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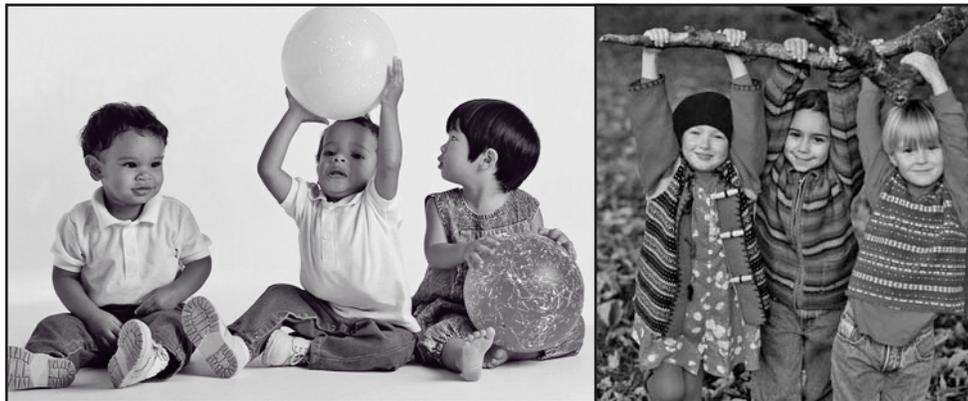
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Prevention of Hepatitis A Through Active or Passive Immunization

Recommendations of the Advisory Committee on Immunization Practices (ACIP)



INSIDE: Continuing Education Examination

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION**

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Prevention of Hepatitis A Through Active or Passive Immunization

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Prepared by
Anthony E. Fiore, MD
Annemarie Wasley, DrPH
Beth P. Bell, MD

Division of Viral Hepatitis, National Center for Infectious Diseases

Summary

Routine vaccination of children is an effective way to reduce hepatitis A incidence in the United States. Since licensure of hepatitis A vaccine during 1995–1996, the hepatitis A childhood immunization strategy has been implemented incrementally, starting with the recommendation of the Advisory Committee on Immunization Practices (ACIP) in 1996 to vaccinate children living in communities with the highest disease rates and continuing in 1999 with ACIP's recommendations for vaccination of children living in states, counties, and communities with consistently elevated hepatitis A rates. These updated recommendations represent the final step in the childhood hepatitis A immunization strategy, routine hepatitis A vaccination of children nationwide. Implementation of these recommendations will reinforce existing vaccination programs, extend the benefits associated with hepatitis A vaccination to the rest of the country, and create the foundation for eventual consideration of elimination of indigenous hepatitis A virus transmission.

This report updates ACIP's 1999 recommendations concerning the prevention of hepatitis A through immunization (CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1999;48[No. RR-12]:1–37) and includes 1) new data on the epidemiology of hepatitis A in the era of hepatitis A vaccination of children in selected U.S. areas, 2) results of analyses of the economics of nationwide routine vaccination of children, and 3) recommendations for the routine vaccination of children in the United States. Previous recommendations for vaccination of persons in groups at increased risk for hepatitis A or its adverse consequences and recommendations regarding the use of immune globulin for protection against hepatitis A are unchanged from the 1999 recommendations.

Introduction

During 1980–1995, approximately 22,000–36,000 cases of hepatitis A were reported annually in the United States, representing an estimated average of 271,000 infections per year when anicteric disease and asymptomatic infections are taken in account (1). During 1995–1996, highly effective hepatitis A vaccines became available in the United States for use among persons aged ≥ 2 years, providing an opportunity to reduce hepatitis A incidence substantially and potentially eliminate indigenous transmission of hepatitis A virus (HAV).

In 1996, the Advisory Committee on Immunization Practices (ACIP) first made recommendations to prevent hepatitis A through immunization, focusing primarily on vaccinating

persons in groups shown to be at high risk for infection and children living in communities with high rates of disease (2). In 1999, as the next step in a strategy of incremental implementation of recommendations for routine vaccination of children, ACIP expanded the recommendations to include vaccination of children living in states, counties, and communities in which hepatitis A rates were consistently above the national average (3). Coincident with implementation of these recommendations, hepatitis A rates have declined to the lowest level ever recorded (4). Because declines were largest in the areas in which routine vaccination of children was occurring, rates are now more equivalent across regions, with the highest rates occurring among children in parts of the country where vaccination has not been recommended (5). This statement includes recommendations for the final step in this incremental strategy, routine hepatitis A vaccination of children nationwide. Implementation of these recommendations will reinforce existing vaccination programs, extend the benefits associated with hepatitis A vaccination to the rest of the country, and create the foundation for eventual consideration of elimination of indigenous HAV transmission.

The material in this report originated in the National Center for Infectious Diseases, Rima Khabbaz, MD, Director; and the Division of Viral Hepatitis, John Ward, MD, Director.

Corresponding preparer: Beth P. Bell, MD, Division of Viral Hepatitis, National Center for Infectious Diseases, 1600 Clifton Road, NE, MS G-37, Atlanta, GA 30333. Telephone: 404-371-5910; Fax: 404-371-5221; E-mail: bbell@cdc.gov.

Primary Changes in the Statement

Changes in recommendations include the following:

- updated data regarding the epidemiology of hepatitis A since the advent of hepatitis A vaccination of children in selected areas of the United States,
- results of recent economic analyses of nationwide routine vaccination of children, and
- recommendations for the routine vaccination of children aged ≥ 1 year in the United States.

Previous recommendations for 1) vaccination of persons in groups at increased risk for hepatitis A or its adverse consequences and 2) use of immune globulin (IG) for protection against hepatitis A are unchanged (3).

Clinical and Diagnostic Features of Hepatitis A

Clinical Illness

HAV, a 27-nm RNA agent classified as a picornavirus, can produce either asymptomatic or symptomatic infection in humans after an average incubation period of 28 days (range: 15–50 days) (6). Illness caused by HAV infection typically has an abrupt onset that can include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, and jaundice. The likelihood of having symptoms with HAV infection is related to age. In children aged < 6 years, 70% of infections are asymptomatic; if illness does occur, it is typically not accompanied by jaundice (7). Among older children and adults, infection typically is symptomatic, with jaundice occurring in $> 70\%$ of patients (8). Signs and symptoms typically last < 2 months, although 10%–15% of symptomatic persons have prolonged or relapsing disease lasting up to 6 months (9). The overall case-fatality ratio among cases reported through the National Notifiable Diseases Surveillance System is approximately 0.3%–0.6% but reaches 1.8% among adults aged > 50 years; persons with chronic liver disease are at increased risk for acute liver failure (5,10–15).

In infected persons, HAV replicates in the liver, is excreted in bile, and is shed in stool. Peak infectivity of infected persons occurs during the 2-week period before onset of jaundice or elevation of liver enzymes, when concentration of virus in stool is highest (16). Concentration of virus in stool declines after jaundice appears. Children can shed HAV for longer periods than do adults, lasting up to 10 weeks (17) after onset of clinical illness; infants infected as neonates in one nosocomial outbreak shed HAV for up to 6 months (18). Chronic shedding of HAV in feces does not occur; however, recurrent shedding occurs during relapses among persons who have relapsing

illness (19). Viremia occurs soon after infection and persists through the period of liver enzyme elevation, but at concentrations several orders of magnitude lower than in stool (20,21).

Diagnosis

Hepatitis A cannot be differentiated from other types of viral hepatitis on the basis of clinical or epidemiologic features alone. Serologic testing to detect immunoglobulin M (IgM) antibody to the capsid proteins of HAV (IgM anti-HAV) is required to confirm a diagnosis of acute HAV infection. Sensitive tests for IgM and immunoglobulin G (IgG) anti-HAV in saliva have been developed but are not licensed in the United States (22). In the majority of persons, serum IgM anti-HAV becomes detectable 5–10 days before onset of symptoms (21,23). IgG anti-HAV, which appears early in the course of infection, remains detectable for the person's lifetime and provides lifelong protection against the disease. Two serologic tests are licensed for the detection of antibodies to HAV: 1) IgM anti-HAV and 2) total anti-HAV (i.e., IgM and IgG anti-HAV, referred to in this report as anti-HAV) (24). In the majority of patients, IgM anti-HAV declines to undetectable levels < 6 months after infection (23). However, persons who test positive for IgM anti-HAV > 1 year after infection have been reported, as have likely false-positive tests in persons without evidence of recent HAV infection (25–27). Total anti-HAV testing is used in epidemiologic studies to measure the prevalence of previous infection or by clinicians to determine whether a person with an indication for pre-exposure prophylaxis is already immune.

HAV RNA can be detected in the blood and stool of the majority of persons during the acute phase of infection by using nucleic acid amplification methods, and nucleic acid sequencing has been used to determine the relatedness of HAV isolates for epidemiologic investigations (28–30). However, only a limited number of research laboratories have the capacity to use these methods.

Epidemiology of Hepatitis A

Modes of Transmission

Person-to-person transmission through the fecal-oral route is the primary means of HAV transmission in the United States. Transmission occurs most frequently among close contacts, especially in households and extended family settings (31). Because the majority of children have asymptomatic or unrecognized infections, they play a key role in HAV transmission and serve as a source of infection for others (32,33). In one study of adults without an identified source, 52% of

their households included a child aged <6 years, and the presence of a young child was associated with HAV transmission in the household (32). In studies in which serologic testing of the household contacts of adults without an identified source of infection was performed, 25%–40% of contacts aged <6 years had serologic evidence of acute HAV infection (IgM anti-HAV) (17,32).

Common-source outbreaks and sporadic cases also can occur from exposure to fecally contaminated food or water. Uncooked foods have been recognized frequently as a source of outbreaks (34). Cooked foods also can transmit HAV if cooking is inadequate to kill the virus or if food is contaminated after cooking, as occurs commonly in outbreaks associated with infected food handlers (34–37). Waterborne outbreaks of hepatitis A are infrequent in developed countries with well-maintained sanitation and water supplies. The majority of waterborne outbreaks are associated with sewage-contaminated or inadequately treated water (38–40). Outbreaks in the context of floods or other natural disasters (e.g., hurricanes) have not been reported in the United States.

Depending on conditions, HAV can be stable in the environment for months (41). Heating foods at temperatures >185°F (>85°C) for 1 minute or disinfecting surfaces with a 1:100 dilution of sodium hypochlorite (i.e., household bleach) in tap water is necessary to inactivate HAV (42).

On rare occasions, HAV infection has been transmitted by transfusion of blood or blood products collected from donors during the viremic phase of their infection (20,43). Since 2002, nucleic acid amplification tests such as polymerase chain reaction (PCR) have been applied to the screening of source plasma used for the manufacture of plasma-derived products (44).

In experimentally infected nonhuman primates, HAV has been detected in saliva during the incubation period (45). However, transmission by saliva has not been demonstrated.

