Epaxal®
Virosomal hepatitis A vaccine
Product Monograph
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**Why choose Epaxal®?**

Epaxal® is the only aluminium-free hepatitis A vaccine. It is based on virosome technology.

Due to its purity, immunogenicity, and good tolerability, Epaxal® is an excellent choice for immunisation against hepatitis A both for people travelling to endemic areas and for people living in endemic areas.

- **Epaxal® is a biodegradable and pure vaccine:** it does not contain aluminium, preservatives or antibiotics.
- **Epaxal® provides fast protection.**
- **Epaxal® has an excellent local tolerability profile.**
- **Epaxal® offers long-term protection after a booster (at least 20 years).**
- **Epaxal® booster can be delayed up to 5 years after primary vaccination.**
- **Epaxal® is indicated for all age groups (≥ 1 year of age).**
- **Epaxal® has a small injection volume of 0.5 ml for all age groups.**
- **Epaxal® can be given simultaneously with other vaccines and prophylactic medicines.**
- **Epaxal® is interchangeable with aluminium-adsorbed hepatitis A vaccines.**
1. Hepatitis A – the disease

- At least 1.5 million clinical cases of hepatitis A occur world-wide each year and numbers are likely to increase.

- The burden of hepatitis A infection is greatest in susceptible adults, who are at higher risk of hospitalisation and death from hepatitis A. Infected children are usually asymptomatic, but represent an important source of infection.

- Hepatitis A virus (HAV) is transmitted by the faecal-oral route. Its endemicity is therefore related to hygiene conditions generally associated with an area’s socio-economic status.

- As living conditions have improved, there has been an ‘epidemiological shift’ from high to transitional endemicity in many countries, which results in more people not previously exposed to HAV and therefore with no natural immunity.

- Without natural immunity the risk of recurring and potentially devastating outbreaks is increased, adding to national health costs and making universal mass HAV vaccination campaigns of special interest.

- Vaccination of specific risk groups, such as travellers, is recommended when travelling from low to high areas of HAV endemicity.

1.1. History of hepatitis A

- Jaundice was first described in ancient Chinese literature, but in vitro cultivation of the virus only started in 1979, allowing the development of hepatitis A vaccines.

Ancient Chinese literature refers to jaundice, but the earliest outbreaks resembling hepatitis in Europe were recorded in the seventeenth and eighteenth centuries. In 1908, McDonald et al. first suggested a virus as the underlying cause of the disease. In 1923, Blumer et al. identified several distinct epidemiological features of the illness after reviewing 63 epidemics of jaundice reported in the United States between 1812 and 1912 (1).

Two epidemiologically and etiologically distinct forms of hepatitis were described during World War II outbreaks among troops and civilians: hepatitis A and hepatitis B. Experimental transmission studies found that hepatitis A was transmitted by the faecal-oral route and had a relatively short incubation period of several weeks, while the hepatitis B virus was spread by the parenteral route, needing several months for incubation (1).

The hepatitis A virus (HAV) was first visualised by electron microscopy in 1973 (2). Once sensitive immunoassays had been developed to detect IgM and IgG specific antibodies in the blood (see section 1.3.2), recent and past infections could be distinguished. By 1979
the virus had been cultivated and serially grown in cell culture. This progress enabled the development of hepatitis A vaccines (3;4).

1.2. The infectious agent

- The highly environmentally adapted and resistant HAV is a small, simple, single-stranded RNA virus with a diameter of 27 – 32 nm, and spreads by the faecal-oral route.

HAV consists of one single-stranded RNA molecule with a number of associated non-structural (enzymes) and capsid proteins. HAV has a roughly cubic, icosahedric structure, which is formed by structural proteins. The diameter of the HAV particle is 27 – 32 nm (Figure 1). It is a unique member of the family Picornaviridae, hence its classification into a new genus, Hepatovirus. HAV is transmitted via the faecal-oral route. It is pathogenic only to humans and some primates and replicates in the liver of the infected host (5). Neutralisation assays have demonstrated the existence of only one serotype of HAV (6).

Figure 1:
Electron micrograph of hepatitis A virus (taken with permission from Locarnini SA (7))

HAV is highly resistant to environmental conditions and therefore remains infectious in the environment over prolonged periods, increasing the likelihood that it will infect people. The virus is stable at temperatures ranging from -20°C to 70°C, in acidic conditions, and during exposure to many common organic solvents and detergents. However, it is inactivated if heated to at least 85°C for 1 minute, autoclaved, or treated with ultraviolet radiation, formalin, iodine, chlorine, or chlorine-containing detergents (1).
1.3. Clinical features of hepatitis A

- The likelihood of symptoms occurring during an HAV infection is related to the person’s age – most childhood infections are asymptomatic.
- Adolescents, adults, and the elderly are at higher risk of symptomatic disease, hospitalisation, and death from fulminant hepatitis.
- The immune response following HAV infection is characterised by a short-lived increase in IgM antibody and a persistent IgG antibody presence providing lifelong immunity.
- HAV-infected asymptomatic children are a common source of infection and thus of adult morbidity.

1.3.1. Infection and clinical course

An HAV infection may be symptomatic or asymptomatic after an average incubation period of 28 days (10–50 days) (1).

The likelihood of suffering symptomatic disease is associated with age. In children less than 6 years of age, a maximum of 10% will develop symptoms after infection, usually without jaundice. On the other hand, more than 70% of infected adults will be symptomatic with jaundice.

HAV replicates in the liver, is excreted in the bile, and shed in the stools of infected subjects. Peak infectivity occurs when the virus load in the stool is highest, i.e. during the 2 weeks before onset of jaundice or when liver enzyme concentrations increase. Once the symptoms start, infectivity decreases. However, children and infants can shed HAV for up to several months and therefore represent an important source of infection. In general HAV transmission is likely to occur during the first weeks after infection before hepatitis A has been diagnosed.

Symptoms start when virus levels in the blood and especially in stools are already decreasing. The illness is characterised by an abrupt onset, which may include fever, malaise, anorexia, nausea, abdominal discomfort, bilirubinuria and jaundice. The duration of illness is usually less than 2 months, but 5–20% of patients experience a prolonged illness for up to 6 months. Chronic infection and carrier states do not occur in hepatitis A.

Most patients recover completely from hepatitis A, but the illness’ severity increases with age and in patients suffering from chronic liver disease (e.g. alcohol-related, hepatitis C). Hospitalisation may be required, especially in adults and elderly patients. If fulminant hepatitis develops, it may cause liver failure, severe coagulation disorders, and even death.
Of the 256 hospitalised hepatitis A cases during an HAV outbreak in the US State of Tennessee, 26% presented with coagulopathy, 21% had a bilirubin level greater than 170 µmol/L, 8% had extrahepatic complications, and 2% died. Patients above 40 years of age were more likely to have complications, including death (8). Two outbreaks in US troops occurred in 1982, when 76–97% of those infected developed symptoms and 40–70% proceeded to icteric complications (9). Patients with chronic liver diseases were reported to be at higher risk of more severe hepatitis A disease (10). Case-fatality rates in England between 1993 and 1997 were 2% in 50–59 year olds and 12.8% in hospitalised HAV-infected people over the age of 70 years (11) (Figure 2).

