Epidemiologic Reviews
Vol. 28, 2006
DOI: 10.1093/epirev/mxj012
Advance Access publication June 14, 2006
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Hepatitis A in the Era of Vaccination

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Accepted for publication March 27, 2006.

The World Health Organization estimates an annual total of 1.5 million clinical cases of hepatitis A worldwide, but seroprevalence data indicate that tens of millions of hepatitis A virus infections occur each year. In the United States in the 1980s–1990s, an average of 26,000 acute hepatitis A cases were reported per year, representing approximately 270,000 infections annually. Since licensure of effective hepatitis A vaccines in the mid-1990s, US hepatitis A rates have fallen precipitously—particularly since 1999, when routine childhood vaccination was recommended in states with consistently elevated rates. By 2004, the overall rate had declined to 1.9/100,000 population, the lowest rate ever recorded and 79% lower than any previously recorded nadir. These marked declines occurred with relatively modest vaccination coverage, suggesting that strong herd immunity accompanies the initiation of routine vaccination programs. Routine childhood vaccination has produced similar results in Israel and selected regions of Italy, Spain, and Australia. Hepatitis A vaccination will probably remain a low priority for some time in the poorest countries, where most persons are infected as young children. However, shifts in the epidemiologic patterns of disease associated with declining hepatitis A virus transmission are occurring in many regions of the world. These shifts are likely to create circumstances where strategically targeted vaccination of children could produce substantial public health benefits.

hepatitis A; hepatitis A vaccine; hepatitis A virus; vaccines

Abbreviations: anti-HAV, antibodies to hepatitis A virus; HAV, hepatitis A virus; HIV, human immunodeficiency virus; IgM, immunoglobulin M.

INTRODUCTION

The first conclusive characterization of the etiologic agent causing hepatitis A and the routes by which it is transmitted occurred in the mid-20th century (1, 2), but outbreaks of disease which, on the basis of their epidemiologic characteristics, appear to have been hepatitis A were described as early as the 17th and 18th centuries (3). According to the World Health Organization, approximately 1.5 million clinical cases of hepatitis A occur worldwide annually (4), but seroprevalence data indicate that tens of millions of hepatitis A virus (HAV) infections occur each year. HAV is transmitted via the fecal-oral route by either person-to-person contact or consumption of contaminated food or water. The incidence of infection is highly related to the prevailing level of hygiene and sanitation, and the disease is most endemic in the less developed parts of the world, where poor socioeconomic conditions facilitate transmission of the virus. In the developed world and in some developing countries, the seroprevalence of HAV infection has declined, presumably because of improvements in hygiene associated with rising socioeconomic conditions (5). However, the introduction of effective hepatitis A vaccines in the mid-1990s provided the first specific tool for preventing HAV infection. In this review, we describe hepatitis A vaccines, the epidemiologic basis for their recommended use, and the impact of hepatitis A vaccination in different epidemiologic settings.

HAV AND HEPATITIS A

HAV is a 27-nm nonenveloped RNA virus in the Picornaviridae family. HAV can remain infectious in the environment for weeks, but the virus is inactivated by heating it

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to more than 85°C for at least 1 minute or by exposure to bleach. There is no animal reservoir of infection.

The illness caused by HAV infection (hepatitis A) typically has an abrupt onset that can include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, and jaundice. Symptoms develop approximately 28 days (range, 15–50 days) after exposure (6). Children under 6 years of age are often asymptomatic (70 percent); even symptomatic illness is not usually accompanied by jaundice (7). Older children and adults with HAV infection are usually symptomatic, with jaundice occurring in more than 70 percent of patients (8). Levels of alanine aminotransferase and aspartate aminotransferase may be elevated to over 1,000 IU/liter, even among asymptomatic persons. However, some asymptomatic persons have normal alanine aminotransferase and aspartate aminotransferase levels (9). Signs and symptoms usually last for less than 2 months, although 10–15 percent of symptomatic persons have prolonged or relapsing illness lasting up to 6 months (10). Immunity after infection persists for life.

No specific therapy exists for hepatitis A. Although most persons with hepatitis A recover fully with no subsequent liver disease, acute liver failure resulting in death or requiring liver transplant occurs in less than 1 percent of cases. Based on surveillance data, the overall case-fatality ratio among persons with acute hepatitis A is 0.6 percent; for those over 60 years of age, the ratio is 1.5 percent (11). Persons with chronic liver disease are also at increased risk of acute liver failure (12, 13).

HAV replicates in the liver, is excreted in bile, and is shed in the stool. The peak infectivity of infected persons occurs during the 2 weeks before onset of jaundice or elevation of liver enzyme levels, when the concentration of virus in stool is highest. The viral concentration in stool declines after jaundice appears, and most persons are noninfectious 1 week after jaundice appears (14). Recurrent shedding may occur in persons with relapsing illness (15), and prolonged shedding as long as several months after illness onset has been described in infants and children (16, 17). However, chronic shedding of HAV does not occur.

