7 Hepatitis A

Key information

Mode of transmission	Faecal–oral route, either from person-to-person contact or through contaminated food or drink. It is also occasionally spread by injected drug use.
Incubation period	28–30 days average (range 15–50 days).
Period of communicability	The 1–2 weeks before and the first few days after the onset of jaundice.
Burden of disease	Infants and children are usually asymptomatic. Severity in adults increases with age. The disease is more serious in those with chronic liver disease and the immunocompromised. There is no carrier state.
Vaccines (registered and available)	Monovalent inactivated hepatitis A virus (HAV) vaccine (Havrix; Avaxim). Combined inactivated HAV-recombinant HBsAg protein vaccine (Twinrix). Combined HAV-purified *Salmonella typhi* Vi polysaccharide vaccine (Hepatyrix; Vivaxim).
Dose, presentation, route	Havrix, Twinrix, Hepatyrix, Vivaxim: 1.0 mL per dose. Havrix Junior, Twinrix Junior, Avaxim: 0.5 mL per dose. Pre-filled syringe. Intramuscular injection.
Funded vaccine indications	HAV vaccine (Havrix) is recommended and funded for: • transplant patients – 2 doses • children with chronic liver disease – 2 doses • close contacts of hepatitis A cases – 1 dose.
Vaccine efficacy/ effectiveness	High efficacy: HAV infection has been almost eliminated in immunised populations.
Public health measures	In an outbreak (if within 2 weeks of exposure): • age <12 months, human normal immunoglobulin is recommended • ≥12 months, age-appropriate vaccination is recommended.

7.1 Virology

Hepatitis A virus (HAV) is a ribonucleic acid (RNA) virus belonging to the picornavirus group, which also contains enteroviruses and rhinoviruses. The virus is usually transmitted by the faecal–oral route, either from person-to-person contact or through contaminated food or drink.

HAV primarily replicates in the liver and is excreted in large quantities via the biliary tract into the faeces. It is a hardy virus and can survive outside the body for prolonged periods in food and water. It causes a self-limiting illness with no carrier state.

7.2 Clinical features

The incubation period between ingestion of the virus and clinical symptoms is 15 to 50 days, with an average of 28 to 30 days. The virus can be detected in blood and faeces within a few days of ingestion, and it increases to a peak in the two weeks prior to the onset of clinical illness, which is the time that subjects are most likely to spread the infection. Faecal viral shedding continues for one to three weeks in adults, but has been reported to last longer in young children. Virus excretion falls sharply in the week following the onset of hepatitis.

In infants and preschool children, most infections are either asymptomatic or cause only mild, non-specific symptoms without jaundice. Most adults and adolescents develop symptomatic disease, the severity of which generally increases with age. Symptomatic HAV infection is characterised by an acute febrile illness with jaundice, anorexia, nausea, abdominal discomfort, malaise and dark urine. Signs and symptoms usually last less than two months, although 10–15 percent of symptomatic persons have prolonged or relapsing illness lasting up to six months. Liver enzymes almost always return to normal by six months after the illness, and often much sooner. The disease is more serious in people with chronic liver disease or those who are immunocompromised (including people with HIV infection). Chronic carrier states do not occur following hepatitis A infection and persisting liver damage is very rare.

7.3 Epidemiology

7.3.1 Global burden of disease

HAV is common in areas with poor sanitary conditions and limited access to clean water.[1] In highly endemic areas, such as parts of Africa and Asia, the disease is virtually confined to early childhood and is not an important cause of morbidity.[1, 2] Almost all adults in these areas are immune, and hepatitis A epidemics are uncommon. In intermediate endemicity areas, such as Central and South America, Eastern Europe and parts of Asia, children may not be infected in early childhood and reach adulthood without immunity. A high proportion of adolescents and adults are susceptible and large outbreaks are common. In low endemicity areas, such as the US and Western Europe, infection is less common but can occur in high-risk groups. Large outbreaks are usually rare, due to high levels of sanitation that stops person-to-person transmission.

Viral spread occurs readily in households, in early childhood services and in residential facilities that care for the chronically ill, disabled or those with a weakened immune system. In early childhood services, typically the adult guardian develops symptomatic disease while the primary source, the infected young child, is asymptomatic. The risk of spread in early childhood centres is proportional to the number of children aged under 2 years wearing nappies. Infection in these early childhood services is an important source of outbreaks for whole communities.

Other groups at the highest risk of contracting the disease include people in close contact with an infected person, and travellers to areas with high or intermediate rates of hepatitis A infection. Others also at greater risk of contracting HAV are people who have oral–anal sexual contact, illicit drug users, those with chronic liver disease, food handlers, and laboratory workers who handle the virus.

