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Abbreviations and acronyms

ACIP  Advisory Committee on Immunization Practices (United States)
ALT  Alanine aminotransferase
ASP  Aspartate transaminase
BMI  Body mass index
CDC  Centers for Disease Control and Prevention (United States)
cDNA  Complementary deoxyribonucleic acid
DTaP  Diphtheria, tetanus, acellular pertussis vaccine
EIA  Enzyme-linked Immunoassay
ELISA  Enzyme-linked immunosorbent assay
EL.U  ELISA units
EPI  Expanded Programme on Immunization
GBD  Global burden of disease
GMC  Geometric mean concentration
HAART  Highly active antiretroviral therapy
HAV  Hepatitis A virus
eHAV  enveloped HAV
HAVCR1  HAV with an attachment cellular receptor TIM 1
HBV  Hepatitis B virus
HCV  Hepatitis C virus
Hib  Haemophilus influenzae type b
HIV  human immune deficiency virus
HLA  Histocompatibility leukocyte antigen
Ig  Immunoglobulin
MAVS  Mitochondrial antiviral signaling protein
MMR  Measles, mumps and rubella vaccine
MSM  Men who have sex with men
LAK  Lymphokine-activated killer cells
NK cells  Natural killer cells
PBMC  Peripheral blood mononuclear cells
RIFIT  Radioimmunofocus assay
RNA  Ribonucleic acid
TCID  Tissue culture-infective dose
UV  Universal vaccination
WHO  WHO  World Health Organization
Preface

This module is part of the WHO series The immunological basis for immunization, which was initially developed in 1993 as a set of eight modules comprising one module on general immunology and seven modules each devoted to one of the vaccines recommended for the Expanded Programme on Immunization (EPI) – i.e. vaccines against diphtheria, measles, pertussis, polio, tetanus, tuberculosis and yellow fever. Since then, this series has been updated and extended to include other vaccines of international importance.

The main purpose of the modules is to provide national immunization managers and vaccination professionals with an overview of the scientific basis for vaccination against a range of important infectious diseases. The modules developed since 1993 continue to be vaccine-specific, reflecting the biological differences in immune responses to individual pathogens and the differing strategies employed to create the best possible level of protection that can be provided by vaccination. The modules also serve as a record of the immunological basis for the WHO recommendations on vaccine use, published in the WHO vaccine position papers1.

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Conflict of interest

Daniel Shouval co-authored a publication with employees of GlaxoSmithKline:


This interest was assessed as personal, specific and financially insignificant.4

Pierre Van Damme: The University of Antwerp (Belgium) obtains research grants from vaccine manufacturers for the conduct of vaccine trials by the clinical trial team within the Centre for the Evaluation of Vaccination (led by Pierre Van Damme), and for the organization of the meetings and activities of the Viral Hepatitis Prevention Board. Some of the clinical trials reports were published in co-authorship with employees of the respective companies.

This interest was assessed as non-personal, non-specific and financially significant.

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4 According to WHO’s Guidelines for Declaration of Interests (WHO expert), an interest is considered “personal” if it generates financial or nonfinancial gain to the expert, such as consulting income or a patent. “Specificity” indicates whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has “financial significance” if the honoraria, consultancy fees or other received funding, including those received by expert’s organization, from any single vaccine manufacturer or other vaccine-related company exceeds US$ 5000 in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of US$ 1000 would also constitute a “significant shareholding”.
1. The hepatitis A virus, the infection, the disease and the vaccine

1.1 Hepatitis A virus

The hepatitis A virus (HAV) has been infecting humans for centuries. The distinction between HAV and non-HAV viruses involved in clinical hepatitis was originally made in the 1940s. HAV was first identified in 1973 through immune electron microscopy. Today, it is classified as hepatovirus genus within the Picornaviridae family. HAV is a 27–32 nm, non-enveloped, icosahedral positive single-stranded linear ribonucleic acid (RNA) virus with a ~7.5 kb genome. The genome contains three regions, namely: a 5’ untranslated region with 734–742 nucleotides, a single open reading frame, and a 3’ non-coding region of 40–80 nucleotides. There are two forms of infectious HAV – naked, non-enveloped virions containing the HAV RNA genome, shed in faeces and detectable by capsid antigen ELISA, and quasi-enveloped virions (eHAV) which are released non-lytically from infected cells as an enveloped form and are undetectable by the same ELISA. eHAV is found in the blood of HAV-infected patients as well as in supernatants of HAV-infected cell lines. HAV is resistant to low pH and heat (60ºC for 60 minutes) as well to freezing temperatures but becomes inactivated at 81ºC for 10 minutes. The virus may persist in faeces and soil for a prolonged period.

The exact pathway of eHAV through the gut wall is not fully known. Infection usually occurs through ingestion of HAV-contaminated food or fluid, with HAV passing through intestinal epithelial crypt cells, reaching the liver via the portal blood and being secreted into the bile. On the basis of the detection of HAV antigen in epithelial crypt cells in the gut in experimentally infected owl monkeys, HAV replication in the gut mucosa is presumed but not proven beyond doubt.

