2012 Antigen Review for the New Zealand National Immunisation Schedule: Hepatitis A

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Executive summary

This report summarises new research on hepatitis A virus (HAV) vaccines and vaccination published during the four years 2009-2012.

HAV is an enterovirus of the family Piconoviridae. There is only one HAV serotype throughout the world; within this serotype there are seven recognised genotypes, of which four affect humans. The disease is spread from person to person by close contact, mostly within families and between sexual partners. A small number of outbreaks are associated with contaminated food, including raw or undercooked shellfish, raw fruit and vegetables. People at highest risk of infection are those who engage in personal contact with an infected person and travellers to countries with high rates of HAV infection.

Most young children in endemic countries have asymptomatic or mild infections that confer long-term immunity. As living standards improve, such as sanitation, fewer younger children are infected and a greater proportion of the population become susceptible to infection.

NZ Epidemiology

The incidence of notified HAV infection in New Zealand has steadily declined in recent decades, from a rate of 145.7 per 100,000 in the population in 1971, to 0.6 in 2011. In 2012, there were a total of 26 cases, and there have been no deaths since 2002. Overseas travel is the most common risk factor, followed by consumption of contaminated food or water. Over two-thirds of cases had travelled overseas during the incubation period of the disease with the most commonly reported country being India. Most cases are from the Auckland region, primarily in Asian ethnic groups, and are distributed mostly across children and younger adults.

Vaccines

All currently available international inactivated HAV strain vaccines are grown in cell-culture, as of early 2013. They use aluminium or liposome adjuvants and most monovalent vaccines do not use preservatives. Combination inactivated HAV vaccines are available, combined with a hepatitis B or typhoid vaccine; these vaccines use aluminium adjuvant and the preservative phenoxyethanol.

One live-attenuated vaccine is produced in China.

Safety

There are no safety concerns with widespread use of the inactivated HAV vaccines. They appear safe when used in immunosuppressed recipients, including HIV-infected children. There is insufficient data to draw conclusions on the safety profile for live attenuated vaccines.

Immunogenicity, efficacy, effectiveness

A clear correlate of protection has not been established, and measures vary with different assays used. Despite this, all the inactivated HAV vaccines appear highly immunogenic after a single dose in all recipients over 12 months of age. A booster dose is likely to be important for long-term protection, in the absence of wild boosting. Immunogenicity rates are lower in HIV-infected patients, but still likely to be effective.

Duration of immunity after a single dose is likely to be up to 10 years in children and at least 15 years in adults. A second dose is likely to give protection for 25 years or longer.

Universal vaccination programmes show strong herd immunity effects with herd immunity accounting for around one third of the cases prevented.

HAV vaccines are highly effective in preventing clinical disease with efficacy measures of 94-100% from six weeks post-vaccination.
**Age and High Risk Specific Issues**

As of early 2013, NZ currently has low rates of HAV notification with a concentration in children and young adults, particularly travellers. Countries with low endemicity, comparable to NZ, show the second-highest risk group, after returning travellers, to be illicit drug users. Other high-risk groups to consider are men who have sex with men, poor food preparation environments and waterborne contamination from sewage. Individuals with chronic liver disease are not at higher risk of exposure, but at higher risk of severe outcomes.

**Options for scheduling**

For countries with low endemicity of HAV disease, there are two options: a universal schedule, usually a single vaccine dose from one year of age, or a targeted schedule focused on those at higher risk of contracting the disease and/or higher risk of poor outcomes. The WHO recommends a single dose HAV vaccine if used as a national schedule vaccine. The evidence for the additional need for a booster is currently unclear. Combination vaccines are available with hepatitis B vaccine.

Outbreak control can be effectively managed with vaccinations in healthy persons 40 years and younger both with pre- and post-exposure prophylaxis. For those over 40 years immunoglobulin is recommended.

Eradication is theoretically possible, but current international focus is on improving living conditions and the strategic application of vaccination.

**Implementation Issues**

Prevaccination serological testing is not recommended in children, but can be undertaken in others, particularly in populations with a high prevalence of infection. The most recent list of recommendations for administering the HAV vaccine to those considered at highest risk, as reported by the US ACIP, is reported in Table 3.

Recent data on concomitant use shows that co-administration with MMR-V, PCV-7, and DTaP and Hib in the second year of life has no safety or immunogenicity concerns. Mixed schedules can be used with all commonly used monovalent inactivated vaccines. Vaccine safety in pregnancy is unknown, however, is theoretically, unlikely to be a concern with an inactivated vaccine.

**International Practice**

Since, in most developed countries the incidence of HAV is low and only at-risk groups are recommended for vaccination, the majority of developed countries do not have HAV vaccination as part of their childhood immunisation schedule. There are some countries with medium to low endemicity that offer a universal HAV programme, usually given at 12 months of age; Israel was the first country to offer this. The US offers a two dose regime at 12 months and a booster six-18 months later. The UK and European countries offer vaccination to high-risk groups only. Australia offers universal vaccination to all Aboriginal and Torres Strait Islander children at 12 – 24 months of age, and to other high-risk groups only.
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<tr>
<td>AEFI</td>
<td>Adverse Events Following Immunisation</td>
</tr>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices (US)</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunisation</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention (US)</td>
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<tr>
<td>DHB</td>
<td>District health board</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
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<tr>
<td>FDA</td>
<td>US Federal Drug Agency</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain-Barré Syndrome</td>
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<tr>
<td>GMC</td>
<td>Geometric mean concentration</td>
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<tr>
<td>Ig</td>
<td>Immunoglobulin</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>HAV</td>
<td>Hepatitis A Virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>MELAA</td>
<td>Middle Eastern, Latin American, African</td>
</tr>
<tr>
<td>NMDS</td>
<td>National Minimum Data Set</td>
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<tr>
<td>NZ</td>
<td>New Zealand</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VAERS</td>
<td>Vaccine Adverse Events Reporting System</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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1. Background – hepatitis A

This report summarises new research on hepatitis A virus (HAV) vaccines and vaccination published during the four years 2009-2012. A full review of data and vaccination schedules was not conducted during an edit in 2014.