Universal and targeted programmes for childhood immunisation have been introduced in several countries, including Israel, the US and Australia. Acute HAV infection has almost been eradicated in areas with HAV immunisation programmes.

7.3.2 New Zealand epidemiology

The rate of HAV in New Zealand has declined from 145.7 per 100,000 in 1971 to 1.0 per 100,000 in 2015.[3] This fall in rate is attributable to the use of HAV vaccination in travellers and a reduction in HAV prevalence overseas.

In 2015, 47 cases were notified compared with 74 in 2014.[3] Hospitalisation status was recorded for 46 cases, of which, 24 (52.2 percent) were hospitalised.

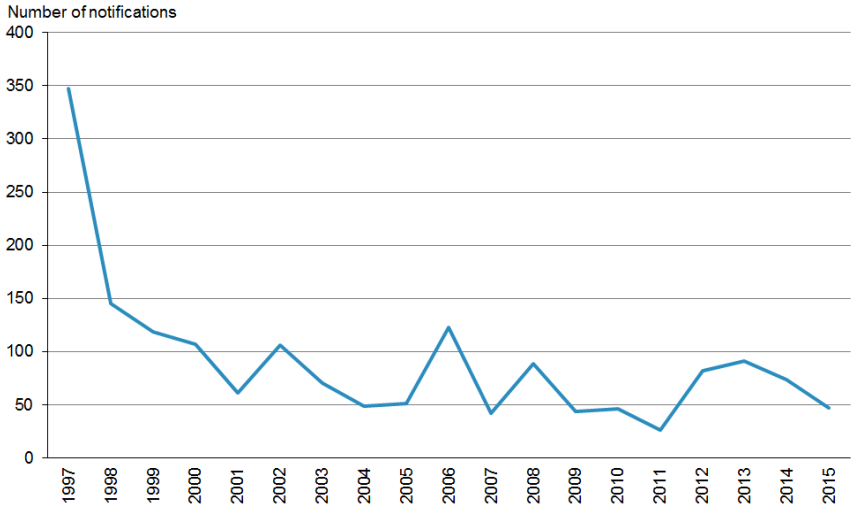
The highest rates occurred in the 20–29 years and 40–49 years age groups (both 1.8 per 100,000), followed by the 15–19 years age group (1.6 per 100,000).[3] Of the 44 cases with ethnicity information recorded, Pacific peoples had the highest notification rate (2.5 per 100,000), followed by the Asian (1.7 per 100,000) and Māori (0.9 per 100,000) ethnic groups.

Travel information was recorded for all cases: 24 cases (51.1 percent) had travelled overseas during the incubation period of the disease.[3] The countries most frequently visited included Samoa (5 cases) and Fiji (4 cases).

Hepatitis A outbreaks continue to occur (see Figure 7.1). There were two outbreaks in 2015, involving nine cases.[3] One outbreak, involving seven cases of hepatitis A reported from five DHBs, was food related.[4] The cases were epidemiologically linked to the consumption of imported frozen berries.

Figure 7.1 illustrates the overall national downward trend since a peak of notifications in 1997.

Figure 7.1: Hepatitis A notifications, by year, 1997–2015



Source: ESR

7.4 Vaccines

7.4.1 Available vaccines

Two inactivated HAV vaccines are currently registered (approved for use) and available (marketed) in New Zealand, as well as a combined HAV and HBV vaccine and two HAV and typhoid combined vaccines.

Funded vaccine

HAV vaccine is not on the Schedule, but is recommended and funded for certain high-risk groups, as shown in Table 7.1.

Each 1.0 mL dose of Havrix (GSK) contains 1,440 EU (enzyme-linked immunosorbent assay [ELISA] units) of inactivated HAV adsorbed onto aluminium hydroxide. Each 0.5 mL dose of Havrix Junior contains 720 EU of inactivated HAV. Other components and residuals include neomycin sulphate, 2-phenoxyethanol, polysorbate 20, amino acid supplement in a phosphate buffered saline solution.

Other vaccines

Inactivated HAV vaccine

- Avaxim (Sanofi) contains 160 antigen units of inactivated HAV in each 0.5 mL dose; other components and residuals include aluminium hydroxide, phenoxyethanol, formaldehyde, Medium 199, neomycin and bovine serum albumin.

Combined HAV and HBV vaccine

- Twinrix (GSK) contains 720 EU of inactivated HAV and 20 µg of recombinant DNA HBsAg vaccine in each 1.0 mL dose. The Twinrix Junior preparation (0.5 mL per dose) contains half these amounts. The vaccines are adsorbed onto aluminium adjuvants. Other components and residuals include aluminium hydroxide, aluminium phosphate, sodium chloride, amino acids, dibasic sodium phosphate, formaldehyde, monobasic sodium phosphate, neomycin sulphate, polysorbate 20 and trometamol.

