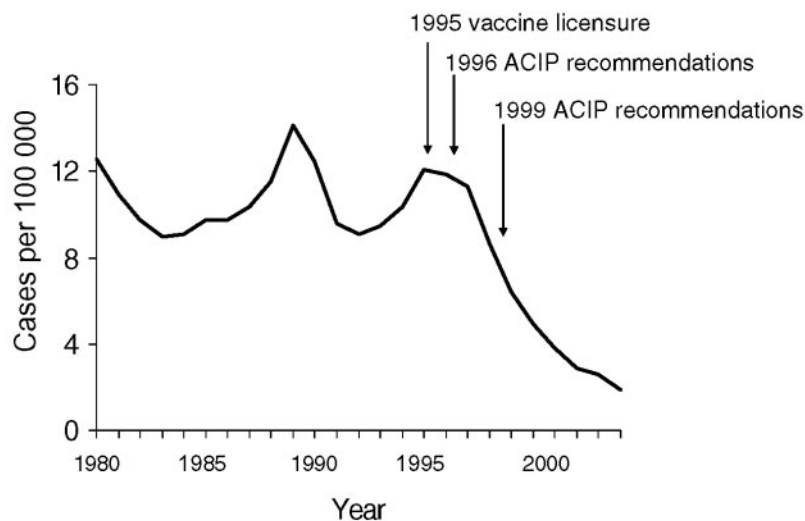


FIGURE 2  
Incidence of hepatitis A according to age: United States, 1990–2004.

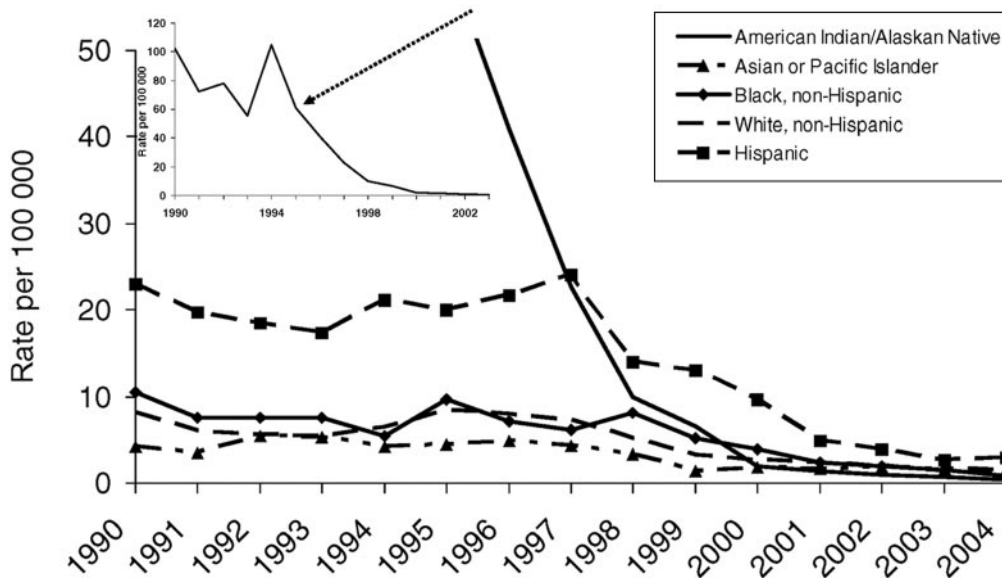
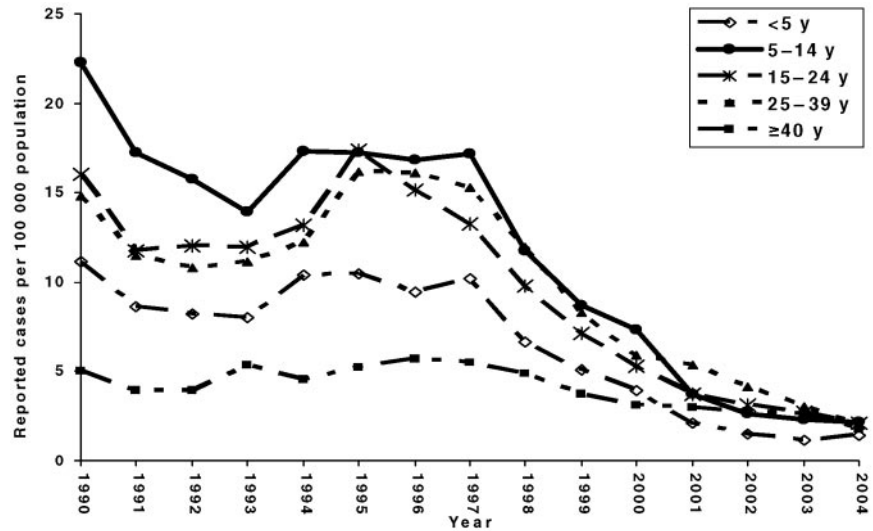