Disease Patterns

Prevaccine Era

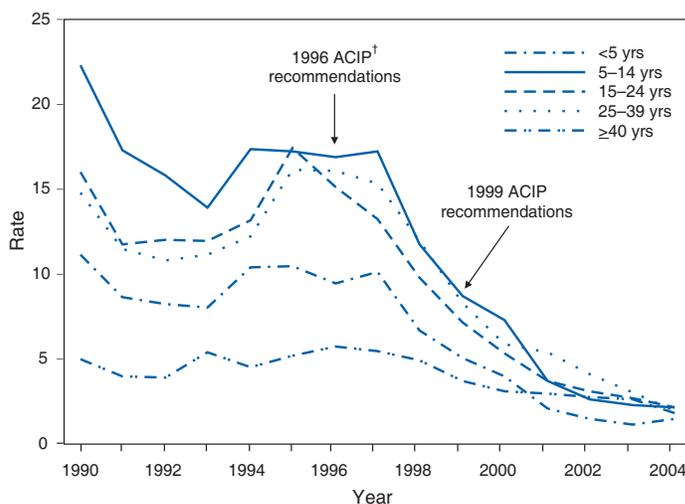
Hepatitis A epidemiology in the United States has fundamentally changed with licensure of hepatitis A vaccine and implementation of national ACIP recommendations for its use. Before vaccine licensure during 1995–1996, hepatitis A incidence was primarily cyclic, with peaks occurring every 10–15 years. In the United States, during 1980–1995, approximately 22,000–36,000 hepatitis A cases were reported annually to CDC (rate: 9.0–14.5 cases per 100,000 population), but incidence models indicate that the number of infections was substantially higher (1,5). One such analysis estimated an average of 271,000 infections per year during 1980–1999, representing 10.4 times the reported number of

cases (1). Each year in the United States, an estimated 100 persons died as a result of acute liver failure attributed to hepatitis A.

The costs associated with hepatitis A are substantial. Surveillance data indicate that 11%–22% of persons with hepatitis A are hospitalized (3). The average duration of work loss for adults who become ill has been estimated at 15.5 days for nonhospitalized patients and 33.2 days for hospitalized patients (46). Estimates of the annual direct and indirect costs of hepatitis A in the United States have ranged from \$300 million to \$488.8 million in 1997 dollars (3,46). A recent Markov model analysis estimated economic costs of \$133.5 million during the lifetime of a single age cohort of children born in 2005, in the absence of vaccination (CDC, unpublished data, 2005).

Variation by Age, Race/Ethnicity, and Region. During the prevaccine era, the reported incidence of hepatitis A was highest among children aged 5–14 years, with approximately one third of reported cases involving children aged <15 years (Figure 1) (5). Because young children frequently have unrecognized or asymptomatic infection, a relatively smaller proportion of infections among children than adults are detected by routine disease surveillance. Incidence models indicate that during 1980–1999, the majority of HAV infections occurred among children aged <10 years, and the highest incidence was among those aged 0–4 years (1). Before the use of hepatitis A vaccine, rates among American Indians and Alaska Natives were more than five times higher than rates in other racial/ethnic populations, and rates among Hispanics were ap-

FIGURE 1. Rate* of reported hepatitis A, by age group and year — United States, 1990–2004



SOURCE: National Notifiable Diseases Surveillance System.

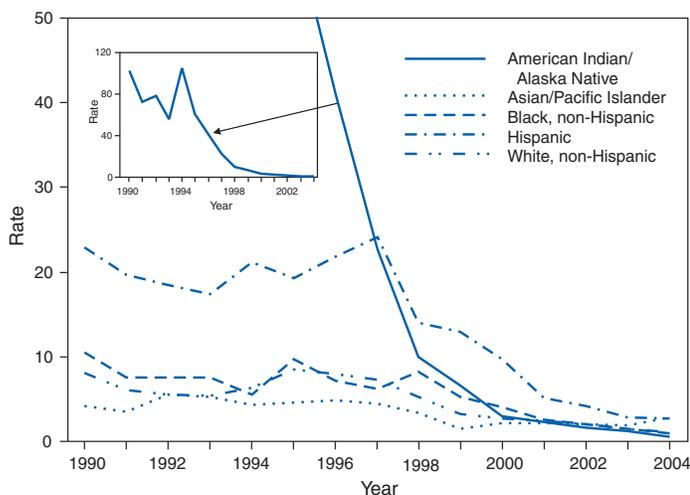
* Per 100,000 population.

† Advisory Committee on Immunization Practices.

proximately three times higher than rates among non-Hispanics (Figure 2) (5,47–49).

Since the 1960s, the highest hepatitis A rates and the majority of cases occurred in a limited number of states and counties concentrated in the western and southwestern United States (Figure 3) (4). Despite year-to-year fluctuations, rates in these areas consistently remained above the national average. In 11 states (Alaska, Arizona, California, Idaho, Nevada,

FIGURE 2. Rate* of reported hepatitis A, by race/ethnicity — United States, 1990–2004



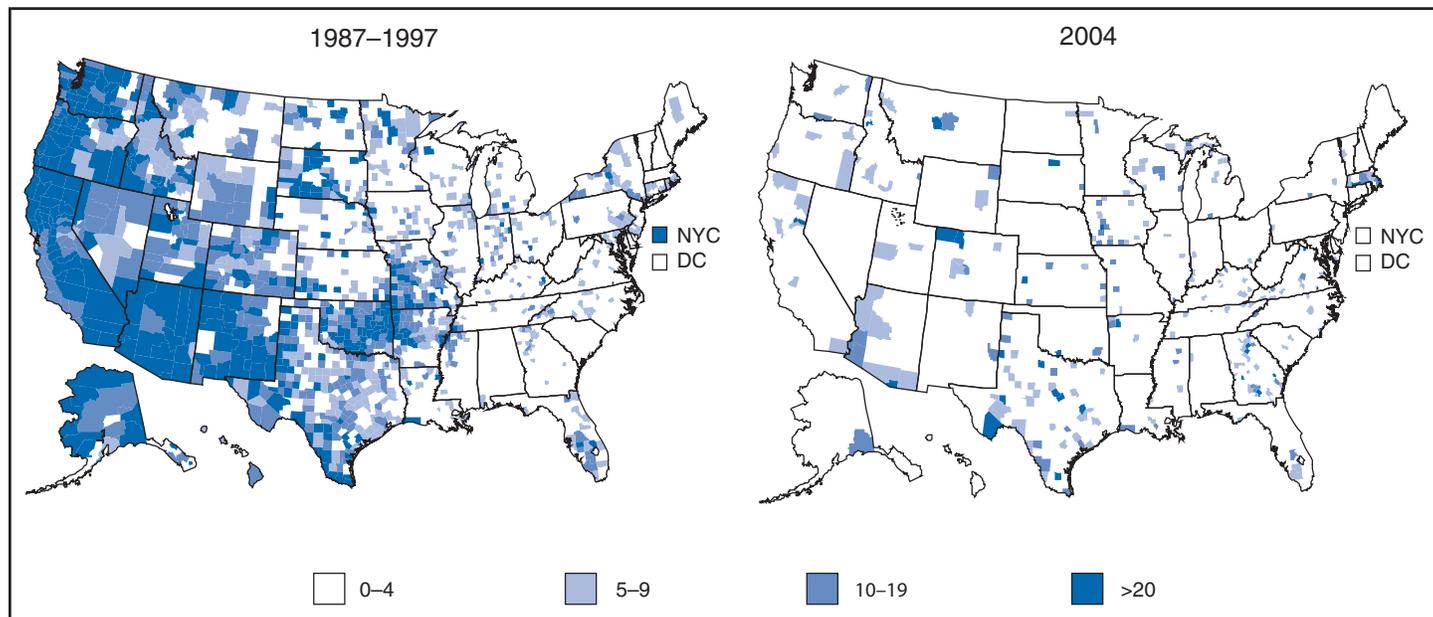
SOURCE: National Notifiable Diseases Surveillance System.
* Per 100,000 population.

New Mexico, Oklahoma, Oregon, South Dakota, Utah, and Washington) with consistently elevated rates, representing 22% of the U.S. population, average annual hepatitis A incidence was ≥ 20 cases per 100,000 during 1987–1997 (twice the national average of approximately 10 cases per 100,000 population); cases among residents of these states accounted for an average of 50% of reported cases (3). An additional 18% of cases occurred among residents of six states (Arkansas, Colorado, Missouri, Montana, Texas, and Wyoming) with average annual rates above (but less than twice) the national average during this time.

Approximately 31% of the U.S. population had serologic evidence of previous HAV infection, when measured in the Third National Health and Nutrition Examination Survey (NHANES-III) conducted during 1988–1994 (50). Anti-HAV prevalence varied directly with age: among persons aged 6–11 years, prevalence was 9%; 20–29 years, 19%; 40–49 years, 33%; and >70 years, 75%. Age-adjusted anti-HAV prevalence was considerably higher among Mexican-American (70%) compared with black (39%) and white (23%) participants, and among foreign-born (69%) compared with U.S.-born (25%) participants.

Sources of Infection. In the prevaccine era, the majority of U.S. cases of hepatitis A resulted from person-to-person transmission of HAV during communitywide outbreaks (31,51). The most frequently reported source of infection (in 12%–26% of cases) was household or sexual contact with a person with hepatitis A (52). Cyclic outbreaks occurred among users

FIGURE 3. Rate* of hepatitis A, by county — United States, 1987–1997 and 2004



SOURCE: National Notifiable Diseases Surveillance System.
* Per 100,000 population.

of injection and noninjection drugs and among men who have sex with men (MSM) (53–57), and up to 15% of nationally reported cases occurred among persons reporting one or more of these behaviors. Other potential sources of infection (e.g., international travel and recognized foodborne outbreaks) were reported among 3%–6% of cases (52). For approximately 50% of persons with hepatitis A, no source was identified for their infection.

Communitywide Epidemics. During communitywide epidemics, infection was transmitted from person to person in households and extended family settings. These epidemics typically spread throughout the community, and no single risk factor or risk group could be identified that accounted for the majority of cases (31). Once initiated, epidemics often persisted for 1–2 years and proved difficult to control (58,59). Because children often have unrecognized or asymptomatic infection, they played a key role in sustaining HAV transmission during these epidemics.

Vaccine Era

With the licensure of inactivated hepatitis A vaccines by the Food and Drug Administration (FDA) during 1995–1996, hepatitis A became a disease that was not only common but also vaccine-preventable. Since 1996, and particularly since ACIP's 1999 recommendations for routine vaccination of children living in areas with consistently elevated hepatitis A rates, national hepatitis A rates have declined sharply (4). The 1999 recommendations called for routine vaccination of children living in states and communities in which the average hepatitis A rate during a baseline period of 1987–1997 was ≥ 20 cases per 100,000 population, approximately twice the national average, and for consideration of hepatitis A vaccination of children in those states and communities in which the average rate during the baseline period was at least the national average (3).