1.1 Introduction

HAV is an enterovirus of the family Picornaviridae with seven recognised genotypes; four of these genotypes affect humans. No correlations have been observed between infecting genotype, clinical characteristics or clinical outcomes (1). There is only one HAV serotype throughout the world, and so individuals infected in any part of the world are not susceptible to infection in another part (2).

Clinically, HAV, in its acute form, can be indistinguishable from other forms of hepatitis. Symptomatic illness can be abrupt in onset characterised by fatigue, malaise, anorexia, fever, myalgia, abdominal pain, nausea and vomiting. Children may also have diarrhoea with pale coloured stools and dark urine. Jaundice appears after approximately one week and is noticeable in the sclera and urine. Physical findings may also include an enlarged liver and upper abdominal tenderness. The average incubation period is 28 days. HAV cannot be distinguished from other causes of acute hepatitis without serological testing for antibodies to HAV. Serology includes total anti-HAV antibody and anti-HAV IgM, the latter being a marker of acute infection. IgG antibody eventually replaces anti-HAV IgM and confers life-long immunity. Only anti-HAV IgG is detected following vaccination or resolved infection.

The disease is spread from person to person by close contact, mostly within families and between sexual partners. A small number of outbreaks are associated with contaminated food, including raw or undercooked shellfish, raw fruit and vegetables. While heating to 85°Celsius will inactivate the virus, freezing the food will not.

People at highest risk for infection are those who engage in personal contact with an infected person. Others at risk include those who travel to countries with high or intermediate rates of HAV, especially Africa, Asia (except Japan), Eastern Europe, the Middle East, South and Central America, Mexico, and Greenland, those who have oral-anal sexual contact, illegal drugs users, chronic liver disease patients, laboratory workers handling the virus, those with blood clotting disorders or who receive clotting factor concentrates, children in day-care centres in communities with high rates of HAV, food handlers, residents and staff of institutions that care for the chronically ill or disabled and people with a weakened immune system due to cancer, human immunodeficiency virus (HIV), chronic steroid medications or organ transplantation.

Hepatitis A virus occurs worldwide and infects more than 80% of the population of many developing countries by late adolescence and is also common in developed countries (3). The World Health Organization (WHO) estimate for HAV disease is a conservative 1.5 million cases per year worldwide. Most young children in endemic countries have asymptomatic or mild infections that confer long-term immunity. Older children and adults are generally symptomatic. As living standards improve, such as sanitation, fewer younger children get infected and a greater proportion of the population become susceptible to infection (4).

Major geographical differences exist in endemicity and resulting epidemiology. The degree of endemicity is related to hygiene and sanitation conditions; this is often more of a problem in the least developed countries, as in parts of Africa, Asia and Central and South America (3). Susceptible adults are at high risk of infection in these areas, but overall reported disease rates are generally low and outbreaks are rare because of the high prevalence of population immunity. In more developed countries, such as NZ, endemicity of the virus is low. This means that relatively fewer children are infected and disease is more likely to occur in the context of community outbreaks and childcare centre outbreaks. Some countries see a cyclic pattern of disease incidence with peaks every 5 to 10 years. Seroprevalence studies show a gradual increase in the prevalence of anti-HAV with increasing age. In countries with very low endemicity, such as the Scandinavian countries, most cases occur in defined risk groups such as returning travellers and intravenous (IV) drug users (3).
2. Methodology for review

2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 NZ antigen review and the specific specifications for HAV vaccines. These are listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around HAV vaccines for New Zealand.

- General specifications
  - Safety
  - Effectiveness
  - Implementation issues (practicality and possible impact on uptake)
  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination
  - Different options of placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparisons between the options

2.2 New Zealand epidemiology

In NZ, HAV is an infectious disease notifiable to Medical Officers of Health. The NZ epidemiological information presented is based on national notification and laboratory-based surveillance summarised in the Notifiable and Other diseases in New Zealand, 2011 (5).

2.3 Literature search strategy

The points below have formed the focus of the literature search:

1. Safety
2. Effectiveness in disease control
   - Effect on i. Indirect effects/herd immunity ii. Duration of protection - Immunogenicity
3. Implementation issues (practicality of and possible impact on uptake)
4. Differences that need to be considered for each age group, and groups with particular needs
   - Age
   - High-risk groups – definition of which groups most likely to benefit and which vaccines/s
5. Different option for placement on the schedule, based on international findings and best practice
6. Different vaccine options and comparison between the options
7. Current international research and evidence around use of vaccines

2.3.1 Medline search terms and strategy

MeSH term: Hepatitis A Vaccin* including sub groups Vaccines, Inactivated, Hepatitis A vaccine*, Viral Hepatitis Vaccine, focus search

3991 Limit to Humans, English, 2009 - current
343 NOT Physician, Survey, Interview, Qualitative, Self-report
309 NOT Cost*, Attitud*
275
2.3.2 Cochrane Library search terms and strategy

Search term Hepatitis A Vaccin*
Limit to Cochrane Reviews, Other Reviews, Trials 2009-present
3 results (keep and view)

2.3.3 Scopus search terms and strategy

Hepatitis A Vaccin* Published 2011 - present
2705
Limit to: Medicine, Humans, English
1728
Exclude Letter, Short survey, Book, Editorial
1640
Reject Veterinary, Arts and Humanities, Social science articles.
1354
Reject Hepatitis B
491 (keep and view)
Delete duplicates
Final Endnote Library 198 Articles

2.3.4 Grey literature

Conference abstracts were sought to include data that has not yet been published, particularly from the key infectious diseases conferences for 2011 and 2012 – there were no abstracts or posters accessed.

2.3.5 Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further 18 articles were accessed.

2.3.6 Final library

The final library includes 218 references. Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

2.4 Participants/populations

The population for a universal programme are Infants and targeted vaccination all ages, children and adults.

2.4.1 Vaccine performance in high risk

High risk groups include the immunocompromised (including HIV patients), healthcare workers, research workers in labs, international travellers, pregnant women, men who have sex with men, illicit drug users, infants, children aged two-18 years, persons with chronic liver disease, persons receiving clotting factor concentrates and household contacts.