HAV is most commonly transmitted through close person-to-person contact in households and extended family settings. Young children have the highest infection rates, and in most communities with sustained transmission, asymptomatic young children are the primary source of infection (18). Serologic studies conducted within households of hepatitis A patients in these communities have shown that an asymptomatic HAV-infected child is often present in the case-patient's household and presumably was the source of infection (19). However, transmission can also be sustained in communities of adults with risk factors for infection, such as men who have sex with men or illicit drug users (20–23).

Additionally, foodborne or waterborne transmission can occur when fecal material from HAV-infected persons contaminates food or water. In the developed world, foodborne transmission is most commonly identified when an HAV-infected food service worker contaminates food that is served to others without being cooked (24, 25). However, outbreaks caused by food items contaminated during harvest or before distribution have also been reported. Produce (typically green onions, lettuce, or strawberries) (26–28) has been the most common source of these outbreaks. Outbreaks associated with shellfish are rare in the United States but have occurred (29) and continue to be reported elsewhere (30). Waterborne outbreaks are uncommon in developed countries. Transmission of HAV via transfused blood or blood derivatives has been reported but is rare, and recent advances in blood processing and better donor screening have further reduced this risk (31–33).

DIAGNOSIS

The symptoms of acute hepatitis A are similar to those of other viral hepatitides, and serologic testing for detection of immunoglobulin M (IgM) antibodies to HAV (anti-HAV) is required to confirm the diagnosis. Commercial diagnostic tests are available for the detection of IgM and total (both IgM and immunoglobulin G) anti-HAV in serum. IgM anti-HAV is usually detectable when symptoms appear, and concentrations decline to undetectable levels within 6 months of infection for most patients (34). However, cases of patients' testing positive for IgM anti-HAV more than 1 year after infection have been reported (35, 36). Immunoglobulin G anti-HAV appears early in the course of infection and remains detectable throughout the person's lifetime. Total anti-HAV tests are often used in epidemiologic investigations or in determining susceptibility to HAV infection but do not identify acute infection.

PROPHYLAXIS AGAINST HAV INFECTION

Immune globulin

Immune globulin provides protection against hepatitis A through passive transfer of antibody. Immune globulin is a sterile preparation of concentrated antibodies (immunoglobulins) made from pooled human plasma that has undergone viral inactivation. When administered for preexposure prophylaxis, a dose of 0.02 ml/kg administered intramuscularly confers protection for up to 3 months, and 0.06 ml/kg protects for up to 5 months (37). When administered within 2 weeks following exposure to HAV (0.02 ml/kg), immune globulin is more than 85 percent effective in preventing hepatitis A. Efficacy is greatest when immune globulin is administered early in the incubation period; when administered later in the incubation period, immune globulin sometimes only attenuates the clinical expression of HAV infection (38). No transmission of hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), or other viruses, which are inactivated in the processing of plasma to produce immune globulin, has been reported from the intramuscular administration of immune globulin. Although anti-HAV concentrations in immune globulin have decreased as the prevalence of previous HAV infection among plasma donors has declined, no evidence of decreased protection has been reported. Periodic shortages and distribution problems can sometimes make obtaining immune globulin a challenge for health departments.

Vaccines

Two single-antigen hepatitis A vaccines are currently licensed for use in the United States: HAVRIX

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TABLE 1. Hepatitis A virus vaccines licensed for use in the United States and their administration schedules

Vaccine	Age group (years)	Dose	Volume (ml)	No. of doses	Schedule (months)
HAVRIX*	1–18	720 ELISA† units	0.5	2	0, 6–12
	≥19	1,440 ELISA units	1.0	2	0, 6–12
VAQTA‡	1–18	25 units	0.5	2	0, 6–18
	≥19	50 units	1.0	2	0, 6–18
TWINRIX§	≥18	720 ELISA units/20 μg hepatitis B vaccine	1.0	3	0, 1, 6

* Hepatitis A vaccine, inactivated (GlaxoSmithKline Biologicals, Rixensart, Belgium).
† ELISA, enzyme-linked immunosorbent assay.
‡ Hepatitis A vaccine, inactivated (Merck & Company, Inc., Whitehouse Station, New Jersey).
§ Combined hepatitis A and hepatitis B vaccine (GlaxoSmithKline).

(GlaxoSmithKline Biologicals, Rixensart, Belgium) and VAQTA (Merck & Company, Inc., Whitehouse Station, New Jersey). Both are prepared from inactivated HAV and are equivalent in terms of immunogenicity and efficacy (39). Dosages and schedules for administration of these vaccines are shown in table 1. Both vaccines can now be used in children aged 12 months or older. The combination vaccine TWINRIX (GlaxoSmithKline) contains both hepatitis A (inactivated) and hepatitis B (recombinant) antigens (table 1). Completing a series using one licensed vaccine after starting the series using the other does not diminish immunogenicity (40, 41).