HAV has a special tropism for liver cells but is non-cytopathic; liver cell injury occurs through an immune-mediated mechanism. Several hypotheses address the mechanism(s) involved in cell entry of HAV through the hepatocyte membrane. These include the formation of virus-IgA complexes and uptake through the asialoglycoprotein receptor (such HAV-IgA complexes are able to pass into blood after oral uptake). Furthermore, interaction of HAV with an attachment cellular receptor TIM 1 (HAVCR1) expressed on the hepatocyte surface facilitates hepatocyte membrane penetration. HAVCR1 may not be the only or essential entry factor and the virus may enter the liver cell through other or additional mechanisms. Cell wall penetration seems to occur via endocytosis followed by removal of membranes around the capsid by bile acids which expose the virus to neutralizing antibodies when present. The virus replicates in the liver and is then shed into the bile and faeces and to a lesser degree into the bloodstream. Free or IgA-HAV immune complexes reach the small intestine.
Upon hepatocyte cell entry, host cell ribosomes bind to the viral uncoated RNA. HAV-RNA is then translated into a major protein of 2225 amino acids. The HAV replication cycle commences with translation of the polyprotein. The polyprotein is processed co-translationally into 10 mature viral proteins. These include, from the N-terminus, four structural proteins that form the capsid – VP4, VP2, VP3 and VP1pX (numbered according to molecular mass) – and six nonstructural proteins that are essential for amplification of the RNA genome. HAV RNA can be detected in body fluids and faeces by using nucleic acid amplification and sequencing techniques. Such methods, mainly used by research laboratories, have been utilized for studies on the genetic organization of HAV infection as well as for investigating outbreaks through phylogenetic analysis. Seven HAV genotypes I-VII were originally identified among a global collection of HAV samples using a 168 nucleotide fragment containing the VP1/2A junction. These were then reclassified into six genotypes based on sequences derived from the complete VP1 region. Genotypes are defined by a sequence variability of ~15% in these regions while subgenotypes differ by 7.0–7.5%. Three genotypes, namely I−III, were identified in infected humans, while genotypes IV−VI have been found in infected nonhuman primates (Figure 1). All HAV genotypes share a common serotype, irrespective of their origin and whether they derive from wild-type or attenuated strains. Consequently, all HAV vaccines – irrespective of attenuated strain used for manufacturing – provide protection against HAV infection. The identification of the various HAV genotypes and subgenotypes has significantly enhanced the ability to investigate the molecular epidemiology of hepatitis A outbreaks. Phylogenetic analysis is particularly helpful in investigations of sources and transmission routes as well as in discrimination between outbreak and non-outbreak cases.

Figure 1: HAV genotypes classification.
Phylogenetic analysis of the six currently recognized HAV genotypes

![Figure 1: HAV genotypes classification.](image)
1.2 Epidemiology of hepatitis A virus infection

The epidemiology of hepatitis A in various geographic regions is changing worldwide. A rise in the world population and improving socioeconomic conditions, as well as immunization campaigns, are divergent factors with an impact on the incidence of HAV infections. It is estimated that more than 100 million hepatitis A virus infections occur annually worldwide, resulting in 15,000 to 30,000 deaths per year. Most of the HAV burden occurs in low- and middle-income countries. According to a WHO assessment, some 1.5 million HAV infections are reported annually. Estimates of HAV infections are often based either on modelling or on age-adjusted prevalence of anti-HAV (IgG) serology. There is no accurate figure of the number of new HAV infections worldwide because of the large number of asymptomatic infections in the younger population and an assumed underreporting of 80% and more.

In 2010, the WHO reported the results of a reassessment of the global burden of disease (GBD) for hepatitis A. As a first step, WHO reviewed 637 eligible reports out of 2932 papers pooled into 21 GBD regions. Results revealed a global increase from 117 million infections in 1990 to 121 million infections in 2005. According to this assessment, an increase in incidence was observed in the age groups 2–14 years and 30 years and older. Deaths increased from 30,283 in 1990 to 35,245 in 2005. Globalization – manifested by increased travel from non-endemic to endemic regions, the import of contaminated food products from HAV-endemic countries and the presence of men who have sex with men (MSM) – contribute to an increased risk for acquiring HAV, especially in countries of low or intermediate HAV endemicity. On the other hand, improving socioeconomic conditions, safer water and food supplies, and universal vaccination programmes (albeit available so far in only a relatively small number of countries) contribute to decreased exposure to HAV but also to increased susceptibility to infection, especially in young and even middle-aged adults. These phenomena create a shift in HAV exposure and, consequently, in the epidemiology of hepatitis A. This paradox is manifested in a decrease in HAV endemicity – i.e. from a high to an intermediate endemic situation – resulting in a growing population of susceptible persons at risk of contracting HAV infection (including children, adolescents and adults) and to lower population immunity. At the same time, the increasing likelihood of exposure at adult age will make a somewhat asymptomatic disease more visible with more pronounced symptomatology when contracted later in life. This shift in susceptibility is reflected in the higher number of symptomatic infections in the recent years.

There are two main types of sources of information that can be used to estimate the burden of disease associated with HAV infection: 1) serological surveys estimating the prevalence of past infections, and 2) reporting systems measuring the incidence of morbidity or mortality from acute hepatitis A disease.
1. **Measurement of prevalence:** The global spread of HAV infection can be assessed by monitoring overall and age-specific prevalence, thus also enabling indirect measurement of incidence rates. Historically, several classifications have been employed by public health agencies to estimate HAV prevalence. Prevalence has been classified into high (> 50% of population), intermediate (15–50%) and low levels (< 15%) of endemicity, based on detection of anti-HAV immunoglobulin G (IgG) antibodies in selected populations. Another categorization based on seroprevalence data suggests classifying endemicity as high (≥ 90% by age 10 years), intermediate (≥ 50% by age 15 years, with < 90% by age 10 years), low (≥ 50% by age 30 years, with < 50% by age 15 years) and very low (< 50% by age 30 years). Recently, the European Centre for Disease Prevention and Control (ECDC) has defined HAV prevalence as very low (< 2 cases per 10 000), low (2–19 cases per 100 000), intermediate (20–199 cases per 100 000) and high (> 200 cases per 100 000). This ECDC classification has been used in the present review to assess the susceptibility to HAV infection in Europe (see below). Age-specific prevalence is considered to be a more accurate marker to classify endemicity. High endemicity of HAV infection is found in countries with poor sanitary and socioeconomic conditions, where infection typically occurs before the age of 5 years. Intermediate endemicity of HAV is typically found in countries in transition from a low socioeconomic status to improved housing and hygienic conditions, mainly in specific segments of the population. In such countries, the paediatric population may escape HAV infection in early childhood. As a result, susceptible individuals are infected by HAV later in life during outbreaks or following person-to-person contact. HAV infection in these populations is associated with a higher proportion of more severe clinical manifestations as compared to the subclinical presentations in babies. In countries with low HAV endemicity, the risk of acquiring HAV infection is low or very low for the general population, although this may be substantially higher in individuals belonging to specific risk groups (Table 1).

