Hepatitis A

Prevention in travellers

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This article is the final in our travel medicine series for 2010, providing a summary of prevention strategies and vaccinations for infections that may be acquired by travellers. The series aims to provide practical strategies to assist general practitioners in giving travel advice, as a synthesis of multiple information sources which must otherwise be consulted.

Background
Hepatitis A is the second most common vaccine preventable infection in travellers. Highly effective vaccines exist for its prevention for travellers from 12 months of age, including last minute travellers and those in special risk groups.

Objective
Information about hepatitis A infection, its epidemiology and existing vaccine options is presented for use in travel related consultations in general practice.

Discussion
Most travellers at risk of hepatitis A should be vaccinated, as the vaccine is a safe and effective means of prevention. Combination vaccines – hepatitis A/hepatitis B and hepatitis A/typhoid – aim to facilitate the vaccination process for travellers, who are often also at risk of exposure to hepatitis B and typhoid fever.

Keywords: travel; preventive medicine; immunisation; communicable diseases; hepatitis A

Hepatitis A is the second most common vaccine preventable infection in travellers, influenza being most common,[1] and the most common form of viral hepatitis.[2] It is an acute liver infection caused by a hepatovirus of the Picornavirus family, the hepatitis A virus (HAV). Hepatitis A virus is a ribonucleic acid (RNA) virus shed in large quantities in the stool of infected persons. It can survive for weeks in water, marine sediment, shellfish or soil, and can persist on the hands for several hours and much longer in food kept at room temperature. It is also resistant to heat and freezing.[3,4–6]

Hepatitis A is a human infection, with no animal reservoir.[4,6] It is associated with poor hygiene and overcrowding.[7] Globally approximately 1.2 billion people have no clean drinking water, while a further 2.6 billion lack adequate sanitation services.[8] Transmission is via the faecal/oral route and can occur through direct person-to-person contact,[3,4–6] with occasional transmission through sexual contact and blood transfusions.[3] There are seven human genotypes of HAV[3] and many strains but only one serotype, so immunity to one strain is protective against all hepatitis A viruses.[4,6]

The incubation period of HAV is 15–50 days.[4,5] Childhood infection is generally asymptomatic, while 75% of adults develop icteric disease. Patients usually have 4–10 days of systemic prodromal symptoms including fever, malaise, weakness, anorexia, nausea and vomiting. Acute hepatitis then manifests as dark urine, followed by jaundice and pale stools 1–2 days later, with gradual resolution of the other symptoms. Malaise and anorexia may persist and hepatic discomfort and pruritus may occur. Liver function usually returns to normal or near normal within a month. Complications are unusual but rarely include fulminant hepatitis.[4] Chronic infection does not occur, although 10% have prolonged or relapsing symptoms over 6–9 months.[5]

The case fatality rate rises with age: 27 per 1000 in those aged 50+ years, but only 0.004 per 1000 in the 5–14 years age group. It is also higher in individuals with chronic liver disease including chronic viral hepatitis,[6] and possibly in women.[9]

Diagnosis is by detection of anti-HAV immunoglobulin M (IgM) in acute phase serum. Immunoglobulin M persists for 3–6 months after the acute illness. Serum anti-HAV immunoglobulin G (IgG) is an indication of past infection or immunisation and is likely to persist for life.[2,4,5] There is no specific treatment; supportive measures are used, usually with complete recovery.[3,5]

Epidemiology

Hepatitis A occurs sporadically and in epidemics worldwide and tends to recur cyclically. An

estimated 1.4 million cases occur each year,[3,10] however this is likely to be an underestimate due to incomplete reporting,[2] and the actual incidence may be up to 10 times higher.[10] Geographic regions are divided into three broad categories according to HAV endemicity (*Table 1*).

