

Hepatitis A Virus and the Traveler

Bradley A. Connor, MD, Brian R. Landzberg, MD

Weill Medical College of Cornell University, New York
New York Center for Travel and Tropical Medicine, New York

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The low seroprevalence of hepatitis A virus (HAV) in North America and Northern and Western Europe relative to the developing world (Figure), coupled with its ease of transmission through the fecal-oral route, makes HAV infection the most frequent vaccine-preventable disease acquired by travelers. Although the risk increases with length of stay, many cases of HAV infection are seen following brief, "standard" tourist itineraries. Historically, the risk of acquiring HAV infection during a 1-month stay in a developing country has been estimated to range from 3 cases per 1000 nonimmune vacationers and business travelers to 20 cases per 1000 nonimmune backpackers and travelers who eat and drink under poor hygienic conditions.¹ This translates to a risk 10- to 100-fold that of typhoid fever and 1000-fold that of cholera.

HAV is a pathogen in the family Picornaviridae and genus Heparnavirus, a nomenclature that reminds us that it is a small RNA virus and is acquired enterically. It is usually transmitted through contaminated food and water and by person-to-person spread. Travelers are typically infected via fecally contaminated drinking water, shellfish taken from water contaminated by sewage, food prepared by infected workers, or high-risk sexual behaviors. HAV is a markedly stable virus, which allows for its survival in inadequately cooked shellfish, thawed frozen foods, and swimming water.

HAV infection demonstrates an average incubation period of 2 to 6 weeks, and it progresses to an acute illness that can vary in severity from being subclinical to flu-like syndromes to icteric illness and even fulminant hepatic failure. Children younger than 6 years are much less likely to become icteric, or even symptomatic. Ten percent of infected children aged 1 to 14 years are hospitalized, compared with 20% of patients aged 15 to 39 years. Infected

adults miss an average of 27 days of work, and annual costs of HAV infection in the United States are estimated to be as high as \$488.8 million. More important, there is a mortality rate of 2% in adults older than 40 years; every 8 days, 1 American dies of fulminant hepatic failure caused by HAV infection, making it clear that this is not simply a "nuisance" illness. Despite its ability to cause severe acute liver disease, however, it is not a cause of chronic liver disease.

As shown in the Figure, the disease demonstrates an intermediate endemicity in countries with "transitional economies," such as those in Eastern Europe and parts of the Middle East. In these countries, improving sanitation and socioeconomic conditions have increasingly spared children from acquiring the usually clinically silent or mild cases that occur in childhood; the children thus mature to become seronegative adults who are susceptible to more clinically apparent disease.

VACCINATION

Given the potentially serious nature of HAV infection and the remarkably benign side-effect profile of the available vaccines, it is little wonder that in a field often divided with controversy, there is unanimity among most groups, including the World Health Organization and the CDC, that prophylaxis against HAV infection should be offered to all travelers to areas where HAV is intermediately or highly endemic. An additional concern is that travelers are possible vectors of illness, particularly if they travel to areas of low endemicity, affording an added public health benefit of HAV vaccination in travelers.

Vaccination for HAV alone is commercially available in 2 forms, Havrix (GlaxoSmithKline) and Vaqta (Merck Vaccine Division), both of which contain inactivated monovalent HAV adsorbed to aluminum hydroxide as an adjuvant. It is difficult to perform head-to-head comparisons of the 2 vaccines, since both use "in-house" assays to determine antibody response. Both vaccines, however, are quite safe, are proved effective, and carry a recommendation for

Dr Connor is clinical associate professor of medicine, and *Dr Landzberg* is clinical assistant professor of medicine, division of gastroenterology and hepatology, department of medicine, Weill Medical College of Cornell University, New York. They are also affiliated with the New York Center for Travel and Tropical Medicine, New York.

a booster shot 6 months after the initial dose. HAV immunization is also available in the form of a combination vaccine with hepatitis B virus, marketed under the name Twinrix (GlaxoSmithKline), a preparation that confers comparable immunity and the convenience of fewer inoculations in patients who require vaccination against both viruses.