Other inactivated vaccines are available in some countries. AVAXIM (Aventis Pasteur, Lyon, France) is prepared similarly to the US-licensed single-antigen vaccines (42). The hepatitis A antigen in EPAXAL (Berna Biotech Ltd., Berne, Switzerland) is incorporated into a virosome consisting of phospholipids and influenza virus surface glycoproteins (43, 44).

Immunogenicity. Vaccination induces concentrations of anti-HAV that are lower than those produced after natural infection and can be below the detection level of some commercially available diagnostic assays. In immunogenicity studies, testing has often been done using commercial assays that have been modified to have a lower detection limit of approximately 10–33 mIU/ml. The lower limit of antibody required to prevent HAV infection has not been defined (45), but persons who develop anti-HAV above this detection limit are considered to be protected from HAV infection (46, 47).

All US-licensed vaccines are highly immunogenic. Studies found that protective anti-HAV levels developed in 94–100 percent of adults 1 month after receiving the first dose of HAVRIX or VAQTA and that, after the second dose, 100 percent had protective antibody levels with high geometric mean antibody concentrations (39, 48). After three doses of TWINRIX, more than 99 percent of adults developed protective levels of anti-HAV (49, 50). Among children aged 1–18 years, 97–100 percent had protective antibody levels 1 month after receiving the first dose of vaccine, and 100 percent had protective levels with high geometric mean antibody concentrations 1 month after the second dose (51, 52). Hepatitis A vaccine is highly immunogenic in children under age 1 year who do not have passively acquired maternal antibodies (53, 54). Studies indicate that AVAXIM and EPAXAL have immunogenicity similar to that of US-licensed vaccines (42–44).

Limited data are available regarding response to a delayed second dose of vaccine. However, several small studies have indicated that delays of as long as 2–6 years do not reduce immunogenicity (55, 56). Hepatitis A vaccines can be administered concomitantly with other vaccines without affecting immunogenicity or reactogenicity (54, 57).

Efficacy as preexposure prophylaxis. The efficacy of HAVRIX was evaluated in a double-blind, controlled, randomized clinical trial in Thailand among approximately 40,000 children aged 1–16 years living in villages that had high rates of hepatitis A. After two doses of vaccine administered 1 month apart, the efficacy of vaccine in protecting recipients against clinical hepatitis A was 94 percent (95 percent confidence interval: 79, 99) (58). A similarly controlled clinical trial using VAQTA that was conducted among approximately 1,000 children aged 2–16 years living in an Upstate New York community with a high rate of hepatitis A found a protective efficacy against clinical hepatitis A of 100 percent (lower bound of 95 percent confidence interval: 87) after one dose of vaccine (59).

Efficacy as postexposure prophylaxis. Limited data indicate that hepatitis A vaccine can prevent infection even if given after exposure. In a small randomized trial, hepatitis A vaccine was 79 percent (95 percent confidence interval: 7, 95) efficacious in preventing infection (defined as the appearance of IgM anti-HAV) after household exposure to hepatitis A when compared with no treatment (60). Immune globulin continues to be recommended by most US advisory groups for postexposure prophylaxis, but Canadian and some European authorities now recommend hepatitis A vaccine for postexposure prophylaxis. Clinical trials comparing the postexposure efficacy of vaccine with that of immune globulin are under way to determine whether hepatitis A vaccine without immune globulin could be recommended to prevent hepatitis A after exposure.

Long-term protection. To monitor vaccine recipients for breakthrough infections and to determine the persistence of protective levels of anti-HAV, investigators have monitored

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cohorts of vaccinated persons for cases of symptomatic hepatitis A and have tested them periodically. No cases of symptomatic hepatitis A were detected in a cohort of children followed for 9 years after vaccination (61). Protective levels of anti-HAV were still observed in more than 99 percent of children and adults 5–12 years after receipt of hepatitis A vaccine (62, 63). Estimates of antibody persistence derived from kinetic models of antibody decline indicate that protective levels of anti-HAV could be present for at least 25 years in adults and at least 14–20 years in children (64). Whether other mechanisms (e.g., cellular memory) also contribute to long-term protection is unknown.

Factors associated with reduced immunogenicity. At the time of vaccination, the presence of anti-HAV from previous or concurrent administration of immune globulin results in lower final anti-HAV concentrations, but the proportion of persons who develop protective levels of anti-HAV is not significantly diminished (65, 66). Therefore, persons with indications for vaccination can receive hepatitis A vaccine at the same time that immune globulin is given for either preexposure or postexposure prophylaxis.

