

# 14 Hepatitis A

## 14.1 Introduction

Hepatitis A virus (HAV) is an RNA virus belonging to the Picornavirus group. Denhart and his colleagues first demonstrated the viral nature of the disease in the 1960s when they transmitted the infection to marmosets. Subsequently, HAV was adapted to grow in a clonal line of fetal rhesus monkey kidney cells, a development that opened the way for the preparation of vaccine strains.

## 14.2 The illness

HAV infection is characterised by an acute febrile illness with jaundice, anorexia, nausea, abdominal discomfort, malaise and dark urine. In infants and preschool children most infections are either asymptomatic or cause only mild non-specific symptoms without jaundice. Adults have higher rates of symptomatic disease: 70 percent of adults have symptoms of illness, and the severity of illness generally increases with age. The case fatality rate is 1.8 percent in adults over the age of 50 years.<sup>1</sup> Fulminant infections with hepatitis A are rare, and chronic carrier states do not occur. Permanent liver damage is extremely unlikely. Signs and symptoms usually last less than two months, although 10–15 percent of symptomatic persons have prolonged or relapsing disease lasting up to six months. The illness may be more severe in those infected with hepatitis B or hepatitis C viruses.

The incubation period is 15 to 50 days, with an average of 28 to 30 days. Faecal viral shedding continues for one to three weeks in adults, but has been reported to last longer in young children. The highest titre of HAV in the stool has been demonstrated in the two weeks prior to the onset of clinical illness, which is the time that subjects are most likely to spread the infection. Virus excretion falls sharply in the week following the onset of jaundice.

### Diagnostic tests

Commercial serological test kits are available for the detection of anti-HAV antibodies. The presence of immunoglobulin M (IgM) specific antibody indicates recent infection. This can be detected 5–10 days after exposure, before the onset of symptoms, and can persist for up to six months. Immunoglobulin G (IgG) antibody is detectable shortly after the appearance of IgM. The presence of HAV IgG indicates previous infection and immunity, or vaccination conferring immunity. Routine virus culture for HAV is not available.

## 14.3 Epidemiology

The virus is usually transmitted by the faecal–oral route, either from person to person contact or through contaminated food or drink. In areas of the world with low living standards, poor hygiene and high population density, the disease is virtually confined to early childhood and is not an important cause of morbidity. Almost all adults in these countries are immune. In industrialised countries the infection is less common in childhood and only 20–40 percent of adults are immune.

Viral spread occurs readily in households and in early childhood services, which, in the United States (US) and (probably) New Zealand, are important sources of outbreaks in the community. In the early childhood service, typically the adult caregiver develops symptomatic disease while the primary source, the infected young child, is asymptomatic. The risk of spread in an early childhood service is proportional to the number of children under two years of age who are still in napkins.

Epidemics have arisen from eating shellfish contaminated by human sewage. Nosocomial outbreaks in newborn nurseries have been reported. Transmission by blood transfusion has also been reported, but is very rare. There have been outbreaks among injecting drug users, and among men who have sex with men.

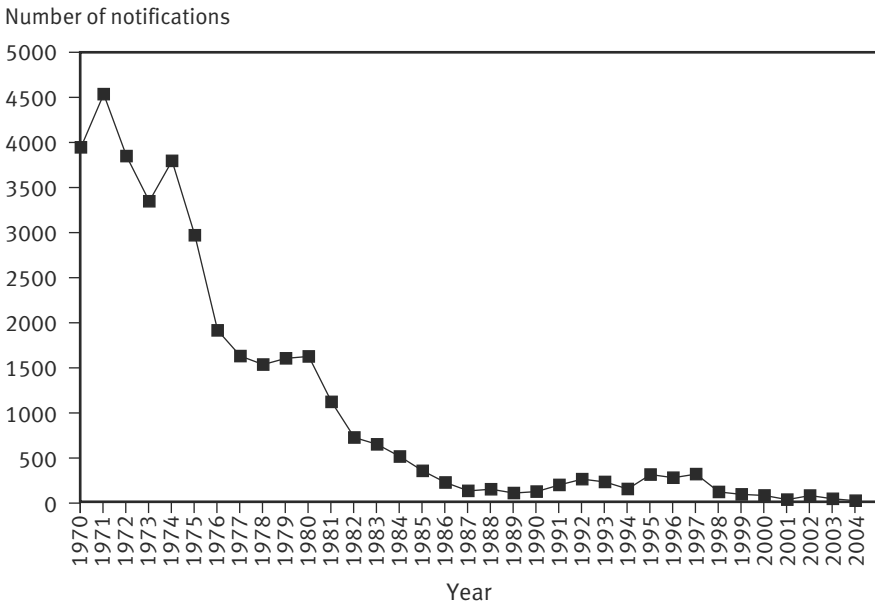
Universal and targeted programmes for childhood immunisation have been introduced in the US and Australia. In north Queensland hepatitis A vaccine was introduced in 1999 for indigenous children at the age of 18 months and a second dose at two years of age, and there was a catch up for children up to their sixth birthday. The average annual notification rate of hepatitis A during 1996–99 was 110 cases per 100,000 in the indigenous population and 25 cases per 100,000 in the non-indigenous population; whereas during 2000–2003 the notification rates in the indigenous and non-indigenous populations were 4 and 2.5 cases per 100,000 persons, respectively. The vaccination programme in the indigenous community reduced the incidence of disease in the broader community.<sup>2</sup>