Figure 2:
Age-specific case fatality due to hepatitis A (11)

1.3.2. Immune response

The development of antibodies against HAV coincides with the start of symptoms and decreased virus shedding (Figure 3).
The primary replication site of HAV is the liver cell (hepatocyte). HAV does not destroy hepatocytes in cell culture, but in vivo cellular immune response leads to necrosis of periportal cells and inflammation of the portal tract in the liver (5).

Serum anti-HAV IgM antibodies are generally detectable in the first 1 to 3 weeks after infection. Antibody levels then increase rapidly over the following 4–8 weeks before declining again to undetectable levels, usually within 6 months (5). Anti-HAV IgG antibodies are also detectable early in the course of HAV infection, they continue to rise to a high level over several months, and subsequently slowly decline over decades. It is this IgG antibody response that provides life-long immunity to further HAV infections. The immune memory is based on priming of T-cells, which is also induced by booster vaccinations (12) (Figure 3).

Several biochemical serum parameters may be elevated during an infection with hepatitis A. Total bilirubin reaches a peak 1 to 2 weeks following the onset of symptoms and then declines gradually within the following 6 weeks. In uncomplicated viral hepatitis, alanine aminotransferase (ALT) levels are significantly higher than aspartate aminotransferase (AST) levels – both highly sensitive indicators of hepatocellular injury. A sharp increase in ALT is observed within 1 month of virus exposure, which slowly declines in activity over the next 1 to 2 months (1) (Figure 3).
1.3.3. Diagnosis

Acute hepatitis A cannot be distinguished clinically from other liver diseases as jaundice is a general sign of liver disorders. Initial laboratory evaluation of a patient with jaundice involves liver function tests, including a complete blood count and blood coagulation tests. An increase in bilirubin and ALT levels are typical features of liver disorders, and the prothrombin time is elevated. The patient generally has a normal or slightly reduced number of segmented leucocytes and a relative lymphocytosis.

Diagnosis of hepatitis A is usually made by enzyme-linked immunosorbent assay (ELISA). Acute hepatitis A infection is diagnosed when anti-HAV IgM antibodies are present in the serum. The presence of anti-HAV IgG alone indicates a past infection or successful immunisation. However, disease-induced IgG antibody titres (mIU/mL serum) are up to 1000-fold higher than those induced by vaccination. Alternatively, diagnosis of hepatitis A may be confirmed by detecting the virus in the stool by polymerase chain reaction (PCR) methods (13;14).

The total anti-HAV assay (IgM plus IgG) is used to assess an individual’s susceptibility to infection, to diagnose a past infection, or to determine the subject’s immune response to vaccination.

1.3.4. Treatment

There are no specific antiviral drugs for hepatitis A, so treatment concentrates on providing supportive care.

As there are no effective antiviral agents, treatment for hepatitis A aims to keep the patient comfortable, while maintaining adequate nutrition. Hospitalisation is usually not indicated in children, with increasing age it will, however, be required in 10-50% of cases or more (see 1.4.2). Administration of anti-HAV antibodies (immunoglobulin) from human serum can mitigate symptoms if given within 2 weeks of infection; it is, however, ineffective in the acute phase of the disease (15;16). The same principles apply for vaccines when used for outbreak control. Liver transplantation is being performed increasingly to treat acute liver failure due to hepatitis A.
1.4. Epidemiology of hepatitis A

- At least 1.5 million clinical hepatitis A cases occur world-wide each year and up to 2% of people infected die.
- Endemicity and the risk of infection and outbreaks of hepatitis A are highly dependent on the region’s socio-economic status and related hygiene conditions, highlighting the importance of protecting travellers coming from low endemic areas.
- Improving economic and hygiene conditions in lower income countries leads to an “epidemiological shift” characterised by an increase in the average age for infection, resulting in a higher number of susceptible older individuals and clinical cases.
- Universal mass vaccination reduces the risk of infection and recurring outbreaks in countries with transitional endemicity and decreases related national health costs.

1.4.1. Transmission

As HAV is transmitted via the faecal-oral route, infection may occur through ingestion of poorly prepared food or polluted water, as well as by direct or indirect contact with contaminated hands or surfaces. Raw or inadequately cooked shellfish from contaminated areas are an important source of HAV infection, because they filter large quantities of polluted water and concentrate the virus in their gills. Investigations of outbreaks have confirmed that food (including shellfish and water) and close contacts (person-to-person) are the main causes of hepatitis A epidemics.

Transmission of HAV through the use of blood or blood products from donors who were in the viraemic phase of their illness has also been reported, and hepatitis A outbreaks have occurred in intravenous drug abusers (17).

1.4.2. The disease burden of hepatitis A

Hepatitis A occurs world-wide endemically and sporadically, with a tendency to cyclic epidemic recurrences.

At least 1.5 million people suffer from clinical hepatitis A world-wide per year with numbers likely to increase in the future. About 10% of infected children and up to 90% of infected adults will develop symptoms and may require hospitalisation. Hospitalisation rates due to
hepatitis A vary by country and age. In the USA, hospitalisation rates were estimated at 11% for all ages, varying from 3% to 13% for subjects under and over 18 years of age, respectively (17). In England and Wales the ratio of admissions to notifications for the period from 1993 until 1998 ranged from 20% to 70% with higher ratios as age increased (11). Mortality from hepatitis A is very low in children and about 0.1% in under 14-year-olds, rising to over 2% in over 40-year-old subjects (18).

The incidence of hepatitis A is likely to be under-reported because of lack of symptoms in children or failures in the reporting system. Based on model estimates, more than 10 times as many hepatitis A cases are thought to have occurred in the US in the past 20 years than were reported to the national health system (19). A large pool of infected individuals acting as a potential source of infection to others can therefore be assumed.

Global seroprevalence ranges from 2% to 100% in subjects over 20 years of age (20). While North European countries, such as Sweden, have about 2% anti-HAV prevalence in 20–50 year old adults, low-income countries, such as Somalia, already have over 90% anti-HAV prevalence in children after the age of 1 year (20). High endemic countries –most countries with developing economies – are characterised by high environmental virus load and poor hygiene conditions, leading to asymptomatic infections early in life and life-long immunity in adulthood. In contrast, people living in low endemic countries – most of the established economies – may be infected later in life and are therefore at high risk of suffering from symptomatic hepatitis A in adulthood.