2.5 Interventions

The interventions included are

- Inactivated hepatitis A vaccines
- Live attenuated hepatitis A vaccines

2.6 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching.
3. Recent epidemiology

3.1 Recent NZ epidemiology

The incidence of notified HAV in New Zealand has declined in recent decades, from a rate of 145.7 per 100,000 in the population in 1971, to 0.6 in 2011. The number of notified cases of acute HAV infection in New Zealand has steadily decreased since 1980. The fall in rates is presumably at least in part due to the use of HAV vaccination in travellers, and falling rates overseas. Overseas travel is currently the most common risk factor reported by notified cases, followed by consumption of known or potentially contaminated food or water.

In 2011, a total of 26 cases of HAV were notified, compared with 46 notifications in 2010. Since a peak of notifications in 1997 (347 cases), there has been an overall downward trend in the number of HAV notifications reported, although an increase in notifications (primarily due to outbreaks of disease) was observed in 2002, 2006 and 2008 (Figure 2).

The national HAV notification rate for 2011 was 0.6 per 100 000, which was a significant decrease from the 2010 rate of 1.1 per 100 000 (46 cases). Auckland (8 cases) and Counties Manukau (5 cases) district health boards (DHBs) had the highest numbers of cases in 2011. Final counts for notifications in 2012 are not yet available but preliminary analysis indicates a considerable increase accompanied by a disproportionate increase in hospitalisation. Most cases were from the Auckland region.

Age was recorded for all cases. The highest case counts occurred in the five-nine years (6 cases), 20–29 years (6 cases) and one-four years (4 cases) age groups.

Sex was recorded for 25 (96.2%) cases. Of these, males (0.7 per 100 000 population, 16 cases) had a higher notification rate than females (0.4 per 100 000, 9 cases).

Ethnicity was recorded for 25 (96.2%) HAV cases. The highest number of notifications was reported for those in the Asian ethnic group (12 cases), followed by the European or Other (6 cases), Pacific Peoples (3 cases), Māori (2 cases) and Middle Eastern, Latin American, African (MELAA) (2 cases) ethnic groups.

Hospitalisation status was recorded for 25 (96.2%) cases. Of these, six cases (24.0%) were hospitalised.

Of the 24 cases with travel information recorded, 16 (66.7%) had travelled overseas during the incubation period of the disease. The countries most frequently visited by HAV cases included India (9 cases), Samoa, United Arab Emirates and Thailand (2 cases each).
3.1.1 Hospitalisations
Hospitalisations can be used as a proxy for disease severity. Comparison of available data from Episurv and National Minimum Data Set (NMDS) indicates a shortfall in Episurv numbers. This is due to the inclusion of HAV associated admissions in the NMDS. Episurv can also be used (see Figure 2) to determine the proportion of hospital admissions from all notifications that included the required information. There appears to be a substantial increase in the numbers hospitalised in 2012.

![Figure 3. Trends in hospital admissions, 2002-2012. ESR Episurv and NMDS](image)

3.1.2 Mortality
The last death due to HAV in New Zealand was in 2002.

3.2 Summary of recent NZ epidemiology
The incidence of notified HAV in New Zealand has steadily declined in recent decades, from a rate of 145.7 per 100,000 in 1971 to 0.6 per 100,000 in 2011, with a total of 26 cases in this year. There have been no deaths since 2002. Overseas travel is the most common risk factor, followed by consumption of contaminated food or water. Over two-thirds of cases had travelled overseas during the incubation period of the disease with the most common country reported country being India. Most cases are from the Auckland region, highest in Asian ethnic groups, and are distributed mostly across children and younger adults.
4. Safety

4.1 Objective

The objective of this section is to review the most recent safety data for currently licensed HAV vaccines. Consideration is given to vaccines undergoing clinical trials and vaccines not currently licensed in New Zealand but which have been approved in countries of similar stature.

4.2 Outcomes

Outcomes are general vaccine safety including adverse events following immunisation (AEFI) and serious adverse events (SAE).

4.3 Review

The common injection-site reactions for inactivated HAV vaccines such as pain, swelling and redness have been reported in 21% of children and 56% of adults vaccinated (6, 7). Systemic reactions are rare. The vaccine adverse events reporting system (VAERS) maintained by the US FDA and CDC received 6000 reports of adverse events over a 10-year period between 1995 and 2005 from over 50 million doses sold. Of these, 871 events were categorised as serious and included Guillain-Barré Syndrome (GBS), transaminitis, idiopathic thrombocytopenic purpura and seizures among children (8). Rare events reported included syncope, jaundice, erythema multiforme, anaphylaxis, brachial plexus neuropathy, transverse myelitis and encephalopathy (9). No serious adverse events could be directly attributed to the HAV vaccine (7, 8).

4.3.1 Live Attenuated Vaccines

A multicentre study of the immunogenicity and safety of a single dose of live attenuated HAV vaccine given to a paediatric population of 505 children aged 18 to 60 months in four metropolitan cities of India has been reported (10). This is a freeze-dried liver attenuated vaccine (H2 strain) developed by the Zhejiang Pukang Biotechnological Company, Ltd, China. There is limited methodology reported as to how safety monitoring was undertaken. The authors report that ‘parents were advised to report to the hospital for any untoward incidence and to keep a record of fever, local pain, erythema and induration at the site of vaccination.’ A follow up 6 weeks post vaccination was also undertaken. The authors reported that vaccine-induced local and systemic adverse events were insignificant at all the centres, except swelling and induration in a few. Overall the safety data presented was limited, and it is therefore difficult to assess its adequacy.

4.3.2 Cochrane Review

A 2012 meta-analysis conducted by the Cochrane Collaboration on Hepatitis A immunisation included 11 studies that attempted to determine the clinical protective efficacy, sero-protective efficacy, and safety and harms of HAV vaccination in persons not previously exposed to HAV (11). Nine randomised trials addressed the primary outcome of clinically confirmed HAV. Of these, four trials assessed the inactivated HAV vaccine (41,690 participants) and five trials assessed the live attenuated HAV vaccine (690,690 participants).

