
Another Success for Hepatitis A Vaccine

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Before the licensure of the first inactivated hepatitis A vaccine in 1995, hepatitis A caused a substantial disease burden in the United States. Annual cases reported to the Centers for Disease Control and Prevention (CDC) numbered 25,000 to 30,000, but a more accurate estimate approached 300,000, since infection in young children often was subclinical and mild and self-limited disease in adults was underreported.¹ Infection rates were highest among children younger than 5 years of age, but only 30% of these children were symptomatic. Older children and adults had lower infection rates, but in approximately 70% of cases they were symptomatic. Most symptomatic patients had a self-limited illness manifested by fever, malaise, nausea, vomiting, and jaundice, but up to 15% of adults had prolonged or relapsing illness for up to 6 months. Death from fulmi-

nant hepatitis was rare, typically occurring in people with underlying chronic liver disease.

Since the introduction of the second hepatitis A vaccine in the United States in 1996, recommendations for the use of the two hepatitis A vaccines in children have gradually expanded. Initially, both vaccines were recommended for use in children 2 years of age or older living in states and counties with rates of hepatitis A that were historically above the national average. This regional strategy for children at higher risk for exposure to hepatitis A was so successful that infection rates in states where immunization was recommended decreased to levels below those in states where immunization was not recommended, suggesting robust herd immunity (i.e., protection of nonvaccinated children and adults).² The next logical step was to recommend hepati-

tis A vaccine for 2-year-old children in all 50 states. Finally, results from studies in toddlers led the Food and Drug Administration to license both hepatitis A vaccines in 2005 for children 12 to 23 months of age. This licensing permitted the vaccine's two-dose schedule to be completed by the time children were 2 years of age, and it facilitated the addition of hepatitis A vaccine into the routine childhood immunization schedule.¹ Provisional data from the CDC indicate that in 2006, reported cases of hepatitis A were at their lowest number (<4000 cases) in 40 years of U.S. surveillance.²

With the number of hepatitis A cases now at a record low, a greater proportion of cases arise from foodborne outbreaks. As compared with endemic hepatitis A infection, in which fecal-oral spread within a household results from direct contact with a person who excretes the virus, in foodborne outbreaks, the virus is transmitted through food that often has been contaminated by the inadequately cleansed hands of a food handler. Although foodborne outbreaks of hepatitis A typically involve a few hundred persons who are exposed to the virus, such outbreaks can sometimes involve thousands of persons³ who require postexposure prophylaxis.

Historically, prophylaxis consisted of the administration of immune globulin within 14 days after exposure. This intervention antedated the development of hepatitis A vaccine, and it has continued to be recommended by the CDC's Advisory Committee on Immunization Practices (ACIP) because of its effectiveness. However, in June 2007 a new strategy for postexposure prophylaxis was approved by the ACIP.⁴ This strategy involved the use of hepatitis A vaccine in preference to immune globulin for postexposure prophylaxis. What changed?

On the basis of encouraging results from investigators in the United States who used hepatitis A vaccine as postexposure prophylaxis in animal models,⁵ in 1997 Sagliocca et al.⁶ performed a randomized trial involving 212 household contacts of patients with hepatitis A; these contacts were 1 to 40 years of age. Within 1 week after exposure, the contacts received either hepatitis A vaccine or no intervention. This trial was discontinued when statistical significance was reached; the vaccine efficacy was 79% (95% confidence interval [CI], 7 to 95). These data led to recommendations for the routine use of hepatitis A vac-

cine for postexposure prophylaxis in Italy and in several other European countries.

Until the study reported by Victor et al.⁷ in this issue of the *Journal*, there were few data to allow direct comparison of immune globulin with hepatitis A vaccine for postexposure prophylaxis. As of the beginning of 2007, the U.S. recommendation for a single intramuscular dose of immune globulin within 14 days after exposure to the virus remained the intervention for postexposure protection against hepatitis A. However, in the United States, reliance on immune globulin in this clinical setting has met with new problems. Immune globulin currently is manufactured only by one company, its supply is limited, and its price has increased considerably during the past year.

Victor and colleagues⁷ present an alternative approach to postexposure prophylaxis. They report the results of a randomized, double-blind, active-control, noninferiority trial comparing the efficacy of hepatitis A vaccine with that of immune globulin in Almaty, Kazakhstan. Laboratory-confirmed, symptomatic hepatitis A infection occurring between 15 and 56 days after exposure was diagnosed in index patients and their contacts on the basis of clinical symptoms, positivity for IgM antibodies to hepatitis A in blood specimens, elevated liver alanine aminotransferase levels, and polymerase chain reaction for the hepatitis A virus in serum and stool specimens. Vaccine and immune globulin were administered at age-appropriate or weight-appropriate doses. After a baseline serologic analysis to determine susceptibility to hepatitis A, more than 4500 contacts of patients with hepatitis A underwent randomization to receive a study intervention. Among the 31% of contacts (primarily children or young adults) determined to be susceptible to the virus, 568 received vaccine and 522 received immune globulin at a mean interval of 10 days after exposure to an index patient. Symptomatic hepatitis A was confirmed in 25 contacts who received vaccine (4.4%) and in 17 contacts who received immune globulin (3.3%) (relative risk, 1.35; 95% CI, 0.70 to 2.67), proving that hepatitis A vaccine and immune globulin each provide good protection. More important, vaccine in the United States has several advantages over immune globulin. It provides long-term protection, its supply is abundant, its administration is easy, and vaccine now approaches the cost of immune globulin.

The data have some limitations. The subjects in the Kazakhstan trial were persons 2 to 40 years of age with no history of hepatitis A infection or other liver disease and no contraindications for study interventions; thus, the use of immune globulin with or without hepatitis A vaccine should be continued for postexposure prophylaxis in children younger than 2 years of age, in adults older than 40 years of age, and in persons who are immunocompromised or who have chronic liver disease. Also, even though this large trial used excellent epidemiologic and virologic definitions of primary and secondary outcomes, the slightly higher, nonsignificant rates of hepatitis A infection among vaccine recipients could signal a true difference between the interventions.

The investigators in the United States and Kazakhstan successfully executed a well-designed clinical trial. The study suggests that hepatitis A vaccine is effective for the prevention of secondary infections. The results provide support for the recent change in U.S. policy to the preference for hepatitis A vaccine over immune globulin for postexposure prophylaxis in healthy persons 2 to 40 years of age, with the continued use of immune globulin in contacts outside this age range and in those who are immunocompromised or who have chronic liver disease.

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