1.4.3. The ‘epidemiological shift’

Due to the mode of transmission of the virus and the age-specific susceptibility of the population (Figure 4), the incidence and prevalence of hepatitis A differs greatly between regions and populations (20). For practical reasons, regions have been classified into high, transitional, intermediate, and low endemicity areas (Figure 5), but considerable differences in hepatitis A endemicity may exist within the same country, state, or city. Although definitions for categorising countries according to their HAV endemicity vary, countries with a life time risk of HAV infection greater than 90% are generally classified as highly endemic. Disease rates in these countries will be low, as infection occurs at an early age (21). In countries with transitional HAV endemicity, seroprevalence has decreased markedly in the last 10–20 years, and the average age of HAV infection is rising. Areas with intermediate HAV endemicity are characterised by high disease rates and potentially large outbreaks due to high environmental virus load and a high proportion of susceptible individuals. In low endemic countries, infection is generally rare and restricted to specific risk groups (22) (see Section 1.4.5).
Figure 4: Seroprevalence by age in various countries with varying endemicity (23-31)
Countries with transitional and intermediate endemicity have experienced this ‘epidemiological shift’ due to socio-economic development in the last 20 years (e.g. South America, Eastern Asia) (20;24;30;32;33). At the same time, the number of clinical hepatitis A cases and the accompanying national health costs have risen because of the remaining high environmental virus load. Interventions that interrupt transmission of hepatitis A early in life and are affordable are likely to benefit national and regional health systems significantly.

1.4.4. Risk of outbreaks

The ‘epidemiological shift’ leads to an increased risk of potentially large hepatitis A epidemics (22). Outbreaks can be devastating, as they may involve large numbers of patients suffering severe outcomes. A large hepatitis A epidemic occurred in Shanghai in 1988, an area characterised by intermediate endemicity situated in a high endemic country. A previous serological survey indicated that about 50% of the population under 30 years of age were susceptible to infection. This outbreak was caused by the consumption of contaminated shellfish and affected about 300,000 people, representing an estimated overall attack rate of 4% (34). Other large outbreaks were reported in Central Asia and Uzbekistan with peak incidence rates of 1,000/100,000 leading to overflowing of hospitals and closing of schools (22). The magnitude of any outbreak will be dependent on the proportion of susceptible adults in the population.
1.4.5. Who should be protected?

The risk of exposure to HAV is increased in specific population groups, depending on their occupation, behaviour, mobility, sexual preferences, or environmental factors (Table 1).

<table>
<thead>
<tr>
<th>Low endemic area</th>
<th>Endemic area</th>
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</thead>
<tbody>
<tr>
<td>Travellers to HAV endemic areas</td>
<td>Individuals living under improved socio-economic, hygienic, and housing conditions</td>
</tr>
<tr>
<td>Medical and paramedical personnel</td>
<td>Individuals with access to improved water and sanitation facilities</td>
</tr>
<tr>
<td>Individuals in households with infected persons</td>
<td>Individuals with higher parental or personal education</td>
</tr>
<tr>
<td>Individuals with occupational exposure (e.g. food handlers)</td>
<td></td>
</tr>
<tr>
<td>Homosexually active men</td>
<td></td>
</tr>
<tr>
<td>Intravenous drug users sharing or reusing needles</td>
<td></td>
</tr>
<tr>
<td>Military personnel</td>
<td></td>
</tr>
</tbody>
</table>

Table 1:
High-risk groups for HAV infection (1;17)

About 1 million people cross the borders of developed and developing countries every week. Susceptible persons travelling to areas of higher HAV endemicity are of crucial relevance. They may not only get infected and become ill, but may further carry the virus back to their own country.

Studies have shown that hepatitis A is the most frequent vaccine-preventable disease in travellers to developing countries (35). The risk of HAV-infection for travellers depends on travel styles. Incidence rates for unprotected travellers residing in endemic areas range between 3/1000 and 20/1000 per month; the latter rate was seen when individuals travelled under conditions of poor hygiene (36).

Risk groups in endemic countries are less clearly identifiable than in countries with low endemicity. Increasing socio-economic levels, which relate to improvements in household income, housing, water supply, and hygiene conditions will lower the incidence of HAV in this specific group, and therefore render people growing up under these improved conditions susceptible to later infection and disease. Natural immunity to HAV is associated with poor living conditions in endemic areas. Vaccination becomes necessary with increasing wealth.
1.5. Prevention

- Assuring high personal and environmental hygiene standards can reduce HAV infection.
- Vaccination against HAV provides long-term protection and is considered the most efficient prophylaxis.

1.5.1. Hygiene

HAV infections in industrialised countries started to decrease decades before the introduction of vaccines in the 1990s, due to improved hygienic conditions and increased economic prosperity (1). Other markers of socio-economic status than household income and wealth are also clearly related to the risk of HAV infection. Low levels of parental or personal education are associated with high HAV seroprevalence rates (20). Increased socio-economic status diminishes crowding within households, reducing the likelihood of spread of HAV. The proportion of the population with access to clean drinking water is also one of the inverse predictors of HAV infection rates (37).

1.5.2. Passive immunisation

Passive immunisation by the administration of immunoglobulins provides temporary protection against hepatitis A – potentially useful in HAV outbreaks – but is not effective in controlling hepatitis A at a community level.

The efficacy of human immunoglobulins for the prevention of hepatitis A was first demonstrated in 1945, and they were subsequently used to support HAV prevention efforts (38) until HAV vaccination became broadly available. One prophylactic dose of 0.05 ml/kg body weight of immunoglobulin provides protection for 4 to 6 months (13;17).

As immunoglobulins only provide short-term protection and vaccines rapidly induce a protective immune response, immunoglobulins have been replaced by vaccines in many parts of the world (39).
1.5.3. Active immunisation

1.5.3.1 Development of vaccines

HAV vaccination is considered the most efficient preventive measure against HAV infection today. Development of an inactivated hepatitis A vaccine began in 1978 with the demonstration that formalin-treated HAV particles from an infected marmoset liver induced anti-HAV antibodies when inoculated into seronegative marmosets. These animals were shown to be fully protected from later challenge with the live virus (40). The successful propagation of the virus in human-derived cell-line cultures in vitro in 1979 (3; 4) paved the way for the development of inactivated vaccines.

Similar to other small viruses or subunit antigens, inactivated HAVs are poorly immunogenic on their own and need some form of immunostimulation in order to be effective as a vaccine (41). Adsorption to aluminium salts was the only approved adjuvant method for inactivated vaccines for many years (42) and was used for the development of the first generation hepatitis A vaccine, marketed in 1992 (43). A new approach has been the development of an aluminium-free, virosome-adjuvanted hepatitis A vaccine, Epaxal®, which was first marketed in 1994 (see section 2.2). Both types of vaccines are highly immunogenic and have been shown to protect against hepatitis A (44-46).

The absolute lower limit of antibody required to prevent HAV infection has not been adequately defined. Early in vitro experiments and studies in chimpanzees demonstrated that minimum antibody titres are probably between 10 mIU/ml and 20 mIU/mL (47; 48). There is, however, consensus that the lower cut-off for seroprotection of a vaccine-induced HAV antibody titre is 10 mIU/ml (17).

Since the introduction of hepatitis A vaccines, several strategies for their use have been developed: individual prophylaxis of persons at risk and universal mass vaccination (UMV) as a disease control measure and outbreak control.

1.5.3.2 Universal mass vaccination (UMV)

Introduction of hepatitis A vaccination into the childhood immunisation schedule interrupts virus transmission. It therefore protects those who have no naturally acquired immunity to hepatitis A from the associated disease and possible complications later in their life.

