Update: Prevention of Hepatitis A After Exposure to Hepatitis A Virus and in International Travelers. Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP)

In 1995, highly effective inactivated hepatitis A vaccines were first licensed in the United States for preexposure prophylaxis against hepatitis A virus (HAV) among persons aged ≥2 years. In 2005, vaccine manufacturers received Food and Drug Administration approval for use of the vaccines in children aged 12--23 months (1).

The Advisory Committee on Immunization Practices (ACIP) issued recommendations for preexposure use of hepatitis A vaccine in 1996, 1999, and 2006 (1). Currently, ACIP recommends hepatitis A vaccination of all children at age 12--23 months, catch-up vaccination of older children in selected areas, and vaccination of persons at increased risk for hepatitis A (e.g., travelers to endemic areas, users of illicit drugs, or men who have sex with men) (1).

For decades, immune globulin (IG) has been recommended for prophylaxis after exposure to HAV (1). IG also has been recommended in addition to hepatitis A vaccine for preexposure prophylaxis for travelers to countries with high or intermediate hepatitis A endemicity who are scheduled to depart <4 weeks after receiving the initial vaccine dose. This report details updated recommendations, made by ACIP in June 2007, for prevention of hepatitis A after exposure to HAV and in departing international travelers (Box) and incorporates existing ACIP recommendations for prevention of hepatitis A (1).

Rationale and Methods for Updated Recommendations

When administered within 2 weeks of last exposure, IG is 80%--90% effective in preventing clinical hepatitis A. Despite previously available limited data suggesting that hepatitis A vaccine might be efficacious when administered after exposure (2), in the absence of an appropriately designed clinical trial comparing...
the postexposure efficacy of vaccine with that of IG, ACIP continued to recommend IG exclusively for postexposure use (1). Hepatitis A vaccine, if recommended for other reasons, could be given at the same time. ACIP was prompted to revisit these recommendations when findings became available from a randomized, double-blind noninferiority clinical trial comparing the efficacy of hepatitis A vaccine and IG after exposure to HAV (3).

The results of this clinical trial were presented to ACIP at its February 2007 meeting. During April--May 2007, the ACIP Hepatitis Vaccines Workgroup considered these results in a series of teleconferences. During these teleconferences, the workgroup also considered the experiences of other countries (e.g., Canada and the United Kingdom) where hepatitis A vaccine has been recommended for postexposure use for >5 years and reviewed data on the immunogenicity of hepatitis A vaccine, the risk for HAV transmission in various settings, and factors known to affect the severity of hepatitis A. Additionally, the workgroup took into account potential advantages of vaccine, recognized disadvantages of IG, and relevance of these data to existing recommendations for use of hepatitis A vaccine and IG in international travelers departing <4 weeks after receiving the first dose of hepatitis A vaccine. The workgroup also considered the likelihood that no additional postexposure efficacy data would become available, because of the difficulties of conducting postexposure efficacy studies of IG and vaccine.

On the basis of this evidence and the expert opinions of workgroup members, other scientists, and feedback from ACIP partner organizations, the ACIP Hepatitis Vaccines Workgroup drafted a revision of the hepatitis A postexposure prophylaxis and travel recommendations. These updated recommendations were deliberated and approved by ACIP at the June 2007 meeting.

I. Prevention of Hepatitis A After Exposure to HAV

Efficacy of hepatitis A vaccine versus IG. The clinical trial comparing hepatitis A vaccine with IG was conducted among 1,090 persons aged 2--40 years who were contacts of hepatitis A cases and susceptible to HAV infection. The trial compared the efficacy of hepatitis A vaccine and IG in preventing laboratory-confirmed symptomatic hepatitis A (i.e., the primary outcome) when administered ≤14 days after exposure to HAV (3). The primary outcome occurred among 25 (4.4%) of 568 recipients of hepatitis A vaccine and 17 (3.3%) of 522 IG recipients (relative risk: 1.35; 95% confidence interval [CI] = 0.70--2.67); the prespecified statistical criterion for noninferiority was met. The low frequency of study endpoints among IG and vaccine recipients indicated that both interventions provided good protection. The risk for hepatitis A in the vaccine group was never more than 1.5 percentage points greater than that for the IG group for the primary outcome or any secondary study endpoint. Assuming IG is 90% efficacious, the point estimate for hepatitis A vaccine efficacy relative to IG in preventing clinical hepatitis A was 86% (CI = 73%--93%) (3). This clinical trial suggested that the performance of vaccine, when administered <14 days after exposure, approaches that of IG in healthy children and adults aged ≤40 years. However, these findings might not be generalizable to all populations and settings. In contrast, years of experience have demonstrated that IG performs well as postexposure prophylaxis in all populations and settings.

Advantages of hepatitis A vaccine. The ability to use hepatitis A vaccine for postexposure prophylaxis
provides numerous public health advantages, including the induction of active immunity and longer protection, greater ease of administration, higher acceptability and availability, and a cost per dose that is similar to IG. Also, the greater availability and ease of administration of hepatitis A vaccine might increase the number of persons at risk for infection who receive postexposure prophylaxis.

