North American And European Health Care Workers Traveling To Countries Highly Endemic For Hepatitis A: Information And Recommendations

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Citation

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Abstract

Hepatitis A (HAV) continues to be a significant infectious disease in today's world. Although it does not progress to chronic liver disease and in most cases is a self-limited disease, acute HAV will result in life-threatening fulminant liver failure in a minority of patients and varying degrees of morbidity, with social and economic consequences, in the majority. Despite the fact that HAV is entirely preventable by vaccination, travelers from areas of low endemicity to high endemicity still remain at risk. In this article, we review the epidemiology and clinical features of HAV and the efficacy and safety of the currently available HAV vaccines.

INTRODUCTION

Hepatitis A was first isolated in 1973 ([1]). It is a non-enveloped RNA virus belonging to the Picornaviridae family and Hepatovirus genus. Worldwide, there are approximately 1.5 million reported human cases of clinical hepatitis A per year and, along with influenza, it is considered one of the most common vaccine-preventable infections ([2]). The virus is known to cause disease in both humans and non-human primates ([3]), and while more than 95% of infections are transmitted via the fecal-oral route, parenteral and vertical transmission have been documented ([4]). Anti-HAV positivity, reflecting exposure to hepatitis A virus, is associated with older age, lower socioeconomic status and urbanization level, certain ethnic origins and lack of access to clean water and sanitation facilities ([5]). Health care workers and travelers to areas where hepatitis is highly endemic are particularly at risk ([6,7,8]). Here we review the epidemiology and clinical course of hepatitis A and the use of hepatitis A vaccinations, particularly in health care workers traveling to areas highly endemic for hepatitis A.

EPIDEMIOLOGY

Studies conducted in many African countries suggest that HAV is highly endemic on the continent, with over 90% of children demonstrating anti-HAV antibodies by age 5 ([5]). In South Africa, however, seroprevalence is somewhat variable, with almost all black individuals becoming anti-HAV positive by 12 years of age, while the seroprevalence rate in the white population is approximately 60% in the 40-49 year age group ([9]). Canada, the United States, Japan, Australia, New Zealand and most European countries have significantly lower anti-HAV positive rates, while much of Asia, South America and the Middle East continue to experience a substantial rate of infection ([5]).

Hepatitis A occurs at a rate of 0.1 to 1.0 per 1000 travelers to developing countries ([2]). For non-immunized Canadians traveling to developing countries, the incidence of hepatitis A infection is approximately 1 case per 3000 month-long trips ([10]). In a case-control study conducted by De Serres et al., the risk of acquiring hepatitis A was 5 times high in travelers who did not visit a travel clinic compared to those who did ([11]). The same study found that among the five most common destinations for Canadian travelers, Mexico had the high incidence of 11 cases per 100,000 months of travel. An Italian study found that the risk of acquiring HAV infection was three times higher among those traveling to Asia, Africa and Latin America compared to those traveling to southern Italy, the Mediterranean or Eastern Europe ([7]).

In a cross-sectional study, Nubling et al. analyzed anti-HAV serology and questionnaire information in 511 German-born, non-HAV vaccinated health care workers ([8]). In multivariate analysis, age greater than 40 years, increasing number of siblings or children, work in a children's psychiatry

department and travel to Argentina or Uruguay were significant predictors of anti-HAV positivity. Livni et al. detected HAV antibodies in 48.3% of almost 500 staff at a tertiary pediatric hospital in Israel ([12]). In multivariate analysis, including country of birth, duration of employment at the hospital and contact with pediatric patients, only older age, crowding during childhood and history of hepatitis were significantly associated with HAV antibody seropositivity. A study by Lerman et al. in Israel identified physicians, dentists, therapists and medical technicians as being in occupational groups at increased risk of hepatitis A infection ([6]).

HEPATITIS A CLINICAL COURSE & IMPACT

Replication of HAV appears to occur exclusively in hepatocytes and gastrointestinal cells, with viral particles being present in the blood, bile and stool ([13]). The virus does not to damage the liver directly, but damage occurs as a result of immune activation in response to viral infection ([3]). Following initial inoculation, the prototypical disease progresses through a 15 to 50 day incubation period, a symptomatic phase of up to a week of flu-like symptoms which may be followed by jaundice and clinical hepatitis for one to four weeks, and finally a convalescent or recovery period of up to 12 months ([3,4,13]). However, substantial variation in disease presentation and length of illness may be observed. Immunoglobulin M (IgM) and IgA are initially elevated in response to HAV infection, waning relatively quickly, while the delayed IgG response is persistent for years ([13]). Viral load of stool is highest one to two weeks prior to the appearance of symptoms and virus may continue to be present in feces at lower levels for several weeks after symptom resolution ([14]).

Hepatitis A infection may be asymptomatic or symptomatic, with increasing symptomatology associated with increasing age ([4]). Common symptoms associated with hepatitis A include nausea, vomiting and diarrhea, abdominal pain, fatigue, anorexia, fever, jaundice and dark urine. Biochemical abnormalities, particularly elevated liver transaminases, are not uncommon. Extrahepatic manifestations, such as acute renal failure, pleural or pericardial effusion, pancreatitis, hemolysis and cholecystitis, are uncommon but may be associated with HAV disease ([13]).