FIGURE 3  
Incidence of hepatitis A according to race/ethnicity: United States, 1990–2004.

zation schedule also is aided by the finding that coadministration of hepatitis A vaccines with other routinely administered immunizations has not been associated with impairment of vaccine-induced immunity. In addition, the equalization of disease rates among regions as well as among ethnic and age groups across the United States precludes sustainability of a vaccine program based on the rationale used to implement the interim strategy. Extending the program to routine immunization of infants nationwide should result in further lowering of disease incidence in the country and possibly could lead to an environment for the eventual elimination of indigenous hepatitis A infection in the United States.

## EPIDEMIOLOGY

### Incidence and Prevalence

Hepatitis A virus has a worldwide distribution, although prevalence of infection varies considerably on the basis of hygiene and sanitation conditions. In areas with overcrowding, limited access to clean water, and inadequate sewage systems, hepatitis A infection occurs almost universally in people early in life. Because most young children who acquire hepatitis A are asymptomatic, disease rates in highly endemic areas of the world are low. Although seronegative adults in such areas of the world are at high risk of infection and disease, outbreaks are unusual because of the high prevalence of antibody to

hepatitis A virus in the population.<sup>9</sup> High endemicity patterns also can be seen in geographic regions or ethnic groups within developed countries, including the United States before this decade.<sup>10–12</sup>

Historically, hepatitis A disease incidence has been cyclic in nature. In developed countries with temperate climates, incidence has commonly peaked every 10 to 15 years. Dramatic decreases in hepatitis A virus infection rates during the decade before and after licensure of the first hepatitis A vaccine have dampened this epidemic pattern significantly in the United States.<sup>5,13</sup> In the prevaccine era, hepatitis A infection rates were highest among young children and American Indian/Alaska Native and Hispanic individuals; these differences virtually have disappeared as of 2006.<sup>5</sup> Success of the hepatitis A immunization program has resulted in the virtual elimination of age, ethnic, racial, and regional differences in the incidence of hepatitis A infection in the past decade.<sup>5,14</sup>

### Mode of Transmission

Humans, great apes, and some species of monkeys can be infected with hepatitis A virus. The primary source of hepatitis A for human transmission is person-to-person spread through the fecal-oral route. On rare occasions, hepatitis A infection has been transmitted by transfusion of blood or blood products collected from donors during the viremic phase of infection.<sup>15,16</sup> Since 2002, nucleic acid amplification tests, such as the polymerase chain reaction (PCR) assay, have been applied to the screening of source plasma used for the manufacture of plasma-derived products.<sup>17</sup>

Transmission generally is limited to close contacts, and hepatitis A rarely is spread by casual interactions. Spread of hepatitis A within families is common, with disease occurring more commonly in older family members after being introduced into the household by an asymptotically infected young child.<sup>12</sup> In child care center outbreaks, contact with feces and subsequent personal contact are important means by which transmission occurs, and cases have occurred in child care center workers and household members of children who attend the center.<sup>18,19</sup> Foodborne hepatitis A transmission can occur from food that is contaminated during preparation by an infected food handler (foods not cooked after handling, such as salads and sandwiches) or during growing or processing (eg, produce), but this mode of transmission accounts for a relatively small proportion of reported hepatitis A cases in the United States.<sup>20</sup> Waterborne outbreaks are rare in developed countries with adequate sanitation systems. Approximately half of the people with sporadic, community-acquired hepatitis A infection have no known source of infection.<sup>12,13,21</sup>