Reduced vaccine immunogenicity also has been observed in infants who had passively acquired antibodies because of prior maternal HAV infection. In most studies, these infants all developed protective levels of antibody, but their final geometric mean antibody concentrations were significantly lower than those of vaccinated infants born to anti-HAV-negative mothers (53, 54). In one study, infants who had passively acquired antibodies at the time of vaccination had significantly lower concentrations of anti-HAV 6 years later as compared with vaccinated infants with no passively acquired antibodies, and a higher proportion had undetectable levels of antibody. However, most vaccinated infants with passively acquired antibodies exhibit an anamnestic response to a booster dose given 1–6 years later (54, 67, 68). Passively acquired maternal antibodies usually become undetectable by 12–15 months of age (69), and hepatitis A vaccine is highly immunogenic for children beginning vaccination at age 1 year or older, regardless of maternal anti-HAV status (70).

Hepatitis A vaccine is immunogenic for children and adults with medical conditions that might reduce immune response. Persons with chronic liver disease or HIV infection with nearly normal CD4 cell counts have similar rates of response but lower antibody levels compared with healthy persons (71–77). Persons with more advanced HIV infection and recipients of liver or kidney transplants have lower rates of response (71, 75, 78–80). Lower final anti-HAV levels have been observed among persons over age 40 years in some studies (48, 81).

Side effects and adverse events. In clinical trials, the most frequently reported side effects include soreness at the injection site, headache, and malaise (82, 83). These symptoms rarely last for more than 48 hours. Over 188 million doses of hepatitis A vaccine have been sold worldwide, including more than 50 million doses in the United States (GlaxoSmithKline, unpublished data; Merck & Company, Inc., unpublished data). None of the licensed hepatitis A vaccines have been associated with any serious adverse events in large prelicensure or postmarketing studies (48, 84, 85). Hepatitis A vaccine should not be administered to persons with a history of a severe reaction to a prior dose of hepatitis A vaccine or to a vaccine component.

HEPATITIS A: EPIDEMIOLOGY IN THE PREVACCINE ERA

Global patterns of disease

Hepatitis A occurs worldwide, but major geographic differences in endemicity exist which closely correlate with hygienic and sanitary conditions and other indicators of the level of development (86, 87) (figure 1). In areas of high endemicity (i.e., parts of Africa, Asia, Central and South America), HAV spreads easily as a result of poor socioeconomic conditions. Most infections in these areas occur in early childhood when asymptomatic infection predominates, and essentially the entire population has been infected before reaching adolescence (88, 89) (figure 2). Susceptible adults in these areas are at high risk of infection and disease, but overall disease rates are generally low and outbreaks rare because of the high prevalence of immunity in the population.

In areas of moderate endemicity, HAV is not transmitted as readily because of better sanitary and living conditions, and the average age of infection is higher in these areas than in areas of high endemicity (90) (figure 2). Transmission among young children remains relatively common. Paradoxically, the potential for large outbreaks of hepatitis A can be increased in comparison with highly endemic areas, because there is a larger pool of susceptible older children and adults (compared with high-endemicity countries) who are at high risk of infection and who, when infected with HAV, are likely to develop symptomatic illness (91). Large food- and water-associated outbreaks occur because of the relatively high rate of virus transmission and the large number of susceptible persons. Such an outbreak occurred in Shanghai, China, in 1988; it involved over 300,000 cases associated with consumption of clams harvested from sewage-contaminated water (30). Nevertheless, person-to-person transmission in community-wide epidemics continues to account for much of the disease in these countries.

In the United States, Canada, Western Europe, and other developed areas, the endemicity of HAV infection is low. Relatively few children are infected, and the incidence of disease is generally low. Most cases occur in the context of cyclic, community-wide outbreaks that feature transmission among preschool and school-age children and their adult contacts (18, 92–95). The prevalence of anti-HAV increases gradually with age, primarily reflecting declining incidence, changing endemicity, and resultant lower childhood infection rates over time (figure 2). Some regions (e.g., Scandinavia) have very low endemicity, with most cases occurring in defined risk groups, such as travelers returning from endemic areas and injection drug users (96).

