3.5 HEPATITIS A

Virology

Hepatitis A is an acute infection of the liver caused by a hepatovirus, the hepatitis A virus (HAV).[1] The virus survives well in the environment – it persists on hands for several hours and in food kept at room temperature for considerably longer – and is relatively resistant to heat and freezing.

Clinical features

Hepatitis A is an infection of humans; there is no animal reservoir. HAV is predominantly transmitted by the faecal-oral route. The infecting dose is unknown but it is presumed to be low. The incubation period of hepatitis A is 15 to 50 days, with a mean of about 30 days.[1] HAV is excreted in faeces for up to 2 weeks before the onset of illness and for at least 1 week afterwards.[1]

In young children, HAV usually causes either an asymptomatic infection or a very mild illness without jaundice. Patients with symptomatic illness typically have a 4 to 10 day prodrome of systemic (fever, malaise, weakness and anorexia) and gastrointestinal (nausea and vomiting) symptoms. Dark urine is usually the first specific manifestation of acute hepatitis A, followed a day or 2 later by jaundice and pale faeces. The prodromal symptoms tend to wane with the onset of jaundice, although the anorexia and malaise may persist; pruritus and localised hepatic discomfort or pain may follow.[1] The duration of illness varies but most patients feel better and have normal, or near normal, liver function tests within a month of the onset of illness. Complications of hepatitis A are uncommon but include, on rare occasion, fulminant hepatitis.[2] Hepatitis A does not cause chronic liver disease.

The diagnosis is made by detecting anti-HAV IgM in serum during the acute illness. Anti-HAV IgM is invariably present by the time the patient presents and persists for 3 to 6 months after the acute illness.[1] Serum anti-HAV IgG indicates past infection (or possibly immunisation) and therefore immunity; it probably persists for life.

Epidemiology

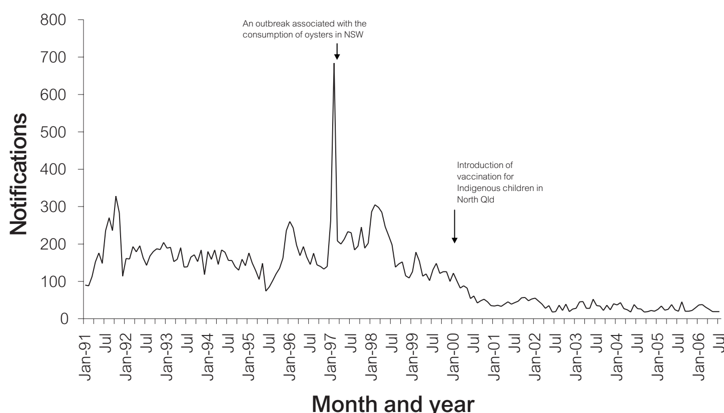
Hepatitis A was a considerable public health problem in Australia in the 1990s. During this time numerous outbreaks occurred in child day-care centres and preschools,[3] communities of men who have sex with men,[4] schools and residential facilities for the intellectually disabled,[5] and communities of injecting drug users.[4] A very large outbreak of hepatitis A associated with the consumption of raw oysters occurred in New South Wales in 1997 (see Figure 3.5.1).[6]

However, there has been a marked decline in notifications of hepatitis A in Australia in recent years (see Figure 3.5.1). This is probably a consequence of

the liberal use of hepatitis A vaccine among travellers, and those at increased risk because of lifestyle or occupation. A hepatitis A vaccination program for Indigenous children in north Queensland that began in 1999 has also contributed substantially to the decline in notifications.[7]

Nevertheless, Indigenous Australian children remain at considerably greater risk, not only of acquiring hepatitis A but also for being hospitalised with the infection, compared to non-Indigenous children.[8] This is particularly true for Indigenous children residing in other regions of Queensland, the Northern Territory, South Australia and Western Australia.

Figure 3.5.1: Notifications of hepatitis A in Australia, 1991 to 2006



Vaccines

- **Avaxim** – Sanofi Pasteur Pty Ltd (formaldehyde inactivated hepatitis A virus (GBM strain)). Each 0.5 mL pre-filled syringe contains 160 ELISA units of hepatitis A virus (HAV) antigens inactivated by formaldehyde; 0.3 mg aluminium hydroxide; 2.5 µL phenoxyethanol; 12.5 µg formaldehyde; trace of neomycin.

- **Havrix Junior** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain)). Each 0.5 mL monodose vial or pre-filled syringe contains 720 ELISA units of HAV antigens; 0.25 mg as aluminium hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin.

- **Havrix 1440** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain)). Each 1.0 mL monodose vial or pre-filled syringe contains 1440 ELISA units of HAV antigens; 0.5 mg aluminium hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin.