Stools from a hepatitis A virus-infected person are most infectious from approximately 14 to 21 days before to approximately 8 days after onset of jaundice.<sup>22</sup> Hepa-

titis A RNA has been reported to be detectable in stool by polymerase chain reaction assay for up to 3 months after the acute illness,<sup>23</sup> and children can shed hepatitis A for up to 10 weeks after onset of clinical illness.<sup>24</sup> Although hepatitis A virus is not excreted chronically, clinical relapses may occur in 10% to 15% of patients and may be associated with recurrence of excretion of the virus in stool.<sup>25,26</sup> Hepatitis A virus can be detected in the serum through the period of jaundice and liver enzyme elevation, which is consistent with the possible transmission of the infection by the bloodborne route.<sup>15</sup>

Hepatitis A is the most important vaccine-preventable disease for travelers. The risk of hepatitis A is 4 to 30 cases per 100 000 months of stay in an area with endemic hepatitis A for travelers who are not immunized against hepatitis A.<sup>27</sup> In 2003, international travel was the source of hepatitis A for more than 25% of cases among children younger than 15 years. Although often not perceived as international travel by either the parents or the child's physician, children returning from visiting family members who live in areas with endemic hepatitis A is not an uncommon source of infection among cases reported in the United States.<sup>28</sup> Spread of hepatitis A virus in child care settings has occurred because of exposure to children who acquired hepatitis A after visiting in the countries of their parent's birth.

### CLINICAL MANIFESTATIONS OF DISEASE

Hepatitis A is an RNA virus in the Picornaviridae family. Hepatitis A virus infects the liver; the infection may be either icteric or anicteric. The likelihood of icteric (clinically apparent) disease is related inversely to the age of the person acquiring hepatitis A. In children younger than 6 years, more than 90% of hepatitis A infections are asymptomatic. In contrast, more than two thirds of older children and adults will develop jaundice after hepatitis A infection.<sup>29</sup> These statistics explain why hepatitis A outbreaks in child care settings frequently are detected for the first time when adult contacts become jaundiced.<sup>30</sup>

Hepatitis A virus is resistant to acid, which allows for passage through the stomach to the lower intestine. After an average incubation period of 28 days (range: 15–50 days),<sup>31</sup> infected people often experience vague and nonspecific symptoms. One of the first symptoms for which medical attention frequently is sought is dark urine, which usually is preceded by a 1- to 7-day mild prodromal illness that can include anorexia, malaise, fever, nausea, and vomiting.<sup>32,33</sup> Within a few days of the onset of bilirubinuria, feces become clay colored, and sclera, skin, and mucous membranes become jaundiced. Hepatomegaly can be noted on physical examination. Discoloration of the stool resolves within 2 to 3 weeks, which frequently indicates resolution of disease. Pruritus occurs uncommonly. Duration of illness is variable, but most patients are significantly better within 3 to 4

weeks, including resolution of elevated hepatocellular enzyme concentrations. Among women in the United States, pregnancy is not a risk factor for more severe hepatitis A virus infections. Although transmission to the fetus is unusual, there have been 2 case reports in which mothers developed hepatitis A during the first trimester of pregnancy and their infants subsequently developed meconium peritonitis.<sup>34,35</sup> The risk of transmission from a woman who develops hepatitis A in the third trimester of pregnancy to the infant seems to be low.<sup>36</sup> Infants infected through this means typically are asymptomatic, but an outbreak among hospital staff related to the exposure to such an infant has been reported.<sup>37</sup>

The pathologic effects of hepatitis A are limited to the liver. As hepatitis A replicates in liver cells, virions are shed from infected hepatocytes into the hepatic sinusoids and the bile canaliculi, where they pass into the intestine and are excreted in feces. Peak infectivity occurs during the 2 weeks before onset of jaundice or serum elevation of liver enzymes.<sup>38</sup> Viremia occurs soon after infection is acquired and persists through the period of elevated hepatocellular enzyme concentrations, but blood viral concentrations are much lower than those that occur in the stool.<sup>39</sup>