In 2004, a total of 5,683 cases (rate: 1.9 cases per 100,000 population) were reported, representing an estimated 24,000 acute clinical cases when underreporting is taken into account. This rate was the lowest ever recorded and was 79% lower than the previously recorded low in 1992 (5). This decline is reflected in other fundamental shifts in hepatitis A epidemiology.

Variation by Age, Race/Ethnicity, and Region. Beginning in the late 1990s, national age-specific rates declined more rapidly among children than adults; as a result, in recent years, rates have been similar among all age groups (Figure 1) (4). Historic differences in rates among racial/ethnic populations also have narrowed in the vaccine era. For example, recent rates among American Indians and Alaska Natives represent a

99% decline compared with the prevaccine era and are now approximately the same or lower than those of other racial/ethnic populations (49). Rates among Hispanics also declined 87% during this period, from 20.6 cases per 100,000 population during 1990–1997 to 2.7 per 100,000 in 2004, but remain higher than those for non-Hispanics (Figure 2) (4,5). Elimination of historic geographic differences in incidence rates has also occurred, and since 2001, rates in states where vaccination was recommended have been approximately equal to the rest of the United States (5). In recent years, counties with higher rates have varied from year to year and have been distributed throughout the country (Figure 3) (4).

Incidence declined sharply in states with historically consistently elevated rates included in the 1999 ACIP recommendations for routine vaccination of children. As a result, the majority of hepatitis A cases during recent years have been reported from states with historically low rates in which hepatitis A vaccination of children has not been widely implemented (4). In addition, the narrowing or elimination of national differences in age, race/ethnicity, and state-specific rates can be attributed largely to changes that occurred in the states in which routine hepatitis A vaccination of children was recommended and implemented. In 2004, for example, approximately two thirds of the nearly 6,000 cases were reported from states without childhood vaccination recommendations (60). The 2004 rate among all Hispanics in these states remained four times higher than among non-Hispanics and was seven times higher among Hispanic compared with non-Hispanic children. The highest rate in any demographic subgroup occurred among Hispanic children in states for which routine hepatitis A vaccination of children is not recommended (60).

Sources of Infection. In recent years, sexual or household contact with a person with hepatitis A has been reported in a smaller proportion of cases but continued to account for 13% of cases during 2002–2004 (5). The proportion of persons with hepatitis A reporting exposure to child care centers also has declined to approximately 9% (5). The number of international travel-associated cases has remained approximately the same, but as overall incidence has declined, the proportion of cases attributable to this exposure has increased, accounting for an average of 13% of cases during 2002–2004 (5). During this time, >25% of cases among children aged <15 years could be attributed to international travel. Approximately 75% of all travel-related cases were associated with travel to Mexico or to Central or South America (5). Outbreaks among MSM and users of illicit drugs also continue to occur (5,57).

Groups at Increased Risk for Hepatitis A

Travelers

Persons from developed countries who travel to developing countries are at substantial risk for acquiring hepatitis A (61). Such persons include tourists, immigrants and their children returning to their country of origin to visit friends or relatives, military personnel, missionaries, and others who work or study abroad in countries that have high or intermediate endemicity of hepatitis A (Figure 4). Hepatitis A remains one of the most common vaccine-preventable diseases acquired during travel. One study estimated the risk among persons who did not receive IG or vaccine before departure to be four to 30 cases per 100,000 months of stay in developing countries (62). The risk might be higher among travelers staying in areas with poor hygienic conditions, varies according to the region and the length of stay, and appears to be increased even among travelers who reported observing protective measures and staying in urban areas or luxury hotels (CDC, unpublished data, 2005). In the United States, children account for approximately 50% of reported travel-related cases (5). In one study of Hispanic children in San Diego with hepatitis A, two thirds reported international travel (to Mexico) during the incubation period; travel was the only exposure associated with infection in a case-control study (63). Travelers who acquire hepatitis A during their trips also might transmit to others on their return.

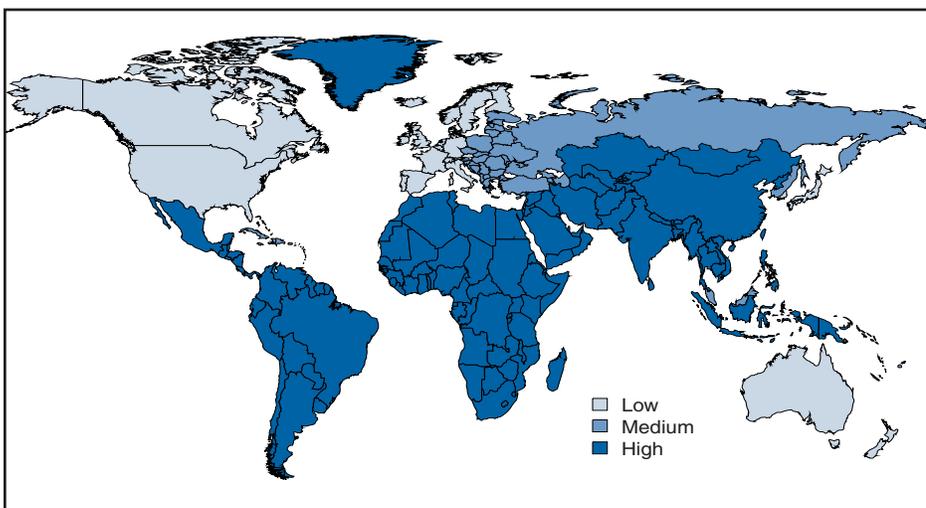
MSM

Hepatitis A outbreaks among MSM have been reported frequently. Cyclic outbreaks have occurred in urban areas in the United States, Canada, Europe, and Australia and can occur in the context of an outbreak in the larger community (28,31,53,64–67). Seroprevalence surveys have not consistently demonstrated an elevated prevalence of anti-HAV compared with a similarly aged general population (68,69). Certain studies have identified specific sex practices associated with illness, whereas others have not demonstrated such associations (53,67,68). Since 1996, ACIP has recommended hepatitis A vaccination of MSM (2). Although precise data are lacking, vaccine coverage appears to be low (53).

Users of Injection and Noninjection Drugs

During the preceding 2 decades, outbreaks have been reported with increasing frequency among users of injection and noninjection drugs in Australia, Europe, and North America (31,54,56,57,70). In the United States, outbreaks have frequently involved users of injected and noninjected methamphetamine, who have accounted for up to 48% of reported cases during outbreaks (57,71). Cross-sectional serologic surveys have demonstrated that injection-drug users have a higher prevalence of anti-HAV than the general U.S. population (68,72). Transmission among injection-drug users probably occurs through both percutaneous and fecal-oral routes (71). Since 1996, ACIP has recommended hepatitis A vaccination of users of illicit drugs, but vaccine coverage data are not available (2).

FIGURE 4. Geographic distribution of hepatitis A endemicity, 2005*



*For multiple countries, estimates of prevalence of antibody to hepatitis A virus (anti-HAV), a marker of previous HAV infection, are based on limited data and might not reflect current prevalence. In addition, anti-HAV prevalence might vary within countries by subpopulation and locality. As used on this map, the terms “high,” “medium,” and “low” endemicity reflect available evidence of how widespread infection is within each country rather than precise quantitative assessments.

Persons with Clotting-Factor Disorders

During 1992–1993, outbreaks of hepatitis A were reported in Europe among persons with clotting-factor disorders who had been administered solvent-detergent-treated, “high-purity” factor VIII concentrates that presumably had been contaminated from plasma donors incubating hepatitis A (73). In the United States, data from one serologic study suggested that persons with hemophilia might be at increased risk for HAV infection (74). HAV is resistant to solvent-detergent treatment, and during 1995–1996, one study identified six patients with clotting-factor disorders who had hepatitis A after having been administered solvent-detergent-treated factor VIII

and factor IX concentrates (43). However, changes in viral inactivation procedures, high hepatitis A vaccine coverage, and improved donor screening have decreased the risk for HAV transmission from clotting factors. During May 1998–July 2002, no new cases of HAV infection attributed to blood products were identified in an analysis of serosurveillance data from 140 participating hemophilia treatment centers (75).

Persons Working with Nonhuman Primates

Outbreaks of hepatitis A have been reported among persons working with nonhuman primates that are susceptible to HAV infection, including Old and New World species (76,77). Primates that were infected were those that had been born in the wild, not those born and raised in captivity.

Risk for Severe Adverse Consequences of Hepatitis A Among Persons with Chronic Liver Disease

Although not at increased risk for HAV infection, persons with chronic liver disease are at increased risk for fulminant hepatitis A (12,14,15). Death certificate data indicate a higher prevalence of chronic liver disease among persons who died of fulminant hepatitis A compared with persons who died of other causes (10).

Risk for Hepatitis A in Other Groups and Settings

Food-Service Establishments and Food Handlers

Foodborne hepatitis A outbreaks are recognized relatively infrequently in the United States. Outbreaks typically are associated with contamination of food during preparation by an HAV-infected food handler; a single infected food handler can transmit HAV to dozens or even hundreds of persons (34,36,37,78–81). However, the majority of food handlers with hepatitis A do not transmit HAV. Food handlers are not at increased risk for hepatitis A because of their occupation. However, among the approximately 40,000 adults with hepatitis A reported during 1992–2000 for whom an occupation was known, 8% were identified as food handlers, reflecting the large number of persons employed in the food service industry (34). Evaluating HAV-infected food handlers is a common and labor-intensive task for public health departments. In a 1992 common-source outbreak involving 43 persons, the estimated total medical and disease control cost was approximately \$800,000 (82).

Outbreaks associated with food, especially green onions and other raw produce, that has been contaminated before reaching a food-service establishment have been recognized increasingly in recent years (29,30,83–88). Low attack rates are common, and outbreaks often have been recognized in association with a single restaurant in which no infected food handler was identified on subsequent investigation (29,83,88).

Child Care Centers

Outbreaks among children attending child care centers and persons employed at these centers have been recognized since the 1970s, but their frequency has decreased as overall hepatitis A incidence among children has declined in recent years (5,7,89). Because infection among children is typically mild or asymptomatic, outbreaks often are identified only when adult contacts (typically parents) become ill (7,90). Poor hygiene among children who wear diapers and the handling and changing of diapers by staff contribute to the spread of HAV infection; outbreaks rarely occur in child care centers in which care is provided only to children who are toilet trained.

Although child care centers might have been the source of outbreaks of hepatitis A in certain communities, disease in child care centers more commonly reflects extended transmission from the community. Despite the occurrence of outbreaks when HAV is introduced into child care centers, results of serologic surveys do not indicate a substantially increased prevalence of HAV infection among staff at child care centers compared with prevalence among control populations (91).