### New Zealand epidemiology

The number of notified cases of acute hepatitis A infection in New Zealand decreased from 1970 to 1989, but since then the number has fluctuated (see Figure 14.1). It is likely that part of the sharp decrease in the number of cases notified as hepatitis A resulted from changes in diagnostic testing, including the introduction of testing for hepatitis B. In 2000 a total of 107 cases of acute hepatitis A were notified to medical officers of health, a rate of 3.0 per 100,000, compared with 119 cases and a rate of 3.3 per 100,000 in 1999. Since 2000 the number of cases of hepatitis A notified has decreased further (see Figure 14.1). In 2003 there were 70 cases (a rate of 1.9 per 100,000) of hepatitis A notified, and there were 49 cases in 2004 (a rate of 1.3 per 100,000 population). In 2004 rates were highest in Tairāwhiti (2.3 per 100,000), followed by Lakes (2.1 per 100,000) and Auckland (1.9 per 100,000) District Health

Boards. In 2004 there was a single outbreak of three cases of hepatitis A associated with the consumption of contaminated blueberries. Nineteen (39 percent) of the 49 cases notified in 2004 had a history of overseas travel identified as a risk factor.

**Figure 14.1: Hepatitis A notifications, 1970–2004**



Over recent years outbreaks in New Zealand have been associated with contaminated food, person to person spread in community outbreaks, and sexual transmission in men.<sup>3</sup>

## 14.4 Vaccines

Four inactivated hepatitis A vaccines are currently licensed in New Zealand, as well as a combined hepatitis A and B vaccine, and two hepatitis A and typhoid combined vaccines. Three of the hepatitis A vaccines – AVAXIM™ (Pasteur Mérieux-Connaught), HAVRIX (GSK) and VAQTA® (MSD) – are manufactured from cell culture adapted hepatitis A propagated in human fibroblasts. The HAV preparation is formalin inactivated and adsorbed to an aluminium adjuvant.

The fourth hepatitis A vaccine, Epaxal Berna (Swiss Serum and Vaccine Institute), is manufactured from HAV purified from infected human diploid cell cultures and inactivated with formalin. The preparation is adsorbed to biodegradable phospholipid vesicles spiked with influenza haemagglutinin and neuramidase.

The four hepatitis A vaccines are similar in terms of efficacy and side effect profile. The immunisation schedule, ages for which the vaccine is licensed and whether

there is a paediatric as well as an adult formulation varies from vaccine to vaccine. These are shown in Table 14.1. (See below for information on the combination vaccines, and section 3.4 for further information regarding the TWINRIX vaccine.)

**Table 14.1: Hepatitis A vaccines, by age, dose, and timing**

Age	Vaccine	Dose	Volume (mL)	Number of doses	Schedule*
1–15 years	HAVRIX JUNIOR	720 EU	0.5	2	0 and 6–12 months
1–17 years	VAQTA®	25 U	0.5	2	0 and 6–18 months
2 years – adult	AVAXIM™	160 antigen units	0.5	2	0 and 6–12 months
1 year – adult	Epaxal Berna		0.5	2	0 and 1–6 months in immune suppressed, including those with splenectomy; others 0 and 12 months
Adults 16 years and over	HAVRIX 1440	1440 EU	1	2	0 and 6–12 months
Adults 18 years and over	VAQTA®	50 U	1	2	0 and 6–18 months

Key: EU = enzyme-linked immunosorbent assay (ELISA); U = units of hepatitis A virus protein.