### Table 1. Risk groups for contracting hepatitis A

- Travellers from non-endemic to HAV endemic countries
- Family members and close contacts of an individual with acute hepatitis A
- Men who have sex with men (MSM)
- Patients with chronic liver disease
- Day-care center staff
- Garbage and sewage workers
- Laboratory workers handling infected specimens
- Immune-suppressed patients living in areas of intermediate HAV endemicity
- People who inject drugs
- Food-handlers
- Frequent recipients of blood products
- Military personnel from non-endemic countries deployed overseas
- Caretakers of nonhuman primates
- Children of migrants from HAV-endemic countries
- Family members of adoptees from HAV-endemic regions
- Homeless and street persons
- Prisoners

2. **Measurement of incidence:** Direct assessment of incidence by anti-HAV(IgM) testing requires adequate surveillance with reliable reporting which is often missing. Detection of anti-HAV(IgM) antibodies is not necessarily discriminatory between acute HAV infection and recent vaccination, although anti-HAV(IgM) titers are much lower in vaccinees as compared to patients recovering from acute hepatitis A. Furthermore, anti-HAV(IgM) testing is not always available in countries that are endemic for HAV. When such data are available (i.e. in countries with improving socioeconomic and sanitary conditions as well as adequate serological testing facilities), endemicity to HAV can also be classified as high (> 150 cases/10^5), intermediate (15–150 cases/10^5), low (5–15 cases/10^5), or very low with an estimated incidence of 5 cases/10^5.b

As already indicated, an epidemiological shift from high to intermediate endemicity of HAV has been observed in many countries, especially those with improving socioeconomic and sanitary conditions. This transition in endemicity often results in a paradoxical individual susceptibility to infection leading to an increase in disease incidence later in life, with consequent increased disease severity despite the presence of improved socioeconomic and sanitary conditions for part of the population.a,b,c,d,e,f

An example for the potential consequences of such a shift in endemicity was clearly observed in the clinical manifestation of the HAV infections during the massive outbreak of hepatitis A in Shanghai in 1988 where over 300,000 persons contracted HAV infection within a short period.

Up-to-date data on the GBD, based on age-adjusted seroprevalence, are still incomplete. Yet the increased incidence of HAV infection in adults is expected to have an impact on the magnitude and severity of clinical disease, as already reported from the Republic of Korea. Furthermore, in countries in transition, pockets of intermediate endemicity may exist within the same areas of high endemicity, facilitating HAV exposure in still susceptible age groups. Finally, despite the observed low attack rates of clinical hepatitis, especially in areas of high endemicity but also in countries with intermediate endemicity in transition, HAV infection has been identified as a leading cause of fulminant hepatic failure in a growing number of countries including in Argentina, Brazil, and the Republic of Korea.

HAV transmission occurs mainly through common source outbreaks (such as frozen food and waterborne outbreaks) as well as through person-to-person contact via a faecal-oral route. Shellfish are able to ingest and concentrate HAV and, as a result, become a reservoir for the spread of the virus. HAV is very rarely transmitted through blood products or iatrogenic medical procedures. Risk groups in low and very low endemic settings include: populations of low socioeconomic status living in crowded conditions; household contacts of infected individuals; children visiting day-care centres and kindergartens; institutionalized patients; prisoners and related caretakers; sewage and garbage collection workers; parents in low endemicity countries of children newly adopted from countries with high or intermediate endemicity; MSM; homeless persons; people who inject drugs; patients with chronic liver disease; immune-suppressed patients such as those with HIV; food handlers; caretakers of nonhuman primates and patients with blood-clotting disorders (Table 1).

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Although sequencing and phylogenetic analysis have improved significantly, the accuracy in identification of the source and routes of HAV transmission 43,44 the source remains unidentified in over 50% of cases 45. The constant changes in the epidemiology of HAV worldwide – especially, though not exclusively, in resource-poor countries in transition – justify continuous surveillance which will be essential for public health decision-makers 33,43,44.

### 1.3 Acute viral hepatitis A — clinical manifestations

Acute hepatitis A virus infection causes an acute necro-inflammatory process in the liver which normally resolves spontaneously without chronic sequelae. The median incubation period of acute HAV is usually about 28 days, ranging from 14 to 50 days. Symptoms include malaise, fatigue, anorexia, vomiting, abdominal discomfort, diarrhoea and, less commonly, fever, headaches, arthralgia and myalgia. Five clinical/subclinical patterns are recognized: 1) asymptomatic HAV infection, often present in children under the age of 5 years; 2) symptomatic HAV infection associated with hepatocellular injury manifested with high alanine aminotransferase/aspartate transaminase (ALT/AST) elevation with the appearance of dark urine and sometimes clay-coloured stools, often accompanied or followed by jaundice; 3) cholestatic hepatitis characterized by pruritus, prolonged rise of alkaline phosphates, gamma glutamyl transpeptidase, bilirubinemia and weight loss; 4) relapsing hepatitis A infection manifested by reappearance of the clinical, biochemical and virological markers of acute hepatitis A after initial resolution; and 5) fulminant hepatitis, which frequently resolves spontaneously but which occasionally may require liver transplantation.