Health-Care Institutions

Nosocomial HAV transmission is rare. Outbreaks have occasionally been observed in neonatal intensive-care units because of infants acquiring infection from transfused blood and subsequently transmitting hepatitis A to other infants and staff (18,92,93). Outbreaks of hepatitis A caused by transmission from adult patients to health-care workers are typically associated with fecal incontinence, although the majority of hospitalized patients who have hepatitis A are admitted after onset of jaundice, when they are beyond the point of peak infectivity (94,95). Data from serologic surveys of health-care workers have not indicated an increased prevalence of HAV infection in these groups compared with that in control populations (96).

Institutions for Persons with Developmental Disabilities

Historically, HAV infection was highly endemic in institutions for persons with developmental disabilities (97). As fewer children have been institutionalized and as conditions in institutions have improved, the incidence and prevalence of HAV infection have decreased, although outbreaks can occur in these settings.

Schools

In the United States, the occurrence of cases of hepatitis A in elementary or secondary schools typically reflects disease acquisition in the community. Child-to-child disease transmission in the school setting is uncommon; if multiple cases occur among children at a school, the possibility of a common source of infection should be investigated (30,84).

Workers Exposed to Sewage

Data from serologic studies conducted outside the United States indicate that workers who had been exposed to sewage had a possible elevated risk for HAV infection; however, these analyses did not control for other risk factors (e.g., socioeconomic status) (98–100). In published reports of three serologic surveys conducted among U.S. wastewater workers and appropriate comparison populations, no substantial or consistent increase in the prevalence of anti-HAV was identified among wastewater workers (101–103). No work-related instances of HAV transmission have been reported among wastewater workers in the United States.

Strategy to Prevent and Control Hepatitis A Through Vaccination

With the availability of hepatitis A vaccines beginning in 1995, hepatitis A became a disease that was not only common but also vaccine-preventable (104). Use of these highly effective vaccines provided the opportunity to protect persons from infection, reduce disease incidence by preventing transmission, and ultimately eliminate indigenous HAV transmission.

Soon after hepatitis A vaccines became available in the United States, a strategy of routine vaccination of children was recognized to have the potential to achieve a sustained reduction in the overall incidence of hepatitis A by preventing infection among persons in age groups that accounted for at least one third of cases and eliminating a major source of infection for others. However, hepatitis A vaccines could not be readily incorporated into the routine infant and early childhood schedule because they were not licensed for children aged <2 years. To overcome these logistical barriers to use of hepatitis A vaccines among children, a novel vaccination strategy was developed on the basis of distinct features of hepatitis A epidemiology and experience gathered from demonstration projects and other research and involving incremental implementation of routine childhood hepatitis A vaccination.

Initial recommendations primarily involved vaccination of persons in populations at increased risk for hepatitis A and, as the first step in the incremental strategy, of children living in

communities with the highest disease rates (2). Vaccination of persons in groups at increased risk for hepatitis A (e.g., travelers) or its adverse outcomes (e.g., persons with chronic liver disease) provided protection to these persons but had little effect on national disease rates because the majority of cases did not occur among persons in these groups. Although routine vaccination of children living in communities with the highest rates of disease was effective in reducing disease rates in these communities, the impact on national disease incidence was limited because the majority of nationally reported cases occurred outside these communities.

A further step in the incremental implementation of routine vaccination of children was possible because areas with consistently elevated hepatitis A rates could be identified that contributed the majority of cases to the national disease burden (3). To date, the 1999 ACIP recommendations for routine vaccination of children living in these areas with consistently elevated rates have been implemented primarily by voluntary measures. The 2004 National Immunization Survey among children aged 24–35 months indicated first-dose coverage of approximately 54% in states for which vaccination is recommended, 27% in states for which it is to be considered, and 2% in the rest of the country (CDC, unpublished data, 2005). Although limited information on trends is available, these coverage estimates represent increases of 2%–3% compared with the previous year (105). Coincident with implementation of these recommendations, national disease incidence has declined to historic lows, with the largest declines occurring in the age groups and parts of the country for which vaccination is recommended (4). The majority of disease (and the highest incidence) occurs in areas for which hepatitis A vaccination of children has not been recommended previously. Examination of historical incidence trends in these areas and theoretic models of incidence dynamics after introduction of a new vaccine suggest that incidence might increase again, although to what level is unknown (106).

A decade has passed since hepatitis A vaccines first became available in the United States. Multiple considerations make this an appropriate time to implement the final step in the incremental strategy, thereby bringing hepatitis A vaccination policy into line with that of other routinely recommended childhood vaccines. First, hepatitis A vaccine became available for children aged 12–23 months in 2005, allowing for its incorporation into the routine early childhood vaccination schedule. Second, as disease rates equalize across regions of the United States, questions remain regarding the validity and ultimate sustainability of the interim limited strategy. Continuation of this policy in light of current hepatitis A epidemiology means that vaccination of children is not presently recommended for the areas with the highest overall and age-

specific disease incidence. Nationwide hepatitis A vaccination of children is likely to result in further narrowing of current demographic disparities and in lower overall rates. Ultimately, elimination of indigenous HAV transmission in the United States is an attainable goal.

Prophylaxis Against Hepatitis A Virus Infection

Immune Globulin

IG is a sterile preparation of concentrated antibodies (immunoglobulins) made from pooled human plasma processed by cold ethanol fractionation (107). In the United States, only plasma that has tested negative for hepatitis B surface antigen (HBsAg), antibody to human immunodeficiency virus (HIV), and antibody to hepatitis C virus (HCV) is used to produce IG. In addition, FDA requires that the process used to produce IG include a viral inactivation step or that final products test negative for HCV RNA by PCR. Anti-HAV concentrations differ among IG lots, and slightly lower concentrations have been observed over the preceding 30 years, probably because of the decreasing prevalence of previous HAV infection among plasma donors (108). However, no clinical or epidemiologic evidence of decreased protection has been observed.

IG provides protection against hepatitis A through passive transfer of antibody. Both IG administered intramuscularly (IM) and IG for intravenous administration (IGIV) contain anti-HAV, but IG administered intramuscularly is the product used for the prevention of HAV infection. No transmission of hepatitis B virus (HBV), HIV, HCV, or other viruses has been reported from intramuscular IG (109,110). The concentrations of IgG anti-HAV achieved after administration of IG intramuscularly are below the level of detection of the majority of commercially available diagnostic tests (111). When administered for preexposure prophylaxis, 1 dose of 0.02 mL/kg IM confers protection for <3 months, and 1 dose of 0.06 mL/kg IM confers protection for 3–5 months (Table 1). When administered within 2 weeks after an exposure to HAV (0.02 mL/kg IM), IG is 80%–90% effective in preventing hepatitis A. Efficacy is greatest when IG is administered early in the incubation period; when administered later in the incubation period, IG might only attenuate the clinical expression of HAV infection (112).

IG is available in single-use (2 mL) and multidose (10 mL) vials. Preparations are formulated without a preservative. For administration of IG, an appropriate muscle mass (i.e., the deltoid or gluteal muscle) should be chosen into which a substantial volume can be injected, using a needle length appro-

TABLE 1. Recommended doses of immune globulin (IG) for hepatitis A preexposure and postexposure prophylaxis

Setting	Duration of coverage	Dose (mL/kg)*
Preexposure	Short-term (1–2 mos)	0.02
	Long-term (3–5 mos)	0.06†
Postexposure		0.02

* IG should be administered by intramuscular injection into either the deltoid or gluteal muscle. For children aged <24 months, IG can be administered in the anterolateral thigh muscle.

† Repeat every 5 months if continued exposure to hepatitis A virus occurs.

priate for the person's age and size. If a gluteal muscle is used, the central region of the buttock should be avoided; only the upper outer quadrant should be used, and the needle should be directed anteriorly to minimize the possibility of injury to the sciatic nerve (113).

Serious adverse events from IG are rare. Anaphylaxis has been reported after repeated administration to persons with known immunoglobulin A (IgA) deficiency; thus, IG should not be administered to these persons (114). Pregnancy or lactation is not a contraindication to IG administration.

IG does not interfere with the immune response to oral poliovirus vaccine or yellow fever vaccine, or, in general, to inactivated vaccines. However, IG can interfere with the response to other live, attenuated vaccines (e.g., measles, mumps, and rubella [MMR] vaccine and varicella vaccine) when administered either as individual or combination vaccines. Administration of MMR should be delayed for >3 months and varicella vaccine for >5 months after administration of IG for hepatitis A prophylaxis. IG should not be administered <2 weeks after administration of MMR or <3 weeks after varicella vaccine unless the benefits of IG administration exceed the benefits of vaccination (113,115). If IG is administered <2 weeks after administration of MMR or <3 weeks after administration of varicella vaccine, the person should be revaccinated, but not sooner than 3 months after IG administration for MMR or 5 months for varicella vaccine (113).

Hepatitis A Vaccine

Inactivated and attenuated hepatitis A vaccines have been developed and evaluated in human clinical trials and in non-human primate models of HAV infection (116); however, only vaccines made from inactivated HAV have been evaluated for efficacy in controlled clinical trials (117–119). The vaccines containing HAV antigen that are currently licensed in the United States are the single-antigen vaccines HAVRIX® (manufactured by GlaxoSmithKline, Rixensart, Belgium) and VAQTA® (manufactured by Merck & Co., Inc., Whitehouse Station, New Jersey) and the combination vaccine TWINRIX® (containing both HAV and HBV antigens; manufactured by GlaxoSmithKline). All are inactivated vaccines.

Preparation

Inactivated hepatitis A vaccines are prepared by methods similar to those used for inactivated poliovirus vaccine (120,121). Cell-culture–adapted virus is propagated in human fibroblasts, purified from cell lysates by ultrafiltration and exclusion gel chromatography or other methods, formalin inactivated, and adsorbed to an aluminum hydroxide adjuvant; 2-phenoxyethanol is used as a preservative for HAVRIX and TWINRIX, and VAQTA is formulated without a preservative. For HAVRIX and TWINRIX, the antigen content of the final aqueous preparation is determined by reactivity in a quantitative immunoassay for HAV antigen, and final vaccine potency (per dose) is expressed as enzyme-linked immunosorbent assay (ELISA) units (EL.U.). For VAQTA, the antigen content is expressed as units (U) of HAV antigen.

Vaccine Storage and Shipment

Hepatitis A vaccine should be stored and shipped at temperatures ranging from 35.6°F–46.4°F (2°C–8°C) and should not be frozen. However, the reactogenicity and immunogenicity of HAVRIX after storage at 98.6°F (37°C) for 1 week and the stability profile of VAQTA when stored at this temperature for >12 months do not differ from those of vaccines stored at the recommended temperature (122; Merck & Co., Inc., unpublished data, 1996).

Route of Administration, Vaccination Schedule, and Dosage

The vaccine should be administered intramuscularly into the deltoid muscle. A needle length appropriate for the person's age and size should be used (113).

VAQTA is licensed in two formulations, which differ according to the person's age. Persons aged 12 months–18 years should receive 25 U per dose in a 2-dose schedule; persons aged >18 years should receive 50 U per dose in a 2-dose schedule (Table 2).