\* Even after a longer interval between the first and second doses there is no need to restart the series. A substantial anamnestic response occurs after a second dose given up to eight years after the initial dose.<sup>4,5</sup>

### Hepatitis A and B combination vaccines (TWINRIX)

TWINRIX (GSK) is an inactivated hepatitis A virus and recombinant DNA hepatitis B surface antigen vaccine. A 1 mL dose of TWINRIX contains not less than 720 ELISA units of inactivated hepatitis A virus, and 20 micrograms of recombinant HBsAg protein. The 0.5 mL TWINRIX JUNIOR preparation contains half these quantities.

#### *Dosage of TWINRIX*

For adults 16 years of age and over, three 1 mL doses are given at zero, one and six months. For children 1–15 years of age (inclusive), the dose is 0.5 mL at zero, one and six months.

TWINRIX may be used for rapid protection, with doses given at zero, seven and 21 days and a booster at one year. Refer to the current data sheet. There is a two-dose schedule for children 1–15 years of age using the adult vaccine.

(See also section 3.4 for further information regarding the TWINRIX vaccine.)

## Hepatitis A and typhoid vaccines

### *HEPATYRIX™*

This combination vaccine with inactivated hepatitis A and purified Vi polysaccharide typhoid vaccine (HEPATYRIX™, GSK) is available for adults and adolescents older than 15 years of age. The vaccine is given as a single 1 mL dose of HEPATYRIX™ at least two weeks before departure overseas to a high risk country. A booster of hepatitis A vaccine (HAVRIX 1440) is recommended 6–12 months after the dose of HEPATYRIX™. If the individual remains at risk from typhoid fever, a single dose of the Vi vaccine, TYPHERIX®, is recommended every three years.

### *VIVAXIM®*

VIVAXIM® (Aventis Pasteur) contains inactivated hepatitis A virus vaccine and *Salmonella typhi* Vi polysaccharide vaccine. It is available for use in adults from the age of 16 years and given as a single 1 mL dose at least 14 days before travel; a booster of hepatitis A vaccine is given 6–12 months after the dose of VIVAXIM®. Revaccination with typhoid vaccine is recommended every three years in subjects who remain at risk.

## Method of administration

The hepatitis A and hepatitis A combination vaccines should be injected intramuscularly into the deltoid region of the upper arm in adults and older children, or the antero-lateral aspect of the thigh in infants. (See section 2.3 for needle sites and sizes.)

These vaccines should *not* be administered into the gluteal region because this may result in a less than optimal antibody response.

## Administration with other vaccines

The Advisory Committee on Immunization Practices (ACIP) has reported that limited data from studies in adults indicates that simultaneous administration of hepatitis A vaccine with any one of the diphtheria, poliovirus (oral and inactivated), tetanus, typhoid (both oral and intramuscular), cholera, Japanese encephalitis, rabies or yellow fever vaccines does not decrease the immune response to either vaccine or increase the frequency of reported adverse events. Studies indicate that hepatitis B vaccine can be administered simultaneously with hepatitis A vaccine without affecting either vaccine's immunogenicity or increasing the frequency of adverse events. Several studies are being conducted among infants and young children to

evaluate whether simultaneous administration of hepatitis A vaccine with DTaP, Hib, hepatitis B, measles-mumps-rubella, or oral and inactivated poliovirus vaccines affects the immunogenicity and reactogenicity of these vaccines.<sup>6</sup> Those reported to date suggest that there is no interference.

When hepatitis A vaccine is administered concurrently with other vaccines, it should be given in a separate syringe and needle at a different injection site.

For individuals requiring post-exposure prophylaxis, the hepatitis A vaccine may be administered concomitantly with immunoglobulin (IG) using separate sites and syringes.

### **Efficacy**

AVAXIM™, Epaxal Berna, HAVRIX and VAQTA® are highly immunogenic in both adults and children, with 94 to 100 percent of recipients developing protective antibody levels one month after the first dose.<sup>7</sup>

Although there are minor differences between vaccines, the administration and efficacy of these vaccines are essentially the same. They all require a booster 6–18 months after the first dose (see Table 14.1, and check the manufacturer's data sheet for more information).