- **Twinrix Junior (360/10)** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine). Each 0.5 mL monodose vial or pre-filled syringe contains 360 ELISA units of HAV antigens, 10 µg recombinant DNA hepatitis B surface antigen protein; 0.225 mg aluminium phosphate/hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin. May contain yeast proteins.
- **Twinrix (720/20)** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine). Each 1.0 mL monodose vial or syringe contains 720 ELISA units of HAV antigens, 20 µg recombinant DNA hepatitis B surface antigen protein; 0.45 mg aluminium phosphate/hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin. May contain yeast proteins.
- **VAQTA Paediatric/Adolescent formulation** – CSL Biotherapies/Merck & Co Inc (formaldehyde inactivated hepatitis A virus (CR326F strain)). Each 0.5 mL monodose vial contains approximately 25 units (U) of hepatitis A virus protein; 0.225 mg aluminium hydroxide; 35 µg borax; trace of formaldehyde.
- **VAQTA Adult formulation** – CSL Biotherapies/Merck & Co Inc (formaldehyde inactivated hepatitis A virus (CR326F strain)). Each 1.0 mL monodose vial contains approximately 50 units (U) of hepatitis A virus protein; aluminium 0.45 mg as aluminium hydroxide; 70 µg borax; trace of formaldehyde.
- **Vivaxim** – Sanofi Pasteur Pty Ltd (inactivated hepatitis A virus and typhoid Vi capsular polysaccharide). Supplied in a unique dual-chamber syringe which enables the 2 vaccines to be mixed just before administration. Each 1.0 mL dose of mixed vaccine contains 160 ELISA units of inactivated hepatitis A virus antigens, 25 µg purified typhoid capsular polysaccharide; 0.3 mg aluminium hydroxide; 2.5 µL phenoxyethanol; formaldehyde; traces of neomycin and bovine serum albumin.

The inactivated hepatitis A vaccines are prepared from HAV harvested from human diploid cell cultures, which are then purified by ultrafiltration and chromatography, inactivated by formaldehyde, and then adsorbed onto aluminium hydroxide adjuvant. Although the vaccines are prepared from differing strains of HAV, there is only one known serotype; immunity induced by a particular strain probably provides protection against all strains.[1]

The Avaxim, Havrix, Twinrix and Vivaxim vaccines contain a preservative, 2-phenoxyethanol. All the vaccines contain minute amounts of residual formaldehyde. Although the manufacturers use slightly different production methods and quantify the HAV antigen content in their respective vaccines

differently, the 'equivalent' vaccines of the different manufacturers are interchangeable.

The inactivated hepatitis A vaccines induce HAV antibodies (anti-HAV) at titres many-fold greater than that provided by the recommended dose of normal human immunoglobulin. Although the vaccines are highly immunogenic (see below), the titres are usually below the detection limits of the routinely available commercial tests for anti-HAV.[1] *Therefore, serological testing to assess immunity after vaccination against hepatitis A is neither necessary nor appropriate.* Likewise, it is also inappropriate to undertake testing if an individual cannot recall if he/she has been vaccinated against hepatitis A in the past; if no vaccination records are available, vaccination should be advised.

Hepatitis A vaccines are highly immunogenic in both children and adults, with virtually universal seroconversion 4 weeks after vaccination.[1] Two randomised clinical trials conducted in the early 1990s showed that the vaccines have a very high protective efficacy, approaching 100%.[9,10] This finding is supported by the apparent eradication of hepatitis A from Indigenous communities in north Queensland since the introduction of the vaccination program in the region.[7]

The duration of immunity and, therefore, protection following vaccination is not certain. However, vaccine-induced anti-HAV probably persists for many years. There is no current evidence that booster doses are required; in healthy individuals, it is quite possible that they will never be required.[11]

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[12] Hepatitis A vaccines should be transported and stored at +2°C to +8°C. Do not freeze.

Dosage and administration

The inactivated hepatitis A vaccines are administered by IM injection. The recommended dosages and schedules for use in Australia are given in Table 3.5.1.

Table 3.5.1: Recommended dosages and schedules for use of the inactivated hepatitis A vaccines

Vaccine	Vaccinee's age (years)	Dose (HAV antigen)	Volume per dose (mL)	Vaccination schedule (mo=months)
Monovalent hepatitis A vaccines				
Avaxim	≥2	160 EIA U	0.5	0, 6 to 12 mo
Havrix Junior	2– <16	720 EIA U	0.5	0, 6 to 12 mo
Havrix 1440	≥16	1440 EIA U	1.0	0, 6 to 12 mo
VAQTA Paediatric/ Adolescent	1– <18	25 U	0.5	0, 6 to 18 mo
VAQTA Adult	≥18	50 U	1.0	0, 6 to 18 mo
Combination hepatitis A/hepatitis B vaccines				
Twinrix Junior (360/10)	1– <16	360 EIA U	0.5	0, 1, 6 mo
Twinrix (720/20)	≥16	720 EIA U	1.0	0, 1, 6 mo
Twinrix (720/20)*	1– <16	720 EIA U	1.0	0, 6 to 12 mo
Twinrix (720/20)†	≥16	720 EIA U	1.0	0, 7, 21 days, 12 mo
Combination hepatitis A/typhoid vaccine				
Vivaxim	≥16	160 EIA U	1.0 (mixed vaccine)	0; a single dose of monovalent adult formulation hepatitis A vaccine should be given at 6 to 36 mo.