The social and economic impact of hepatitis A can be substantial, with one study in airline employees demonstrating an inability to work for 4 to 10 weeks following infection ([15]). Costs associated with HAV infection worldwide have been estimated to be between US$1.5 and $3.0 billion ([3]). Fulminant hepatitis, occurring at a rate of less than 1% of all hepatitis A cases, is associated with approximately 80% mortality ([4,16]). While the overall proportion of cases resulting in fulminant hepatitis is low, 10 to 20% of liver failure and liver transplant cases have been found to be due to hepatitis A infection in some regions ([4,17,18]). Several analyses have assessed the cost-effectiveness of hepatitis A vaccination. Jacobs et al. modeled the vaccination of health and public safety workers in Western United States with hepatitis B or combined hepatitis A and B vaccines ([19]). Extensive use of the combined vaccine was found to be cost-effective, with the US$5.4 million higher cost of vaccination offset by US$8.0 million reduction in treatment and loss of work related to hepatitis A infection. In another assessment, vaccination of travelers for hepatitis A, with or without prior screening for immunity, was significantly more cost-effective than passive immunization in Belgian travelers to high HAV endemic countries ([20]). Similarly, a cost-utility analysis of hepatitis A prevention among health care workers in Israel recommended selective vaccination of non-immune physicians and paramedical workers ([21]).

REVIEWS OF VACCINE IMMUNOGENICITY, EFFICACY AND SAFETY

At least eight vaccines conferring immunity against hepatitis A are currently available in various parts of the world (Table 1). The World Health Organization ([3]), Health Canada, and the United States Centers for Disease Control endorse the use of currently available inactivated hepatitis A vaccines ([3, 22, 23]). While there is limited English-language information available about the live attenuated hepatitis A vaccine Biovac A®, several recent reviews of the safety and efficacy of various hepatitis A vaccine formulations have recently been published ([24,25,26,27,28,29]).

Andre et al. reviewed the immunogenicity, efficacy, safety and official recommendations for the use of Havrix® hepatitis A vaccine ([24]). In two studies involving almost 800 adults, over 97% of participants seroconverted, defined as the achievement of anti-HAV antibody levels greater then or equal to 20 mIU/mL, following two doses of vaccine spaced six to twelve months apart. In other studies, 77 to 88% of adults seroconverted within fifteen days of vaccination, with younger adults demonstrating a faster rate of seroconversion

compared to older adults. Protective antibody levels were projected to persist for more than 25 years following two vaccines doses.

A systematic review of the effectiveness and safety of hepatitis A vaccines in randomized trials by Demicheli and Tiberti identified eight relevant trials ([25]). In children, pooled inactivated hepatitis A vaccine effectiveness was 86% (95% CI 63 – 95%) and live attenuated vaccine effectiveness was 95% (95% CI 81 – 99%). The effectiveness of the vaccine in preventing secondary cases of hepatitis A infection in 404 healthy young children and adults was 82% (95% CI 23 – 96%) and no significant difference in local adverse effects was identified when active vaccine and placebo were compared.

Franco et al. also reviewed data on hepatitis A vaccines ([26]). They found that in trials of the vaccine Havrix®, involving approximately one thousand individuals 17 years or older, three doses of 720 ELISA units at 0, 1 and 6 months led to seroconversion rates of 88 to 100% after 1 month and almost 100% after 7 months. In an efficacy trial, Vaqta® was found to be 100% efficacious after 50 days when 519 immunized children were compared with 518 controls, and a trial of Havrix® involving almost 40,000 Thai children demonstrated a 94% HAV protection rate after two vaccine doses and 100% protection after booster doses were completed.

Stoffel et al. investigated the immunogenicity of Twinrix®, a combined hepatitis A and B vaccine, in adults aged 40 years and above ([27]). Data from five clinical trials involving older adults were retrospectively combined. Following three doses of at least 720 ELISA units at 0, 1 and 6 months, the rate of seroconversion was 99.4% in the 41 to 50 year age group and 100% in the 51 to 60 and over 50 year age groups. There was a trend toward higher geometric mean concentrations of anti-HAV antibodies in younger subjects. The immune response induced by the combination vaccine Twinrix® was at least as good as the response elicited when separate hepatitis A vaccine Havrix® and hepatitis B vaccine Engerix-B® were given simultaneously (93% versus 91.5% seroconversion rates).

Vidor et al. reviewed immunogenicity data from 37 clinical trials in 20 countries with the Aventis Pasteur vaccines Avaxim® and Vivaxim®, both of which contain inactivated HAV ([28]). Of individuals 16 years of age and older immunized with vaccines containing 160 ELISA units of HAV, almost 100% achieved protective levels of anti-HAV antibodies four weeks after the primary vaccine dose. No clinically significant effects on serological response to hepatitis A vaccination were detected when given in combination with other vaccines, either as monovalent or multivalent formulations. Similarly, no clinically significant differences in immunogenicity were detected in studies where patients received hepatitis A vaccines from different manufacturers at different time points during their dosing schedule, including Havrix-Avaxim®, Vaqta-Havrix® and Havrix-Epaxal®.