Universal mass vaccination programmes have been implemented in several intermediate and transitional countries in the last decade. A ‘toddlers only vaccination programme’ in place in Israel since 1999 not only reduced the incidence of HAV infection in children, but also in older age groups by over 90%, which suggests a herd protection effect (Figure 6) (49).
Figure 6: 
Reported HAV cases in Israel from 1993 to 2003 (49)

In Puglia, Italy, recurrent outbreaks were successfully stopped after the introduction of universal mass vaccination of toddlers (aged 15-18 months) and of all children aged 12 years in 1997. Vaccination of these age groups is now part of the routine vaccination schedule (50).

In the USA, the introduction of routine vaccination programmes for children in 11 high-incidence states in 1999 resulted in an overall hepatitis A decline of 76%, with 87% less cases in children and 69% less cases in individuals over 18 years of age (51).

In 2005, Argentina introduced universal hepatitis A vaccination of all 1-year-old children into the national childhood immunisation programme by using a 1-dose schedule. Close monitoring and review will evaluate the necessity of a second dose in the future.

Even though evidence is increasing that universal mass vaccination is highly beneficial in transitional and intermediate areas, thorough cost-effectiveness evaluations and tailoring of individual strategies are recommended before programme introduction (21).
1.5.3.3. Outbreak control

Vaccination programmes were reported to stop cyclic epidemics in Italy and Alaska (50, 52). Over 10,000 hepatitis A cases were reported in Puglia between 1996 and 1997. The introduction of universal mass vaccination in the childhood vaccination programme in 1997 prevented further epidemics in the following years (50). In Alaska, immunisation of several communities during a regional outbreak stopped the epidemic in 6 to 8 weeks, whereas, in one large community with less than 50% immunisation coverage, the outbreak continued for 50 weeks (52). The virome-adsorbed hepatitis A vaccine, Epaxal®, controlled a small outbreak of hepatitis A among a class of students in Thailand after administration of a single intramuscular dose of the vaccine (53). The control of outbreaks with active immunisation is likely to be due to the prevention of secondary cases, as reported from a randomised controlled trial involving household contacts of people with primary HAV infection (54). This was further confirmed by David et al., who developed a model for a hepatitis A outbreak control programme providing a framework for action, including immunisation of family members, in countries and specific areas where the disease remains a problem (55).

1.5.3.4. Vaccines for travellers

Active vaccination prevents infection in specific risk groups such as travellers. Vaccination is recommended for frequent travellers and travellers to endemic countries. However, only 52.1% of individuals seek health advice before travelling to a developing country, as reported in a recent study in 8 European airports involving 2779 travellers. Hepatitis A was perceived as the most likely infection abroad, but only 22.0% had received at least 2 doses of hepatitis A vaccine in the past or were naturally immune (56). Non-compliance was partly due to the fear of side effects from vaccination (18.4%), although 83.4% of the interviewees perceived vaccines in general to provide essential protection.

Besides communicating the risk of exposure to infectious diseases, such as hepatitis A, more efforts need to be made to increase awareness in travellers to comply with travel health advice (56).

The proportion of elderly subjects in the population is increasing, as are the number of elderly travellers. HAV immunisation schedules may need to be adapted to elderly subjects. Their immune response to hepatitis A vaccines may not always be satisfactory after a single dose, possibly leaving them unprotected until the booster dose, which is routinely scheduled 6-12 months later (57).
1.6. Health Economic aspects of hepatitis A vaccination

• Current evidence from national universal childhood vaccination campaigns show an impressive reduction in case numbers of more than 90% which results in cost-savings over prolonged periods.

• Considering the high risk of hepatitis A infection for travellers, immunisation is generally recommended.

1.6.1. Burden and costs of hepatitis A

Even though most infected individuals recover completely, the burden of hepatitis A and associated costs are considerable. Hepatitis A infection is usually self-limited to a period of up to 8 weeks; in general, infected adults miss an average of 30 days of work (58;59). Children often have mild or no symptoms; however, they can initiate and perpetuate community outbreaks. In the United States, between 11% and 22% of individuals who have hepatitis A are hospitalised and additional costs are incurred in providing post-exposure prophylaxis to an average of 11 contacts per case (17).

The direct and indirect costs of hepatitis A in the US have been estimated at an average of $1817 to $4150 (60) per case for adults and $433 to $1492 per case for individuals less than 18 years of age (61). The economic burden of symptomatic hepatitis A infections in adolescents and adults was estimated by Berge, et al as US$ 488.8 million in 1997 (62). Because of the occurrence of outbreaks, which are mainly food-borne, the cost of hepatitis A can be much higher. Estimated total costs of an epidemic in Puglia, Italy were US$43.5 million (1996 figures) and in the mid-1990s an epidemic in Denver, Colorado cost approximately US$689,000 (63;64).

The cost-effectiveness of a hepatitis A vaccination strategy depends on various factors (Table 2): (65-68)

<table>
<thead>
<tr>
<th>Factors affecting cost-effectiveness</th>
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</thead>
<tbody>
<tr>
<td>Travel destination and endemic conditions (i.e. risk of infection in a particular region)</td>
</tr>
<tr>
<td>Frequency, duration and type of travel</td>
</tr>
<tr>
<td>Natural immunity (prevalence of anti-HAV antibodies in country of origin)</td>
</tr>
<tr>
<td>Behavioural characteristics including compliance with vaccination schedule</td>
</tr>
<tr>
<td>Price of vaccine</td>
</tr>
<tr>
<td>Price of screening tests</td>
</tr>
<tr>
<td>Direct and indirect costs of morbidity</td>
</tr>
</tbody>
</table>

Table 2:
Factors affecting cost-effectiveness of hepatitis A vaccination

During illness adults usually miss 30 days of work.
1.6.2. Economic benefits of universal mass vaccination

The changing epidemiology of hepatitis A (see Section 1.4.3) leads to a reduced prevalence of naturally acquired anti-HAV antibodies and to an increased susceptibility in adults and hence to more symptomatic and more severe cases of hepatitis A. The increased age at which susceptible individuals have contact with the hepatitis A virus is reflected in an increase of the cost of hepatitis A illness to society (10;49;63;66;69-71).

The optimal, most cost-effective, strategy for the prevention of hepatitis A infections in regions of low to intermediate HAV endemicity seems to be universal vaccination. For Ireland it was shown that the threshold seroprevalence is 45%, below which universal vaccination should be recommended (72).

Recent studies, observations, and modelling on the adoption of universal vaccination of children – as already implemented in Israel – confirmed this to be a cost-effective strategy, with societal benefit to cost ratios up to 2.54, i.e. for US$1 invested in hepatitis A vaccination a return of US$2.54 on societal benefits is achieved (68;73;74). In Israel, a region of intermediate risk of acquiring hepatitis A, this programme was calculated to result in net savings of US$66.5 million to the society (73). This was supported by the findings after 5 years of universal mass vaccination in Israel which reduced hepatitis A incidence by more than 96% (49). Jacobs and colleagues showed by an health economic evaluation for the US that a national hepatitis A immunisation policy would be cost effective with US$9100 per quality adjusted life year (QALY) gained, similar to other childhood immunisations (75). A model for Chile calculated universal vaccination to be a cost effective strategy with less than US$726 per QALY gained, which is well below the country’s per capita gross domestic product (76).