Extra-hepatic manifestations of acute hepatitis A may occur; they include skin involvement (rash, vasculitis, cryoglobulinemia), pancreatitis, mononeuritis, meningo-encephalitis, Guillain–Barré syndrome, carditis, glomerulonephritis, pneumonitis, haemolysis (especially in patients with glucose-6 phosphate dehydrogenase syndrome) and aplastic anaemia. Other manifestations include prolonged fatigue, right upper quadrant discomfort, fat intolerance and indigestion, weight loss, emotional instability and prolonged indirect bilirubinaemia. Acute HAV infection resolves spontaneously in over 99% of infected persons. Relapsing hepatitis A with subsequent complete resolution has been reported in 3–20% of patients with clinical hepatitis 46,47,48. Fulminant hepatitis is relatively rare, with a wide range of estimates. Some reports on incidence of fulminant hepatitis, liver failure and death are based on data obtained 20–30 years ago or on information obtained in non-endemic countries. Immune-suppressed patients and patients with chronic liver disease (i.e. chronic HCV infection with HAV super-infection) are at an increased risk of developing severe or fulminant hepatitis 49,50. Before widespread use of HAV vaccines, the reported fatality rate of HAV-associated acute liver failure ranged between 0.015 and 0.5% in children and adults over 40 years of age, respectively 51,52. According to a recent GAVI estimate, in 2015 HAV caused approximately 11 000 deaths, reflecting an 0.8% mortality rate. Following the massive outbreak of hepatitis A in Shanghai in 1988, 47 deaths were reported among more than 300 000 infected patients (a case fatality of 0.015 rising to 0.05 in patients with underlying chronic liver diseases, i.e. with persistent HCV infection). In this massive outbreak, fatality in hepatitis B surface antigen (HBsAg+) carriers infected with HAV reached 0.05%, as compared to 0.015% in non-HBV carriers 35. In Western countries, reports suggest a case fatality rate of 0.3–0.6% in age groups over 40 years. In age groups of 50 years and older, case fatality may rise to 1.8–5.4% (these data reported from the United Kingdom and the USA were obtained prior to introduction of liver transplantation for HAV-induced liver failure) 53–59.
Two reports from the Republic of Korea and the USA, based on a relatively small sample size, revealed a spontaneous recovery from fulminant HAV infection in 55–57% of patients with acute liver failure, while 31–38% underwent liver transplantation and 6–14% of non-transplanted patients died \(^{60,61}\). Although not confirmed, increased susceptibility for development of severe or fulminant hepatitis A has been linked to a mutation of the HAVCR1 receptor \(^{62}\). Reports from South America and the Republic of Korea have raised concerns that the incidence of fulminant hepatitis A may be rising, particularly in children. Before the introduction of universal HAV vaccination in Argentina, hepatitis A was reported to be the main cause of fulminant hepatic failure (58–61% of cases in children diagnosed with liver failure). Overall in Argentina, 0.4% of paediatric cases with acute HAV infection developed fulminant hepatitis, of which 60% were fatal \(^{61}\). A retrospective analysis in Brazil reported that 39% of fulminant hepatic failure cases in children were associated with hepatitis A infection. In a multicentre, prospective study on fulminant hepatic failure cases in Latin America, 43% of the cases were associated with hepatitis A \(^{64,65}\). The incidence of fulminant hepatic failure caused by hepatitis A in children was used as one of the indicators to measure the impact of universal hepatitis A immunization in Latin American countries. Indeed, introduction of infant immunization against HAV is leading to a decline in incidence of fulminant hepatitis A, as reported from Argentina and the Republic of Korea \(^{38,39,41,42,66}\).

1.4 Hepatitis A vaccines

Prevention of HAV infection requires a broad spectrum of general measures of hygiene which are closely linked to the level of socioeconomic standards. These measures include the maintenance of adequate sanitation, access to clean irrigation and drinking water, effective supervision of food handlers and food products, and proper surveillance of nursing staff caring for toddlers. Not less important, hepatitis A is a vaccine preventable disease and thus, immunization is the most effective mean for prevention of hepatitis A.

1.4.1 Monovalent and combined hepatitis A vaccines

Attenuation of HAV through serial propagation in tissue cell culture in 1979 \(^{67}\) led to the development of several HAV vaccines that were tested initially in nonhuman primates and then in clinical trials in humans. Two types of HAV vaccines are currently used worldwide: 1) formaldehyde-inactivated hepatitis A virus vaccines are used in most countries (Table 2a) \(^{68-72}\) and 2) live attenuated vaccines manufactured and mainly used in China \(^{73-77}\) and sporadically in India in the private sector (Table 2b) \(^{78}\).
Table 2a. Monovalent hepatitis A vaccines with attenuated, formaldehyde-inactivated hepatitis A virus, available worldwide

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Attenuated HAV strain</th>
<th>Adjuvant</th>
<th>HAV antigen dose/injection</th>
<th>Manufacturers</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pediatric</td>
<td>Adult</td>
<td></td>
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<tr>
<td>HAVRIX®</td>
<td>HM-175</td>
<td>Aluminium hydroxide</td>
<td>720 EU</td>
<td>1440 EU</td>
<td>GSK</td>
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<td>VAQTA®</td>
<td>CR-326</td>
<td>Aluminium hydroxide</td>
<td>25 U</td>
<td>50 U</td>
<td>MSD</td>
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<tr>
<td>AVAXIM®</td>
<td>GBM</td>
<td>Aluminium hydroxide</td>
<td>80 U</td>
<td>160 U</td>
<td>Sanofi Pasteur</td>
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<td>HEALIVE</td>
<td>TZ84</td>
<td>Aluminium hydroxide</td>
<td>250 U</td>
<td>500 U</td>
<td>Sinovac Biotech Co., Ltd</td>
</tr>
<tr>
<td>Weisairuiian</td>
<td>Lv-8</td>
<td>Aluminium hydroxide</td>
<td>320 EU</td>
<td>640 EU</td>
<td>Inst. Of Medical biology, Chinese Academy of Medical Sciences</td>
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<tr>
<td>Aimugen</td>
<td>KRM003</td>
<td>Aluminium hydroxide</td>
<td>0.5mcg</td>
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<td>VERAXIMR</td>
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<td>1600 EU</td>
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<tr>
<td>EPAXAL®</td>
<td>RG-SB</td>
<td>Virosome</td>
<td>24U</td>
<td>24 U</td>
<td>Crucell/ Berna Biotech/ Janssen-Cilag Ltd</td>
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</table>

Table 2b. Monovalent hepatitis A vaccines manufactured in China (reproduced by permission Wang et al. 61,77)

<table>
<thead>
<tr>
<th>Type</th>
<th>Trade name</th>
<th>Attenuated HAV strain</th>
<th>Year licensed</th>
<th>Adjuvant</th>
<th>HAV antigen dose-injection</th>
<th>Manufacturers</th>
</tr>
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<tr>
<td>Live attenuated</td>
<td>Weisairuiji,</td>
<td>H2</td>
<td>1992</td>
<td>None</td>
<td>1.0 mL (6.50 lg CCID50)</td>
<td>Institute of Medical Biology of the Chinese Academy of Medical Sciences, Kunming</td>
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<td>vaccine initially</td>
<td>Biovac-A, Mevac-A</td>
<td></td>
<td>2003</td>
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<tr>
<td>in liquid form,</td>
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<tr>
<td>now freeze-dried;</td>
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<td>(the liquid form</td>
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<td>the market¨)</td>
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<tr>
<td></td>
<td>HAVAC LA-1</td>
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<td>1997</td>
<td>None</td>
<td>1.0 mL (6.50 lg CCID50)</td>
<td>Changchun Institute of Biological Products</td>
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<td>2000</td>
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</table>

* Not available at present
1.4.1.1 Formaldehyde-inactivated vaccines

Formaldehyde-inactivated HAV vaccines include the monovalent HAVRIX®, VAQTA® , EPAXAL®, AVAXIM® and four inactivated vaccines which are available in China (TZ 84 HEALIVE®, Lv-8 Weisairuiian, Aimugen and Veraxim) (Table 2a) .