**Risk for HAV transmission in various settings.** The risk for transmission of HAV is influenced by host and environmental factors and varies considerably in different settings. For example, without postexposure prophylaxis, secondary attack rates of 15%--30% have been reported in households, with higher rates of transmission occurring from infected young children than from infected adolescents and adults (4--6). In contrast, attack rates among patrons of food service establishments who have been exposed to HAV-infected food handlers generally are low (7). Indeed, most food handlers with hepatitis A do not transmit HAV to exposed consumers or restaurant patrons (7). Given the wide range of HAV transmission risks in various settings for which postexposure prophylaxis is recommended, magnitude of risk in each situation is an important factor in determining whether to use IG or vaccine.

**Factors affecting clinical manifestations of hepatitis A.** Older persons and persons with chronic liver disease are more likely to have severe manifestations of hepatitis A. Among older children and adults, infection typically is symptomatic, with jaundice occurring in >70% of patients (8). The case-fatality rate among cases reported through national surveillance reaches a high of 1.8% among persons aged ≥60 years, and fulminant hepatitis has been reported more frequently among older patients with hepatitis A (9). Although not at increased risk for HAV infection, persons with chronic liver disease also are at increased risk for fulminant hepatitis A (10). Because of the frequency of severe consequences, preventing hepatitis A among exposed older persons and persons with chronic liver disease is particularly vital. The performance of hepatitis A vaccine as postexposure prophylaxis in these groups was not assessed in the recent clinical trial and remains unknown. In contrast, IG has been recommended and used successfully for many years in these groups and in the general population.

These recommendations replace previous ACIP recommendations for postexposure prophylaxis with IG (1), incorporating new recommendations for use of single-antigen hepatitis A vaccine and updated recommendations for use of IG postexposure. These recommendations also incorporate and consolidate existing recommendations regarding recommended settings for which postexposure prophylaxis is indicated, including close personal contact with a person with hepatitis A and selected circumstances in which hepatitis A is recognized in a food handler or in a child care center (1). Also, the updated recommendations leave unchanged the recommendation that postexposure prophylaxis (using vaccine or IG) should be administered as soon as possible. No information exists regarding the efficacy of IG or vaccine if administered >2 weeks after exposure (1). The updated recommendations for use of hepatitis A vaccine alone for postexposure prophylaxis do not apply to the combination hepatitis A/hepatitis B vaccine because no data exist regarding the performance of the combination vaccine for prophylaxis after exposure to HAV. The concentration of HAV antigen in the currently available combination vaccine formulation is half that included in the single-antigen vaccine available from the same manufacturer (1).

**Recommendations for postexposure prophylaxis with IG or hepatitis A vaccine.** Persons who
recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of single-antigen vaccine or IG (0.02 mL/kg) as soon as possible. Information about the relative efficacy of vaccine compared with IG postexposure is limited, and no data are available for persons aged >40 years or those with underlying medical conditions. Therefore, decisions to use vaccine or IG should take into account patient characteristics associated with more severe manifestations of hepatitis A, including older age and chronic liver disease.

For healthy persons aged 12 months--40 years, single-antigen hepatitis A vaccine at the age-appropriate dose is preferred to IG because of vaccine advantages that include long-term protection and ease of administration. For persons aged >40 years, IG is preferred because of the absence of information regarding vaccine performance and the more severe manifestations of hepatitis A in this age group; vaccine can be used if IG cannot be obtained. The magnitude of the risk for HAV transmission from the exposure should be considered in decisions to use IG or vaccine. IG should be used for children aged <12 months, immunocompromised persons, persons who have had chronic liver disease diagnosed, and persons for whom vaccine is contraindicated.

Persons administered IG for whom hepatitis A vaccine also is recommended for other reasons should receive a dose of vaccine simultaneously with IG. For persons who receive vaccine, the second dose should be administered according to the licensed schedule to complete the series. The efficacy of IG or vaccine when administered >2 weeks after exposure has not been established.

Close personal contact. Hepatitis A vaccine or 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 hepatitis A vaccine, or IG and hepatitis A vaccine simultaneously. Consideration also should be given to providing IG or hepatitis A vaccine to persons with other types of ongoing, close personal contact (e.g., regular babysitting) with a person with hepatitis A.

Child care centers. Hepatitis A vaccine or IG should be administered to all previously unvaccinated staff members 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, hepatitis A vaccine or IG need be administered only to classroom contacts of the index patient. When an outbreak occurs (i.e., hepatitis A cases in three or more families), hepatitis A vaccine or IG also should be considered for members of households that have children (center attendees) in diapers.

Common-source exposure. If a food handler receives a diagnosis of hepatitis A, vaccine or IG should be administered to other food handlers at the same establishment. Because common-source transmission to patrons is unlikely, hepatitis A vaccine or 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 or cooked foods 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 hepatitis A vaccine or IG use could be warranted. In the event of a common-source outbreak, postexposure prophylaxis should not be provided to exposed persons after cases have begun to occur because the 2-week period after exposure during which IG or hepatitis A vaccine is known to be effective will have been exceeded.