Combined HAV and typhoid vaccines

The two HAV-typhoid combination vaccines contain inactivated HAV and purified *Salmonella typhi* Vi polysaccharide.

- Hepatyrix (GSK) contains 1,440 EU of HAV and 25 µg of purified *Salmonella typhi* Vi polysaccharide in each 1.0 mL dose; other components and residuals include aluminium hydroxide, sodium chloride, formaldehyde, polysorbate 20, amino acids, trometamol and neomycin.
- Vivaxim (Sanofi) contains 160 antigen units of HAV and 25 µg of purified *Salmonella typhi* Vi polysaccharide in each 1.0 mL dose; other components and residuals include sodium chloride, sodium phosphate, aluminium hydroxide, phenoxyethanol, formaldehyde, Medium 199, neomycin and bovine serum albumin.

7.4.2 Efficacy and effectiveness

After one dose of monovalent HAV vaccine in healthy people, protective levels of antibody have been demonstrated by two weeks, and 94–100 percent of people vaccinated will seroconvert by four weeks.[5]

A second dose 6 to 18 months after the first is thought to be important for long-term protection, particularly in the absence of exposure to HAV.[6, 7] In subjects with an impaired immune system, adequate anti-HAV antibody titres may not be obtained after a single dose.

HAV vaccines have not yet been approved for children aged under 12 months. The limited data on immunogenicity in infants indicates high levels of seroconversion, but those with passively acquired maternal anti-HAV have lower serum antibody titres.

HAV vaccines are highly effective in preventing clinical disease, with recorded efficacy measures of around 94–100 percent from six weeks post-vaccination. Where children, adolescents and young adults have been vaccinated in targeted and/or national programmes, there has been a rapid decline in disease incidence. This decline is through both direct and indirect (herd immunity) effects.[6]

Duration of immunity

Antibodies to two doses of HAV vaccine have been shown to persist in vaccinated adults for at least 17 years after vaccination, and up to 15 years in vaccinated children and adolescents.[8] Mathematical models estimate that following completion of a two-dose series, protective levels of antibody will persist for 25 years or longer in adults and 14–20 years in children.[8] Given that HAV has a long incubation period, it is possible that immune memory with no detectable circulating antibody may be sufficient for protection, as is the case with HBV and HepB.

7.4.3 Transport, storage and handling

Transport according to the *National Standards for Vaccine Storage and Transportation for Immunisation Providers 2017*.[9] Store at +2˚C to +8˚C. Do not freeze.

7.4.4 Dosage and administration

See Table 7.2 for dosage and scheduling information.

The monovalent HAV and HAV combination vaccines should be administered by intramuscular injection into the deltoid region of the

upper arm in adults and older children, or the anterolateral aspect of the thigh in younger children (see section 2.2.3).

Co-administration with other vaccines

The monovalent HAV and HAV combination vaccines may be administered concurrently with other vaccines.[8, 10] The vaccines should be given in separate syringes and at different injection sites.

Interchangeability of hepatitis A vaccines

The monovalent HAV vaccines may be used interchangeably to complete a two-dose course.[10]

7.5 Recommended immunisation schedule

7.5.1 Recommendations

Hepatitis A vaccines are not on the Schedule, but are recommended and funded for the high-risk groups in the shaded section of Table 7.1 below. They may also be employer-funded or funded during an outbreak (see section 7.8).

Table 7.1: Hepatitis A vaccine recommendations

Note: Funded conditions are in the shaded rows. See the Pharmaceutical Schedule (www.pharmac.govt.nz) for the number of funded doses and any changes to the funding decisions.

Recommended and funded
Transplant patients[a]
Children with chronic liver disease[a]
Close contacts[b] of hepatitis A cases
Recommended but not funded
Adults with chronic liver disease: • chronic hepatitis B or C infection • other chronic liver disease.
Men who have sex with men
Travellers – including occupational[c] and recreational travel.
Occupational groups[c] exposed to faeces, including: • employees of early childhood services, particularly where there are children too young to be toilet trained • health care workers exposed to faeces • sewage workers • those who work with non-human primates (eg, zoos, research laboratories).
Food handlers[c] during community outbreaks.
Military personnel[c] who are likely to be deployed to high-risk areas.

a See also sections 4.2 and 4.3.

b Only one dose is funded for close contacts as protection is only required for the duration of the outbreak. For long-term protection, contacts may seek a second (unfunded) dose, after an interval of at least 6 months. Refer to the *Communicable Disease Control Manual 2012*[11] for a definition of contacts.

c May be employer-funded. See also section 4.6.