The available evidence justifies a much wider application of the strategy of universal childhood immunisation against HAV infection (60;77).

Universal vaccination in young children will reduce the risk of infection in adolescents and adults through a herd immunity effect (49). Nevertheless travelling to endemic countries will remain an important risk factor for susceptible adults (60;78), as shown with a 3-fold increased risk for travellers to southern or eastern Europe (79).

1.6.3. Economic benefits of immunising travellers and specific risk groups

Immunity to hepatitis A infection is limited in low endemic areas such as in European countries. However, about 14 million Europeans are estimated to travel to higher HAV endemic countries each year, and 3 of every 1000 travellers per month will return with symptomatic hepatitis A. This number rises to 20 per 1000 travellers per month for people travelling un-
der less hygienic conditions (80). Active immunisation of travellers without prior screening for immune status seems to be the most cost-effective preventive strategy, as calculated by Tormans et al. for Belgian travellers (81). As hepatitis A was a childhood illness until 40-50 years ago in most industrialised countries, it is economically justifiable to screen travellers residing in low to intermediate endemic areas and above a certain age (>35 to >60 years) for naturally acquired anti-HAV antibodies prior to vaccination (17;82;83).

For other risk groups, like health care workers, selective vaccination after screening for anti-HAV antibodies was reported to be more cost-effective than mass vaccination in Israel (84). For patients with chronic liver disease, routine hepatitis A vaccination would substantially reduce morbidity and mortality in all age groups, being most cost effective if performed in younger patients. Immunisation of military personnel without previous screening proved the optimal strategy for regularly deployed Dutch troops (85).

Despite regional and socio-economic differences, active immunisation is generally recommended for individuals travelling to areas with higher endemicity. For other risk groups, some recommendations already suggest immunising all individuals at risk, or any person wishing to obtain immunity (17). However, targeted vaccination has not been very successful in protecting society from sporadic outbreaks and episodic increases in reported cases. Therefore universal vaccination against hepatitis A might be more appropriate to eliminate the risk of new infections in low endemic countries (72;77).

Vaccination is considered ‘cost-effective’ in all high risk groups such as in populations living in low endemic areas, and in those of highest risk of death (68).
2. Epaxal®: Properties and mechanism of action

• Epaxal®'s innovative technology utilises virosomes as an adjuvant, providing a natural presentation of the antigen to the immune system.

• Epaxal® results in excellent immunostimulation without inducing a non-specific inflammatory response at the site of administration.

2.1. Development of the virosomal hepatitis A vaccine

To be efficacious, vaccines against hepatitis A need adjuvants capable of improving the immunogenicity of the small inactivated hepatitis A virus (HAV) (41). The most common adjuvants approved for human use are aluminium salt derivatives. Although widely accepted as safe and effective, aluminium salt-based adjuvants induce protection against an associated antigen through a depot effect and a local inflammatory response. This adjuvant action is non-specific in terms of the immune response induced, and results in undesirable local effects, including pain and swelling at the injection site (42;86).

Epaxal® uses virosomes, a carrier and adjuvant technology free of aluminium salts. Virosome technology has been used to induce immunity to a variety of antigens without the adverse reactions associated with other adjuvants (87). The novelty of this biodegradable delivery system lies in the natural presentation of antigens and the stimulation of a specific immune response, induced by the active targeting of antigens to immunocompetent cells (88). Virosomes have been shown to elicit both cell-mediated and humoral immune responses (89;90).

2.2. Epaxal® – structure

• Virosomes, at least 100 times smaller than the particles in aluminium-adsorbed vaccines, are based on phospholipid membranes to which the inactivated HAV attaches.

Epaxal® virosomes are spherical vesicles made up of unilamellar phospholipid bilayers of a defined size, approximately 150 nm in diameter – at least 100 times smaller than the particles in aluminium-adjuvanted vaccines. The phospholipids forming the virosome bilayers are lecithin (phosphatidylcholine) and cephalin (phosphatidylethanolamine). Lecithin was chosen as it is well tolerated in humans; it is an important constituent in many commercial solutions for intravenous applications (91). Cephalin aids in the binding of the HAV virions to the virosomes (Figure 7) (92;93).

Intercalation of purified haemagglutinin (HA) and neuraminidase (NA) influenza surface glycoproteins, isolated from the influenza A/Singapore 6/86 (H1N1) virus strain, into the phos-
pholipid bilayer is intrinsic to the adjuvant properties of Epaxal® virosomes. It is these fusion active glycoproteins, projecting from the phospholipid bilayers (Figure 7), that facilitate the targeted delivery of the HAV antigen to immunocompetent cells (94) (see Section 2.3).

The final step in the production of Epaxal® is the adsorption of the formalin-inactivated, highly purified HAV virions of the RG-SB strain to the virosome surface. The virions attach themselves to the phospholipids of the virosome membrane (95).

Figure 7:
Virosomal hepatitis A vaccine (Epaxal®)

2.3. Induced immune responses

- Epaxal® results in excellent immunostimulation without inducing the non-specific inflammatory response characteristic of aluminium-salt based vaccines

The proposed mechanism of action of Epaxal®, virosomes is shown in 6 steps in Figure 8. It has been shown that the influenza virus HA component of the virosome enables binding to immunocompetent cells such as macrophages (95-97). HA-mediated endocytosis ❼ occurs. Exposure to the low pH (~ 5) of the cell endosome ❽ causes conformational changes in HA, resulting in fusion ❺ of the virosome and endosome membranes. Within the endosome, the virus antigen is proteolysed ❻ to antigenic peptides. Thereafter, the antigen-containing endosomes join ❼ with vacuoles containing major histocompatibility class II (MHC II) molecules. The resulting MHC II-antigen complex is transported to the surface of the cell ❼ where it initiates either a specific humoral response and/or a cellular immune response.
The natural process of antigen presentation provided by Epaxal® enables effective HAV antigen processing and the stimulation of protective immune responses without inducing the non-specific inflammatory response characteristic of aluminium-salt based vaccines. The purity of the components and the exclusion of aluminium, preservatives, and detergents adds to the excellent tolerability of virosome formulations.

Figure 8:  
Mechanism of action of Epaxal®

2.4. Proof of principle of the virosome concept

- The virosome-based antigen delivery used in Epaxal® is superior to the aluminium-adsorbed antigen presentation.

Initial clinical work demonstrated that the selected HAV antigen, RG-SB, was immunogenic in man when administered as an aluminium-hydroxide-adsorbed formulation. The RG-SB strain was then used for the novel virosome-adjuvanted vaccine formulation for further clinical testing. In a comparative trial of the virosome-formulated vaccine, the aluminium-adsorbed formulation and the soluble HAV-antigen (no adjuvant), all administered intramuscularly, were assessed for immunogenicity and tolerability (see Table 3) (98).
• All recipients (100%) of the virosome vaccine were seroprotected (≥20 mIU/ml) after 14 days compared with 71% of those receiving the aluminium-adsorbed antigen and 32% of those receiving the soluble antigen.

• HAV antibody titres were higher in the individuals receiving the virome formulation in comparison with groups receiving the other two formulations.