## COMPLICATIONS

Approximately 10% to 15% of patients with illness attributable to hepatitis A have relapsing disease lasting up to 6 months, and approximately 20% of these people have multiple relapses.<sup>25,40</sup> Hepatitis A virus can be detected in stool of some patients during the relapse.<sup>25,26</sup> Even with relapsing disease, overall outcomes are very good.<sup>26,41</sup> The clinical, laboratory, and pathologic findings in people with prolonged jaundice are associated with cholestatic hepatitis. A short course of rapidly tapered corticosteroids can reduce symptoms and hasten resolution of disease.<sup>42</sup>

Hepatitis A infection rarely results in fatalities. Before the recent success with hepatitis A immunization in the United States, there were approximately 100 deaths from hepatitis A viral infections each year in the United States. Reported case fatality rates for hepatitis A viral infections range from 0.01% to 2%. Fulminant hepatitis A viral infection is characterized by increasing severity of jaundice, deterioration in liver function, coagulation problems, and encephalopathy. Fulminant disease is more common among people older than 50 years<sup>43</sup> and patients with chronic liver disease, including chronic hepatitis B or hepatitis C infections.<sup>44-46</sup> Notably, serious and even fatal hepatitis A virus infection can occur in children,<sup>47,48</sup> albeit less commonly than in people with these other risk factors. Spontaneous recovery occurs in 30% to 60% of people with fulminant hepatitis A virus disease, with survivors regaining full liver function.

Prognosis is influenced by age, clotting-factor levels, stage of coma, and presence of renal disease.

## VACCINE

### Description

Hepatitis A vaccines licensed in the United States are inactivated, whole-cell virus vaccines that are produced from hepatitis A virus grown in human diploid fibroblast cells. There are 2 single-antigen vaccines, Vaqta<sup>49</sup> and Havrix,<sup>50</sup> and a combined hepatitis A/hepatitis B vaccine, Twinrix (GlaxoSmithKline). Once hepatitis A virus is adapted to growth in cell culture, it becomes attenuated. The purified virus is then formalin inactivated and adsorbed to aluminum hydroxide.<sup>51</sup> Havrix and Twinrix have 2-phenoxyethanol added as a preservative, whereas Vaqta is preservative free. All hepatitis A vaccine preparations are administered intramuscularly. No vaccine containing hepatitis A licensed in the United States has ever contained thimerosal.

Vaccine activity in Havrix is referenced to a standard by using an enzyme-linked immunosorbent assay and is expressed, therefore, in terms of enzyme-linked immunosorbent assay units (ELU). Vaqta antigen content is expressed as units (U) of the hepatitis A antigen. The pediatric/adolescent (12 months to 18 years) dose of Havrix is 0.5 mL and contains approximately 720 ELU of hepatitis A antigen, and the 1-mL adult formulation contains approximately 1440 ELU of hepatitis A antigen. Vaqta also is supplied in 2 formulations, one for use in children 12 months to 18 years of age and another for use in individuals 19 years of age and older. Twinrix contains a combination of hepatitis A antigen (720 ELU) and hepatitis B antigen (20  $\mu$ g) and is administered as a 3-dose series on a 0-, 1-, and 6-month schedule. In the United States, Twinrix is only licensed for administration to people 18 years and older. After completion of the 3-dose Twinrix series, immunogenicity to hepatitis A and B is equivalent to immunogenicity of people who received single-antigen vaccines administered separately according to standard schedules.<sup>52</sup>

### Immunogenicity

Within 1 month of receiving a first dose of hepatitis A vaccine, 97% of children and adolescents and 95% of adults developed protective concentrations of antibody, with the second dose resulting in virtually 100% of individuals being protected against the infection.<sup>53</sup> Although data are limited, the vaccine is less immunogenic in patients with chronic liver disease, immunocompromised people, transplant recipients, and elderly individuals. Because of the high rate of seroconversion in healthy children and the insensitivity of the standardly available assays, testing for antibodies after immunization is not recommended.