In high and very high endemicity areas, most children are infected early and clinical disease is uncommon.[6] Disease incidence may vary from 1–150 per 100 000 per year.[2] In intermediate endemicity areas, clinical disease may be an important public health problem as sporadic cases and outbreaks occur among adolescents and young adults.[6] Disease incidence may equal that of high endemicity areas,[2] with flooding potentially increasing the outbreak frequency.[11] In low and very low endemicity areas, infections occur in specific settings and mainly during travel. Downward shifts in endemicity have occurred in parts of Asia and Europe due to improvements in clean water supplies and food hygiene, leaving adolescents and adults susceptible to infection.[2,6] Disease incidence is 5–15 per 100 000 per year in low endemicity areas and less than 5 per 100 000 per year in very low endemicity areas.[2]

Australia has moved from intermediate to low endemicity since the 1950s, with immunity found in 60% of those aged >60 years due to asymptomatic childhood infection, but in only 1–2% of young adults. While >90% of children in remote Aboriginal communities had previously been infected by 5 years of age, improved living conditions have shifted endemicity to intermediate, with subsequent outbreaks in older age groups.[6] In Australia during the 1990s, numerous outbreaks occurred in childcare centres and kindergartens, in communities of men who have sex with men, schools, residential units for the intellectually disabled, and in communities of injecting drug users (where inadequate hygiene was an issue); a large 1997 New South Wales outbreak was associated with raw oysters. Since then, HAV notifications have markedly declined,[4] although a Victorian outbreak in 2009 was linked to semidried tomatoes.[12] Immunisation programs for northern Queensland toddlers have effectively prevented both disease and infection.[6] Indigenous children remain at greater risk of infection and severe disease compared to nonindigenous children.[4]

Risk to travellers

The risk to nonimmune travellers was considered to be three per 1000 per month of travel to a developing country in good quality accommodation, rising to 20 per 1000 per month for budget travellers including backpackers and trekkers.[6,13] Now the overall risk for nonimmune travellers has reduced to 6–30 per 100 000 per month in areas of high or intermediate endemicity[14] due to an improvement in hygiene standards. Older nonimmune travellers are at greater risk of severe disease.[2] It is important to give appropriate preventive information to travellers visiting friends and relatives who are at increased risk of infection (especially individuals who have grown up in a developed country and lack immunity).[15–17]

Prevention in travellers

The mainstay of HAV prevention in travellers is education regarding hygiene and food and water precautions, and vaccination.

Vaccines

Hepatitis A vaccines are highly immunogenic,[17] with virtually universal seroconversion by 4 weeks.[4] *Table 2* summarises HAV vaccines available in Australia. Vaccines may be administered simultaneously, with, or within any time of other travel related

Table 1. Worldwide endemicity of HAV infection[2,3]

HAV endemicity*	Region by epidemiological pattern	Average age of patient	Most likely mode of transmission
Very high	Africa, parts of South America, the Middle East, parts of Asia (including India, China, Nepal, Vietnam)	<5 years	Person-to-person Contaminated food and water
High	Brazil – Amazon Basin Some parts of China Latin America (shifting toward intermediate endemicity in Mexico, Chile, Dominican Republic, Brazil in general, Venezuela, Argentina)	5–14 years	Person-to-person Outbreaks Contaminated food or water
Intermediate	Southern and Eastern Europe (shifting toward low endemicity) Some regions of the Middle East and Asia (including Indonesia, Korea, Malaysia, Philippines, Thailand)	5–24 years	Person to person Outbreaks Cntaminated food or water
Low	Australia, USA, western Europe Some parts of Asia (including Hong Kong, Singapore, Taiwan)	5–40 years	Common source outbreaks (contaminated food/water)
Very low	Northern Europe, Japan	>20 years	Exposure during travel to high endemicity areas Uncommon source outbreaks

* Endemicity can vary between regions and population groups within countries

Table 2. Inactivated hepatitis A vaccines available in Australia – recommended dosages and schedules[4]