HAVRIX is available in two formulations, which differ according to the person's age: for persons aged 12 months–18 years, 720 EL.U. per dose in a 2-dose schedule; and for persons aged >18 years, 1,440 EL.U. per dose in a 2-dose schedule (Table 3). A pediatric formulation of 360 EL.U. per dose administered in a 3-dose schedule is no longer available.

TWINRIX is licensed for use in persons aged ≥18 years. TWINRIX is a combined hepatitis A and hepatitis B vaccine containing 720 EL.U. of hepatitis A antigen (half of the HAVRIX adult dose) and 20 mcg of recombinant hepatitis B surface antigen protein (the same as the ENGERIX-B adult dose) (Table 4). Primary immunization consists of 3 doses, administered on a 0-, 1-, and 6-month schedule, the same schedule as that commonly used for single-antigen hepatitis

TABLE 2. Licensed dosages of VAQTA®*

Vaccine recipient's age	Dose (U) [†]	Vol. (mL)	No. doses	Schedule (mos) [§]
12 mos–18 yrs	25	0.5	2	0, 6–18
≥19 yrs	50	1.0	2	0, 6–18

* Hepatitis A vaccine, inactivated, Merck & Co., Inc. (Whitehouse Station, New Jersey).

[†] Units.

[§] 0 months represents timing of initial dose; subsequent numbers represent months after the initial dose.

TABLE 3. Licensed dosages of HAVRIX®*

Vaccine recipient's age	Dose (EL.U.) [†]	Vol. (mL)	No. doses	Schedule (mos) [§]
12 mos–18 yrs	720	0.5	2	0, 6–12
≥19 yrs	1,440	1.0	2	0, 6–12

* Hepatitis A vaccine, inactivated, GlaxoSmithKline (Rixensart, Belgium).

[†] Enzyme-linked immunosorbent assay units.

[§] 0 months represents timing of initial dose; subsequent numbers represent months after the initial dose.

TABLE 4. Licensed dosages of TWINRIX®*

Vaccine recipient's age	Dose (hepatitis A/ hepatitis B)	Vol. (mL)	No. doses	Schedule (mos) [†]
≥18 yrs	720 EL.U./20 µg	1.0	3	0, 1, 6

* Combined hepatitis A and hepatitis B vaccine, GlaxoSmithKline (Rixensart, Belgium).

[†] 0 months represents timing of initial dose; subsequent numbers represent months after the initial dose.

[§] Enzyme-linked immunosorbent assay units.

B vaccine. TWINRIX contains aluminum phosphate and aluminum hydroxide as adjuvant and 2-phenoxyethanol as a preservative. After 3 doses of TWINRIX, antibody responses to both antigens are equivalent to responses seen after the single-antigen vaccines are administered separately on standard schedules (123,124).

Vaccine Performance

Detection of Anti-HAV After Vaccination. Concentrations of antibody achieved after passive transfer by IG or active induction by vaccination are 10- to 100-fold lower than those produced after natural infection and can be below the level of detection of certain commercially available diagnostic assays (111). To measure lower levels of antibody, more sensitive immunoassays were developed for immunogenicity studies that correlate more closely with neutralizing antibody assays (111). Anti-HAV concentrations are measured in comparison with a World Health Organization reference immunoglobulin reagent and are expressed as milli-International Units per milliliter (mIU/mL). The lower limits of detection have typically been approximately 100 mIU/mL by unmodified commercially available assays and 10 mIU/mL by more sensitive assays. A positive anti-HAV result by a standard assay indicates protection. However, after vaccination, persons who are anti-HAV negative by

standard assays might nevertheless have protective levels of antibody.

The absolute lower limit of anti-HAV required to prevent HAV infection has not been defined. In vitro studies using cell-culture-derived virus indicate that low levels of antibody (e.g., <20 mIU/mL) can be neutralizing (125). Clinical studies have yielded limited data from which a minimum protective antibody level can be derived because vaccine-induced levels of antibody have been high and few infections have been detected among vaccinated persons. Experimental studies in chimpanzees indicate that low levels of passively transferred antibody (<10 mIU/mL) obtained from immunized persons do not protect against infection but do prevent clinical hepatitis and virus shedding (126). To define a protective antibody response, clinical studies conducted with HAVRIX have used levels >20 mIU/mL, or >33 mIU/mL in more recent studies, as measured with modified enzyme immunoassays, and studies conducted with VAQTA have used levels >10 mIU/mL as measured with a modified radioimmunoassay (127,128).

Immunogenicity in Adults. All licensed vaccines are highly immunogenic in persons aged ≥ 18 years when administered according to the recommended schedules (128–130). Protective antibody levels were identified in 94%–100% of adults 1 month after the first dose. After the second dose, all persons had protective levels of antibody, with high geometric mean antibody concentrations (GMCs).

Limited data are available regarding the timing of the appearance of neutralizing antibody. Among a sample of vaccinated persons, 54%–62% were positive for neutralizing antibody 14 days after the first dose, and 94%–100% were positive at 1 month (128; GlaxoSmithKline, unpublished data, 1994).

Immunogenicity in Children and Adolescents. Both vaccines are highly immunogenic when administered to children and adolescents according to multiple schedules; 97%–100% of persons aged 2–18 years had protective levels of antibody 1 month after receiving the first dose, and 100% had protective levels 1 month after the second dose, with high GMCs (128–133). Children with Down syndrome responded to vaccination as well as other children and had similar levels of protective antibody (134).

Immunogenicity in Infants. Available data indicate that inactivated hepatitis A vaccines are immunogenic in children aged <2 years who do not have passively acquired maternal antibody. All such infants administered hepatitis A vaccine subsequently had protective antibody levels, with the final GMCs varying depending on the dosage and schedule (135–139). Infants with passively acquired maternal antibody had reduced GMCs after vaccination (see Factors Associated with Reduced Immunogenicity) (135,136).

IgM Anti-HAV After Vaccination. Hepatitis A vaccination can induce IgM anti-HAV that is detectable by standard assays, particularly if the test is conducted soon after vaccination. IgM anti-HAV has been detected 2–3 weeks after administration of one dose of vaccine in 8%–20% of adults (140; CDC, unpublished data, 1995).

Efficacy. The efficacy of HAVRIX was evaluated in a double-blind, controlled, randomized clinical trial conducted in Thailand among approximately 40,000 children aged 1–16 years living in villages that had high rates of hepatitis A (117). After 2 doses of vaccine (360 EL.U. per dose) administered 1 month apart, the efficacy of vaccine in protecting against clinical hepatitis A was 94% (95% confidence interval [CI] = 79%–99%). A double-blind, placebo-controlled, randomized clinical trial using VAQTA was conducted among approximately 1,000 children aged 2–16 years living in a New York community that had a high rate of hepatitis A (118). The protective efficacy against clinical hepatitis A was 100% (lower bound of the 95% CI = 87%) after administration of 1 dose (25 U) of vaccine.

Efficacy After Exposure. Studies of chimpanzees indicate that hepatitis A vaccine can prevent HAV infection if administered shortly after exposure (141). Because the incubation period of hepatitis A can be 50 days, the fact that during a clinical efficacy trial, no cases of hepatitis A occurred in vaccine recipients beginning 17 days after vaccination also suggests a possible postexposure effect (118,142). In a limited randomized trial, investigators determined that hepatitis A vaccine was 79% efficacious in preventing IgM anti-HAV positivity after household exposure to hepatitis A compared with no treatment. However, the CI was extremely wide (7%–95%), and investigators did not assess the efficacy of the vaccine compared with IG (143). Results of an appropriately designed clinical trial comparing the postexposure efficacy of vaccine with that of IG are needed to determine if hepatitis A vaccine without IG can be recommended to prevent hepatitis A after exposure (144).

Effectiveness in Populations. The effectiveness of hepatitis A vaccine in populations has been studied in demonstration projects and by analysis of surveillance and vaccine coverage data. The earliest such studies focused on communities with the historically highest hepatitis A rates, such as Alaska Native and American Indian communities. Demonstration projects conducted soon after hepatitis A vaccines became available indicated that routine vaccination of children living in these communities was feasible and that when relatively high vaccination coverage was achieved and sustained, ongoing epidemics were interrupted and a reduction in disease incidence was sustained (145–147). For example, a 1992–1993 communitywide epidemic among Alaska Natives in one rural area ended within 4–8 weeks of vaccinating

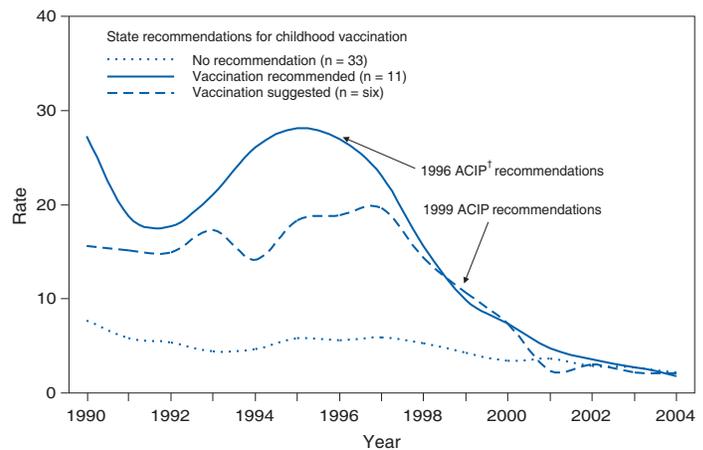
approximately 80% of children and young adults (146). After publication in 1996 of ACIP recommendations for routine vaccination of children in these areas, surveys indicated that vaccine coverage among preschool- and school-aged American Indian and Alaska Native children was 50%–80%, suggesting that recommendations were being implemented (2,49). By 2000, hepatitis A incidence among American Indians and Alaska Natives had declined 97% compared with the beginning of the decade and was lower than the overall U.S. rate (49). These low rates have been sustained in subsequent years; the 2004 rate of 0.1 case per 100,000 population among American Indian and Alaska Natives was the lowest of any racial/ethnic population (5).

Results of a demonstration project in Butte County, California, provided evidence that considerable reductions in overall incidence also could be achieved in populations with consistently elevated hepatitis A rates with a program of ongoing routine vaccination of children that achieved fairly modest coverage (148). During the 6-year project, 66% of the approximately 45,000 eligible children aged ≥ 2 years received ≥ 1 dose of hepatitis A vaccine. The number of reported cases declined 94%, and the four cases reported in 2000 during the last year of the project was the lowest number ever reported in the county since hepatitis surveillance began in 1966.