Monovalent inactivated HAV vaccines manufactured in the western hemisphere are available in paediatric (≥ 1 year old) and adult doses and are licensed for two intramuscular injections given 6 months apart. The interval between the two doses is, however, flexible and under certain circumstances can be extended to 18–36 months (Table 2a).

In addition to monovalent HAV vaccines, formaldehyde-inactivated combination vaccines have been developed in Europe, including TWINRIX® and AMBIRIX® (hepatitis A and B) , VIATIM®/VIVAXIM® and HEPATYRIX® (hepatitis A and typhoid).

1.4.1.2 Live attenuated hepatitis A vaccines

In China, two live attenuated hepatitis A vaccines are available and are distributed under various trade names and provided in a freeze-dried form. These live attenuated vaccines contain the H2 strain under the trade names of WEISAIRUIJI, BIOVAC A, MEVAC A and the LA-1 strain (HAVAC) . These vaccines are administered using a subcutaneous single-dose immunization schedule . The vaccines, which have a suggested shelf-life of 18 months, were tested in clinical trials in China (Table 2b) . Live attenuated HAV vaccines manufactured in China are also available in the, Guatemala, India, Philippines and Thailand.

Both the live attenuated vaccines administered subcutaneously as a single dose and as three formaldehyde-inactivated vaccines administered in two i.m. doses were tested in clinical trials in China and integrated into the Chinese Expanded Programme on Immunization (EPI) in 2007 . Immunization with a single dose of the live attenuated H2 strain led to a median seroconversion rate of 94% at 2 months following injection of 6.5 log 10 cell culture infectious units and remaining at 91% at month 6. Recent reviews summarize the immunogenicity of six controlled clinical trials with the attenuated HAV vaccine conducted in children in China, reporting 72–97.9% seroconversion rates and a good safety profile . However, surveillance provided evidence for horizontal transmission of the faecally-shedded attenuated virus by vaccinees with, so far, no signs for reversion to virulence or clinical significance. Comparative immunogenicity studies between formaldehyde-inactivated and live attenuated HAV vaccines suggest a somewhat slower seroconversion rate in the latter with similar long-term seroprotection rates for at least 14–15 years .

1.4.2 Attenuated hepatitis A virus strains

All HAV vaccines contain HAV antigens derived from virus attenuated through serial propagation in cell cultures. (Tables 2a and 2b). HAV has been adapted to grow in human and nonhuman mammalian cells, including fibroblasts, African green monkey kidney cells, fetal rhesus monkey kidney cells, and human fetal lung diploid fibroblasts. Adaptation of HAV to propagation in tissue culture and attenuation is associated with a number of mutations, particularly in the 2B and 2C proteins, generated through serial passage of wild-type HAV 89,90. Cultured cells persistently infected with HAV produce relatively low amounts of viral antigen 6,7. Comparison of the nucleotide sequence of complementary DNA (cDNA) cloned from wild-type virus (propagated in vivo in liver of marmosets) with attenuated HM-175/7 and MK-5 HAV strain (propagated in tissue culture) revealed only a small number of nucleotide changes. These were distributed throughout the genome, some being apparently associated with growth adaptation in culture and attenuation 91. Limited information is available on the genomic organization of the Chinese attenuated strains of HAV as compared to strains propagated in Europe or the USA 92,93.

Most attenuated virus strains used for vaccine production in the western hemisphere are grown in human diploid MRC-5 fibroblasts, and the nucleotide and amino acid sequences of the virus are about 95% identical in different strains. Cell culture-derived HAV antigen is purified in a number of steps, including ultrafiltration and gel chromatography, inactivated by formaldehyde, and adsorbed to aluminium hydroxide (HAVRIX®, VAQTA®, AVAXIM®) or formulated in influenza-reconstituted virosomes (EPAXAL®) which substitute alum hydroxide as an immune-stimulating adjuvant. VAQTA®, HAVRIX®, EPAXAL®, HEALIVE® and the Chinese Lv-8 vaccine are at present preservative-free and some vaccines contain additional excipients.

1.4.3 Vaccine potency

The biological activity of cell culture-derived virus, or its inactivated viral antigens, is determined by different methods for the various hepatitis A vaccines. Methods used to quantitate infectivity of HAV harvested from cell culture before inactivation include radioimmunofocus assay, fluorescent focus assay, in situ radioimmunoassay and in situ hybridization 6,7,94,95. The inactivated antigen immune reactivity and dose are measured for HAVRIX® through an enzyme-linked immunosorbent assay (ELISA) using a standard reference and expressed in ELISA units (EL.U). Paediatric and adult formulations contain 720 EL.U in 0.5 mL and 1440 EL.U in 1.0 mL respectively. Antigen potency for VAQTA® is measured through an enzyme-linked immunoassay using a standard reference reagent in which 1 VAQTA® unit corresponds approximately to 1 ng of viral protein antigen confirmed by amino-acid analysis. Paediatric/adolescent and adult formulations of VAQTA® contain approximately 25 and 50 antigen units in 0.5 and 1.0 mL respectively. AVAXIM® is available at 80 and 160 antigen units for paediatric and adult populations respectively. Potency is measured by an in-house assay. EPAXAL®, the aluminium-free HAV vaccine formulated in virosomes, contains a dose of 12 and 24 international units (IU) of HAV antigen in 0.25mL and 0.5mL for paediatric and adult use respectively.
IU are measured by an ELISA using an international reference serum of 100 IU (NIBSC code #95/500). Paediatric and adult doses for HEALIVE® contain 250 U/0.5 mL and 500 U/1.0 mL respectively. Weisairuian, another inactivated HAV vaccine manufactured in China, contains 320 and 640 EU for paediatric and adult formulations respectively. Veraxim® is the third inactivated HAV vaccine manufactured in China (Table 2a). Recently, the European Pharmacopoeia has updated its biological reference preparation for measurement of in vitro non-adsorbed, inactivated HAV vaccine potency 96.

Two of the live freeze-dried HAV vaccines manufactured in China contain a 6.5 tissue culture-infecting dose (TCID₅₀) derived from the H₂ and LA1 attenuated HAV strains (Table 2b).