	Age (years)	Volume per dose (contains***)	Vaccination schedule
Monovalent	**Hepatitis A**		
Avaxim (Sanofi Pasteur)	>2	0.5 mL (160 ELISA units of inactivated HAV antigens)	0, 6–12 months
Havrix Junior (GlaxoSmithKline)	2–16	0.5 mL (720 ELISA units of inactivated HAV antigens)	0, 6–12 months
Havrix 1440 (GlaxoSmithKline)	>16	1 mL (1440 ELISA units of inactivated HAV antigens)	0, 6–12 months
VAQTA Paed (CSL/Merck Sharp&Dohme)	1–18	0.5 mL (25 units of inactivated HAV protein)	0, 6–18 months
VAQTA Adult (CSL/Merck Sharp&Dohme)	>18	1 mL (50 units of inactivated HAV protein)	0, 6–18 months
Combination	**Hepatitis A/B**		
Twinrix Junior (GlaxoSmithKline)	1–16	0.5 mL (360 ELISA units of HAV antigens and 10 µg recombinant hepatitis B surface antigen protein)	0, 1, 6 months
Twinrix 720/20 (GlaxoSmithKline)	>16	1.0 mL (720 ELISA units of HAV antigens and 20 µg recombinant hepatitis B surface antigen protein)	0, 1, 6 months
Twinrix 720/20*	1–16	1.0 mL	0, 6–12 months
Twinrix 720/20**	>16	1.0 mL	0, 7, 21 days, 12 months
Combination	**Hepatitis A/ typhoid**		
Vivaxim (Sanofi Pasteur)	>16	1.0 mL (160 ELISA units of inactivated HAV antigens and 25 µg of purified typhoid capsular polysaccharide)	0 and a single dose of monovalent adult HAV at 6–36 months; a booster dose of monovalent typhoid vaccine 3 yearly as required

* Not appropriate if rapid protection against hepatitis B is required (eg. close contact with known hepatitis B carrier)

** 'Rapid schedule' used if limited time before departure to high or intermediate endemic areas

*** Different units used due to the lack of an accepted standard. Units are not directly comparable[6]

Note: Vaqta contains no preservative. Havrix and Avaxim contain 2-phenoxyethanol. All vaccines other than Vaqta contain trace amounts of neomycin. All contain trace amounts of formaldehyde[6]

Other HA vaccines, including a live attenuated vaccine produced and widely used in China and the inactivated vaccine Epaxal (Berna), are available overseas[3,6]

vaccines.[4] Monovalent vaccine brands are interchangeable.[4,5] An interrupted course of HAV vaccine does not need to be restarted,[5,6,10] even without detectable antibody levels.[10] The first dose provides protective anti-HAV levels for at least 12 months. The second dose increases the duration of protection;[4] antibodies persist for 20 years or more.[3] Postvaccination testing for serological response is not indicated.[5] Booster doses are currently considered unnecessary in fully vaccinated individuals.[10,13] Further studies are needed to establish booster requirements in immunocompromised individuals.[10]

Hepatitis A vaccines can be administered at the last minute as the incubation period of HAV is prolonged, and immunisation may even be effective after exposure to HAV,[6,13,17–19] although they cannot be used reliably for postexposure prophylaxis.[4]

Screening for natural immunity using anti-HAV IgG to avoid unnecessary vaccination is recommended in those born before 1950; those who spent their childhood in endemic areas, including in indigenous communities; and in those with a past history of unexplained hepatitis or jaundice. If total HAV antibodies or IgG are present, the individual is immune and does not require vaccination.[3,6]

Adverse events include brief mild local reactions, injection site soreness (especially in children), headache (15%) and sometimes malaise or fatigue (5%).[4]

Contraindications include a history of anaphylaxis to a previous dose of HAV vaccine, or anaphylaxis to any of their components. Combination hepatitis A/B vaccines are contraindicated where a history of anaphylaxis to yeast exists. Pregnancy is not a contraindication.[4]

Precautions

Liver function tests are unaffected by HAV vaccines. Hepatitis A vaccines can safely be administered to HIV infected travellers (including children)[4,20] and other immunocompromised

Table 3. Recommended doses of immunoglobulin for pre- and post-exposure prophylaxis against hepatitis A[3,5]