The most comprehensive indication of the performance of hepatitis A vaccines in populations is derived from analysis of trends in hepatitis A incidence after publication of ACIP's 1999 recommendations for routine vaccination of children living in 17 states with consistently elevated hepatitis A rates. The 2003 rate (2.5 cases per 100,000 population) in these states represented a decline of approximately 88% compared with the average rate (21.1 cases per 100,000 population) during the baseline prevaccine period on which the recommendations were based (4). Rates among regions with and without statewide recommendations for routine vaccination of children are now approximately equal (Figure 5). Compared with 1990–1997, rates declined most dramatically among children aged 2–18 years, and the proportion of cases among children declined from 35% to 19%. Because hepatitis A incidence has been cyclic in the United States, the precise contribution of vaccination of children to the observed decline in rates has been difficult to quantify. Modeling studies suggested that during 1995–2001, an estimated 97,800 hepatitis A cases were averted because of the direct effects of immunization and herd immunity, including 39% of potential cases in 2001 (149).

Available information concerning vaccine use indicates that the observed declines in rates among children appear to have been achieved with modest levels of vaccine coverage, suggesting a strong herd immunity effect (105,150). Declines in rates among adults also suggest that vaccination of children

FIGURE 5. Rate* of hepatitis A, by region, recommendation for childhood vaccination, and year — 1990–2004



SOURCE: National Notifiable Diseases Surveillance System.

* Per 100,000 population.

† Advisory Committee on Immunization Practices.

might have reduced transmission in other age groups through herd immunity. Similar findings have been reported from other countries (e.g., Israel and parts of Spain) in which routine hepatitis A vaccination of infants or children has been implemented (151,152). Results of modeling the relationship between hepatitis A incidence and vaccine coverage have also indicated a strong herd immunity effect, accounting for more than one third of the estimated number of cases prevented by vaccination (149).

Interest has been expressed regarding use of hepatitis A vaccine to interrupt ongoing communitywide epidemics by vaccinating children in these populations, but the strategy has proved difficult to implement. Typically, first-dose coverage was low (20%–45%), and the impact of vaccination always was limited to vaccinated age groups that did not represent the majority of cases (59). Efforts are probably better directed towards sustained routine vaccination of children to maintain high levels of immunity and prevent future epidemics.

Long-Term Protection. All 31 adults who received 3 doses of HAVRIX (720 EL.U. per dose at 0-, 1-, and 6-month intervals) had anti-HAV levels >15 mIU/mL 12 years after the initial dose (153). Ten years after vaccination, all 307 adults administered 2 doses of 1,440 EL.U. of HAVRIX had anti-HAV levels >20 mIU/mL (154). Protective levels of anti-HAV were still observed in 544 (99%) of 549 children evaluated 5–6 years after receiving VAQTA (155). A recent review concluded that estimates of antibody persistence derived from kinetic models of antibody decline indicate that protective levels of anti-HAV could be present for ≥ 25 years in adults and ≥ 14 –20 years in children (156). Whether other mecha-

nisms (e.g., cellular memory) also contribute to long-term protection is unknown. Surveillance data and population-based studies are being used to monitor the long-term protective efficacy of hepatitis A vaccine and to determine the possible need for a booster dose. In the longest such follow-up study reported to date, no cases of hepatitis A have been detected among children studied for 9 years after vaccination (157).

Vaccination Schedules. Results of multiple studies indicate that, among adults administered hepatitis A vaccine according to a schedule that mixed the two currently licensed vaccines, the proportion that subsequently had protective antibody levels did not differ from that of adults vaccinated according to the licensed schedules, and final GMCs were high (158,159). Although using the vaccines according to the licensed schedule is preferable, on the basis of the similar immunogenicity of both vaccines in adults and children, these data indicate that the two brands of hepatitis A vaccine can be considered interchangeable.

Limited data are available regarding response to a delayed second vaccine dose. In one study, 85 (97%) of 88 persons aged >18 years who had received 1 dose of VAQTA (50 U) had anti-HAV levels >10 mIU/mL 18 months later. None reported a history of hepatitis A, and all responded to a second dose. Final GMCs were not different compared with persons vaccinated according to a 0-, 6-month schedule (160). In another study, 132 (84%) of 156 persons aged 1 month–64 years who had responded to 1 dose of HAVRIX (720 EL.U. for children aged ≤18 years; 1,440 EL.U. for adults) had anti-HAV levels >20 mIU/mL a mean of 27 months later. None of these persons reported a history of hepatitis A. All but one of these persons responded to a second dose, with a substantial rise in antibody levels (161). In a third study, 18 (72%) of 25 adults who had received 1 dose of HAVRIX 4–8 years previously had anti-HAV levels >10 mIU/mL, and all 25 responded to a second dose of vaccine with a substantial increase in anti-HAV levels (162).

Factors Associated with Reduced Immunogenicity. The presence of passively acquired anti-HAV at the time of vaccination appears to diminish the immune response. Administration of IG concurrently with the first dose of hepatitis A vaccine did not decrease the proportion of adults who subsequently had protective levels of antibody compared with adults who had been administered hepatitis A vaccine alone, but GMCs of adults who received IG were substantially lower 1 month after completion of the vaccine series than GMCs of adults who had been administered hepatitis A vaccine alone (163,164). However, their antibody levels were >100-fold higher than levels considered to be protective, suggesting that the reduced immunogenicity of hepatitis A vaccine that occurs with concurrent administration of IG is not clinically

significant in the short term. The effect of reduced GMCs on long-term protection is unknown.

Reduced vaccine immunogenicity also has been observed in infants who had passively acquired antibody because of previous maternal HAV infection and were administered hepatitis A vaccine according to a number of different schedules (135–137). In the majority of studies, all infants subsequently had protective levels of antibody, but the final GMCs were approximately one third to one tenth those of infants born to anti-HAV–negative mothers and vaccinated according to the same schedule. Infants with passively acquired antibody who receive hepatitis A vaccine had substantially lower concentrations of anti-HAV 6 years later compared with vaccinated infants with no passively acquired antibody (165). Despite lower antibody levels after the primary series, the majority of infants with passively acquired antibody had an anamnestic response to a booster dose 1–6 years later (136,165,166). Passively acquired antibody declines to undetectable levels in the majority of infants by age 1 year (167,168). Hepatitis A vaccine is highly immunogenic for children who begin vaccination at age ≥1 year, regardless of maternal anti-HAV status (136,168).

Hepatitis A vaccine using a standard dose and schedule is immunogenic for children and adults with HIV infection. Those with higher CD4 counts (>300 cells/mm³) respond nearly as well as persons who are not immunocompromised, but adults with lower CD4 counts are less likely to acquire protective levels of antibody. Protective levels of antibody developed after vaccination in 61%–87% of HIV-infected adults (169–171) and in 100% of 32 HIV-infected children (172). Lower CD4 cell count at the time of vaccination, but not the CD4 cell count nadir, was associated with lack of response, suggesting that immunologic reconstitution with highly active antiretroviral therapy might restore the ability to respond to vaccination (173).

Vaccination of children or adults with chronic liver disease of viral or nonviral etiology produced seroprotection rates similar to those observed in healthy adults. However, final antibody levels were substantially lower for each group of chronic liver disease patients than for healthy adults (174–179). Immunogenicity in liver transplant recipients has varied among studies. In one study, none of the eight patients who had received a liver transplant responded to hepatitis A vaccination; in another study, only six (26%) of 23 liver transplant recipients responded (176,179). However, hepatitis A vaccine was immunogenic for liver transplant patients in another study, with 38 (97%) responding to a standard dose and schedule (180). Only 28 (72%) of 39 kidney transplant recipients in this study subsequently had protective levels of antibody. A follow-up study indicated that antibody levels might decline more rapidly for

both liver and kidney transplant recipients compared with typical rates of decline for healthy patients (181).

Limited data indicate that age might reduce the immunogenicity of hepatitis A vaccine. In certain studies, the proportion of persons aged ≥ 40 years who had protective antibody levels was similar to that of persons aged < 40 years, but final antibody levels were lower in the older age group (130, 182–184). Additional factors associated with decreased immunogenicity to other vaccines (e.g., smoking and obesity) have not been evaluated for the currently licensed formulations of hepatitis A vaccine. No data are available pertaining to response rates to revaccination among persons who do not respond to the primary vaccine series.

Simultaneous Administration with Other Vaccines. Limited data from studies conducted among adults indicate that simultaneous administration of hepatitis A vaccine with diphtheria, poliovirus (oral and inactivated), tetanus, typhoid (both oral and IM), cholera, Japanese encephalitis, rabies, or yellow fever vaccines does not decrease the immune response to either vaccine or increase the frequency of reported adverse events (185–187). Studies indicating that hepatitis B vaccine can be administered simultaneously with hepatitis A vaccine without affecting either vaccine's immunogenicity or increasing the frequency of adverse events led to the licensure of TWINRIX (188). Studies conducted among infants and young children aged ≤ 18 months have demonstrated that simultaneous administration of hepatitis A vaccine with diphtheria-tetanus-acellular pertussis (DTaP), *Haemophilus influenzae* type b (Hib), hepatitis B, MMR, or inactivated poliovirus vaccines does not affect the immunogenicity and reactogenicity of these vaccines (136, 189–192).

Side Effects and Adverse Events

Data on adverse events are derived from prelicensure clinical studies worldwide, reports following licensure of HAVRIX in Europe and Asia, other postlicensure studies, and reports to the national Vaccine Adverse Events Reporting System (VAERS) following licensure of HAVRIX and VAQTA in the United States.

Local Reactions

Approximately 50,000 persons were administered HAVRIX in prelicensure clinical studies (190). No serious adverse events were attributed definitively to hepatitis A vaccine. Among adults, the most frequently reported side effects occurring < 3 days after the 1,440-EL.U. dose were soreness at the injection site (56%), headache (14%), and malaise (7%). In clinical studies among children, the most frequently reported side

effects were soreness at the injection site (15%), feeding problems (8%), headache (4%), and injection-site induration (4%). The frequency of side effects after administration of TWINRIX was similar to those reported when the two single-antigen vaccines were administered (123, 124, 191).

Approximately 10,000 persons were administered VAQTA in prelicensure clinical studies, and no serious adverse events were reported among participants (192). Among adults, the most frequent side effects that occurred < 5 days after vaccination included tenderness (53%), pain (51%), and warmth (17%) at the injection site and headache (16%). Among children, the most common side effects reported were pain (19%), tenderness (17%), and warmth (9%) at the injection site. In one placebo-controlled trial among children, adverse reactions among vaccine recipients did not differ substantially from those that occurred among persons who received placebo (118).

Serious Adverse Events

An estimated 1.3 million persons in Europe and Asia were vaccinated with HAVRIX before the vaccine's licensure in the United States in 1995. Reports of serious adverse events, without regard to causality, received by the vaccine manufacturer included anaphylaxis, Guillain-Barré syndrome, brachial plexus neuropathy, transverse myelitis, multiple sclerosis, encephalopathy, and erythema multiforme (SmithKline Beecham Biologicals, unpublished data, 1995). The majority of these events occurred among adults, and approximately one third occurred among persons receiving other vaccines concurrently. For serious adverse events for which background incidence data can be estimated (e.g., Guillain-Barré syndrome and brachial plexus neuropathy), rates for vaccine recipients were not higher than would be expected for an unvaccinated population (CDC, unpublished data, 1995).