Epidemiology of hepatitis A in the United States during the prevaccine era

In the United States, during the 1980s and 1990s, before hepatitis A vaccines were widely available, approximately 26,000 hepatitis A cases were reported annually (range,

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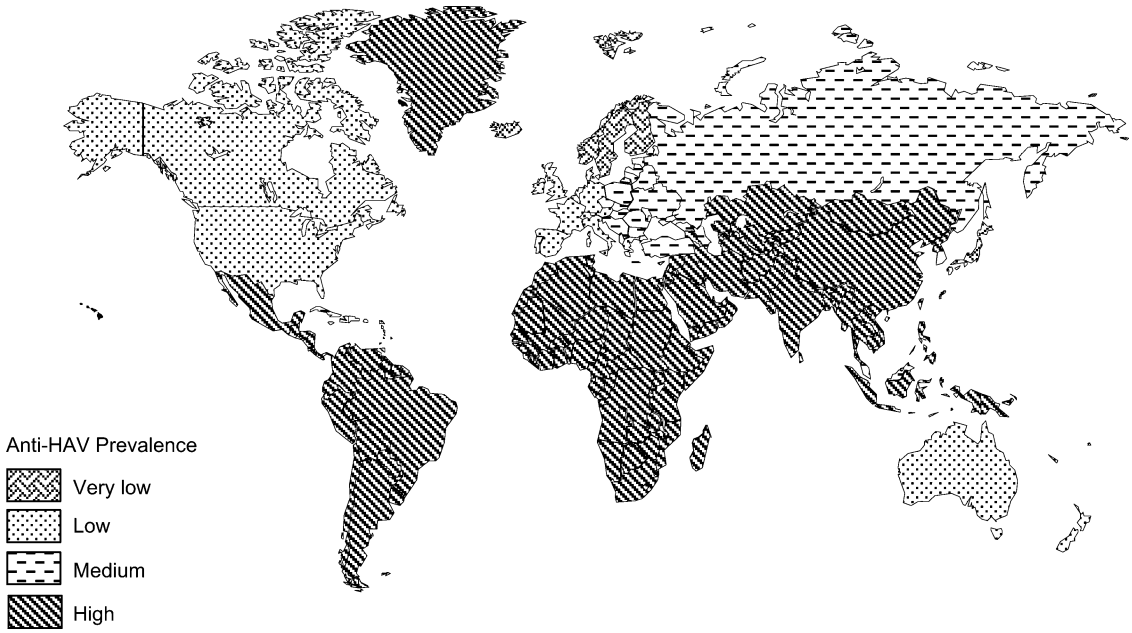

FIGURE 1. Global patterns of endemicity of hepatitis A virus infection (prevalence of antibodies to hepatitis A virus (anti-HAV)) as generalized from available prevalence data. (Source: Centers for Disease Control and Prevention (119).)

17,000–36,000); with asymptomatic infections taken into account, this represented an estimated 270,000 infections per year (97). The incidence of hepatitis A in the United States has varied cyclically, with nationwide increases every 10–15 years. Hepatitis A incidence has historically varied strikingly by region; the highest rates and the majority of cases occur in the western and southwestern states. During the prevaccine years 1987–1997, approximately 70 percent of cases originated from 17 predominantly western states representing only one third of the US population (98). Hepatitis A rates in those states were consistently above the national average.

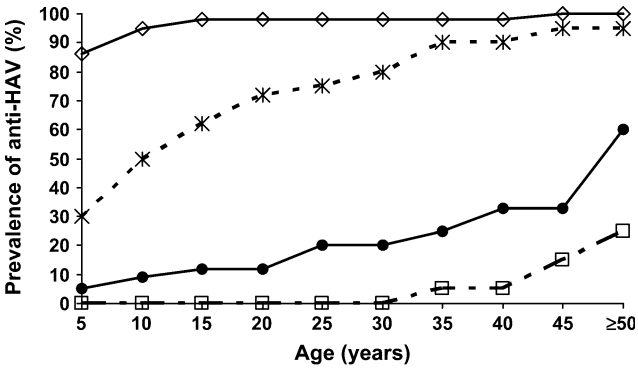

FIGURE 2. Age-specific prevalence of antibodies to hepatitis A virus (anti-HAV) worldwide in areas with differing levels of endemicity. Diamonds, high endemicity; X's, intermediate endemicity; circles, low endemicity; squares, very low endemicity. (Source: Bell et al. (125).)

Nationwide, rates of acute hepatitis A were highest among children aged 5–14 years, with approximately one third of reported symptomatic cases occurring among children under age 15 years (11, 98). Because most infections in children are asymptomatic, reported cases represent only a small proportion of infections in this age group; using incidence models, Armstrong and Bell (97) estimated that more than half of all HAV infections occurred among children under 10 years of age. Rates of symptomatic hepatitis A among American Indians and Alaska Natives were more than five times those in other racial/ethnic groups, and rates among Hispanics were approximately three times higher than those among non-Hispanics (11, 99).