Setting	Duration of coverage	Dose (mL/kg)
Pre-exposure	Short term (1–2 months)	0.02
	Long term (3–5 months)	0.06 (repeat 5 monthly if ongoing HAV exposure)
Postexposure*		0.02

Note: Give IG intramuscularly into deltoid or gluteal muscle, or anterolateral thigh in infants <12 months

* Australian National Health and Medical Research Council guidelines recommend human IG administration as a single intramuscular injection to close contacts of HAV cases. Doses: 0.5 mL if <25 kg, 1.0 mL if 25–50 kg, and 2.0 mL if >50 kg

persons[19] but may be less immunogenic in proportion to the degree of immune dysfunction;[6] for instance, seroconversion rates in HIV positive individuals are related to their CD4+ count.[10]

Human immunoglobulin

Australian guidelines do not recommend the routine use of human immunoglobulin (IG) for HAV prevention in travellers.[4] Concomitant administration of vaccine and IG may reduce postvaccination antibody levels by up to 50%, and in children, IG may interfere with vaccines such as measles/mumps/rubella (MMR) and varicella.[21] In addition, IG is expensive, in short supply, and a blood product with associated theoretical risks.[6] It can be given with vaccination in certain circumstances, such as aid workers deployed at short notice to emergency refugee camps, or contacts of HAV cases.[4] It may also be given in cases of moderate to severe immune dysfunction, where a protective vaccine response is uncertain, and when a history of severe reaction to a previous vaccine dose or component[6] exists (*Table 3*).

In contrast, the Centres for Disease Control and Prevention recommends that high risk travellers departing within 2 weeks – including older adults, immunocompromised persons and those with chronic liver disease or other chronic medical conditions – should receive IG at 0.02 mL/kg at the time of vaccine administration at a separate anatomical site. Those with allergy to a vaccine component, infants <12 months of age and others who for some reason cannot be vaccinated at all should also receive a single dose of IG at 0.02 mL/kg, which provides protection against HAV for up to 3 months.[5,21] The World Health Organization (WHO) recommends IG administration to those with allergies to the vaccines or their components.[3]

Special patient groups

Children

Hepatitis A is rare in developed countries, so nonimmune children travelling to endemic areas are at risk of infection, especially those visiting friends and relatives. Outbreaks have been linked to children returning from endemic areas who can asymptomatically shed HAV for long periods. Children should therefore be immunised regardless of itinerary, duration and accommodation (even those staying in luxury hotels may be affected). Children >2 years of age develop protective antibodies in 97–100% of cases 1 month after the first dose, and in 100% after the second dose. In the under 12 month age group, acquired maternal antibodies can impair the immune response to HAV vaccines. Passively acquired antibodies persist for at least 6 months then decline to undetectable levels by 12 months. Vaccines are not registered for use in infants <12 months of age, although HAV vaccines are safe and immunogenic when administered in this age group. It is unlikely that a booster dose is required after a completed vaccine course in childhood.[17,19,21,22] Human IG in the under 12 month age group is an option in some situations, although not routinely recommended (see earlier). Combination vaccines are preferable where appropriate.[21,22] Schedules for vaccinating premature infants are identical to those for full term infants.[22]

Pregnant women

Pregnancy does not worsen the course of the disease, but HAV infection during pregnancy may result in vertical transmission to the fetus, premature labour, fetal loss and serious maternal consequences. Although the safety of HAV vaccination in pregnancy has not been determined, the theoretical risk to the developing fetus of inactivated HAV vaccine is low, and its use during pregnancy is recommended where otherwise indicated.[4,19]

Mature age

Adults >40 years of age are at much greater risk of serious and even fatal complications of HAV infection. There is limited data showing a decrease in, and slower development of, immune response with age to HAV vaccination in those over 65 years of age.[9,23] Gender, obesity, smoking and comorbidities (eg. renal insufficiency or chronic liver disease) may affect the immune response.[10,23] However, very few vaccine failures have been reported in the elderly.[23] Clear pretravel recommendations specific for this age group have not been established.[23] Suggestions include giving the initial dose at least 1 month before travel.[23] There is no clear evidence to support additional vaccine doses or routine postvaccine antibody testing, although these may be considered in specific situations.[23]