No serious adverse events were reported for approximately 40,000 children who were administered the 360-EL.U. dose of HAVRIX in the protective efficacy study (117). In a postlicensure study of 11,417 children and 25,023 adults who were administered VAQTA, no serious adverse events occurred that were considered to be associated with administration of vaccine (Merck & Co., Inc., unpublished data, 2005). A published postlicensure evaluation of safety among 2,000 child and adult recipients identified no serious adverse events associated with VAQTA (193).

Since vaccine licensure in 1995, approximately 188 million doses of hepatitis A vaccine have been sold worldwide, including 50 million doses in the United States (GlaxoSmithKline, unpublished data, 2005; Merck & Co., Inc., unpublished data, 2005). During January 1995–October 2005, VAERS received 6,136 reports of adverse events among persons who received

hepatitis A vaccine, with or without other vaccines (FDA, unpublished data, 2005). The most common events were fever, injection-site reactions, rash, and headache. The 871 reports of serious adverse events included reports of Guillain-Barré syndrome, transaminitis, and idiopathic thrombocytopenic purpura, which had been described previously in a published safety review, and seizures among children (194). The relation, if any, between the vaccine and reported serious events was not clear. In the original safety review, reported adverse events were similar for VAQTA and HAVRIX (194). The safety of the vaccine will continue to be assessed through ongoing monitoring of data from VAERS and other surveillance systems.

Any adverse event suspected to be associated with hepatitis A vaccination should be reported to VAERS. Information on how to report adverse events is available at <http://www.fda.gov/cber/vaers/vaers.htm>; forms for this purpose can be obtained at telephone 800-822-7967.

Contraindications and Precautions

Hepatitis A vaccine should not be administered to persons with a history of a severe allergic reaction to a previous dose of hepatitis A vaccine or to a vaccine component. The safety of hepatitis A vaccination during pregnancy has not been determined; however, because hepatitis A vaccine is produced from inactivated HAV, the theoretic risk to the developing fetus is expected to be low. The risk associated with vaccination should be weighed against the risk for hepatitis A in pregnant women who might be at high risk for exposure to HAV. Because hepatitis A vaccine is inactivated, no special precautions need to be taken when vaccinating immunocompromised persons.

Prevaccination Serologic Testing for Susceptibility

Antibody production in response to HAV infection results in lifelong immunity to hepatitis A and, presumably, to HAV infection. Vaccination of a person who is immune because of previous infection does not increase the risk for adverse events. In populations that have expected high rates of previous HAV infection, prevaccination testing may be considered to reduce costs by not vaccinating persons who are already immune. Testing of children is not indicated because of their expected low prevalence of infection. For adults, the decision to test should be based on 1) the expected prevalence of immunity, 2) the cost of vaccination compared with the cost of serologic testing (including the cost of an additional visit), and 3) the likelihood that testing will not interfere with initiation of vaccination. For example, if the cost of screening (including laboratory and office visits) is one third the cost of

the vaccine series, then screening potential recipients in populations for which the prevalence of infection is likely to be >33% should be cost-effective (195).

Persons for whom prevaccination testing will likely be most cost-effective include adults who were either born in or lived for extensive periods in geographic areas that have a high or intermediate endemicity of hepatitis A (Figure 4); older adolescents and adults in certain population groups (i.e., American Indians, Alaska Natives, and Hispanics); and adults in certain groups that have a high prevalence of infection (e.g., injection-drug users). In addition, prevalence might be high enough among all older adults to warrant prevaccination testing. Overall anti-HAV prevalence among persons aged >40 years, determined by NHANES-III testing, was >33% (50). Therefore, if the cost of screening is one third the cost of the vaccine series, prevaccination testing of any person aged >40 years would likely be cost-effective. Commercially available tests for total anti-HAV should be used for prevaccination testing.

Postvaccination Testing for Serologic Response

Postvaccination testing is not indicated because of the high rate of vaccine response among adults and children. In addition, not all testing methods approved for routine diagnostic use in the United States have the sensitivity to detect low anti-HAV concentrations after vaccination.

Cost-Effectiveness of Hepatitis A Vaccination of Children

The cost-effectiveness of nationwide routine hepatitis A vaccination was evaluated in an analysis that used a Markov model to follow a single U.S. birth cohort of approximately 4 million persons from birth in 2005 through age 95 years or death. Compared with no childhood vaccination, routine vaccination at age 1 year would result in 183,806 fewer infections and 32 fewer deaths in each cohort (CDC, unpublished data, 2005). The cost-effectiveness ratio was estimated at \$173,000 per life year gained and \$24,000 per quality-adjusted life year (QALY) gained. Compared with 2003 vaccine coverage levels, the incremental cost-effectiveness ratio of routine nationwide vaccination at age 1 year was \$73,000 per QALY gained. When out-of-cohort herd immunity was taken into account, vaccination at age 1 year yielded a societal cost of \$1,000 per QALY gained. Another economic analysis that included the estimated reduction in secondary cases among household contacts of infected children yielded similar results (196).

Recommendations for Use of Hepatitis A Vaccine and Immune Globulin

Preexposure Protection Against HAV Infection

The following recommendations for hepatitis A vaccination are intended to further reduce hepatitis A morbidity and mortality in the United States and make possible consideration of eventual elimination of HAV transmission. Hepatitis A vaccination is recommended routinely for children, for persons who are at increased risk for infection, and for any person wishing to obtain immunity.

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 2 and 3) 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 children aged 1 year 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 aged 2–18 years can be considered. Such programs might especially be warranted in the context of increasing incidence or ongoing outbreaks among children or adolescents.

Persons At Increased Risk for HAV Infection

Persons Traveling to or Working in Countries That Have High or Intermediate Endemicity of Infection

All susceptible persons traveling to or working in countries that have high or intermediate hepatitis A endemicity (Figure 4) should be vaccinated or receive IG before departure (Tables 1–4). Hepatitis A vaccination at the age-appropriate dose is preferred (Tables 2–4). Prevacination testing should be considered for older travelers or for younger persons in certain population groups (see Prevacination Serologic Testing for Susceptibility).

Travelers to Australia, Canada, western Europe, Japan, or New Zealand (i.e., countries in which endemicity is low) are at no greater risk for infection than persons in the United States. Data are not available regarding the risk for hepatitis A for persons traveling to certain areas of the Caribbean, although

vaccine or IG should be considered if travel to areas that have questionable sanitation is anticipated.

The first dose of hepatitis A vaccine should be administered as soon as travel is considered. Travelers who are administered vaccine can be assumed to be protected within 4 weeks after receiving the first vaccine dose. Persons administered single-antigen hepatitis A vaccine often will have detectable anti-HAV by 2 weeks after the first vaccine dose; the proportion of persons who will have detectable anti-HAV at 2 weeks might be lower when lower vaccine dosages are used (e.g., in TWINRIX). However, no data are available regarding the risk for hepatitis A among persons vaccinated 2–4 weeks before departure. Because protection might not be complete until 4 weeks after vaccination, for optimal protection, persons traveling to an area in which risk is high <4 weeks after the initial dose also may be administered IG (0.02 mL/kg), but at a different anatomic injection site. Travelers departing in <4 weeks who do not or cannot receive IG should nonetheless receive hepatitis A vaccine and be informed that they might not be optimally protected from acquiring hepatitis A in the immediate future (i.e., subsequent 2–4 weeks). Completion of the vaccine series according to the licensed schedule (Tables 2–4) is necessary for long-term protection.

Travelers who are allergic to a vaccine component or who elect not to receive vaccine should receive a single dose of IG (0.02 mL/kg), which provides effective protection against hepatitis A for up to 3 months (Table 1). Travelers whose travel period is >2 months should be administered IG at 0.06 mL/kg; administration must be repeated if the travel period is >5 months (Table 1).

MSM

MSM (both adolescents and adults) should be vaccinated. Prevacination testing is not indicated for the vaccination of adolescents and young adults in this population but might be warranted for older adults (see Prevacination Serologic Testing for susceptibility). Studies have suggested that the majority of MSM would accept hepatitis A vaccination if recommended by their providers (53). Health-care providers in primary-care and specialty medical settings in which MSM receive care should offer hepatitis A vaccine to patients at risk. Implementation strategies to overcome barriers and increase coverage (e.g., use of standing orders) should be considered.

Users of Injection and Noninjection Drugs

Vaccination is recommended for users of injection and noninjection illicit drugs. Prevacination testing is not indicated for the vaccination of adolescent users of illicit drugs but might be warranted for certain adults. The need might depend on the particular characteristics of the population of

drug users, including the type and duration of drug use. Providers should obtain a thorough history to identify patients who use or are at risk for using illicit drugs and might benefit from hepatitis A vaccination. Implementation strategies to overcome barriers and increase coverage (e.g., use of standing orders) should be considered.

Persons Who Have Occupational Risk for Infection

Persons who work with HAV-infected primates or with HAV in a research laboratory setting should be vaccinated. Studies conducted among U.S. workers exposed to raw sewage do not indicate increased risk for HAV infection. No other populations have been demonstrated to be at increased risk for HAV infection because of occupational exposure.

Persons with Clotting-Factor Disorders

Susceptible persons who are administered clotting-factor concentrates, especially solvent-detergent-treated preparations, should receive hepatitis A vaccine. Changes in clotting factor preparation practices and donor screening have greatly reduced the risk for hepatitis A for recipients of clotting factors.

Vaccination of Persons with Chronic Liver Disease

Susceptible persons with chronic liver disease should be vaccinated. Available data do not indicate a need for routine vaccination of persons with chronic HBV or HCV infections without evidence of chronic liver disease. Susceptible persons who are either awaiting or have received liver transplants should be vaccinated.

Hepatitis A Vaccination During Outbreaks

The frequency of large communitywide outbreaks has diminished considerably since implementation of the recommended childhood hepatitis A vaccination programs. Implementation of the recommendations in this report should further reduce occurrence of outbreaks. If communitywide outbreaks occur, accelerated vaccination may be considered as an additional control measure. Factors to consider in deciding whether to initiate an outbreak-control vaccination program include the feasibility of rapidly vaccinating the target population of children, adolescents, or young adults, and program cost. Ongoing vaccination of children should be sustained to maintain high levels of immunity and prevent future epidemics.

Limited outbreaks, especially those involving adults at increased risk (e.g., illicit drug users or MSM), are likely to continue to occur until higher vaccine coverage is achieved in

these populations. Vaccination programs to control these outbreaks have been difficult to implement. Programs to control hepatitis A outbreaks among users of illicit drugs, especially methamphetamine, that focused on vaccination in county jails and similar venues (e.g., court-ordered diversion programs) have met with some limited success, at least in terms of the provision of vaccine (57). In general, efforts to control and prevent hepatitis A outbreaks among adults in these populations should be focused primarily on initiating and sustaining routine vaccination of these persons.