There were only three randomised trials considered to have low risk of bias, all assessing inactivated vaccines. The authors concluded that the risk of both non-serious local and systemic adverse events was comparable to placebo for the inactivated HAV vaccines. There were insufficient data to draw conclusions on adverse events for the live attenuated HAV vaccine.
4.3.3 Immune suppression

The administration of the inactivated vaccine to the immune suppressed does not appear to be associated with a greater risk compared to persons with normal immune systems (12-14).

4.3.1.1 HIV-infected

A small study undertaken in 2008/2009 looked at the immunogenicity and safety of a paediatric dose virosomal HAV vaccine (Epaxal®) in 45 HIV-infected children in Thailand (15) aged from 2 to 16 years in a two dose regime at 0 and 6 months. Patients were monitored for 3 days post vaccination with a diary card; there was one report of mild pain at the injection site and no other reported adverse events for both doses.

The risk of both non-serious local and systemic adverse events was comparable to placebo for the inactivated HAV vaccines. There were insufficient data to draw conclusions on adverse events for the live attenuated HAV vaccine.

4.4 Summary vaccine safety

There have been no specific concerns regarding the safety of any of the inactivated HAV vaccines reported on in the recent literature either when used singly or when co-administered. Inactivated HAV vaccines appear safe when used in immunosuppressed recipients, including HIV-infected children. There is to date very limited data on the safety profile of live attenuated vaccines.
5. Immunogenicity, efficacy, effectiveness and vaccine impact

5.1 Objective
The objective of this section is to review the most recent performance data for currently licenced HAV vaccines. Consideration is given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of HAV vaccines and evidence of their impact in populations.

5.2 Outcomes
The outcomes for this review are:
- Immunogenicity
- Efficacy and effectiveness against HAV
- Duration of protection
- Herd Immunity

5.3 Immunogenicity
All the inactivated HAV vaccines are highly immunogenic in both adults and children over 12 months of age, with 90–100% of recipients developing protective antibody levels by one month after the first dose (3). A second dose at 6 to 18 months after the first results in excellent booster antibody concentration for almost all recipients; this is considered protective, but is generally lower than concentrations measured after natural infection. The second dose is likely important for long-term protection (3).

Although there are minor differences between the vaccines, the administration and efficacy of these vaccines are essentially the same. A booster dose is recommended 6–18 months after the first dose. It is not necessary to repeat prior doses, irrespective of the interval between doses.

HAV vaccines have not been approved for children aged less than 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. Almost all recipients develop protective antibodies after a single dose of HAV vaccine, but a second dose is thought to be important for long-term protection, particularly in the absence of exposure to HAV (8, 9). In subjects with an impaired immune system, adequate anti-HAV antibody titres may not be obtained after a single dose.

An open randomised controlled multi-centre parallel-group study was conducted in two sites in Chile to assess the immunogenicity of the paediatric dose of the inactivated vaccine Epaxal® (0.25 mL), compared to the standard dose (0.5 mL) of Epaxal® and to a dose of the control inactivated vaccine Havrix® Junior.

The study included 360 children aged 12 months to <17 years randomised 2:2:1 for vaccination with Epaxal® 0.25mL, (n=146), Epaxal® 0.5 mL (n=142) and Havrix® Junior (n=172). The primary end point was the proportion of subjects seroprotected (anti-HAV antibody concentration >=10 mIU/mL) at month 1 post vaccination. All vaccines elicited high seroprotection rates at month 1: 95.7% with Epaxal® 0.25 mL, 99.3% with Epaxal® 0.5 mL and 94.0% with Havrix® Junior. After the booster vaccination, all subjects demonstrated 100% seroprotection with all vaccines.

All study vaccines were well tolerated. Thus, the paediatric 0.25 mL dose of Epaxal® fulfilled the primary objective of showing non-inferiority to the adult 0.5 mL dose and to Havrix® Junior, in terms of seroprotection rates achieved. The results show the paediatric dose of Epaxal® to be an acceptable option when conducting childhood-vaccination programmes (16).

5.3.1 Correlates of Protection
The absolute lower limit of antibody needed to prevent HAV infection has not been determined. Because no absolute protective level has been defined the lower limit of detection of the particular assay being used has generally been considered the protective level. Clinical studies with Havrix® have used levels greater than 20 or 33 mIU/mL with enzyme immunoassays, and studies with VAQTA® have used levels greater than 10mIU/mL. Antibody concentrations above the defined protective concentration can be measured as early as two weeks after one dose, although this varies with different vaccines. Neutralising antibodies may take up to a month after the first dose, and 2 weeks after the second dose (3).
5.3.2 Duration of immunity

Antibodies to HAV vaccine have been shown to persist in vaccinated adults for at least 15 years after vaccination, and up to 10 years in vaccinated children and adolescents. Protective levels of antibody following completion of a two-dose series are expected to persist for 25 years or longer based on estimates from mathematical models (3).

5.3.2.1 Long term immunogenicity

An open-label randomised study conducted in 1998 in two centres in the Czech Republic compared the immunogenicity of two- and three-dose regimens of a combined HAV and B vaccine 10 years after administration in 300 adolescents aged 12 – 15 years. One hundred and fifty adolescents received Twinrix® Adult, a HAV and B vaccine Adult formulation (720 EL.U of inactivated HAV with 20 µg of HBs antigen) in a 0 and 6 month schedule and 150 received three doses of Twinrix® Paediatric, the combined and B vaccine Paediatric formulation (360 EL.U of inactivated HAV antigen and 10 µg of HBs antigen) in a 0, 1 and 6 month schedule. They reported anti-HAV seropositivity rate of 100% in both groups and similar anti-HAV antibody geometric mean antibody concentration (GMC) response. No vaccine-related serious adverse events were reported. The authors concluded that with respect to long-term antibody persistence, the two-dose schedule of the combined hepatitis A and B vaccine adult formulation was an effective alternative to the conventional three-dose schedule of the paediatric formulation in adolescents (17).

5.3.3 Immunogenicity in high risk groups

5.3.3.1 HIV infected patients

The earlier reported study looked at the immunogenicity and safety of the paediatric dose virosomal HAV vaccine (Epaxal®) in an open label study of HIV-infected children in Thailand (15) aged from 2 to 16 years in a two dose regime at 0 and 6 months. The seroprotection rate was 71% at 1 month and 100% at 7 months. The booster dose increased GMC from 106.5 mIU/ml to 3486.1 mIU/ml. This preliminary data suggests that a paediatric dose of Epaxal® is an effective HAV vaccine for HIV-infected children and could be considered for implementation on a larger scale in the paediatric HIV population.