Data regarding immunologic response when hepatitis A vaccines are administered concomitantly with other

routinely administered immunizations of childhood are limited. However, available data indicate that simultaneous administration of hepatitis A vaccine with diphtheria and tetanus toxoids and acellular pertussis (DTaP), poliovirus (oral and inactivated), *Haemophilus influenzae* type b (Hib), hepatitis B, or measles-mumps-rubella (MMR) vaccines did not affect immunogenicity or reactogenicity.<sup>54</sup> No data are available regarding simultaneous administration of hepatitis A vaccine and pneumococcal conjugate vaccine (Prevnar [Wyeth Pharmaceuticals, Madison, NJ]), but there is no reason to assume that there will be an interaction between the vaccines.

Although vaccines containing hepatitis A effectively stimulate antibody production, the antibody concentrations achieved after immunization are 10 to 100 times less than concentrations that occur after natural infection.<sup>55</sup> In addition, many commercially available tests are not sufficiently sensitive to detect the presence of antibodies against hepatitis A virus elicited by the vaccine.<sup>56</sup> Thus, people who are immunized against hepatitis A virus may be protected against the infection but be antibody-negative according to standard assays.

#### **Efficacy and Effectiveness**

Two large trials have been conducted to evaluate the efficacy of hepatitis A vaccine in children. One trial, conducted in Thailand, enrolled more than 38 000 children aged 1 to 16 years who were randomly assigned to receive 2 doses separated by 1 month of either hepatitis A vaccine (Havrix, 360 ELU per dose) or hepatitis B vaccine.<sup>57</sup> Efficacy was calculated on development of hepatitis A antibodies more than 21 days after receipt of vaccine. Ninety-seven percent of children developed a protective titer within 1 month of immunization, and the efficacy over a 1-year period of observation after immunization was calculated at 94% (95% confidence interval: 79%–99%).<sup>57</sup> The other trial was conducted in 1037 children aged 2 to 16 years who were living in an area of upstate New York with historically sustained high rates of transmission of hepatitis A.<sup>58</sup> Study participants were immunized with 1 dose of Vaqta, and over the period of observation, vaccine efficacy was calculated to be 100% (the lower 95% confidence limit was 87%).<sup>58</sup> Although long-term measurement of vaccine efficacy is needed, mathematical models predict that protective concentrations of antibody will persist more than 25 years after completion of the recommended 2-dose vaccine series.<sup>59</sup>

Postlicensure effectiveness of the hepatitis A vaccine has been shown to be similar to reported efficacy. From 1996–2000, hepatitis A vaccine was provided free of charge to children who were living in Butte County, California.<sup>60</sup> Of the 45 000 children eligible for the program, approximately 30 000 (66%) received 1 dose and 17 600 children received 2 doses of hepatitis A vaccine.

During the 5 years of surveillance, overall hepatitis rates dropped 94% in the county, and vaccine effectiveness was calculated at 98%.<sup>60</sup> Similarly, in Catalonia, Spain, cases of hepatitis A decreased from 10.3 per 100 000 in children 11 to 14 years of age before routine hepatitis A immunization to 1.8 cases per 100 000 after implementation of a hepatitis A immunization program, resulting in an effectiveness rate of 97%.<sup>61</sup>

#### **Safety**

Hepatitis A vaccines have been proven to be extremely safe. In prelicensure clinical trials of both Havrix and Vaqta, adverse events were uncommon and mild when they occurred, with resolution typically occurring in less than 1 day.<sup>57</sup> The most common adverse events, reported in 10% to 15% of subjects, were pain at the site of injection, redness, and swelling. No serious adverse events have been definitively associated with either Vaqta or Havrix. In a study of more than 38 000 Thai children who received Havrix as part of an efficacy trial, no serious adverse events were reported.<sup>57</sup> Since licensure in 1995, millions of doses of hepatitis A vaccine have been administered, and no significant adverse events have been associated with either of the hepatitis A vaccines (Beth Bell, MD, CDC, personal communication, 2006). A postmarketing study for Vaqta was performed in a large health maintenance organization population in Northern California. During an 18-month period, patients were observed for emergency department and clinic use in the month after receipt of hepatitis A vaccine. More than 49 000 doses of hepatitis A vaccine were administered (15 000 to children younger than 18 years), and no serious adverse events were noted.<sup>62</sup> The only vaccine-related adverse event that occurred more commonly after administration of hepatitis A vaccine was mild diarrhea in immunized adults. A summary of adverse events reported through the Vaccine Adverse Event Reporting System (VAERS) showed that 871 adverse events occurred in temporal relationship to receipt of hepatitis A vaccines. However, only fever, injection-site reactions, and allergic reactions seemed to be related to the vaccine. Events reported through the VAERS were similar in type and number for Vaqta and Havrix.