The frequency of outbreaks in child care centers has also decreased in recent years and should continue to decrease with more widespread vaccination of young children. Limited data exist regarding the role of hepatitis A vaccine in controlling outbreaks in these settings. If outbreaks are recognized in child care centers, use of IG as recommended is effective in limiting transmission to employees and families of attendees (see Postexposure Prophylaxis with IG). Previously unvaccinated children receiving postexposure prophylaxis with IG should also receive hepatitis A vaccine.

Persons who work as food handlers can contract hepatitis A and potentially transmit HAV to others. One national economic analysis concluded that routine vaccination of all food handlers would not be economical from a societal or restaurant owner's perspective (197). Nonetheless, to decrease the frequency of evaluations of food handlers with hepatitis A and the need for postexposure prophylaxis of patrons, consideration may be given to vaccination of employees who work in areas where state and local health authorities or private employers determine that such vaccination is appropriate. Food handlers who receive hepatitis A vaccine should be provided with a record of the immunization. Those who do not should be informed of the signs and symptoms of hepatitis A and taught food preparation practices that reduce the risk for fecal contamination.

Postexposure Prophylaxis with IG

Persons who have been recently exposed to HAV and who have not previously received hepatitis A vaccine should be administered a single dose of IG (0.02 mL/kg) as soon as possible. Efficacy when administered >2 weeks after exposure has not been established. Persons who have been administered 1 dose of hepatitis A vaccine at ≥ 1 month before exposure to HAV do not need IG.

Because hepatitis A cannot be reliably diagnosed on clinical presentation alone, serologic confirmation of HAV infection in index patients by IgM anti-HAV testing is recommended before postexposure treatment of contacts. Screening of con-

tacts for immunity before administering IG is not recommended because screening would result in delay.

If hepatitis A vaccine is recommended for a person being administered IG (e.g., a person with a recent exposure but also an indication for vaccination), it may be administered simultaneously with IG at a separate anatomic injection site. Unlike IG, hepatitis A vaccine is not licensed for use as postexposure prophylaxis. The completion of studies comparing IG with hepatitis A vaccine for postexposure prophylaxis is needed before vaccine can be recommended in this setting. IG should be administered to previously unvaccinated persons in the following situations.

Close Personal Contact

IG should be administered to all previously unvaccinated household and sexual contacts of persons with serologically confirmed hepatitis A. In addition, persons who have shared illicit drugs with a person who has serologically confirmed hepatitis A should receive IG and hepatitis A vaccine. Consideration should also be given to providing IG to persons with other types of ongoing, close personal contact with a person with hepatitis A (e.g., regular babysitting).

Child Care Centers

IG should be administered to all previously unvaccinated staff and attendees of child care centers or homes if 1) one or more cases of hepatitis A are recognized in children or employees or 2) cases are recognized in two or more households of center attendees. In centers that do not provide care to children who wear diapers, IG need be administered only to classroom contacts of an index patient. When an outbreak occurs (i.e., hepatitis A cases in three or more families), IG also should be considered for members of households that have children (center attendees) in diapers. Hepatitis A vaccine may be administered at the same time as IG for children receiving postexposure prophylaxis in child care centers.

Common-Source Exposure

If a food handler receives a diagnosis of hepatitis A, IG should be administered to other food handlers at the same establishment. Because common-source transmission to patrons is unlikely, IG administration to patrons typically is not indicated but may be considered if 1) during the time when the food handler was likely to be infectious, the food handler both directly handled uncooked foods or foods after cooking and had diarrhea or poor hygienic practices, and 2) patrons can be identified and treated ≤ 2 weeks after the exposure. In settings in which repeated exposures to HAV might have occurred (e.g., institutional cafeterias), stronger consideration of IG use might be warranted. In the event of a common-source out-

break, IG should not be administered to exposed persons after cases have begun to occur because the 2-week period during which IG is effective will have been exceeded.

Schools, Hospitals, and Work Settings

IG is not routinely indicated when a single case occurs in an elementary or secondary school, an office, or other work settings, and the source of infection is outside the school or work setting. Similarly, when a person who has hepatitis A is admitted to a hospital, staff should not routinely be administered IG; instead, careful hygienic practices should be emphasized. IG should be administered to persons who have close contact with index patients if an epidemiologic investigation indicates HAV transmission has occurred among students in a school or among patients or between patients and staff in a hospital.

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MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports

May 19, 2006 / Vol. 55 / No. RR-7

Continuing Education Activity Sponsored by CDC

Prevention of Hepatitis A Through Active or Passive Immunization Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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You must complete and return the response form electronically or by mail by **MAY 19, 2009**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 2.5 hours Continuing Medical Education (CME) credit; 0.2 Continuing Education Units (CEUs); or 2.8

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Goal and Objectives

This report provides updated recommendations made by the Advisory Committee on Immunization Practices (ACIP) concerning vaccination to prevent hepatitis A virus (HAV) infection in the United States. The goal of this report is to guide clinical practice and policy development related to the prevention of HAV infection. Upon completion of this educational activity, the reader should be able to 1) identify recommendations for the routine hepatitis A vaccination of children in the United States, 2) describe the epidemiology of hepatitis A in selected areas of the United States after implementation of ACIP's 1996 and 1999 recommendations for use of hepatitis A vaccine, 3) list the primary target groups for routine hepatitis A vaccination, and 4) describe the characteristics of currently licensed hepatitis A vaccines.

To receive continuing education credit, please answer all of the following questions.

1. **Which of the following recommendations are made regarding children who should be routinely vaccinated or considered for vaccination? (Indicate all that apply.)**
 - A. All children should receive hepatitis A vaccine at age 1 year (i.e., 12–23 months).
 - B. States, counties, and communities with existing hepatitis A vaccination programs for children aged 2–18 years are encouraged to maintain these programs.
 - C. In areas without existing hepatitis A vaccination programs, catch-up vaccination of unvaccinated children aged 2–18 years may be considered.
 - D. All of the above.
2. **The 2004 national rate of reported cases of hepatitis A (1.9 cases per 100,000 population, representing 5,683 reported cases) was the lowest ever recorded and was 79% lower than the previously recorded low.**
 - A. True.
 - B. False.
3. **The following persons are at increased risk for HAV infection and should be routinely vaccinated:**
 - A. Persons traveling to or working in countries that have high or intermediate levels of HAV infection.
 - B. Men who have sex with men.
 - C. Users of illegal drugs (both injecting and noninjecting).
 - D. Persons who have an occupational risk for infection.
 - E. Persons who have a clotting-factor disorder.
 - F. Susceptible persons who have chronic liver disease.
 - G. All of the above.
4. **Recent hepatitis A rates among American Indians and Alaska Natives represent a 99% decline from the prevaccine era and are now approximately the same or lower than those of other racial and ethnic populations.**
 - A. True.
 - B. False.
5. **In the era of hepatitis A vaccination, hepatitis A rates among Hispanics have declined...**
 - A. 87%.
 - B. 73%.
 - C. 53%.
 - D. 23%.
6. **In recent years, the majority of hepatitis A cases have been reported from states with historically low rates of hepatitis A in which hepatitis A vaccination of children has not been implemented widely.**
 - A. True.
 - B. False.
7. **Which best describes your professional activities?**
 - A. Physician.
 - B. Nurse.
 - C. Health educator.
 - D. Office staff.
 - E. Other.
8. **I plan to use these recommendations as the basis for...(Indicate all that apply.)**
 - A. health education materials.
 - B. insurance reimbursement policies.
 - C. local practice guidelines.
 - D. public policy.
 - E. other.
9. **Overall, the length of the journal report was...**
 - A. much too long.
 - B. a little too long.
 - C. just right.
 - D. a little too short.
 - E. much too short.
10. **After reading this report, I am confident I can identify recommendations for the routine hepatitis A vaccination of children in the United States.**
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
11. **After reading this report, I am confident I can describe the epidemiology of hepatitis A in selected areas of the United States after implementation of ACIP's 1996 and 1999 recommendations for use of hepatitis A vaccine.**
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
12. **After reading this report, I am confident I can list the primary target groups for routine hepatitis A vaccination.**
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.

- 13. After reading this report, I am confident I can describe the characteristics of currently licensed hepatitis A vaccines.
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
- 14. The learning outcomes (objectives) were relevant to the goals of this report.
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
- 15. The instructional strategies used in this report (text, tables, and figures) helped me learn the material.
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
- 16. The content was appropriate given the stated objectives of the report.
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.

- 17. The content expert(s) demonstrated expertise in the subject matter.
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
- 18. Overall, the quality of the journal report was excellent.
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
- 19. These recommendations will improve the quality of my practice.
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
- 20. The availability of continuing education credit influenced my decision to read this report.
 - A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.

(Continued on pg CE-4)

**MMWR Response Form for Continuing Education Credit
May 19, 2006/Vol. 55/No. RR-7**

**Prevention of Hepatitis A Through Active or Passive Immunization
Recommendations of the Advisory Committee
on Immunization Practices (ACIP)**

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Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1. [] A [] B [] C [] D	13. [] A [] B [] C [] D [] E
2. [] A [] B [] C [] D [] E	14. [] A [] B [] C [] D [] E
3. [] A [] B [] C [] D [] E [] F [] G	15. [] A [] B [] C [] D [] E
4. [] A [] B [] C [] D [] E	16. [] A [] B [] C [] D [] E
5. [] A [] B [] C [] D	17. [] A [] B [] C [] D [] E
6. [] A [] B [] C [] D [] E	18. [] A [] B [] C [] D [] E
7. [] A [] B [] C [] D [] E	19. [] A [] B [] C [] D [] E
8. [] A [] B [] C [] D [] E	20. [] A [] B [] C [] D [] E
9. [] A [] B [] C [] D [] E	21. [] A [] B [] C [] D [] E
10. [] A [] B [] C [] D [] E	22. [] A [] B [] C [] D [] E
11. [] A [] B [] C [] D [] E	23. [] A [] B [] C [] D [] E [] F
12. [] A [] B [] C [] D [] E	

Signature _____ Date / Completed Exam _____

21. The *MMWR* format was conducive to learning this content.

- A. Strongly agree.
- B. Agree.
- C. Undecided.
- D. Disagree.
- E. Strongly disagree.

22. Do you feel this course was commercially biased? (*Indicate yes or no; if yes, please explain in the space provided.*)

- A. Yes.
- B. No.

23. How did you learn about the continuing education activity?

- A. Internet.
- B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
- C. Coworker/supervisor.
- D. Conference presentation.
- E. *MMWR* subscription.
- F. Other.

Correct answers for questions 1-6.
1. D; 2. A; 3. G; 4. A; 5. A; 6. A.

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