A double blind study compared 90 HIV-non infected adults with 90 HIV-infected adults all randomised to be given a single dose of either inactivated HAV vaccine (VAQTA®) or placebo. Seroconversion rates at week 28 of the study were 87% - 94% among HIV-infected and 100% among HIV non-infected. HIV infected patients seroconvert but show concentrations lower than those detected in non-HIV patients (19).

5.3.3.2 Other high risk groups

Acute HAV superimposed on pre-existing chronic liver disease has been associated with severe or fulminant hepatitis. A study on 475 adults over the age of 18 years consisted of five groups: healthy adults, chronic hepatitis B, chronic hepatitis and other chronic liver disease not caused by viral hepatitis. All groups were vaccinated with two doses of an inactivated HAV vaccine at 0 and 6 months. Although a higher percentage of healthy subjects (93%) seroconverted after a single dose of the vaccine than did subjects with chronic hepatitis C (73.7%) or chronic disease of non-viral origin (83.1%), after the complete vaccination course more that 94% of all vaccines were seropositive (20).

5.3.4 Immunogenicity of a live attenuated hepatitis A vaccine

The multicentre study referred to in the safety section looked at the immunogenicity and safety of a single dose of live attenuated HAV vaccine given to a paediatric population of 505 children aged 18 to 60 months in four metropolitan cities of India has been reported (21). This is a freeze-dried liver attenuated vaccine (H2 strain) developed by the Zhejiang Pukang Biotechnological Company, Ltd, China. At 6 weeks, 95.1% seroconverted and at the end of 6 months, 97.9 % had seroconverted.
5.4 Efficacy and effectiveness

HAV vaccines are highly effective in preventing clinical disease, with recorded efficacy measures of around 94-100% from 6 weeks post vaccination (3). Effectiveness has been demonstrated in many communities with national programmes vaccinating children or adolescents and young adults, resulting in a rapid decline in disease incidence, both through direct and indirect (herd immunity) effects (3).

5.4.1 Cochrane meta-analysis

A 2012 meta-analysis conducted by the Cochrane Collaboration on HAV immunisation included 11 studies that attempted to determine the clinical protective efficacy, sero-protective efficacy, and safety and harms of HAV vaccination in persons not previously exposed to HAV (11). Nine randomised trials addressed the primary outcome of clinically confirmed HAV. Of these, four trials assessed the inactivated HAV vaccine (41,690 participants) and five trials assessed the live attenuated HAV vaccine (690,690 participants).

There were only three randomised trials considered to have low risk of bias, all assessing inactivated vaccines. In these 3 trials clinically apparent HAV occurred in 9/20,684 (0.04% of vaccinees versus 92/20,746 (0.44%) of the control group giving a RR of 0.09, 95% CI 0.03 – 0.3).

Inactivated HAV vaccines had a significant effect on immunogenicity when measuring seroprotective thresholds levels at less than 20 mIU/L (RR 0.01, 95% CI 0.00 to 0.03). No trial reported on a seroprotective threshold less than 10 mIU/L.

In all the nine randomised trials, clinically apparent HAV occurred in 31/375,726 (0.01%) versus 505/356,654 (0.18%) participants in the HAV vaccine and control groups respectively (RR 0.09, 95% CI 0.05 to 0.17). Subgroup analyses confirmed the clinical effectiveness of both inactivated HAV vaccines (RR 0.09, 95% CI 0.03 to 0.30) and live attenuated HAV vaccines (RR 0.07, 95% CI 0.03 to 0.17) on clinically confirmed HAV. The review demonstrated significant protection for at least two years with the inactivated HAV vaccine and at least five years with the live attenuated HAV vaccine (11).

5.4.2 Herd immunity

As with all disease prevention in vaccinated populations, the benefits of immunisation against HAV extends beyond the protection of those vaccinated. In populations with high endemic levels of the disease, vaccination programmes with even sub-optimal uptake have produced dramatic falls in disease incidence (3). Summarising the data (3): In Israel the incidence of HAV declined by 95% within three years after initiation of an immunisation programme to 18-24 month old children, even though no catch up vaccination in other groups was undertaken. Routine vaccination of 12 year olds in Catalonia, Spain was followed by a 58% reduction overall in disease incidence. A United States (US) study modelled the relationship between incidence and vaccination coverage in the US and estimated that herd immunity accounted for one third of the cases prevented (22).

An economic modelling exercise conducted in the US commencing in 2005, demonstrated the fraction of the population that would have been prevented from getting the disease by herd immunity using previously published analyses of the relationship between vaccine coverage and hepatitis incidence decline. The authors demonstrated that herd immunity more than doubles the savings from vaccination during the first 10 years of the programme (3).

5.5 Summary of immunogenicity, efficacy and effectiveness

A clear correlate of protection has not been established, and measures vary with different assays used. Despite this, all the inactivated HAV vaccines appear highly immunogenic after a single dose in all recipients over 12 months of age. Seroprotection has been demonstrated for at least two years with inactivated vaccines and at least five years with live attenuated vaccines. A booster dose is likely to be important for long-term protection, in the absence of wild boosting. Immunogenicity rates are lower in HIV-infected patients but still likely to be effective.

Duration of immunity after a single dose with inactivated vaccines is likely to be up to 10 years in children and at least 15 years in adults. A second dose is likely to give protection for 25 years or longer.

Universal vaccination programmes show strong herd immunity effects with herd immunity accounting for around one third of the cases prevented.

HAV vaccines are highly effective in preventing clinical disease with efficacy measures of 94-100% from 6 weeks post-vaccination.
6. Age-specific and high-risk specific issues

6.1 Objective
This section considers the differences that need to be considered for various age groups and high-risk groups. Issues around the use of available vaccines in age groups other than infants and young children are also considered.

6.2 Review

6.2.1 Vaccine issues for different age groups
Current NZ epidemiology shows overall low rates of hepatitis with a concentration in children and young adults, particularly travellers.