• The virosomal HAV vaccine was significantly better tolerated than the aluminium-adsorbed antigen in terms of pain, swelling, and induration.

The Epaxal® formulation is currently marketed in over 40 countries world-wide as 0.5 ml pre-filled syringes for intramuscular injection.

<table>
<thead>
<tr>
<th>Type of antigen presentation</th>
<th>Seroprotection</th>
<th>GMT (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virosomal (n=40)</td>
<td>100 %</td>
<td>92 283 1550</td>
</tr>
<tr>
<td>Aluminium-based (n=10)</td>
<td>71 %</td>
<td>43 267 604</td>
</tr>
<tr>
<td>Soluble (n=28)</td>
<td>32 %</td>
<td>22 160 622</td>
</tr>
</tbody>
</table>

All subjects received 1000 RIA units of HAV antigen as a single dose.

Table 3: Immune response after vaccination with three formulations of hepatitis A antigen
3. Epaxal®: Clinical experience

- Epaxal® is highly immunogenic, well tolerated, and confers fast and long-lasting protection against hepatitis A.
- Epaxal® is interchangeable with other hepatitis A vaccines and can be co-administered with other vaccines and prophylactic medicines.

3.1. Protective efficacy against hepatitis A

- Epaxal® protected 100% of vaccinated children in a highly endemic area.

The protective efficacy of a vaccine is best demonstrated by comparison of the incidence of infection in two groups that were either immunised or received placebo – a so-called placebo-controlled trial.

The protective efficacy of Epaxal® was shown in a double-blind, placebo-controlled field trial carried out in Nicaragua (45), a country with high endemicity for hepatitis A, i.e. where by the age of 10 years, more than 90% of children have antibodies against the disease (21). Over 900 children (aged 1.5 - 6 years) were screened 4-6 weeks prior to study start for past exposure to HAV by measuring anti-HAV IgG antibodies. Only non-exposed, i.e. seronegative, children were enrolled and randomised to receive vaccine or placebo. The use of a placebo group was ethically justifiable as HAV infection in children below the age of 6 years is usually asymptomatic. HAV infections were diagnosed by the detection of raised anti-HAV IgM antibody titres, which is indicative of an acute infection. At the end of the trial, all subjects in the placebo group without exposure to HAV infection were vaccinated with Epaxal®.

After excluding 33 children infected between screening and study start, 239 children could be evaluated for primary efficacy (Table 4). Up to week 6 (the maximum duration of the incubation period for HAV infection), 4 of the 122 vaccinated and 5 of the 117 placebo children were serologically diagnosed with an acute HAV infection, i.e. they had been incubating hepatitis A at study start. All 118 (100%) vaccinated children who were seronegative for anti-HAV IgM antibodies at week 6 remained infection-free for the following 15 months. In the placebo group 17 children became infected between week 6 and month 15. Hence Epaxal® demonstrated 100% protective efficacy compared with placebo (p<0.0001) in a highly endemic area (Figure 9) (45). All children were followed for several years and this data indicated that protection may last for several decades (99).
Table 4:
Protective efficacy of Epaxal® in children (primary efficacy population, n=239) in Nicaragua (45)

<table>
<thead>
<tr>
<th></th>
<th>Number with infections</th>
<th>% efficacy (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 0 to week 6</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine</td>
<td>4</td>
<td>22.5 (not significant)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Week 6 to month 15</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine</td>
<td>0</td>
<td>100 (P=0.0001)</td>
</tr>
<tr>
<td>Placebo</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

Figure 9:
Epaxal® field efficacy trial: Immunoglobulin M (IgM) values at baseline and during follow-up in all 272 children screened and vaccinated (45).
Epaxal® is effective in all age groups.

Epaxal® is immunogenic in all age groups

- Epaxal® is at least as effective in eliciting protective antibody levels as conventional hepatitis A vaccines in all age groups.

3.2. Epaxal® is immunogenic in all age groups

3.2.1. Immunogenicity in infants and children

Four clinical studies included over 400 seronegative children from different countries, in which they received a single intramuscular dose of Epaxal® (0.5 ml) and a booster dose 12 months later.

In Chile, 94% of toddlers aged 12–16 months (n=20) and 99% of children aged 5–17 years (n=80) had seroconverted 4 weeks after immunisation. All toddlers and children showed a strong rise in antibody after the booster vaccination (100). In two studies in 70 and 55 Thai children, one dose of the virosomal vaccine induced seroconversion in 93% and 100% of previously seronegative children (25). In a study in Lithuania, the primary dose of Epaxal® induced a 100% seroconversion in 30 infants aged 6–7 months and 30 children aged 5–7 years (101). In Nicaragua, 98.4% of children (1.5 years to 6 years old) seroconverted successfully after priming and 100% after the booster dose. Epaxal® conferred protection from week 6 to month 15 in all vaccinated and previously seronegative children (45) (see Section 3.1).

All of these studies demonstrate that seroprotection can be achieved in 93-100% of infants and children 4 weeks after primary immunisation with Epaxal®. A strong antibody response was seen in all children following the booster dose (Table 5).

The response to active immunisation may be down-regulated by maternal antibodies present in infants below 1 year of age. In the study conducted in Lithuania, 16 infants had maternal anti-HAV antibodies at the start. Seroprotection (≥20 mIU/ml) was achieved in all infants and children at 1 month to 12 months after primary vaccination. The response to booster vaccination was strong, although lower than in the infants without maternal antibodies (101). A previous study from Israel had reported that infants without maternal HAV antibodies showed a higher response than those with maternal HAV antibodies (102). In conclusion, infants can be primed successfully even in the presence of maternal antibodies, as documented by the strong rise in antibody titres following the booster dose (101;102).

3.2.2. Immunogenicity in adults

In several open, controlled and uncontrolled studies, which enrolled over 800 adults aged ≥18 years, a single dose of Epaxal® elicited good antibody responses with seroprotection rates of 96–100% and 91–100% after 1 and 12 months, respectively. A 20- to 30-fold rise
in GMT and 100% seroprotection always followed the booster dose at 12 months (Table 5) (103-109). Epaxal® was shown to be highly immunogenic in adults, with less local adverse events than aluminium-adsorbed HAV vaccines in 2 controlled studies (105,107).

3.2.3. Immunogenicity in the elderly

The limited data published on hepatitis A vaccination in subjects over 40 years of age show that the elderly have a lower antibody response compared with younger age groups (57,110-112).

In an open, uncontrolled study, seroprotection rates 1 month after immunisation with a single dose of Epaxal® and after a booster dose 12 months later were compared between 53 younger subjects (18-45 years old) and 31 individuals (50-73 years of age). Seroprotection rates (≥20 mIU/ml) in younger and older subjects were 100% and 70% (age 50-60 years) and 60% (age >60 years) after the baseline immunisation and 100% and 97% after the booster dose, respectively. The proportional rise in GMT after the booster dose was similar in both groups (113).

Epaxal® can therefore successfully prime the ageing immune system. Elderly travellers may benefit from an earlier booster dose (57), but immune response to a single dose may already be sufficient to protect them against disease, since experience with all HAV vaccines has shown few failures in elderly individuals.