#### **Cost-effectiveness**

The cost-effectiveness of nationwide routine hepatitis A immunization has been evaluated. Compared with no childhood immunization against hepatitis A, routine immunization at 1 year of age would result in 183 806 fewer infections and 32 fewer deaths in each cohort.<sup>63</sup> The cost-effectiveness ratio was estimated at \$173 000 per life-year gained and \$24 000 per quality-adjusted life-year (QALY) gained. When out-of-cohort herd immunity was considered, immunization at 1 year of age yielded a societal cost of \$1000 per QALY gained. Another economic analysis that included the estimated re-

**TABLE 1 Recommended Doses and Schedules for Inactivated Hepatitis A Vaccines**

Age, y	Vaccine (Manufacturer)	Dose	Volume per Dose, mL	Route of Injection	No. of Doses	Schedule, mo
1–18 y	Vaqta (Merck)	25 U	0.5	IM	2	0, 6–18
	Havrix (GlaxoSmithKline)	720 ELU	0.5	IM	2	0, 6–12
≥19 y	Vaqta (Merck)	50 U	1	IM	2	0, 6–18
	Havrix (GlaxoSmithKline)	1440 ELU	1	IM	2	0, 6–12
	Twinrix (GlaxoSmithKline)	720 ELU (hepatitis A), 20 µg (hepatitis B)	1	IM	3	0, 1, 6

IM indicates intramuscular.

duction in secondary cases among household contacts of infected children yielded similar results.<sup>64</sup> When these values are placed in context, the projected costs of implementation of a universal hepatitis A vaccine program is equivalent to an acellular pertussis vaccine program in adolescents and approximately 10% of the cost of the meningococcal vaccine program based on QALYs.

### Vaccine Administration and Storage

Before administration, vaccine preparations should be shaken and, when well mixed, will be a slightly opaque, white-colored suspension. The vaccine should be administered intramuscularly with needle length based on age and size of the patient (see Table 1.5: Site and Needle Length by Age for Intramuscular Administration in *Red Book*<sup>65</sup>). Hepatitis A vaccine in children is administered in a 2-dose series, with the first dose of Vaqta or Havrix administered to children as young as 12 months. The second dose of Havrix should be given 6 to 12 months after the first dose, and the second dose of Vaqta can be administered 6 to 18 months after the first dose. Twinrix is a 3-dose series given on a 0-, 1-, and 6-month schedule. If the immunization schedule for vaccines containing hepatitis A is interrupted, only the required immunization needs to be administered rather than restarting the series.<sup>66</sup>

Hepatitis A vaccine is to be stored and shipped between 2 and 8°C (36 and 46°F). However, neither the immunogenicity nor reactogenicity of either Vaqta or Havrix was affected by storage at up to 37°C (98°F) for up to 1 week.<sup>67</sup> The vaccine should not be frozen, because it will destroy vaccine potency.

### RECOMMENDATIONS

As the next step in the incremental immunization strategy to prevent hepatitis A, the following recommendations are made.