6.2.2 Other high-risk groups
In low endemicity countries, except for travellers, groups that are at highest risk of symptomatic HAV infection are primarily illicit drug users – both injected and non-injected. Illicit drug users can account for up to 30% of reported cases in communities during outbreaks (3). Transmission is probably both via percutaneous and faecal-oral routes.

Other sources of high risk include men who have sex with men, food-borne infection from poor food preparation and waterborne generally related to sewage contamination or inadequate treatment of water. Rates of exposure may be higher among sewage workers.

Transfusion-related and nosocomial transmission were historically reported, but these are now very rare.

Other high-risk groups to consider include those who work with non-human primates e.g. zoos and those who may be exposed to the virus in research and laboratory settings. HAV vaccination is also recommended for those who have a high risk of severe outcomes from the disease including people with chronic liver disease.

Healthy adults, who do not fit into the above categories, do not require the vaccine particularly as post-exposure prophylaxis for HAV can be given. While the use of immunoglobulin for this purpose is well documented, recent studies have indicated that the vaccine itself is effective in preventing secondary infection (23-25). Immunoglobulin will still be required for those who are immunocompromised, those with chronic liver disease and those in whom the vaccine is contraindicated (26).
7. Vaccine options

7.1 Objective

The objectives for this section are to consider the different vaccine options available to NZ in terms of available vaccines and schedules.

7.2 Review

7.2.1 Inactivated Vaccines

All HAV vaccines currently available internationally are adapted inactivated HAV strains grown in cell-culture, harvested by cell lysis and inactivated with formalin.

The table below lists the major internationally available vaccines.

Table 1. Major Constituents and Recommended Schedules for Selected Inactivated Hepatitis A Vaccines; with permission (3)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Trade name</th>
<th>HAV strain</th>
<th>Adjuvant</th>
<th>Dosage*</th>
<th>Age</th>
<th>Volume (mL)</th>
<th>Schedule (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck &amp; Co</td>
<td>VAQTA</td>
<td>CR326F</td>
<td>Aluminium hydroxyphosphate sulphate</td>
<td>25 U</td>
<td>12mo-18y</td>
<td>0.5</td>
<td>0, 6-18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 U</td>
<td>≥19y</td>
<td>1.0</td>
<td>0, 6-18</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>HAVRIX</td>
<td>HM175</td>
<td>Aluminium hydroxide</td>
<td>720EL.U</td>
<td>12mo-18y</td>
<td>0.5</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>Biologicals</td>
<td></td>
<td></td>
<td></td>
<td>1,440EL.U</td>
<td>≥19y</td>
<td>1.0</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>Sanofi Pasteur</td>
<td>AVAXIM</td>
<td>GBM</td>
<td>Aluminium hydroxide</td>
<td>80 U</td>
<td>12mo-15y</td>
<td>0.5</td>
<td>0, 6-18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>160 U</td>
<td>≥16y</td>
<td>0.5</td>
<td>0, 6-18</td>
</tr>
<tr>
<td>Crucell Vaccines</td>
<td>EPAXAL</td>
<td>RG-SB</td>
<td>Virosomes composed of 10µg purified influenza virus haemagglutinin and 100µg of phospholipids (immunopotentiating reconstituted influenza virosome)</td>
<td>25 IU</td>
<td>≥12mo</td>
<td>0.5</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>Sinovac Biotech</td>
<td>Healive</td>
<td>T284</td>
<td>Aluminium hydroxide</td>
<td>250 U</td>
<td>12mo-15y</td>
<td>0.5</td>
<td>0, 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>500 U</td>
<td>≥16y</td>
<td>1.0</td>
<td>0, 6</td>
</tr>
</tbody>
</table>

HAV, hepatitis A virus. * Licensed ages, dosages, and schedules vary among countries. All vaccines are administered two-doses IM. Some vaccines contain other constituents.

Avaxim® is based on the GBM strain of the virus and is licensed in Europe, Canada and several other areas. Epaxal® was developed at the Swiss Serum Institute, is licensed by Cricell Vaccines Inc. and used in most countries in Europe, Canada and many countries in South America. Healive is manufactured by Sinvace Biotech in Beijing and available in China.

All available inactivated vaccines include the HAV antigen, but the units by which the antigen content is expressed are different for each vaccine. It is not possible to directly compare the antigen content of the various vaccines, because of the lack of an accepted standard. Most vaccines use aluminium hydroxide or hydroxyphosphate as
an adjuvant, although Epaxal® uses liposomes as the adjuvant. Avaxim® uses 2-phenoxyethanol as a preservative; the other vaccines do not contain preservatives. None of the vaccines contain antibiotics, although residual traces from the manufacturing processes may be present.

All monovalent inactivated vaccines have formulations available for recipients aged 12 months old and above, all are available in a two-dose schedule and are administered intramuscularly.

Combination vaccines combining HAV and typhoid fever prevention are available in some countries. ViTIM (also called ViVAXIM®, Sanofi Pasteur) contains the same amount of inactivated HAV antigen as Avaxim® and 25µg of Salmonella typhi Vi capsular polysaccharide antigen. It also contains the preservative 2-phenoxyethanol and 0.3mg aluminium hydroxide as adjuvant. Hepatyrix® (GSK) contains 25µg of Salmonella typhi Vi capsular polysaccharide antigen and 1,440 EL.U of HAV antigen with aluminium hydroxide as the adjuvant.

Twinrix® is an inactivated HAV and recombinant DNA hepatitis B surface antigen vaccine. Each 1mL dose of Twinrix® contains not less than 720 ELISA units of inactivated HAV and 20µg of recombinant HBsAg protein. The 0.5mL Twinrix® Junior preparation contains half these quantities.

Combination vaccines seem to perform in similar ways to monovalent, and are offered in a two-dose schedule at 0 and 6 months. Twinrix® is also offered in a three-dose regime at 0, 1 and 6 months for hepatitis B protection. Twinrix® may be used for rapid protection, with doses given at zero, seven and twenty-one day intervals and a booster at one year.

### 7.2.2 Live Attenuated Vaccines

A freeze-dried live attenuated vaccine has been used in China, reported immunogenic in trials in India. It only requires a single dose. Because it is highly attenuated, large inoculums (approx. 10⁷ TCID₅₀) are needed to produce an immune response (3).