Individuals with chronic liver disease

HAV vaccine is recommended and funded for children with chronic liver disease and for children and adults undergoing transplants (see sections 4.2 and 4.3). People with chronic liver disease are not at increased risk for hepatitis A, but acute hepatitis A can have serious or fatal consequences.[6]

Chronic hepatitis B or C infection

Studies have shown that in these individuals, super-infection with HAV leads to increased morbidity and mortality.[6]

Other chronic liver disease

Non-immune individuals who have not been vaccinated should receive HAV vaccine before liver decompensation. It should be given as early as possible before liver transplantation; vaccination may be performed after transplantation, although the response is unlikely to be as good as early in liver disease.[12, 13]

Travellers

The first dose of HAV vaccine should be given as soon as travel is considered.[8] The high and intermediate endemicity areas listed in section 7.3.1 may be used as a guide for recommending hepatitis A vaccination for travel, but there are limits to the data that informs these listings, and variation within countries. Even in low prevalence countries there is a risk of foodborne hepatitis A. In addition, decreasing prevalence in formerly endemic countries leads to large numbers of susceptible people and the risk of large outbreaks, as has recently been reported. The vaccine may be considered for all travellers aged 1 year and older.[1]

Immunoglobulin is not normally available or recommended in New Zealand for pre-travel use.

Certain occupational groups

Immunisation with HAV vaccine is recommended (but not funded) for people in occupational groups exposed to faeces, as listed in Table 7.1 above.

Others at higher risk

Pre-immunisation screening for anti-HAV antibodies is not routinely recommended. There is no danger in vaccinating an already immune person, but some groups with higher probability of prior infection may wish to avoid the expense of vaccination. These include:

- those who are likely to have been exposed as children (born in a country of high endemicity) or in the course of their employment
- those with a history of jaundice.
- Consider HAV vaccine for the following groups:
- intravenous drug users (who account for 30 percent of cases in communities during outbreaks)[6]
- men who have sex with men.

Routine immunisation for children

HAV vaccine is not routinely recommended and is not on the Schedule for children in New Zealand. It should, however, be considered during community outbreaks (see section 7.8).

7.5.2 Immunisation schedule

Immunisation schedules for HAV-containing vaccines are provided in Table 7.2. See the manufacturers' data sheets for more information. For the monovalent HAV vaccines, the first dose is for primary immunisation and the second dose is a booster.

Table 7.2: Hepatitis A-containing vaccines: by age, dose and schedule

Note: Havrix and Havrix Junior are funded for eligible individuals[a] (see Table 7.1).

Age	Vaccine	Dose	Volume (mL)	Number of doses	Schedule
Hepatitis A vaccines					
1–15 years	Havrix Junior	720 EU	0.5	2	0 and 6–12 months[b]
2 years–adult	Avaxim	160 antigen units	0.5	2	0 and 6–36 months
≥16 years	Havrix 1440	1,440 EU	1	2	0 and 6–12 months[b]

Continued overleaf

Age	Vaccine	Dose	Volume (mL)	Number of doses	Schedule
Hepatitis A–Hepatitis B combined vaccine					
1–15 years	Twinrix[c]	720 EU of HAV and 20 µg of HBsAg	1.0	2	0 and 6–12 months
	Twinrix Junior[d]	360 EU of HAV and 10 µg of HBsAg	0.5	3	0, 1 and 6 months
≥16 years	Twinrix	720 EU of HAV and 20 µg of HBsAg	1.0	3	0, 1 and 6 months; or 0, 7, 21 days plus a booster at 1 year
Hepatitis A–Typhoid combined vaccines					
≥15 years	Hepatyrix	1,440 EU of HAV and 25 µg of Vi	1.0	1	At least 14 days before departure; then boost with HAV vaccine at 6–12 months[e]
≥16 years	Vivaxim	160 antigen units of HAV and 25 µg of Vi	1.0	1	At least 14 days before departure; then boost with HAV vaccine at 6–36 months[e]

Key: EU = enzyme-linked immunosorbent assay (ELISA) units of hepatitis A virus protein; HAV = hepatitis A virus; HBsAg = recombinant hepatitis B surface antigen; Vi = *Salmonella typhi* polysaccharide

Notes

a Note that two doses of hepatitis vaccine are funded for transplant patients and children with chronic liver disease; one dose is funded for close contacts of hepatitis A cases.