* This schedule should not be used for those who require prompt protection against hepatitis B; for example, if there is close contact with a known hepatitis B carrier.

† This 'rapid' schedule should be used only if there is very limited time before departure to either moderately or highly endemic regions.

Recommendations

To avoid unnecessary vaccination, it is recommended that the following groups be screened for pre-existing natural immunity to hepatitis A:

- those born before 1950,
- those who spent their early childhood in endemic areas, and
- those with an unexplained previous episode of hepatitis or jaundice. (NB. Such a previous episode cannot be assumed to be hepatitis A.)

If, upon screening, a person has either total hepatitis A antibodies or anti-HAV IgG, he/she has presumably had previous, perhaps unrecognised, HAV infection (or less likely, has been previously immunised) and can be assumed to be immune and, therefore, does not need hepatitis A vaccination.

(i) Hepatitis A vaccination is recommended for:

- **all travellers to, and all expatriates living in, moderately to highly endemic areas (including all developing countries)**

A single dose of a monovalent hepatitis A vaccine provides protective levels of anti-HAV for at least a year;[1] the second dose is recommended to increase the duration of protection. As they do not contain live viruses, hepatitis A vaccines can be administered either simultaneously with, or within a month of, all other vaccines relevant to international travel.[13]

There is no place for the routine use of normal human immunoglobulin to prevent hepatitis A in travellers. It should only be given (at the same time as hepatitis A vaccine) to those, such as aid-workers about to be deployed in emergency refugee camps, who will be living in very inadequate circumstances. Otherwise, it is only recommended for contacts of hepatitis A cases (see 'The public health management of contacts of hepatitis A cases' below).

- **Aboriginal and Torres Strait Islander children residing in the Northern Territory, Queensland, South Australia and Western Australia**

Hepatitis A vaccination for these children should commence in the second year of life. State/Territory health authorities should be contacted about the local hepatitis A vaccination schedules, including catch-up.

- **those whose occupation may put them at risk of acquiring hepatitis A**

This includes those who live or work in rural and remote Indigenous communities, child day-care and preschool personnel, carers of people with intellectual disabilities, healthcare workers who regularly provide care for Aboriginal and Torres Strait Islander children, plumbers or sewage workers, and sex workers.

- **those whose lifestyle may put them at risk of acquiring hepatitis A**

This includes men who have sex with men, and injecting drug users.

- **people with intellectual disabilities**
- **people chronically infected with either hepatitis B or hepatitis C viruses**
- **patients with chronic liver disease**

Hepatitis A vaccination is recommended for patients with chronic liver disease of any aetiology. Those with chronic liver disease of mild to moderate severity mount a satisfactory immune response following vaccination, but those with end-stage liver disease do not respond as well, and liver transplant recipients may not respond at all.[14,15] Nevertheless, all those with chronic liver disease should be vaccinated, preferably as early in the course of the disease as possible.

(ii) Combined hepatitis A/hepatitis B vaccines

Combined hepatitis A/hepatitis B vaccines should be considered for:

- expatriates and long-term visitors to developing countries,

  NB. Twinrix (720/20) can be administered according to a 'rapid' schedule if there is limited time before departure.[16] This consists of a single dose on each of days 0, 7 and 21. It is important that a fourth dose be given as a booster 12 months after the first dose to ensure longer-term protection.
- medical, dental and nursing undergraduate students,
- men who have sex with men,
- sex industry workers,
- injecting drug users,
- patients with chronic liver disease,
- solid organ transplant recipients (see Table 2.3.2 *Recommendations for vaccinations for solid organ transplant (SOT) recipients*),
- people with intellectual disabilities and their carers.

NB. Twinrix (720/20) can be administered in a 2-dose regimen in people 1 to 15 years of age (see Table 3.5.1). However, this regimen should not be used in those who require prompt protection against hepatitis B; for example, if there is close contact with a known hepatitis B carrier.

Combined hepatitis A/hepatitis B vaccines can be administered simultaneously with, or within a month of, all other vaccines relevant to international travel.

(iii) Combined hepatitis A/typhoid vaccine

The combined hepatitis A/typhoid vaccine can be recommended for all those ≥16 years of age who intend travelling to developing countries, and is particularly useful for those already immunised against hepatitis B. The vaccine can be administered simultaneously with, or within a month of, all other vaccines relevant to international travel.