Travellers and other groups

Vaccination is recommended for all travellers to, and all expatriates living in, intermediate to high endemicity areas.[3,4,6] This may be expanded to include travel to any destination.[5] Hepatitis A is in the vaccination schedule for Aboriginal and Torres Strait Islander children living in the Northern Territory, Queensland, South Australia and Western Australia. Those who live or work in rural and remote indigenous communities should receive HAV vaccine. It is also recommended that individuals at occupational risk, lifestyle risk (injecting drug users, men who have sex with men), those with intellectual disabilities, and those at risk of HAV because of pre-existing hepatitis B or C infection or chronic liver disease should be vaccinated.[4,19]

Combination vaccines

Hepatitis B

Hepatitis B virus (HBV) has infected 2 billion people with up to 450 million carriers worldwide

and up to 1.2 million deaths annually caused by cirrhosis and primary hepatocellular carcinoma attributable to HBV infection.[24] Risk factors and endemicity for HAV and HBV infection overlap.[24] Up to one in 4 travellers are considered at increased risk for exposure to HBV due to hospitalisation, sexual activity, body piercing, tattooing and other high risk exposures.[13,24] The monthly incidence of HBV is up to 240 per 100 000 in expatriates working in developing countries, and only 2–10 times less in short term travellers.[13] While HBV vaccination is now routine in most industrialised countries,[13] HAV and HBV are the most commonly indicated travel vaccines,[25] with WHO recommending that they should be considered in virtually all travellers to highly endemic areas.[23]

A combined hepatitis A and B vaccine reduces the number of required injections and increases compliance.[25] This should be considered for longer term travellers and expatriates living in developing countries, as well as the above at risk groups for HAV, including health workers, health students and military personnel, and solid organ transplant recipients.[4] Protection against both HAV and HBV is equal to that conferred by monovalent vaccines,[18] with long term persistence of antibodies and no need for booster doses. A HBV booster is not required in immunocompetent individuals who have responded to a completed primary vaccination course.[10] An accelerated schedule of combined vaccine with a booster dose at 12 months is particularly useful where rapid protection is required, and has been found to be at least as immunogenic and well tolerated as corresponding monovalent vaccines.[13,24,25]

Typhoid fever

Combined protection against HAV and typhoid fever is recommended for all individuals aged more than 16 years travelling to developing countries.[4,13,26] Uptake of both typhoid and HAV vaccines may be increased with a combination vaccine.[2] Both vaccine components in the combination vaccine are of similar efficacy as when administered as monovalent vaccines.[7] Hepatitis A booster doses are not required after a completed primary vaccination course,[10] whereas monovalent typhoid boosters are required every 3 years if there is ongoing risk of exposure.[4]

Conclusion

Hepatitis A is a common vaccine preventable infection in travellers. Highly effective vaccines exist for its prevention for travellers from 12 months of age onward, including last minute travellers and those in special risk groups. Combination vaccines – hepatitis A/hepatitis B and hepatitis A/typhoid – aim to facilitate the vaccination process for travellers. All travellers at risk of HAV should be vaccinated where contraindications do not exist, as the vaccine is a safe and effective means of prevention.

Resource

Centres for Disease Control. Hepatitis A. Available at www.cdc.gov/hepatitis/HAV/index.htm.