### 7.3 Summary for vaccine options

As of early 2013, all currently available international inactivated HAV strain vaccines are grown in cell-culture. They are adjuvanted with aluminium or liposomes, and most monovalent vaccines do not contain preservatives. Inactivated HAV vaccines are available in combination with a hepatitis B or typhoid vaccine; these vaccines use aluminium adjuvant and the preservative phenoxyethanol.

One live attenuated vaccine is produced in China.
8. Options for scheduling

8.1 Objective
The objective for this section is to consider the different vaccine options available internationally that are currently or potentially available to New Zealand for consideration on the national schedule. The focus is on the generic type of vaccine, not the specific trade name.

8.2 Review
Live attenuated vaccines, while safe when given orally or parenterally, do not replicate well in humans and do not induce a satisfactory immune response when given orally. They do not have any significant advantages over the inactivated vaccines (27).

8.3 Schedule Placement

8.3.1 Universal schedule
For universal schedule, a single dose for children from 12 months of age is recommended. Given earlier, there is a risk of interference with the response from maternal passively acquired antibodies.

8.3.2 Targeted schedule
Generally, all those at high risk of contracting the disease or at higher risk of poor outcomes (such as chronic liver disease), or travellers to high endemicity areas are recommended to have a single dose and a second dose six months after the first dose.

8.3.3 Outbreak control
When outbreaks have been recognised, both use of immunoglobulin and vaccination have been shown to be effective in interrupting outbreaks (3). The use of the vaccine in healthy individuals aged 40 years or younger is now recommended in most circumstances for pre-exposure and post-exposure prophylaxis, because of the public health advantages of vaccination compared with use of immunoglobulin. Single antigen vaccine should be used, although immunoglobulin is still recommended for those over 40 years of age (3).

Persons employed as food handlers are not at increased risk of HAV because of their occupation, but they may transmit HAV to others if they contract it. As a result, some areas recommend HAV vaccination of food handlers. However, overall transmission from infected food handlers accounts for a very small proportion of HAV cases in low endemicity countries.

8.3.4 Use of combination vaccines
Combined hepatitis A and B vaccines have been evaluated in terms of their safety, efficacy and effectiveness including duration of protection. An early study had indicated the benefits of using the combined vaccine due to the quicker antibody response and higher immunogenicity particularly in individuals with risk factors for non-response (28). Quicker antibody production at three weeks against both diseases following an accelerated 0, 7 and 21 day schedule were of benefit to travellers leaving at short notice. A two-dose schedule (0 and 6 months) for children and adolescents aged four - 20 years produced a higher antibody response in comparison with monovalent vaccines (29). The combined vaccine was found to be protective after 10-15 years (30).

8.3.5 Strategies for schedules
Developing countries, particularly those with high endemicity, where infection in early childhood is nearly universal and symptomatic disease is uncommon, are not recommended for universal programmes until the epidemiology pattern of the disease shifts (3).

Countries of low or relatively low endemicity, similar to the NZ situation, who have instituted national immunisation programmes have shown good disease control with routine vaccination of young children. Other low-endemicity countries continue with vaccination of high-risk groups and settings only and epidemic outbreaks.

If vaccine were available at a low cost and vaccination was shown to be cost effective, some countries in which a considerable susceptible adolescent and adult population has developed might find it useful to include HAV vaccination among their routine childhood immunizations (31).

The WHO Strategic Advisory Group of Experts (SAGE) reviewed the evidence of efficacy of a single dose of inactivated HAV vaccine from data from an RCT in Nicaragua and from national use of a single dose schedule in Argentina. The group recommended a single dose HAV schedule, and concluded that additional evidence of booster potential and long-term immunogenicity are needed (32).
8.3.6 Eradication

Hepatitis virus is considered to be a target for eradication, but international bodies to date have not made this recommendation, primarily because of considerations around cost and feasibility. The current international focus is on improving living condition in the developing world the strategic application of vaccination in other areas (3).

8.4 Summary

For countries with low HAV disease endemicity, there are two options: either a universal schedule, usually a single dose from 12 months of age; or a targeted schedule to those at high risk of contracting the disease or higher risk of poor outcomes. The WHO recommends a single dose HAV schedule, if used as a national schedule vaccine. The evidence for the additional need for a booster is currently unclear.

Outbreak control can be managed with vaccination in healthy persons aged 40 years and younger, with both pre- and post-exposure prophylaxis. Immunoglobulin is recommended for those over 40 years. Combination vaccines are available with hepatitis B.

Eradication is theoretically possible but current international focus is on improving living conditions and the strategic application of vaccination.
9. Implementation issues

9.1 Objective
The objective of this section is to review the most recent data and issues arising since the 2011 Handbook for currently licensed HAV vaccines with respect to potential implementation issues in the New Zealand context.

9.2 Review

9.2.1. Pre-vaccination serological testing
Serological testing can be undertaken prevaccination, depending on the costs and the likelihood of follow-up. Populations with a high prevalence of infection, such as those born in areas of high HAV endemicity, men who have sex with men or illegal drug users could be considered for testing. General testing of children is not seen as cost effective (3).

9.2.2 High risk groups
The most recent ACIP recommendations for HAV vaccine for those considered at highest risk of disease are listed in table 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children aged 12-23 months</td>
<td>Integrate into routine childhood schedule. Children not vaccinated by 2 years can be vaccinated at subsequent visits.</td>
</tr>
<tr>
<td>Children aged 2 – 18 years</td>
<td>Maintain existing programmes; can be considered in areas without existing programmes.</td>
</tr>
<tr>
<td>International travellers</td>
<td>Except persons travelling to countries with no greater risk than in the US [Canada, Western Europe, Japan, Australia, NZ]</td>
</tr>
<tr>
<td>Persons who anticipate close contact with an international adoptee</td>
<td>Includes unvaccinated household or regular babysitting contacts of adoptee from a country of high or intermediate hepatitis A endemicity during first 60 days following arrival in the US.</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>Includes adolescents</td>
</tr>
<tr>
<td>Illicit drug user</td>
<td>Includes adolescents</td>
</tr>
<tr>
<td>Persons with chronic liver disease</td>
<td>Increased risk of fulminant hepatitis A</td>
</tr>
<tr>
<td>Persons receiving clotting factor concentrates</td>
<td></td>
</tr>
<tr>
<td>Persons who work with HAV in research settings</td>
<td></td>
</tr>
</tbody>
</table>
9.2.3 Co-administration

The US Advisory Committee on Immunization Practices (ACIP) has reported that limited data from studies in adults indicate that simultaneous administration of HAV 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 HAV vaccine without affecting either the immunogenicity of the vaccine or increasing the frequency of adverse events. When administered concurrently with other vaccines, HAV vaccine should be given in a separate syringe and needle at a different injection site.