Hepatitis A virus vaccines should be refrigerated at 2–8 ºC. Freezing should be avoided as this is expected to affect immunogenicity. The shelf-life for formaldehyde-inactivated hepatitis A vaccines manufactured in the western hemisphere ranges from 24 to 36 months, depending on the manufacturer and the time of storage at the recommended temperature. Furthermore, reactogenicity and immunogenicity of HAVRIX® stored at 37 ºC for up to one week, and VAQTA® stored at 37 ºC for up to 12 months, do not differ from what was reported for these vaccines when stored at 2–8 ºC 55,97.

1.4.4 Immune response to “natural” wild-type HAV infection

The mechanism of hepatic cell injury induced by HAV is partially understood. The virus is not directly cytolytic. Available evidence suggests that immune-mediated liver cell injury involves innate, adaptive and cellular immune responses to HAV 9,98,99. It is not known why hepatocyte injury, and as a result also clinical symptoms, are less pronounced in children as compared to adults.

1.5 Innate immune response in acute hepatitis A

Limited information regarding innate immunity to HAV infection is derived from experimentally infected chimpanzees 100 and mice 9,101 (see review) 9. HAV has been shown to actively suppress interferon responses through proteinases which proteolytically degraded mitochondrial antiviral signal protein (MAVS) and TRIF adaptor molecules involved in interferon induction. Thus, HAV has the capacity to evade MAVS mediated intra-hepatic interferon responses. A low interferon stimulating gene (ISG) response translates into resistance to develop an efficient interferon type I release despite high viraemia. Thus, blunted type I interferon production seems to influence the vigour and effectiveness of T-cell immunity against HAV and as a result contributes to the “stealth” property of the virus 100.
1.6 **Humoral immune response in acute hepatitis A**

The humoral immune response during acute hepatitis A includes a concerted generation of specific antibodies of the IGM, IgG and IgA isotypes directed against the HAV capsid. Diagnosis of acute hepatitis A is established through detection of IgM anti-HAV antibodies in patients with clinical/laboratory signs of hepatitis. Post-infection and post-vaccination immunity is established through detection of total anti-HAV(IgG) antibodies. Following acute HAV infection, cross-genotype neutralizing anti-HAV (IgG) antibodies react with an immune-dominant antigenic capsid epitope which is a conformational discontinuous complex structure formed from VP1, VP2 and VP3. Another putative conformational neutralizing epitope was recently located to amino acids on VP2 and VP3, providing lifelong protection against HAV re-infection. The mechanism involved in HAV neutralization is not completely understood. Most circulating HAV particles in blood are cloaked in host-cell membranes (eHAV-quasi-enveloped particles). These membranes are removed from the capsid and the intra-hepatic virus is then inactivated through post-endocytic neutralization by the specific antibodies. Upregulation of specific immunoglobulin genes lead to expansion of multifunctional virus-neutralizing specific CD4+ T cells. Resolution of acute infection is also facilitated through release of antiviral cytokines which, together with the antibodies, lead to decline in intra-hepatic HAV-RNA. The presence of total IgG anti-HAV antibodies in the absence of IgM anti-HAV antibodies signifies previous HAV infection with immunity against HAV (and exclusion of acute HAV infection). Commercially available enzyme-linked immunoassays are used for detection of IgM anti-HAV antibodies (directed against HAV capsid proteins) and for detection of total anti-HAV antibodies (IgG and IgM). IgM anti-HAV assays utilize the principle of direct binding of IgM anti-HAV in the test sample to anti-human IgM-coated matrix or particles. Competitive inhibition assays for measurement of total anti-HAV antibodies are available as qualitative or quantitative assays, the latter containing calibrators standardized against a WHO reference serum.

IgM, IgG and IgA anti-HAV antibodies appear shortly before, or during, the onset of symptoms. Anti-HAV IgM antibodies are detectable in symptomatic and asymptomatic patients alike. In symptomatic patients, IgM anti-HAV antibodies appear within 5–10 days before symptoms, or at the early phase of alanine aminotransferase (ALT) elevation, and persist for about four months (range 30–420 days). In one study, HAV RNA was detected at an average of 17 days before the ALT peak, and viraemia persisted for an average of 79 days after the liver enzyme peak. The average duration of viraemia demonstrated in chimpanzees inoculated intravenously with HAV was 95 days (range 36–391 days) (Figure 2). In patients with relapsing hepatitis A (3–20% of patients), IgM anti-HAV, viraemia and shedding of HAV in the faeces may reappear intermittently for up to 6 months, and occasionally even longer. False positive IgM anti-HAV may rarely be present in patients with hyperglobulinemia. In such cases, HAV RNA testing by PCR may facilitate the distinction between a positive and a false positive anti-HAV(IgM) result.
Figure 2: Virological, immunological and biochemical events during the course of experimental hepatitis A virus infection in chimpanzees inoculated intravenously with human HAV, strain HLD2. ALT, alanine aminotransferase.

Total anti-HAV antibodies, often referred to as IgG anti-HAV, are detectable at the onset of symptoms. Their titre rises slowly parallel to the decrease in titre of anti-HAV IgM antibodies (Figure 2). IgG anti-HAV antibodies established through natural infection provide protection against re-challenge with hepatitis A virus and signify immunity against hepatitis A for life, irrespective of whether the infection was symptomatic or subclinical.\(^6,107\) Immunity to HAV is established by convention once IgG anti-HAV antibodies rise to a titre above 10–20 mIU/mL, depending on the immunoassay used for detection. However, the absolute lower limit of protective antibody level has not been determined.\(^{108}\)

Qualitative assays for total anti-HAV antibodies are used for prevalence studies and, indirectly, for assessment of incidence when adjusted for age of detection. Anti-HAV(IgG) testing may also be used for assessing immunity prior to a decision to vaccinate as well as for confirming protection against HAV post-infection or post-vaccination. However, detection of anti-HAV(IgG) does not enable a clear distinction to be made between immunity generated by “natural”, wild-type HAV infection, and vaccine-induced immunity. Such a differentiation may be possible in part through quantitative IgM and total anti-HAV measurements using modified, more sensitive immunoassays, since the humoral response to immunization is generally weaker compared to the response to wild-type HAV infection.\(^94,109\) The inability to distinguish clearly between these two situations led to an attempt to develop an antibody assay against non-structural proteins such as the 3C\(^{pro}\) protease for differentiating the humoral immune response against replicating virus from the response to a killed-inactivated HAV vaccine.\(^{110–112}\) However, these tests remain research tools only.
There are other sensitive, but also more time-consuming, methods compared to the commercially available assays for identification of neutralizing antibodies against hepatitis A. These assays, which are mainly used as research tools, include the radioimmunofocus inhibition assay (RIFIT), HAVARNA and radioimmunoprecipitation assay.