Most hepatitis A in the United States occurred in the context of community-wide epidemics, during which infection was transmitted from person to person in households and extended family settings (18). In general, no single risk factor or risk group could be identified that accounted for the majority of cases (18). Nearly 50 percent of hepatitis A cases reported nationwide did not involve a recognized source of infection (18), but sources may have been contacts of persons, especially children, with asymptomatic infection. During community-wide outbreaks, studies of household contacts of adult cases without an identified source found that 25–40 percent of contacts under age 6 years had serologic evidence of recent HAV infection (17, 19). In one study, 52 percent of households of adults without an identified source of infection included a child under 6 years old, and the presence of a young child was associated with household transmission of HAV (19). The most commonly reported source of infection was household or sexual contact with another person with hepatitis A (15–25 percent of

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reported cases) (11, 18, 98). Approximately 10–15 percent of reported cases occurred among children and employees of child-care centers and members of their households, although this probably overestimates the amount of disease attributable to day-care exposure, because cases could be ascribed to child-care-center-related contact without any evidence of additional HAV infections in the center (11, 18, 98). International travel (5–7 percent) and suspected food- or waterborne outbreaks (2–5 percent) each accounted for a small proportion of cases (11, 93). Cyclic outbreaks occurred among men who had sex with men and illicit drug users, and during outbreak years, each of these exposures accounted for 5–10 percent of reported cases (18, 22, 100–102). Serologic surveys found a higher prevalence of anti-HAV among illicit drug users than in the general population (103, 104). Similar data for men who had sex with men were not consistent, with some studies showing an elevated prevalence of anti-HAV in this group while others did not (104, 105).

USES OF HEPATITIS A VACCINE IN THE CONTROL AND PREVENTION OF HEPATITIS A

Recommendations for the use of hepatitis A vaccine vary considerably among countries. Guidance from the World Health Organization on hepatitis A vaccines emphasizes the need to consider the cost-benefit and sustainability of various prevention strategies in the context of the epidemiologic characteristics of the setting where vaccination is being considered (4). Hepatitis A vaccination currently has few indications in the developing world, where hepatitis A is highly endemic and where most of the population is already immune as a result of HAV infection in early childhood (86). In areas of intermediate or high endemicity that are transitioning to a lower level of transmission, shifts in the age-specific patterns of disease result in an increasing proportion of susceptible adolescents and adults, often in urban areas or higher socioeconomic classes, among whom outbreaks occur and who might benefit from vaccination. In more developed countries, hepatitis A vaccine is primarily being used to protect persons at increased risk of hepatitis A or its consequences, such as travelers to areas where hepatitis A is endemic (98, 106–109). However, in some of these countries, the epidemiology of hepatitis A is heterogeneous, with much of the disease burden being focused in certain regions where large community-wide epidemics occur (18, 110). These regions have been the focus of programs using routine vaccination of children (98, 111) to reduce HAV transmission.

Vaccination of persons at increased risk of hepatitis A or severe consequences

In the United States, hepatitis A vaccination has been recommended since 1996 for groups who are at increased risk of hepatitis A or its consequences (99). Many developed countries have similar recommendations. Hepatitis A vaccine is recommended for persons who travel to countries where hepatitis A is of high or intermediate endemicity (4, 64, 98, 107). Of particular interest are recent immigrants from high- or intermediate-endemicity countries who return to their country of origin to visit friends and relatives. Although adults in these families are probably immune, many of these travelers are children, who may acquire hepatitis A and transmit it to others when they return (112–114). Hepatitis A cases among children due to foreign travel have been frequently observed among immigrant families in Europe and the United States. Although the number of US patients reporting travel as a risk factor has remained relatively unchanged in recent years, these cases account for an increasing proportion of all cases reported, particularly among children (11). Eighteen percent of US cases occurring in 2004 involved travel, and of these travel-related cases, approximately 50 percent were among children (11).

Vaccination has also been recommended for men who have sex with men and illicit drug users because of the outbreaks that occur among persons engaging in these behaviors. The extent to which these risk-based recommendations have been implemented is unknown. However, vaccine coverage is believed to be low, and outbreaks among men who have sex with men and illicit drug users, particularly users of methamphetamine, continue to occur (21, 23). Only limited vaccine coverage data are available, but in areas experiencing outbreaks among adults with risk factors, few adults are found to have been previously vaccinated (23).

Even if it were completely implemented, vaccination of recommended risk groups could have a substantial impact on overall rates only in situations where transmission was occurring primarily among adults in these risk groups. In the United States, the majority of cases occur in the context of community-wide outbreaks and among persons without an identifiable risk factor, and such cases would not be preventable through vaccination strategies focused on risk groups.

Vaccination of children

In some countries, primarily in the developed world, large, heterogeneous communities with hepatitis A rates that are consistently elevated with respect to a national average can be identified. Examples include the Puglia region of Italy, Catalonia in Spain, and the western and southwestern areas of the United States (18, 19, 111, 115). Periodic community-wide epidemics occur in these communities, but the interepidemic period is variable and the majority of the population remains susceptible to HAV infection into at least middle age (18, 111, 115). To prevent or control large outbreaks in these areas with high rates of disease and, over the longer term, to reduce HAV transmission, recommendations for routine vaccination of selected populations of children have been made in the United States, Israel, and Italy and selected other European countries (98, 108, 111, 116–118).