Hepatitis A vaccine has not yet been approved for children less than one year old. The limited data on immunogenicity in infants indicates high levels of seroconversion, but those with passively acquired maternal anti-HAV have lower serum antibody.

Almost all recipients after a single dose of hepatitis A vaccine have short term protection, and a second dose is thought to be important for long term protection. After the primary course of hepatitis A vaccine, a booster is not recommended and follow-up studies have shown that protective antibodies last for 10 years in healthy individuals.<sup>8</sup>

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

### **Duration of immunity**

Protective levels of antibodies have been observed in almost all immunised children and adults who have received two doses of vaccine, five years after immunisation. Mathematical models suggest protective levels of anti-HAV could persist for 20 years or more, and there is speculation that the induction of immune memory may mean that protection may be lifelong, but ongoing studies are necessary to confirm this hypothesis.

## 14.5 Recommended immunisation schedule

Immunisation against hepatitis A is recommended, but not publicly funded, for the following groups.

### **Individuals with chronic liver disease in whom HAV infection is likely to be more severe**

Immunisation with hepatitis A vaccine is recommended for chronic carriers of hepatitis B and C. Studies have shown that in these individuals super-infection with HAV leads to increased morbidity and mortality.

Susceptible people with chronic liver disease should receive hepatitis A vaccine before liver decompensation and as early as possible before liver transplant. Susceptible people who have not been vaccinated should receive hepatitis A vaccine while awaiting a liver transplant; they may receive vaccination after transplantation, although the response is unlikely to be as good as early in liver disease.<sup>9,10</sup>

### **Travellers**

Individuals travelling from New Zealand to areas of high (Africa, Asia, Central and South America and the Middle East) or intermediate (the Mediterranean, Eastern Europe including Russia, and parts of the Pacific) endemicity should be offered hepatitis A vaccine rather than IG. This is because of the high level of safety and efficacy of the vaccine and the anticipated duration of protection. After one dose, protective levels of antibody have been demonstrated by two weeks, and 95–100 percent of vaccinees seroconvert by four weeks. IG is no longer recommended or available for pre-travel use. Hepatitis A vaccine given at any time prior to the day of departure may provide some protection.

### **Certain occupational groups**

Immunisation with hepatitis A vaccine should be recommended for people in occupational groups exposed to faeces, including:

- employees of early childhood services, particularly where there are children too young to be toilet trained
- those involved in the care and education of the intellectually disabled
- health care workers exposed to faeces
- sewerage and other workers exposed to faeces
- military personnel.

Food handlers are not at specific risk for contracting hepatitis A, nor are they at specific risk for transmitting the infection, but they are expected to use safe food handling practices. Hepatitis A immunisation of food handlers may be considered, particularly when there is a community outbreak.

## Others at higher risk

Consider hepatitis A vaccine for the following groups:

- men who have sex with men, among whom outbreaks of HAV infection have been reported
- injecting drug users
- recipients of blood products such as factor VIII because of the very small risk of hepatitis A transmission from this source.

Pre-immunisation screening for anti-HAV antibodies is not routinely recommended but should be considered for those who may have already been infected, including:

- 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
- men who have sex with men
- injecting drug users
- individuals who have frequently visited areas of high endemicity.

## Routine immunisation for children

Hepatitis A vaccine is not routinely recommended and is not on the National Immunisation Schedule for children in New Zealand. It should, however, be considered during community outbreaks.

In the US, hepatitis A vaccine is recommended for universal immunisation of children if the regional incidence reaches greater than 20 per 100,000 (twice the national average in the US). It is also considered for children in those areas where the rate of infection is above the US national average population rate of 10 per 100,000 but below 20 per 100,000. In one area of California, where the rate of hepatitis A infection was 48 per 100,000, immunisation of children aged two to 12 years followed by ongoing immunisation of two-year-old children decreased the rate of hepatitis A infection by 93 percent. A two-dose schedule was given. The decrease was in both immunised and non-immunised populations.<sup>11</sup>

In Australia, hepatitis A vaccine was offered to aboriginal children in Queensland, Northern Territory, Western Australia and South Australia from 1 November 2005. Eligible children were given two doses of vaccine, with the first given after 12 months of age and the second dose six months later. There was a catch-up programme for children under the age of five years.