3.3. Epaxal®’s immunogenic effect in immunocompromised individuals

• Epaxal® can induce seroprotective antibody levels in immunocompromised individuals.

HIV-positive individuals represent a risk group for HAV with an increased probability of exposure (e.g. intravenous drug) and an increased risk of suffering from serious hepatitis A disease because of the impaired immune system. The disease is often associated with disruption of HIV therapy. HAV immunisation of immunocompromised individuals is therefore clearly desirable but potentially challenging (114). Eleven HIV-positive patients were vaccinated with Epaxal® during an open, uncontrolled single centre study. Immunogenicity was 1.5 – 2 times lower in HIV-positive patients when compared with healthy individuals, but >90% of the patients reached seroprotection after the booster dose (25).
### Infants and Children

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Age group</th>
<th>N</th>
<th>% seroprotection (1 month after 1st dose)</th>
<th>% seroprotection (1 month after booster)</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancharoen (2005)</td>
<td>Thailand</td>
<td>8-12 y</td>
<td>55</td>
<td>100</td>
<td>100</td>
<td>(118)</td>
</tr>
<tr>
<td>Riedemann (2004)</td>
<td>Chile</td>
<td>12-16 m 5-17 y</td>
<td>20</td>
<td>94</td>
<td>99</td>
<td>(100)</td>
</tr>
<tr>
<td>Usonis (2003)</td>
<td>Lithuania</td>
<td>6-7 m 5-7 y</td>
<td>30</td>
<td>100</td>
<td>100</td>
<td>(101)</td>
</tr>
<tr>
<td>Mayorga (2003)</td>
<td>Nicaragua</td>
<td>1.5-6 y</td>
<td>122</td>
<td>98.4</td>
<td>100</td>
<td>(45)</td>
</tr>
<tr>
<td>Poovorawan (1993)</td>
<td>Thailand</td>
<td>3-12 y</td>
<td>70</td>
<td>93</td>
<td>-</td>
<td>(25)</td>
</tr>
</tbody>
</table>

### Adults

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Age group(s)</th>
<th>N</th>
<th>% seroprotection (1 month after 1st dose)</th>
<th>% seroprotection (1 month after booster)</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Acremont (2006)</td>
<td>Switzerland</td>
<td>18-45 y</td>
<td>59</td>
<td>100</td>
<td>100</td>
<td>(113)</td>
</tr>
<tr>
<td>Bovier (2005)</td>
<td>Switzerland</td>
<td>&gt; 18 y</td>
<td>58</td>
<td>100</td>
<td>100</td>
<td>(105)</td>
</tr>
<tr>
<td>Ambrosch (2004)</td>
<td>Austria</td>
<td>18-43 y</td>
<td>30</td>
<td>100</td>
<td>100</td>
<td>(104)</td>
</tr>
<tr>
<td>Bovier (1999)</td>
<td>Switzerland</td>
<td>18-39 y</td>
<td>103</td>
<td>100</td>
<td>100</td>
<td>(124)</td>
</tr>
<tr>
<td>Ambrosch (1997)</td>
<td>Austria</td>
<td>ø 22.2 y</td>
<td>117</td>
<td>99</td>
<td>100</td>
<td>(103)</td>
</tr>
<tr>
<td>Holzer (1996)</td>
<td>Switzerland</td>
<td>ø 29.7 y</td>
<td>201</td>
<td>98</td>
<td>100</td>
<td>(107)</td>
</tr>
<tr>
<td>Poovorawan (1995)</td>
<td>Thailand</td>
<td>17-35 y</td>
<td>79</td>
<td>100</td>
<td>-</td>
<td>(109)</td>
</tr>
<tr>
<td>Loutan (1994)</td>
<td>Switzerland</td>
<td>ø 23.6 y</td>
<td>104</td>
<td>98</td>
<td>100</td>
<td>(108)</td>
</tr>
<tr>
<td>Froesner (1994)</td>
<td>Switzerland</td>
<td>17-56 y</td>
<td>99</td>
<td>100</td>
<td>-</td>
<td>(106)</td>
</tr>
</tbody>
</table>

### Elderly

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Age group(s)</th>
<th>N</th>
<th>% seroprotection (1 month after 1st dose)</th>
<th>% seroprotection (1 month after booster)</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Acremont (2006)</td>
<td>Switzerland</td>
<td>50-60 y &gt; 60-73 y</td>
<td>59</td>
<td>70</td>
<td>100</td>
<td>(113)</td>
</tr>
</tbody>
</table>

**Table 5:**

Efficacy studies of Epaxal® in various age groups and countries
In an earlier study involving 26 subjects who had undergone a splenectomy after trauma, 85% had seroconverted (≥20 mlU/ml) at day 28 after immunisation with Epaxal®. Three patients identified as non-responders seroconverted after a second dose given 4 weeks later. The immune response appeared to be related to the age of the subject at splenectomy, where increasing age was associated with a weaker response (115).

3.4. Excellent local tolerability

*Epaxal® is a pure vaccine with an excellent tolerability profile.*

Epaxal® showed consistent and excellent safety profiles in all clinical studies, which have enrolled more than 6,000 subjects (25).

In a randomised, double-blind, controlled trial in Nicaragua, children vaccinated with Epaxal® did not report significantly more side effects than children receiving the placebo (45).

Early studies comparing local adverse events between the aluminium-free vaccine Epaxal® in comparison with aluminium-adsorbed vaccines found that 3 times fewer local adverse events were reported by individuals receiving Epaxal® than by individuals receiving an aluminium-adsorbed HAV vaccine (17% vs. 66%) (107).

More recent studies reported similar differences in local adverse events between vaccines, such as a post-marketing safety study involving 422 subjects (116). Significantly fewer adverse events were reported by subjects vaccinated with Epaxal® (23.4%) than individuals immunised with Havrix® (57.3%; p<0.0001) (Figure 10). Injection site pain was the most frequently reported adverse event (21% in Epaxal® group vs. 56% in Havrix® group). The adverse events after immunisation with Epaxal® tended to resolve more rapidly and were generally classified as less severe than adverse events after Havrix® immunisation. A significantly lower proportion of subjects reported pain lasting 3 or more days (8.6% vs. 22.7%) when vaccinated with Epaxal®.

A randomised, single-blind, cross-over trial confirmed that pain at the injection site was significantly more common among individuals vaccinated with aluminium-adsorbed vaccine than after immunisation with Epaxal® (105).

The possibility of administering Epaxal® intradermally is further evidence for its excellent tolerability profile and pureness in comparison with other available HAV vaccines (see Section 3.11) (117;118).
-3 times less pain and ~9 times less severe pain than aluminium based vaccine.

3.5. Epaxal® provides rapid protection

- **Epaxal®** induces protective antibody levels within 10 days of primary vaccination.

Rapid protection against hepatitis A after immunisation is especially important for last-minute travellers to endemic regions.