In the United States, routine vaccination has been recommended since 1999 for children living in areas where rates of hepatitis A have been consistently elevated. These areas include 17 states (''vaccinating states''), located primarily in the West and Southwest, which comprise approximately one third of the US population but historically have

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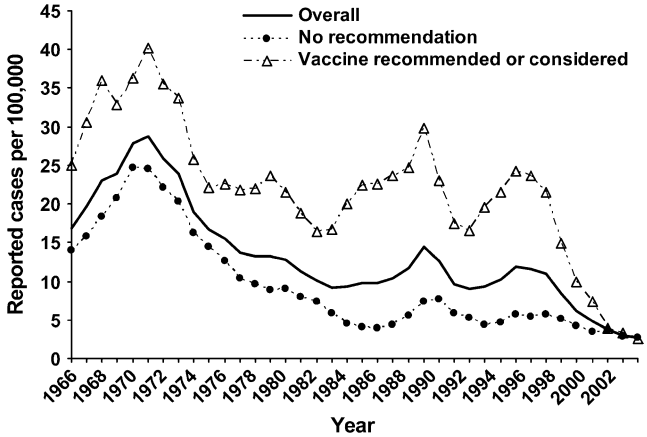

FIGURE 3. Rates of hepatitis A in the United States (reported number of cases per 100,000 population), 1966–2004. The graph shows overall US rates as well as rates in states where routine vaccination of children was recommended/considered and states where it was not. (Source: Wasley et al. (120).)

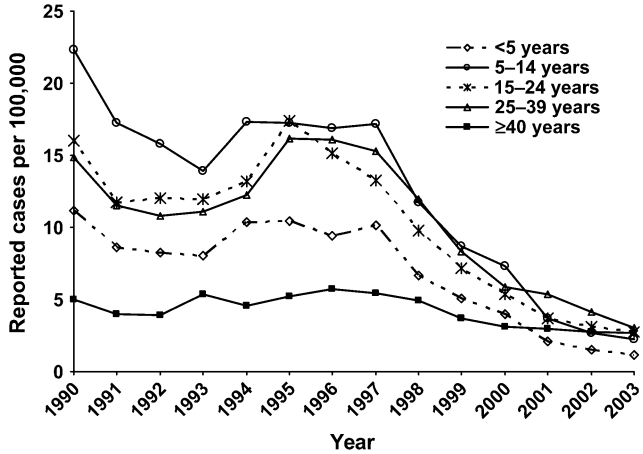

FIGURE 4. Rates of hepatitis A in the United States, by age group, 1990–2003. (Source: Centers for Disease Control and Prevention (11).)

accounted for more than two thirds of hepatitis A cases nationwide (98). In October 2005, the recommendations for routine vaccination were expanded to include nationwide implementation for all children aged 12–23 months (119). In the 10 years since vaccines were first licensed in the United States in 1995, and particularly since the issuance of the 1999 recommendations for routine vaccination of children, hepatitis A rates in the United States have declined precipitously. By 2004, the overall rate had declined to 1.9/100,000 population, the lowest rate ever recorded and 79 percent lower than any previously recorded nadir (120) (figure 3).

The declines in rates were greater in the parts of the country and the age groups covered by the recommendations for routine childhood vaccination (120) (figures 3 and 4). As a result of greater declines among children, the age group which historically had the highest rate of disease, the age profile of the disease has shifted, with the majority of cases now occurring among adults and with similar disease rates across all age groups. Similarly, as a result of greater declines in the "vaccinating states," the geographic differences in hepatitis A incidence that have historically characterized the disease have been eliminated, and rates among US regions have been approximately equal since 2001 (11, 120). In recent years, particular counties with higher rates have varied from year to year and have been distributed throughout the country. The majority of disease cases and the highest rates currently are in areas in which hepatitis A vaccination of children was not recommended (11, 120).

These remarkable declines were echoed in other fundamental shifts in hepatitis A epidemiology. The large community-wide outbreaks that accounted for the majority of cases in past decades (18), driven primarily by infections among children and transmission in households and extended family settings, have virtually disappeared. This is reflected in a shift in the distribution of reported potential sources of infection, with a declining proportion of patients reporting exposure to child day-care centers (11).

Because hepatitis A incidence in the United States has historically exhibited a pattern of cyclic increases (and subsequent decreases) every 10–15 years, determining how much of the recent decline has resulted from vaccination is complicated. The observed decline is certainly not completely due to vaccination. Mathematical models of hepatitis A incidence predicted a 4.5 percent yearly decline among susceptible persons over seven decades before the availability of vaccines (97). After comparing the incidence predicted by the models with actual 2001 incidence data, Samandari et al. (121) concluded that the observed rate was 39 percent lower than that predicted on the basis of historical trends and that this reduction was presumably attributable to vaccination.