The role of secretory immunity in hepatitis A remains unclear. Anti-HAV(IgA) antibodies have been detected in the saliva of experimentally infected animals and humans. Anti-HAV(IgA) antibodies appear in serum closely to generation of anti-HAV(IgM) antibodies. Such antibodies can also be found in some patients as virus-antibody complexes in stools of infected persons.

1.7 Cellular immune response in acute hepatitis A

Hepatocellular injury induced by HAV infection, has been linked to a cellular immune response presumably involved in the immunopathogenesis of the infection. Despite the proven tropism of HAV for liver cells, the virus is not cytolytic and liver cell injury occurs through activation of HAV multispecific cytotoxic T cells. Inflammatory cell infiltrates isolated from liver biopsies of patients with hepatitis A contain CD8-positive T cells which can specifically lyse hepatitis A virus-infected target cells in an histocompatibility leukocyte antigen (HLA) class I restricted manner. Although there is only limited information on involvement of the innate immune system in HAV infection in humans (see section 2.1), there is evidence that secretion of interferon gamma by activated T cells may facilitate the expression of HLA class I determinants on the surface of infected liver cells. On the other hand, HAV is able to induce cleavage of MAVS and TRIF which are signaling molecules for induction of interferon responses. Consequently, HAV is able to block the induction of beta interferon through interference with IRF-3 phosphorylation. Cytolytic T-cell epitopes residing on the structural proteins of HAV (i.e. the dominant epitopes in 2B, 2C and 3D) may be involved in cytolysis of HAV-infected hepatocytes. Little is known about the role of T-helper cells in mounting an immune response to HAV. One putative CD4 T-cell helper lymphocyte epitope was identified on the VP3 102–121 sequence. There is also some evidence that nonspecific immune mechanisms, including natural killer cells (NK) and lymphokine-activated killer cells (LAK), are involved in the induction of hepatocellular injury even before the initiation of cytotoxic T lymphocyte injury. Finally, impaired function of CTL-suppressing CD4+/CD25+ regulatory T cells has been linked to the frequent resolution of acute hepatitis A with spontaneous recovery. Thus, it appears that multiple immune mechanisms contribute to HAV induced acute liver injury and recovery.
2. Immune response to vaccination

Formaldehyde-inactivated hepatitis A vaccines are highly immunogenic and safe, providing rapid, protective immunity to hepatitis A. The extraordinary immunogenicity of these vaccines enables a flexible interval between the first and second dose. Thus, a booster dose is usually administered within 6–12 months after the priming injection. However, the interval may be extended to 18–36 months, depending on the vaccine type. Based on clinical data and mathematical modelling, protection against HAV is estimated to last for decades, and possibly a lifetime \(^{127-129}\).

2.1 The humoral and cellular immune response to vaccination

Infection with live, wild-type HAV involves virus replication in liver cells and is associated with an active cellular and humoral immune response against the virus which induces hepatocellular injury \(^{94,116-122}\). By contrast, viral replication does not occur after immunization with a killed HAV vaccine, and protection against HAV is primarily antibody-based \(^{34,94,130}\). Indeed, experience with immune globulin (Ig) and active immunization initially suggested that vaccine-induced protective immunity against hepatitis A is mainly humoral with little involvement of the cellular immune system \(^{34,108,130}\). Evidence has now been obtained to suggest that immunization against HAV with a killed vaccine also leads to a measurable cellular protective immune response, which is long-lasting for at least 6 years and may be boosted to revive the immune memory \(^{131-135}\).

2.1.1 The humoral response

Many studies have documented the rapid and effective humoral immune response to inactivated hepatitis A vaccines \(^{34,70,94,127,132-139}\).

One example of careful prospective evaluation of the immune response to HAV vaccine was reported in 45 healthy vaccinees (mean age 28.4 years, 23 females) who received 1440 IU of HAVRIX® at 0 and 6 months \(^{131}\) (Figure 3a). Seroprotection after the first dose was already documented in 97.7% of vaccinees by week 2, reaching 100% at week 4. Geometric mean concentration (GMC) of total anti-HAV antibodies (mainly IgG) at week 2 and 4 reached 211 and 812 mIU/mL respectively (range 117–5688 mIU/mL). At month 6, all vaccinees were still seropositive but antibody levels had dropped by 80%. However, a booster dose at month 6 led to a 24-fold rise in total anti-HAV levels, reaching a GMC of 5375 mIU/mL (range 745–34 245 mIU/mL). Similar results were obtained with other inactivated HAV vaccines, including VAQTA® \(^{34},\) in a small-scale comparative randomized trial between HAVRIX® and VAQTA® \(^{34},\) with AVAXIM® \(^{70},\) EPAXAL® \(^{71}\) and HEALIVE® \(^{72}\).
On the basis of this information, the humoral immune response to a single dose of an attenuated vaccine is slower compared to that of formaldehyde-inactivated vaccines. One month after a single-dose injection, 81% of 102 vaccinees had detectable anti-HAV (IgG) antibodies (GMC 56 mIU/mL) rising to a peak of 95% (GMC 131 mIU/mL) at two months. At 96 months, 72% of vaccinees were still anti-HAV (IgG) positive (GMC 89mIU/mL). A booster dose led to an anamnestic response in 100% of vaccinees (GMC 3133mIU/mL). Reports in the Chinese literature indicate seroconversion rates of 68–94% six weeks after single-dose immunization with the attenuated H2 strain and 57–100% at six months. Furthermore, anti-HAV (IgG) antibodies were still detectable in 72–88% of vaccinees at 15 years. It is, however, not known if these vaccinated individuals were naturally exposed to wild-type HAV during this period.
2.1.2 The cellular response

Few studies have examined the cellular response to inactivated HAV vaccines. Interferon gamma secretion as evidence for an HAV-specific proliferative T-cell response was documented in three studies. In one study, a single 1440 EL.U dose of HAVRIX® induced a specific proliferative T-lymphocyte response in up to 100% of vaccinees, starting at day 7 post-injection (Figure 3b). A 60% decline in cellular immune responses was observed by week 12 after primary immunization but rose over 7-fold after a booster dose at month 6. In another study of the innate immune system, production of interferon gamma and interleukin-10 by peripheral blood lymphocytes was documented by day 10 after immunization against HAV. Garner-Spitzer and co-workers have documented a direct correlation between the concentration of cytokines IL-2, interferon gamma and IL-10 with anti-HAV antibody levels before and after booster vaccination. These results provide evidence for the role of cytokines and T-helper cells in induction of protective immunity against hepatitis A through vaccination. More information on the cellular immune response in recipients of the live attenuated HAV vaccine is not yet available.