Van Damme and Van Herck reviewed the efficacy, immunogenicity and tolerability of the combined hepatitis A and B vaccine Twinrix® ([29]). In six randomized, double blinded clinical trials in evolving 843 healthy adults, Twinrix® was given at 0, 1 and 6 months. At one month, 94.3% of participants had seroconverted, 99% had seroconverted at 2 months and 100% of participants seroconverted after the final dose. Seroconversion rates for Twinrix® were found to be comparable to conversion rates following monovalent hepatitis A and hepatitis B vaccination (99.6 – 199% vs. 99.3 – 100%). A retrospective review of 1694 adults given Twinrix® revealed that 79% of participants seroconverted within 13 days of a single vaccine dose and all participants seroconverted within 19 days. Twinrix® has an excellent safety profile in clinical trial and commercial use to date, with allergic-type reactions (1 per 41,055 doses), fever, injection site reactions, abdominal pain, other pain and nausea being the most common adverse effects reported in post-marking surveillance.

Most guidelines and HAV vaccine manufacturers recommend vaccination for hepatitis A approximately four weeks before possible exposure ([23]). However, based on data showing that most healthy individuals demonstrate HAV seroconversion approximately 2 weeks after hepatitis A vaccination and an average HAV incubation period of 15 days, one clinician argues that vaccination up to and including immediately before departure to a hepatitis A endemic area should provide ample protection to at-risk travelers ([30]).

Figure 1

Table 1: Hepatitis A vaccines for adult use

Brand name	Manufacturer	Formulation	Adult Dosage
Havrix® (Hepatitis A vaccine)	GlaxoSmithKline	Inactivated; 1440 ELISA units (E.U.) hepatitis A antigen adsorbed onto aluminum hydroxide	1440 E.U. (1.0mL) IM primary dose + 1440 E.U. booster dose in 6 – 12 months
Twinrix® (combined hepatitis A & B vaccine)	GlaxoSmithKline	Inactivated; 720 ELISA units (E.U.) hepatitis A antigen + 20µg hepatitis B surface antigen adsorbed onto aluminum hydroxide	720 E.U. HAV/20µg HBV (1.0mL) IM dose at 0, 1 and 6 months (3 doses) or 0, 7, 21 days and 12 months (4 doses)
Hepatyrix (Combined typhoid and hepatitis A vaccine)	GlaxoSmithKline	Inactivated;1440 ELISA units (E.U.) hepatitis A antigen adsorbed onto aluminum hydroxide + 25µg typhoid Vi polysaccharide antigen	1440 E.U. HAV/25µg typhoid Vi polysaccharide (1.0mL) primary dose + booster dose in 6 – 12 months.
AVAXIM® (Hepatitis A vaccine)	Sanofi Pasteur	Inactivated; 160 antigen units HAV adsorbed onto aluminum hydroxide	160 antigen units HAV (0.5mL) IM primary dose + booster dose in 6 – 12 months.
ViVAXIM® (Combined typhoid and hepatitis A vaccine)	Sanofi Pasteur	Inactivated; 160 antigen units HAV adsorbed onto aluminum hydroxide and 25µg *Salmonella typhi* Vi capsular polysaccharide	160 antigen units HAV + 25µg typhoid Vi polysaccharide (1.0mL) IM primary dose + booster dose in 6 – 12 months.
Epaxal® (Hepatitis A vaccine)	Berna Biotech	Inactivated; Minimum 500 radioimmunoassay units hepatitis A virus adsorbed onto influenza virosome; aluminum-free	500 radioimmunoassay units HAV (0.5mL) IM primary dose + booster dose in 12 months
Vaqta® (Hepatitis A vaccine)	Merck Frosst	Inactivated; 50 units hepatitis A antigen adsorbed onto aluminum hydroxide	50 U (1.0mL) IM primary dose + identical booster dose in 6-12 months
Biovac A® (Hepatitis A vaccine)	Zhejiang Pukang Biotechnology, Wockhardt	Live attenuated hepatitis A virus (H2 strain)	$10^{6.5}$ $TCID_{50}$ virus (1.0mL) SC as a single dose

IM = intramusculary; HAV = hepatitis A virus; HBV = hepatitis B virus, TCID = tissue culture infecting dose

CONCLUSIONS

More than twenty years after it was first isolated, the hepatitis A virus continues to be a leading cause of infectious disease. Disease severity may range from asymptomatic infection to fulminant liver failure and death. While socioeconomic factors, such as crowding during childhood and lack of access to clean water supplies are major risk factors for disease acquisition, health care workers from developed countries traveling to countries where HAV is highly endemic are also vulnerable. Inactivated vaccines against hepatitis A are highly effective and safe and are universally recommended for this occupational group.

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