## 14.6 Expected responses and adverse events following immunisation (AEFI)

### Expected responses

Expected responses to the vaccine are usually mild and of short duration. Soreness, redness and swelling at the injection site, as well as fever, malaise, headache, nausea and loss of appetite, have been reported for the available vaccines.

### Adverse events following immunisation

Reviews of data from multiple sources have not identified any serious adverse events among children and adults that could be attributed to the hepatitis A vaccine.

Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

## 14.7 Contraindications

The usual general contraindications to immunisation apply to hepatitis A vaccine (see section 1.9). Administration of hepatitis A vaccine should be delayed in individuals suffering from acute severe febrile illness. Hepatitis A vaccine should not be administered to people with a history of a severe reaction to a prior dose of hepatitis A vaccine or to a vaccine component. In individuals with an impaired immune system, adequate anti-HAV antibody titres may not be obtained after a single dose.

The safety of hepatitis A vaccine in pregnancy and during lactation has not been determined. However, because hepatitis A vaccine is produced from inactivated HAV, the risk to the developing fetus and infant is expected to be low. Therefore the risk associated with vaccination in pregnancy and during lactation should be weighed against the risk of hepatitis A. Hepatitis A vaccines should be used during pregnancy and during lactation only when clearly needed.

Hepatitis A vaccines should be administered with caution to individuals with thrombocytopenia or a bleeding disorder, since bleeding may occur following intramuscular administration. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

## 14.8 Control measures and passive immunisation

All cases of hepatitis A should be notified to the local medical officer of health.

Human normal IG provides protection against clinical disease due to hepatitis A and may be offered to close short term contacts of all ages in order to control outbreaks of hepatitis A in households and institutions. IG should be administered as soon as

possible after exposure. The recommended dose is 0.03 mL/kg intramuscular human normal IG. Hepatitis A vaccine should also be offered (see ‘Control of outbreaks’ below). IG is not usually offered if more than two weeks have elapsed since the onset of exposure to the index case.

Human normal IG is no longer recommended as pre-exposure prophylaxis for travellers. Hepatitis A vaccine is advised instead. The hepatitis A vaccine may be considered as an alternative, or in addition, to IG for post-exposure prophylaxis although further studies are needed to confirm its efficacy in these circumstances.

### **Newborn infants of infected mothers**

Perinatal transmission is rare. If the mother develops symptoms two weeks before to one week after delivery, the infant may be given IG (0.02 mL/kg), although its efficacy in these circumstances has not been established. The mother may breastfeed.

### **Early childhood services workers, children and household contacts**

Prevention of spread in these circumstances requires educating people about the modes of spread. For example, HAV can survive on objects in the environment for up to several weeks. IG or immunisation should be considered for unimmunised adult workers and children in the same room as the index case. An outbreak involving children still in napkins usually requires that all children at the facility and adult workers be given IG and/or vaccine. In addition, new workers appointed or children admitted up to six weeks after the outbreak should be vaccinated prior to entry, or offered IG if younger than the recommended age for vaccine.

All household and intimate contacts should receive IG in the dosage noted above, or vaccine as soon as possible after exposure (see ‘Control of outbreaks’ below). Schoolroom exposure does not usually lead to a significant risk of infection, and prophylaxis is not regarded as necessary in these circumstances.

### **Control of outbreaks**

#### *Community wide outbreaks of hepatitis A infection*

IG is of limited use when used as a single agent, but there is strong evidence that hepatitis A vaccine is effective in controlling community wide epidemics of hepatitis A infection.<sup>12</sup> 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.

#### *Common source outbreaks of hepatitis A infection*

IG is effective at limiting transmission in defined outbreaks. IG given as post-exposure prophylaxis is effective at limiting transmission to contacts that have recently been exposed to HAV, if the last contact occurred within the previous two weeks while the case was in the infectious period of the illness.

There is some evidence that hepatitis A vaccine is effective at controlling common source outbreaks. Before the vaccine is used for outbreak control, however, consideration should be given to the current epidemiology in the community, and the population at increased risk needs to be clearly defined.

In the future, consideration may be given to administering hepatitis A vaccine to specific populations in areas where there are high rates of hepatitis A over time.

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