A single dose of a monovalent adult formulation hepatitis A vaccine 6 to 36 months later is required to provide longer-term protection against hepatitis A. A booster dose of typhoid capsular polysaccharide vaccine is required after 3 years if there is a continued risk. The combined hepatitis A/typhoid vaccine may be used as a 'booster' vaccine if a person received a previous dose of a monovalent adult formulation hepatitis A vaccine. This may be given 6 to 36 months after primary vaccination.

Contraindications

The only contraindications to any of the hepatitis A vaccines are:

- anaphylaxis following a previous dose of any of the hepatitis A vaccines, or
- anaphylaxis following any component of the vaccine.

Combination vaccines containing the hepatitis B component are contraindicated where there is a history of anaphylaxis to yeast.

Adverse events

The most common adverse events following administration of hepatitis A vaccines are mild local events of a short duration, probably caused by the aluminium hydroxide adjuvant. About 15% (very common) of adults report headache and approximately 5% (common) report malaise or fatigue following vaccination.[17] Up to 20% (very common) of children who received either Havrix or VAQTA experienced soreness at the injection site. In both adults and children, systemic adverse events such as headache and fever are much less common than local adverse events.[17]

Hepatitis A vaccines do not affect liver enzyme levels. They can be safely given to HIV-infected people, and do not adversely affect either the HIV load or CD4 cell count.[18]

The public health management of contacts of hepatitis A cases

Normal human immunoglobulin (NHIG) can be used to prevent secondary cases in close contacts of hepatitis A cases. (NB. A hepatitis A IgM positive test in an adult without either clinical or epidemiological features of hepatitis A should be considered as a false-positive result.[19] In this circumstance, no interventions are necessary for the close contacts.)

NHIG should be administered to close contacts within 2 weeks (of the last exposure to the cases) in the doses given in Table 3.5.2; NHIG may not be effective if given >2 weeks after the exposure.[17] 'Close contacts' are those who have had contact with a case during the 2 weeks before, up until 1 week after, the onset of jaundice, and usually include only household and/or sexual contacts (but in some circumstances may include close occupational exposure).

Table 3.5.2: Recommended doses of normal human immunoglobulin (NHIG) to be given as a single intramuscular injection to close contacts of hepatitis A cases

Weight	Dose NHIG
Under 25 kg	0.5 mL
25–50 kg	1.0 mL
Over 50 kg	2.0 mL

Although 1 study suggests that hepatitis A vaccine may be effective in preventing secondary cases of hepatitis A in close contacts,[20] there is currently insufficient evidence to be able to recommend it for this purpose.

Further public health considerations

If a person with hepatitis A was a food-handler by occupation while infectious, a review of the food-handling procedures in the food establishment should be undertaken and the staff at the establishment reminded of standard food and personal hygiene practices.[17] If the review identifies issues which raise the possibility of transmission of HAV, NHIG should be administered to the other food-handlers in the establishment. State/Territory public health authorities should determine the need for recall of customers of the establishment for NHIG. A food-handler with hepatitis A should be excluded from work until at least 1 week after the onset of jaundice.

A single case of hepatitis A associated with a day-care or preschool facility (ie. a case in an attendee child, a staff member or a household contact of an attendee or staff member) does not require any mass intervention.[3] However, the supervisor of the facility should be contacted to:

- explore the possibility of within-centre transmission by the case (eg. faecal accidents, other hygiene control concerns), and
- determine if there could be other cases associated with the facility. In particular, it should be ascertained whether an attendee child arrived from an endemic region overseas about a month before the case's onset, and whether any other children at the facility have recently been vaguely unwell with a change in bowel motions.

Should there be any concerns about the potential for further transmission of hepatitis A virus within the facility, mass interventions (as per 2 or more cases below) may be considered. The supervisor should be reminded of the relevant infection control practices that should be in place at all times at the facility, and that hepatitis A vaccine is routinely recommended for day-care and preschool staff (unless they have either had hepatitis A in the past or been vaccinated previously). A useful reference is 'Staying Healthy in Child Care' available at http://www.nhmrc.gov.au/publications/synopses/ch43syn.htm.

Two or more cases of hepatitis A (associated with the same day-care or preschool facility) that occur in different households are strongly suggestive that transmission of HAV is occurring within that facility.[3] These cases may be in attendee children or staff or household contacts of an attendee or staff member. As soon as transmission of HAV is recognised within a day-care or preschool facility, NHIG should be offered to children and susceptible staff in the relevant age groups (or classes) at that facility. Parents and staff need to be reminded that live virus vaccines, MMR and varicella vaccines in particular, should not be administered within 3 months of receiving IM NHIG.[3]

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

None.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.