The "short-notice" traveler

As opposed to vaccination of the general population or selected patients at higher risk for morbidity from HAV infection, such as patients with cirrhosis, vaccination in travelers often poses a challenge of working within difficult time constraints. Patients often present for pretravel counseling and vaccination within 2 weeks of intended departure. Although the average amount of notice observed in a review of travel medicine practice in the United States and Belgium was 23 and 31 days, respectively, 29% and 7.8% of travelers sought care less than 1 week before departure.^{2,3}

The conservative approach to these patients adopted by many health organizations has historically been passive immunization against HAV with immune globulin, based on the belief that complete protection might not develop until 4 weeks after immunization.⁴ However, more recent data from several studies looking at rapid outbreak control and postexposure prophylaxis demonstrate that seroconversion may occur earlier than 2 to 4 weeks and that protection may be achieved at antibody levels that have not yet risen to the threshold of detection of standard assays.⁵ These data, along with concerns over the safety of human-derived blood products, lead us to recommend that active immunization with HAV vaccine should be the preferred approach over immunoglobulin in short-notice travelers.

Long-term immunity

The traveler is well protected during his or her trip from the first dose of HAV vaccine. The booster dose at 6 to 12 months is given to enhance long-term immunity. There has been a concern raised, however, that many patients who receive their first dose of HAV vaccine in pretravel counseling will neglect to return for the second dose on schedule as a result of the vagaries of travel, which may keep the traveler abroad for months or years. Fortunately, recent data show that although more travelers who received delayed booster (even out to 66 months) had lost detectable antibodies compared with patients who received booster on schedule (32% versus 11%), all patients showed an anamnestic response to the booster, with a brisk rise in antibody titer regardless of serologic status.⁶ The implications of this are that delay of the booster may

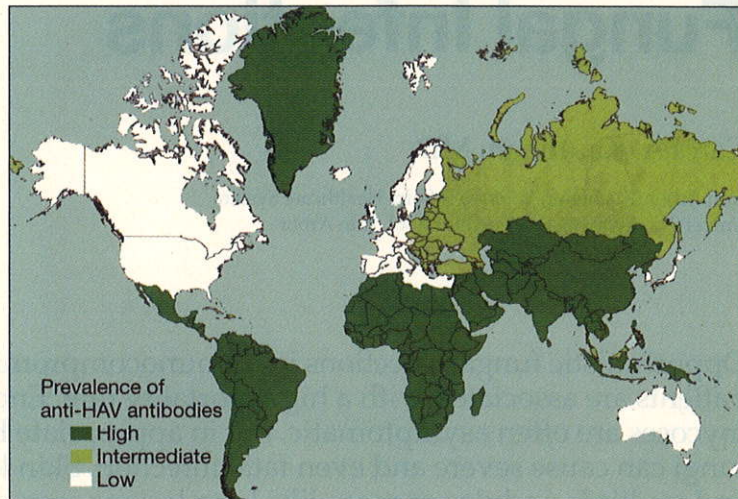


Figure – Global seroprevalence of hepatitis A virus (HAV) in 2002.⁴

not be clinically important, that immunity is achieved with levels of antibody below the threshold of detection of standard testing, that cell-mediated immune memory may play a role, and even that a booster might not be absolutely necessary.

CONCLUSIONS

HAV infection is a potentially serious disease for which travelers are at particular risk. Vaccination against HAV, using either commercially available formulation, should be a cornerstone of pretravel medical care for patients destined for intermediate- or high-prevalence areas. In light of recent data, the short-notice traveler should be offered active vaccination with HAV vaccine, rather than immunoglobulin. Long-term immunity is generally achieved even if the booster vaccine is not given to the traveler until months or years beyond the recommended time interval, although this may only be discernible by observing an anamnestic response or using serologic testing more sensitive than the standard commercially available enzyme-linked immunosorbent assays. ♦

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