#### Children

1. All children who live in the United States should receive hepatitis A vaccine at 1 year of age (ie, 12–23 months of age) as a 2-dose regimen. Immunization should be integrated into the routine childhood immunization schedule and completed according to the approved schedules (Table 1) using Havrix or Vaqta

hepatitis A vaccines. Administration of 2 doses of the same hepatitis A vaccine is preferable. However, data indicate that the vaccines are interchangeable; thus, the 2-dose series may be completed with either of the vaccine preparations approved for children.<sup>68</sup>

2. States, counties, and communities with existing hepatitis A immunization programs for children 2 to 18 years of age are encouraged to maintain these programs and expand to include children who are 12 to 23 months of age. In these areas, new efforts focused on routine immunization of preschool children should enhance, not supplant or replace, ongoing programs that are directed at a broader population of children.
3. In areas without existing hepatitis A immunization programs, catch-up immunization of unimmunized children 2 to 18 years of age can be considered. Such programs might especially be warranted in the context of increasing incidence or ongoing outbreaks among children or adolescents.
4. Immunocompromising conditions are not a contraindication to receiving hepatitis A vaccine. The preparation is an inactivated virus and has not been shown to result in any increased safety risks when administered to people with primary or secondary immunodeficiencies.
5. The vaccine should not be administered to people with a hypersensitivity to any of the vaccine components such as aluminum hydroxide and phenoxyethanol.

#### Persons at Increased Risk of Hepatitis A Virus Infection

1. Children not previously immunized against hepatitis A virus who will be traveling to or living in areas with intermediate or high endemicity for the infection should be immunized before departure. Areas for which hepatitis A immunization is recommended before travel can be found at [www.cdc.gov/travel/vaccinat.htm](http://www.cdc.gov/travel/vaccinat.htm). Protection is reliably present by 4 weeks after administration of the first dose of hepatitis A vaccine and may afford protection as soon as 2 weeks after immunization.
2. Both adolescent and adult males who have sex with men should be immunized against hepatitis A virus.

Preimmunization serologic testing is not recommended for adolescents or young adults.

3. Immunization is recommended for users of either injectable or noninjectable illicit drugs. Again, preimmunization serologic testing is not recommended for adolescents or young adults.
4. Although changes in clotting-factor-preparation practices and donor screening have greatly reduced the risk of acquiring hepatitis A for recipients of clotting factors, susceptible individuals should be immunized against hepatitis A before administration of the clotting factors.
5. Susceptible persons who work with hepatitis A virus in a laboratory setting should be immunized against the virus.

### REPORTING ADVERSE EVENTS

The safety of hepatitis A vaccines will continue to be assessed through ongoing monitoring of data from the VAERS and other surveillance systems. Any adverse event suspected to be associated with hepatitis A immunization should be reported to the VAERS. Information on how to report adverse events is available at [www.fda.gov/cber/vaers/vaers.htm](http://www.fda.gov/cber/vaers/vaers.htm). VAERS forms also can be obtained by telephone at 800-822-7967.

### FUTURE NEEDS AND RESEARCH

#### Ongoing Disease Surveillance

The incidence of hepatitis A is at an all-time low in the United States.<sup>5</sup> The decrease in the rate of disease is temporally associated with implementation of an immunization program against the infection. Although it is likely that immunization has been a major contributor to the decrease, other factors, including improved hygiene or cycling of disease, which have been characteristic of the epidemiology of hepatitis A virus in the past, could have contributed to the decreased hepatitis A incidence during the past decade. Comprehensive information on hepatitis A immunization coverage is vital to fully evaluate the effect that immunization has had on reduction of the incidence of the infection. Unfortunately, only limited data are available, and immunization coverage among adults is not assessed systematically.

Although data from the Third National Health and Nutrition Examination Survey<sup>69</sup> contributed to the understanding of hepatitis A, the information gained focused on prevalence of infection. As vaccine implementation increases, it will be most important to collect prospective data on disease incidence by fully investigating disease outbreaks and encouraging national reporting of cases through state and local health departments to the National Notifiable Diseases Surveillance System. Only with the availability of these data will it be possible

to determine the full impact and added value of these mass-immunization programs.

#### Potential Need for a Catch-up Schedule

Strategies for catch-up immunization are often components of universal immunization programs. However, currently available data from the United States, Israel, and some European countries suggest that there is a significant herd-immunity effect associated with immunization of young children against hepatitis A.<sup>6,7,70</sup> A mandate for catch-up immunization should await further surveillance to determine if the indirect effect on older, nonimmunized groups continues.