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References

1. Steffen R, Amitirigala I, Mutsch M. Health risks among travelers – need for regular updates. J Travel Med 2008;15:145–6.
2. Luxemburger C, Dutta AK. Overlapping epidemiologies of hepatitis A and typhoid fever: the needs of the traveler. J Travel Med 2005;12:S12–21.
3. World Health Organization. Hepatitis. Available at www.who.int/csr/disease/hepatitis/en/index.html [Accessed 29 October 2010].
4. National Health and Medical Research Council The Australian Immunisation Handbook, 9th edn. Canberra: National Health and Medical Research Council, 2008.
5. Centers for Disease Control and Prevention. Travelers' Health: Yellow Book. In: Centers for Disease Control and Prevention. Health Information for International Travel, 2010.
6. Yung A, Ruff T. Manual of travel medicine: a pre-travel guide for health care practitioners. 2nd edn. Melbourne: IP Communications, 2004.
7. Van Hoecke C, Lebacq E, Beran J, Prymula R, Collard F. Concomitant vaccination against hepatitis A and typhoid fever. J Travel Med 1998;5:116–20.
8. Barbour V, Clark J, Jones S, Peiperl L, Veitch E, Yamey G. Clean water should be recognized as a human right. PLoS Med 2009;6:e1000102.
9. Oltmann A, Kämper S, Staeck O, et al. Fatal outcome of hepatitis A virus (HAV) infection in a traveler with incomplete HAV vaccination and evidence of Rift Valley fever virus infection. J Clin Microbiol 2008;46:3850–2.
10. Van Damme P, Banatvala J, Fay O, et al. Hepatitis A booster vaccination: is there a need? Lancet 2003;362:1065–71.
11. Ford TE, Colwell RR, Rose JB, Morse SS, Rogers DJ, Yates TL. Using satellite images of environmental changes to predict infectious disease outbreaks. Emerg Infect Dis 2009;15:1341–6.
12. Department of Human Services. Health warning on semi-dried tomatoes. Media Release Friday, 9 October 2009. Available at http://hnb.dhs.vic.gov.au/web/pubaff/medrel.nsf/LinkView/D8172AF758EDF26ECA25764A002574DE?OpenDocument [Accessed 29 October 2010].
13. Zuckerman JN, Van Damme P, Van Herck K, Löscher T. Vaccination options for last-minute travellers in need of travel-related prophylaxis against hepatitis A and B and typhoid fever: a practical guide. Travel Med Infect Dis 2003;1:219–26.
14. Askling HH, Rombo L, Andersson Y, Martin S, Ekdahl K. Hepatitis A risk in travelers. J Travel Med 2009;16:233–8.
15. Leder K, Tong S, Weld L, et al. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. Clin Infect Dis 2006;43:1185–93.
16. Hagmann S, Benavides V, Neugebauer R, Purswani M. Travel health care for immigrant children visiting friends and relatives abroad: retrospective analysis of a hospital-based travel health service in a US urban underserved area. J Travel Med 2009;16:407–12.
17. Bonanni P, Boccalini S, Bechini A. Vaccination against hepatitis A in children: A review of the evidence. Ther Clin Risk Manag 2007;3:1071–6.
18. Spira AM. Preparing the traveller. Lancet 2003;361:1368–81.
19. Fiore AE, Wasley A, Bell BB. Prevention of hepatitis A through active or passive immunization – Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and Reports 2006;55(RR07);1–23.
20. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep 2009;58(RR-11):1–166.
21. Stauffer WM, Kamat D. Traveling with infants and children. Part 2: Immunizations. J Travel Med 2002;9:82–90.
22. Mackell SM. Vaccinations for the pediatric traveler. Clin Infect Dis 2003;37:1508–16.
23. Genton B, D'Acremont V, Furrer HJ, Hatz C, Loutan L. Hepatitis A vaccines and the elderly. Travel Med Infect Dis 2006;4:303–12.
24. Connor BA, Blatter MM, Beran J, Zou B, Trofa AF. Rapid and sustained immune response against hepatitis A and B achieved with combined vaccine using an accelerated administration schedule. J Travel Med 2007;14:9–15.
25. Steffen R. Immunization against hepatitis A and hepatitis B infections. J Travel Med 2001;8:S9–16.
26. Lankester T. Health care of the long-term traveller. Travel Med Infect Dis 2005;3:143–55.

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