Since 2003, information on hepatitis A vaccine coverage has been collected through the National Immunization Survey, an annual survey that estimates vaccination coverage among children aged 19–35 months in 50 states and 28 selected urban areas. On the basis of National Immunization Survey data from 2003–2004, the proportion of children aged 24–35 months receiving at least one dose of hepatitis A vaccine was approximately 50 percent in the 11 states where it was recommended that routine vaccination be implemented and 25 percent in the six states where routine vaccination was to be considered (122). Coverage in this age group in the remaining states was 1 percent. Further analysis of the National Immunization Survey data found that in addition to living in a state where routine vaccination was recommended, other factors associated with having received hepatitis A vaccine included living in an urban area, being Hispanic or Native American, and having a mother with less than a high school education (123). These results suggest that at least some proportion of vaccination efforts has been focused on the children with the highest risk of hepatitis A. Limited coverage data among somewhat older

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children, available from vaccine registries of selected populations in five states included in the recommendations, indicated that as of 2004, 44–81 percent of children aged 3–5 years had received one or more doses of hepatitis A vaccine (120).

Based on the information on vaccine usage available to date, the observed declines in rates among children appear to have been achieved with relatively modest levels of coverage, supporting the hypothesis of a strong herd immunity effect. Declines in rates among adults in ''vaccinating states'' were larger than those in ''nonvaccinating states,'' suggesting that vaccination of children also might have reduced transmission in other age groups through herd immunity. Additional evidence of such an effect was seen in a demonstration project done in Butte County, California, where vaccination of children (approximately 66 percent coverage with at least one vaccine dose among 45,000 eligible children) resulted in a substantial reduction in disease rates not only in the vaccinated age group but also in adults (115). Mathematical modeling of the relation between hepatitis A incidence and vaccination coverage suggested that more than one third of the total estimated number of cases prevented by vaccination was the result of herd immunity (121).

Similar findings have been reported from other countries in which routine hepatitis A vaccination of infants or children has been implemented. In Israel, where all 18-month-old children have been vaccinated each year since 1999 and the first-dose coverage level among toddlers in 2001–2002 was 90 percent, a 98 percent decline during 2002–2004 in rates in the vaccinated age group was accompanied by a decline in older children and adults of more than 90 percent (117). In Catalonia (Spain), where vaccination of 11- to 12-year-olds has been ongoing since September 1998 and estimated coverage in the vaccinated cohort is 94 percent, the overall average hepatitis A rate in the region declined from 6.2/100,000 population during the 3 years before the vaccination program to 2.6/100,000 population during the subsequent 3 years. The greatest decline occurred in the vaccinated age group, children aged 10–14 years, in which the average rate fell from 10.3/100,000 to 1.8/100,000, but statistically significant declines were also observed in other age groups (124).

FUTURE CONSIDERATIONS

The efficacy of vaccination against hepatitis A is expected to be long-lasting, and no current data support a need for booster doses after completion of the primary series, but additional studies to monitor the duration of protection are needed. In particular, long-term protection after vaccination in childhood must be monitored to avoid inadvertently shifting the age of infection to older children and adults, for whom morbidity is higher. Additional information on the safety of the vaccine will also be important. Results from studies comparing the efficacy of vaccine with that of immune globulin when used for postexposure prophylaxis are eagerly awaited.

In most communities with high incidence rates, transmission among children is the means by which transmission is sustained, and routine vaccination early in childhood would greatly reduce the incidence of HAV infection. In the developing world, asymptomatic HAV infection during early childhood (with subsequent lifetime immunity) is nearly universal, and disease is uncommon. In these areas, vaccination is unlikely to be viewed as an important public health priority, and the primary means of reducing the incidence of HAV infection will be improvements in hygienic and living conditions. However, in areas transitioning from high or intermediate endemicity to lower levels of transmission, use of vaccine to protect adolescents or adults remaining susceptible to infection may be appropriate. Cost and feasibility are the major barriers to implementing hepatitis A vaccination programs in these countries.

In the developed world, hepatitis A immunization programs focused on children in communities where incidence is highest have demonstrated dramatic reductions in hepatitis A incidence rates. Marked declines in incidence with relatively modest vaccination coverage suggest that strong herd immunity occurs soon after the initiation of routine vaccination programs. In the United States, it is anticipated that the expansion of existing recommendations to include nationwide vaccination of 12- to 23-month-olds will result in increasing vaccination coverage and that extending vaccination to multiple cohorts will eventually eliminate HAV transmission among children and their contacts. However, even if high coverage rates are achieved among children, transmission among adults in high-risk groups will continue for several decades unless infrastructure to deliver vaccines to adults is developed.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

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