#### Observing for Need of a Booster Dose for Adults

Hepatitis A infection in childhood typically is mild, and in children younger than 6 years, 90% of infections are asymptomatic. However, acquisition of the infection during adolescence and adulthood typically is associated with symptomatic infections that can be debilitating for weeks. Thus, for a hepatitis A immunization program to be effective, the vaccine has to confer long-term protection. Otherwise, an asymptomatic childhood infection could be replaced by symptomatic disease after exposure later in life. Because the vaccine has been commercially available for only 10 years, data on the persistence of antibody is based largely on information collected from trials that tested the immunogenicity and efficacy of the vaccine. However, the available data are encouraging, finding that protective antibody concentrations persist more than 10 years after immunization.<sup>71</sup> In addition, mathematical modeling suggests that protective antibody concentrations may persist for more than 25 years after immunization.<sup>59</sup> Finally, studies suggest that immunity may be present even beyond the ability to detect circulating antibodies.<sup>71</sup> Thus, although it is not considered necessary for booster immunization in a fully immunized healthy person, observation will be needed to determine if this evidence-based recommendation will need to change over time.

#### Evaluation of Immunogenicity With Coadministration of Vaccines

Limited data are available that indicate that coadministration of hepatitis A vaccine with other vaccines in the recommended childhood series does not affect immunogenicity of the vaccines.<sup>54</sup> Additional studies to assess hepatitis A vaccine immunogenicity in conjunction with other vaccines, particularly varicella and pneumococcal conjugate vaccines, will need to be collected and evaluated. However, unless data become available to the contrary, one should assume that concomitant administration of hepatitis A vaccine with other recommended vaccines of children is safe and immunogenic.



## Evaluating Vaccine Acceptance

The success of a hepatitis A vaccine program will depend on the enthusiasm that physicians and members of the health care team display toward implementation of the program. In addition, the attitudes of families to incorporation of "another vaccine" into the crowded immunization schedule will critically affect the program. In a 2003 survey, only 51% of age-eligible children who lived in the 11 states with recommendation to be immunized with hepatitis A vaccine had received at least 1 dose of vaccine.<sup>72</sup> Only 1% of children who lived in states without a hepatitis A vaccine recommendation had received 1 dose of vaccine. Despite this moderate uptake of vaccine in "vaccine" states, there was a significant decrease in hepatitis A disease, suggesting the vaccine is highly effective and, along with the excellent safety profile of the vaccine, can provide the encouraging information needed to sustain a vaccine program.

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#### “FOR JIMMY AND THE BOYS AND GIRLS OF AMERICA”: PUBLICIZING CHILDHOOD CANCERS IN TWENTIETH-CENTURY AMERICA

“On the evening of 22 May 1948, Ralph Edwards, host of the popular radio program *Truth or Consequences*, introduced his audience to a special guest: ‘Tonight we take you to a little fellow named Jimmy. We’re not going to give you his last name, because he’s just like thousands of other young fellows and girls in private homes and hospitals all over the country.’ Without further explanation, the program commenced as Edwards prompted Jimmy to list his favorite Boston Braves players. Members of the team’s starting lineup filed into his hospital room one by one, and presented the boy with autographed baseball memorabilia. Jimmy then joined the men in singing ‘Take Me Out to the Ballgame’ on air and received special permission to attend a game the next day—a day designated as ‘Jimmy’s Day’ at the ballpark. After his young guest signed off, Edwards told listeners that Jimmy was a twelve-year-old undergoing cancer treatment in Boston. He asked them to contribute money toward a television set for the boy’s room and, more generally, to aid ‘Jimmy and the boys and girls of America.’ Members of the show’s audience responded generously, reportedly donating more than \$200 000 to the fund and sending tens of thousands of ‘get well’ cards to Jimmy. By drawing upon child-centered fund-raising strategies pioneered by other earlier voluntary health agencies, the Jimmy Fund and its mission to direct research and treatment toward childhood cancers were launched with overwhelming public support.”

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