A recent study compared two single-dose tetravalent measles, mumps, rubella, varicella vaccines, Priorix®-tetra (GSK) and ProQuad® (Merck-20C), when co-administered with HAV vaccine and 7-valent pneumococcal conjugate vaccine (PCV7), in 1783 healthy 12-14 month olds. Both vaccines showed acceptable reactogenicity/safety when co-administered with HAV and PCV7 (10).

The immunogenicity and safety of an inactivated HAV vaccine when co-administered with measles-mumps-rubella and varicella vaccines in 324 children less than two years of age has been reported by Rinderknecht et al. The data showed that after two doses of HAV vaccine, nearly all subjects in all groups were seropositive (≥99%). Co-administration did not impact the immunogenicity of any of the vaccines and was well tolerated (35).

A US study published in 2011 investigated the immunogenicity and safety of an inactivated HAV vaccine (Havrix®) when co-administered with diphtheria-tetanus-acellular pertussis (Infanrix® or Pediarix®) and Haemophilus influenzae type B vaccines (HibTITER® or OmmiHiB®) in children 15 months of age (36). This open-labelled, multicentre study randomised healthy participants into three treatment groups (1:1:1). A total of 394 subjects received the first study vaccinations at 15 months of age. Co-administration of the three vaccines did not impact immunogenicity of the HAV, DTaP or Hib vaccines. Vaccines were well tolerated in all groups. The authors concluded that a two-dose schedule of HAV vaccine was well tolerated and immunogenic when administered to children starting at 15 months of age. Immune responses to the DTaP and Hib vaccines were similar whether they were administered alone or were co-administered with the HAV vaccine.

9.2.4 Mixed schedules

Mixed schedules with Epaxal® and Havrix®, and with Avaxim®, Havrix® and VAQTA® have all been shown to be equivalent to schedule that used a single vaccine brand (3).

9.2.5 Pregnancy

Any viral infection during pregnancy could pose specific risks and HAV is no exception. Acute infection has been associated with high rates of gestational complications and pre-term labour (37). The safety of HAV vaccination during pregnancy has not been determined; however, because the vaccine is produced from inactivated HAV, the theoretical risk to the developing fetus is expected to be low (3).

9.3 Summary

Prevaccination serological testing is not recommended in children, and can be undertaken in others, particularly in populations with a high prevalence of infection. Table 2 lists the latest recommendations for HAV vaccine for those considered at highest risk reported by the US ACIP.

Recent data on concomitant use shows that co-administration with MMR-V, PCV7, and DTaP and Hib in the second year of live has no safety or immunogenicity concerns. Mixed schedules can be used with the commonly used monovalent inactivated vaccines. Vaccine safety in pregnancy is unknown, but unlikely to be a concern with an inactivated vaccine from a theoretical basis.
10. International policy and practice

10.1 Objective
Summarise some of the international experience on the use of HAV vaccines and position statements and policies from countries with comparable populations to New Zealand.

10.2 Review
Israel was the first country to introduce universal childhood HAV vaccine, followed by Bahrain in 2004, Argentina in 2005 and Panama and the USA in 2006. By 2010, China, Greece, Saudi Arabia, Uruguay, Kazakhstan and Qatar had all introduced universal childhood vaccination (3).

10.2.1 United States
The US recommends HAV vaccination as part of its childhood immunisation schedule. Two doses of vaccine are given at 12 months of age then six - 18 months later (33). Prior to vaccine introduction, the US had a reported incidence of 12/100 000 cases in 1995 (3). The introduction of the HAV vaccine in the US in 1995-96 was staged and initially targeted people at high risk of disease and children in communities where the rates were high. This was expanded in 1999 to children in states, counties and communities where the rate of disease was higher than the national average, and then finally in 2006 universally to all children. This has significantly reduced the incidence of HAV disease in the US, and in 2009, the rate was the lowest ever recorded at 0.8/100 000, with geography variations disappearing (3). Indigenous populations in the US and Hispanic people had significantly higher rates of disease prior to the introduction of the vaccine.

10.2.2 United Kingdom
The incidence of HAV disease in the UK is low and vaccination is not part of the childhood immunisation schedule. Four monovalent, one combined HepA/HepB and two HepA/typhoid vaccines are licensed in the UK. Vaccination is recommended to travellers visiting countries where the virus is prevalent, patients with chronic liver disease, patients with haemophilia, men who have sex with men, injecting drug users and those at occupational risk of exposure. These are the same groups who are recommended for vaccination in New Zealand.

10.2.3 European Union
None of the European Union countries have the HAV vaccine as part of their routine childhood immunisation schedule (38).

10.2.4 Australia
The Australian immunisation schedule includes vaccination against HAV only for specific groups, all Aboriginal and Torres Strait Islander children at 12 – 24 months of age. Other at-risk groups recommended HAV vaccination is the same as those given for New Zealand and the UK (39). Five HepA and two HepA/ HepB vaccines are available for use.

10.3 Summary of international policy and practice
The majority of developed countries do not have HAV vaccination as part of their childhood immunisation schedule. In these countries, the incidence of HAV is low and only at-risk groups are recommended for vaccination.

There are some countries with medium to low endemicity that offer a universal HAV programme usually given at 12 months of age. The first country to offer this was Israel. The US offers a two dose regime at 12 months and a booster six - 18 months later. The UK and European countries offer vaccination to high risk groups only. Australia offers universal vaccination to all Aboriginal and Torres Strait Islander children at 12 – 24 months of age, and to other high risk groups only.
References