Schools, hospitals, and work settings. Hepatitis A postexposure prophylaxis is not routinely indicated when a single case occurs in an elementary or secondary school or an office or other work setting, 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 members should not routinely be administered hepatitis A postexposure prophylaxis; instead, careful hygienic practices should be emphasized. Hepatitis A vaccine or 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 members in a hospital.

II. Prevention of Hepatitis A Before International Travel

Hepatitis A vaccination is recommended to prevent hepatitis A among travelers to countries with high or intermediate hepatitis A endemicity. Previously, however, because few data were available regarding the immunogenicity of hepatitis A vaccine during the 4 weeks immediately following administration of the first dose, ACIP recommended that, for optimal protection, persons traveling to an area where the risk for transmission was high <4 weeks after the initial vaccine dose also could be administered IG (1). In June 2007, ACIP concluded that if hepatitis A vaccine alone can be recommended for prophylaxis after exposure to HAV, vaccine also should be recommended for healthy international travelers aged <40 years regardless of their scheduled dates for departure. Similar to updated recommendations for postexposure prophylaxis, ACIP recognized that, for certain international travelers (e.g., older adults or those with underlying medical conditions), the performance of vaccine alone is unknown and clinical manifestations of hepatitis A tend to be more severe. Hence, under the updated recommendations for international travelers, for optimal protection, IG can be considered in addition to vaccine for older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions who are traveling to an area within 2 weeks.

The following recommendation updates recommendations for prevention of hepatitis A among travelers departing in <4 weeks to areas where prophylaxis is recommended and consolidates other recommendations for prevention of hepatitis A among international travelers (1). These recommendations replace previous ACIP recommendations for preexposure protection against hepatitis A for travelers (1).

**Recommendations for preexposure protection against hepatitis A for travelers.** All susceptible persons traveling to or working in countries that have high or intermediate hepatitis A endemicity are at increased risk for HAV infection and should be vaccinated or receive IG before departure.* Hepatitis A vaccination at the age-appropriate dose is preferred to IG. Data are not available regarding the risk for hepatitis A for persons traveling to certain areas of the Caribbean, although prophylaxis should be considered if travel to areas with questionable sanitation is anticipated. Travelers to Australia, Canada, western Europe, Japan, or
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New Zealand (i.e., countries in which endemicity is low) are at no greater risk for infection than persons living or traveling in the United States.

The first dose of hepatitis A vaccine should be administered as soon as travel is considered. Based on limited data indicating equivalent postexposure efficacy of IG and vaccine among healthy persons aged <40 years, 1 dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons. However, no data are available for other populations or other hepatitis A vaccine formulations (e.g., Twinrix®). For optimal protection, older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions planning to depart to an area in <2 weeks should receive the initial dose of vaccine and also simultaneously can be administered IG (0.02 mL/kg) at a separate anatomic injection site. Completion of the vaccine series according to the licensed schedule is necessary for long-term protection.

Travelers who elect not to receive vaccine, are aged <12 months, or are allergic to a vaccine component should receive a single dose of IG (0.02 mL/kg), which provides effective protection against hepatitis A for up to 3 months. Such travelers whose travel period is expected to be >2 months should be administered IG at 0.06 mL/kg; administration must be repeated if the travel period is >5 months. The full statement containing licensed vaccination schedule and recommended dose of IG and vaccine has been published previously (1).

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References

4. Victor JC, Surdina TY, Suleimenova SZ, Favorov MO, Bell BP, Monto AS. Person-to-person transmission of


Box
BOX. Summary of updated recommendations for prevention of hepatitis A after exposure to hepatitis A virus (HAV) and in departing international travelers

Postexposure prophylaxis
Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of single-antigen hepatitis A vaccine or immune globulin (IG) (0.02 mL/kg) as soon as possible.

- For healthy persons aged 12 months–40 years, single-antigen hepatitis A vaccine at the age-appropriate dose is preferred.
- For persons aged >40 years, IG is preferred; vaccine can be used if IG cannot be obtained.
- For children aged <12 months, immunocompromised persons, persons who have had chronic liver disease diagnosed, and persons for whom vaccine is contraindicated, IG should be used.

International travel
All susceptible persons traveling to or working in countries that have high or intermediate hepatitis A endemicity should be vaccinated or receive IG before departure. Hepatitis A vaccine at the age-appropriate dose is preferred to IG. The first dose of hepatitis A vaccine should be administered as soon as travel is considered.

- One dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons.
- Older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions planning to depart to an area in ≤2 weeks should receive the initial dose of vaccine and also simultaneously can be administered IG (0.02 mL/kg) at a separate anatomic injection site.
- Travelers who elect not to receive vaccine, are aged <12 months, or are allergic to a vaccine component should receive a single dose of IG (0.02 mL/kg), which provides effective protection for up to 3 months.

NOTE: Previous recommendations remain unchanged regarding 1) settings in which postexposure prophylaxis is indicated, and 2) timing of administration of postexposure prophylaxis.