b Even after a longer interval between the 1st and 2nd doses, there is no need to restart the series. A substantial anamnestic response occurs after a 2nd dose given up to 8 years after the initial dose.[14]

c For children not previously exposed to the hepatitis A or B viruses. Source: GlaxoSmithKline NZ Ltd. 2016. *Twinrix and Twinrix Junior New Zealand Data Sheet*. URL: http://www.medsafe.govt.nz/profs/datasheet/t/Twinrixinj.pdf (accessed 4 December 2016).

d Use when the child is at immediate risk of exposure to hepatitis B (eg, travellers) and did not receive a primary course of HepB as an infant. Source: GlaxoSmithKline NZ Ltd. 2016. *Twinrix and Twinrix Junior New Zealand Data Sheet*. URL: http://www.medsafe.govt.nz/profs/datasheet/t/Twinrixinj.pdf (accessed 4 December 2016).

e If the individual remains at risk from typhoid fever, a single dose of the typhoid vaccine is recommended every 3 years.

7.5.3 Pregnancy and breastfeeding

The safety of HAV vaccine during pregnancy and while breastfeeding has not been determined. However, because HAV vaccine is produced from inactivated HAV, there is not expected to be any risk to the developing fetus and infant. As a precaution, HAV vaccines should be used during pregnancy only when clearly needed, such as when travelling to a country where HAV is endemic.

7.6 Contraindications and precautions

See also section 2.1.3 for pre-vaccination screening guidelines and section 2.1.4 for general contraindications for all vaccines.

7.6.1 Contraindications

Administration of HAV vaccine should be delayed in individuals suffering from acute febrile illness. HAV vaccine should not be administered to people with a history of an anaphylactic reaction to a prior dose of HAV vaccine or to a vaccine component.

7.6.2 Precautions

In individuals with an impaired immune system, adequate anti-HAV antibody titres may not be obtained after a single dose.

Pregnancy is a precaution – see section 7.5.3.

7.7 Expected responses and AEFIs

7.7.1 Expected responses

Soreness, redness and swelling at the injection site, fever, malaise, headache, nausea and loss of appetite have been reported for the monovalent HAV vaccines, but these responses are usually mild and brief.[15] Similar responses are seen with HAV–HBV combination vaccines, and HAV–typhoid combination vaccines.

7.7.2 AEFIs

Review of data from multiple sources has not identified any serious adverse events among children and adults that could be attributed to the HAV vaccine.[15]

7.8 Public health measures

It is a legal requirement that all cases of hepatitis A be notified immediately on suspicion to the local medical officer of health.

7.8.1 Outbreak control

Vaccination

Age-appropriate vaccine is recommended for all close contacts aged older than 1 year. If time allows, consider pre-vaccine serology if there is a history or likelihood of previous HAV vaccination or infection (for example, previous residence in an endemic country). Post-exposure prophylaxis with vaccine should be offered to contacts as soon as possible, and within two weeks of last exposure to an infectious case. The efficacy of vaccine when administered more than two weeks after exposure has not been established.

Immunoglobulin

Where vaccine is contraindicated (or not immediately available), human normal immunoglobulin may be offered to a close contact who may have a reduced response to vaccine or has risk factors for severe disease. The dose is 0.03 mL/kg given by intramuscular injection. Post-exposure prophylaxis should be offered to contacts as soon as possible, and within two weeks of last exposure to an infectious case.

Close contacts aged under 1 year will require human normal immunoglobulin.

Human normal immunoglobulin is available from the New Zealand Blood Service. For further information, refer to the medicine data sheets or the New Zealand Blood Service website (www.nzblood.co.nz).

Early childhood services and other institutional outbreaks

If an outbreak occurs in an early childhood service, vaccination (and/or immunoglobulin if appropriate) may be indicated for all previously unimmunised staff and children at the service and unimmunised new staff and children for up to six weeks after the last case has been identified, including cases in the household of attendees. The number of infected cases should determine the extent of intervention.

Vaccination and/or immunoglobulin may also be indicated for adults and children at a school, hospital or custodial-care institution where an outbreak of hepatitis A is occurring. For sporadic cases in hospitals, schools or work settings, post-exposure prophylaxis is not routinely indicated, but careful hygiene practices should be maintained.

Community-wide outbreaks of hepatitis A infection

HAV vaccine is effective in controlling community-wide epidemics and common-source outbreaks of HAV infection.[16] Before the vaccine is used for outbreak control, consideration should be given to the current epidemiology in the community, the population at risk should be defined, and the feasibility and cost of delivering a programme should be assessed.

For more details on control measures, refer to the 'Hepatitis A' chapter of the *Communicable Disease Control Manual 2012*.[11]

7.9 Variations from the vaccine data sheets

None.

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