Early studies indicated that Epaxal® rapidly induces seroprotection 14 days after immunisation (103). A recent uncontrolled study in 30 healthy individuals found that seroprotection is achieved as early as 10 days after immunisation – as documented by a neutralising antibody assay measuring the virus inactivating activity of the antibodies (Figure 11) (104). As viraemia only starts approximately 14 days after HAV infection, Epaxal® may begin to protect on the day of travel.
Figure 11:
Rapid appearance of neutralising anti-HAV antibodies after a single intramuscular dose of Epaxal® (based on Ambrosch et al., 2004 (104))

3.6. Epaxal® provides long-term protection

- Epaxal® provides seroprotection for at least 20 years.

The current consensus is that 2 doses of hepatitis A vaccine may protect for life (119). At product introduction follow-up data has been used in mathematical models to obtain a 10 year seroprotection claim for aluminium-based vaccines.

For Epaxal®, mathematical modelling of clinical data from individuals immunised between 1992 and 1994 indicated that Epaxal® would provide protection against hepatitis A for at least 20 years (120). First calculations with 5-year post-booster data from 190 volunteers with at least 2 valid assessments of titres from year 3 onwards estimated that 95% of the vaccinated population should still have a titre above the minimum protective level (20 mIU/ml) after 21.5 years. Recent analysis of a 10-year follow-up cohort of 130 volunteers showed that all (100%) were still seroprotected (≥20 mIU/ml) and that the estimated duration of seroprotection by immunisation with Epaxal® was now at least 30 years (121) (Figure 12).
3.7. Epaxal®’s booster timing

Epaxal® provides flexibility for the timing of the booster dose.

The administration of 2 doses of Epaxal® is recommended in order to obtain long-term protection against hepatitis A. Flexibility in the interval between the 2 recommended doses is important as individuals may forget about the booster vaccination.

In a study with 115 subjects previously vaccinated intramuscularly with a primary dose, and 1½ - 4½ years later with a booster dose, of Epaxal®, the mean GMTs after booster were all approximately 2300 mIU/ml and did not differ among groups of individuals receiving the booster immunisation 18-29 months, 30-41 months, or 42-54 months after the primary vaccination (122). The timing of an Epaxal® booster dose is therefore flexible, and no loss of immune response is expected within 5 years of primary immunisation (Table 6).

<table>
<thead>
<tr>
<th>Interval since primary vaccination (months)</th>
<th>Seroprotection (%) pre → post booster</th>
<th>GMT (mIU/ml) pre → post booster</th>
<th>Relative increase in GMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10 mIU/ml</td>
<td>≥ 20 mIU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-30 (n=36)</td>
<td>89 → 100</td>
<td>67 → 100</td>
<td>39 → 2330</td>
</tr>
<tr>
<td>31-42 (n=34)</td>
<td>91 → 100</td>
<td>77 → 100</td>
<td>50 → 2395</td>
</tr>
<tr>
<td>43-54 (n=27)</td>
<td>85 → 100</td>
<td>70 → 100</td>
<td>33 → 2432</td>
</tr>
</tbody>
</table>

Table 6: Seroprotection at extended intervals after primary vaccination (122)
3.8. Interchangeability with aluminium-adsorbed vaccines

- Epaxal® and aluminium-adsorbed hepatitis A vaccines are interchangeable.

Using the same hepatitis A vaccine for the booster dose as was used for primary immunisation may not always be possible. Crossover studies are important to prove interchangeability between hepatitis A vaccines, ensuring that individuals are properly immunised irrespective of the availability of a specific vaccine.

In a randomised, single-blind, cross-over trial, 111 healthy adults were vaccinated with either a virosomal (Epaxal®) or aluminium-adsorbed vaccine (Havrix 1440®), and after 12 months again randomised to receive either vaccine. All subjects were seroprotected one month after the booster dose irrespective of the vaccine combination. GMTs in response to the booster vaccination did not differ between study arms, showing the interchangeability of Epaxal® with a conventional aluminium-adsorbed hepatitis A vaccine (105). This study also confirmed earlier results from a study reporting the successful administration of an Epaxal® booster dose in travellers immunised initially with an aluminium-adsorbed HAV vaccine (123).

3.9. Co-administration with other vaccines

- Epaxal® may be co-administered with other vaccines and prophylactic medicines.

The concomitant administration of Epaxal® and vaccines against yellow fever, typhoid fever, poliomyelitis, diphtheria, tetanus, meningococci A + C, as well as malaria prophylaxis was studied as part of a travel prophylaxis programme in 49 subjects. No major negative interactions were found (124). As yellow fever immunisation has occasionally been found to influence negatively the immune response to concomitantly administered vaccines, a study was conducted assessing 53 volunteers receiving Epaxal® together with a live-attenuated yellow fever vaccine compared with 56 individuals receiving Epaxal® alone. Those who received simultaneous vaccinations had slightly lower anti-HAV titres than individuals receiving Epaxal® alone. However, the difference was not statistically significant and all subjects were fully protected against hepatitis A (124).

A prospective study was performed with 163 subjects concomitantly immunised with Epaxal® and whole-cell influenza vaccine, which showed that the simultaneous administration did not impair the immune response to either hepatitis A or influenza. In addition, the immune response to hepatitis A was independent of the level of influenza pre-immunisation titres (25).

These results indicated that Epaxal® can be administered simultaneously with the above vaccines, but in separate syringes, as well as in conjunction with malaria prophylaxis.
3.10. Co-administration with hepatitis A immunoglobulin

- Epaxal® can be co-administered with human immunoglobulins.

Epaxal® can be co-administered with human immunoglobulins, which would result in an immediate passive response that merges into active vaccine protection (125). However, Epaxal® alone would already provide rapid enough protection if given immediately prior to or within days after exposure (104).

3.11. Alternative routes of administration

- In addition to intramuscular administration, Epaxal® can also be administered subcutaneously and intradermally with no loss in immune response or change in tolerability.

- Epaxal® can be used at a lower dose when administered intradermally, which reduces costs and could therefore be an attractive option for universal mass vaccination against hepatitis A.

Alternative routes of administration of a hepatitis A vaccine, such as subcutaneous administration, are sometimes essential, e.g. for subjects on anticoagulation therapy. Epaxal® administered subcutaneously has been shown to induce a comparable immune response to intramuscular administration and was well-tolerated (126).

In contrast to experiences with Epaxal®, intradermal administration of a reduced dose of aluminium-adsorbed hepatitis A vaccines is less immunogenic compared with the intramuscular administration of a full dose (127) and cannot be recommended due to severe local reactions (128).

Administering 0.1 ml of Epaxal® intradermally is well-tolerated and results in an immune response similar to that seen with intramuscular administration. In a study of 30 healthy volunteers, a single intradermal dose of 0.1 ml resulted in an antibody titre of 72 mIU/ml (GMT) and 97% seroprotection (≥20 mIU/ml) at day 29 (117). An intradermal dose of 0.1 ml given one year later resulted in a strong booster response. A recent study further showed that the intradermal and intramuscular routes of administration were equally well tolerated and effective in 8- to 12-year-old children (118).

The intradermal route of administration of Epaxal® may be especially attractive for universal mass immunisation programmes targeting the local control of hepatitis A, as it requires lower doses and therefore could reduce programme costs while providing effective seroprotection.