Figure 3b: Median-specific proliferative response of peripheral blood mononuclear cells (PBMC) to inactivated hepatitis A virus in 15 adults receiving 1440 EU HAVRIX® at 0 and 26 weeks (vertical reference lines). Data are presented as ∆cpm; upper and lower lines represent the upper and lower quartile ranges

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2.1.3 Summary

In immune competent individuals, vaccination against hepatitis A using a two-dose schedule of formaldehyde-inactivated vaccines leads to a significant cellular and humoral immune response within two weeks of the primary injection, rising to 100% by week 4. A 60–80% decline in T-cell and B-cell responses within 24 weeks is reversed through a booster dose at week 24, leading to a significant rise in cellular and humoral immune response.

2.2 Immunogenicity of hepatitis A vaccines and immune memory

The duration of protective immunity following wild-type HAV infection is thought to be lifelong \(^9\,^{107,129}\). Similarly, primary immunization with the first dose of inactivated hepatitis A vaccines provides the basis for long-term immunity – probably for decades \(^28\,^{128,129,133}\), while non-response to immunization is extremely rare \(^134\). Inactivated hepatitis A vaccines are usually recommended using a 2-dose schedule, with a second dose given at 6–12 months after the priming dose for HAVRIX® and EPAXAL®, at 6–18 months for VAQTA® and AVAXIM® 80U, and at 6–36 months for AVAXIM® 160U. The interval between the priming vaccination and the second dose is flexible. This is particularly important for vaccinees who missed their second dose (e.g. international travellers). Furthermore, in children and young adults, up to 100% of vaccinees will seroconvert with anti-HAV IgG titres over 20 mIU/mL within 2–4 weeks of the first injection (Figure 3a).

In China, where live attenuated vaccines are used with a one-dose schedule, the persistence of anti-HAV(IgG) antibodies was documented after 15 years in 72–88% of subjects immunized with the H2 live attenuated HAV vaccine \(^74\,^{77,141}\). Early studies in chimpanzees immunized against hepatitis A with a formaldehyde-inactivated vaccine and challenged with wild-type HAV revealed that, even in the case of waning anti-HAV IgG antibodies at the time of HAV challenge, animals were protected against hepatitis A \(^136\). A specific gamma interferon-mediated T-cell immune response was documented in human vaccinees within 1.5–6 years of the completion of the original vaccine series \(^135\). In this study, a booster dose was given to 36 subjects 6 years after initially receiving two doses of HAVRIX®, 1440 EL.U at a 6–12-month interval. More than 50% of vaccinees had an HAV-specific proliferative T-cell response in vitro, providing evidence for prolonged immune memory induced through immunization. In another study, protective anti-HAV(IgG) were still detectable in 98% of 1016 travellers tested 10 years after immunization with 720 EL.U HAVRIX® \(^109\). Similar results of long-term persistence were recorded in 98% of Argentinean children 10 years after immunization with a two-dose vaccine schedule \(^142\). While cellular immune memory to HAV vaccines has so far been shown to persist for at least six years, available evidence already suggests that humoral immune memory will most probably persist for 2–3 decades or more, as demonstrated in follow-up studies and through mathematical modelling of antibody decay \(^28\,^{137–139,143,144}\). Challenge of vaccinees 12 years after completion of an HAV immunization series led to a robust anamnestic response, as manifested by a significant rise in anti-HAV antibody titre \(^143\). Furthermore, administration of a booster dose up to 6 years after one vaccine dose led to a 32–100-fold rise in anti-HAV IgG antibodies. A recent small-scale study compared HAV specific memory cellular responses between recipients of a single or two-dose inactivated HAV vaccine and patients following “natural” HAV infection \(^145\).
Proliferation assays revealed that the first vaccine dose induces HAV-specific cellular responses similar to that induced by a second dose or by natural infection. Increase in the frequencies of classical memory B cells, TCD8 cells and central memory TCD4 and TCD8 cells were observed from the first to the second dose. This response was accompanied by increased IL-6, IL-10, TNF and interferon gamma cytokine levels after vaccination. The HAV-specific T-cell immunity induced by primary vaccination persisted independently of the protective plasma antibody level. These results suggest that a single dose of HAV vaccine promotes HAV-specific memory cell responses similar to that induced by a natural infection. Thus, there is to date ample evidence to conclude that immune memory against hepatitis A, established through vaccination, will persist for decades in immune competent persons. The excellent record of immunogenicity of hepatitis A vaccines in children has led to the introduction of a single-dose immunization strategy in the routine childhood immunization programme in Argentina and in other Latin American countries.
3. Protection against hepatitis A

Hepatitis A virus infection is a vaccine-preventable disease. General measures of protection include adequate personal hygiene, especially by food-handlers and by nursing staff at day-care centres, quality control and maintenance of a safe water and food supply, and proper sanitation. Specific measures include: 1) short-term pre- and post-exposure prophylaxis with immune serum globulin (Ig), if available; 2) long-term pre- and post-exposure active prophylaxis using formaldehyde-inactivated HAV vaccines; and 3) pre-exposure prevention using a live attenuated vaccine.

3.1 Measurement of protection

A positive (qualitative) test for total anti-HAV antibodies signifies immunity to hepatitis A. The lowest protective level against challenge with HAV is unknown. Clinical experience suggests that protection against hepatitis A following passive immunization with Ig or active vaccination may still be present even in the absence of detectable anti-HAV antibodies using standard immunoassays. Different thresholds for protective total anti-HAV (mainly IgG) antibody levels have been suggested when studying individual HAV vaccines while using a WHO reference serum. The reported minimal serum levels of total anti-HAV antibodies required for protection against HAV in humans varied between 10–33 mIU/mL, depending on the immunoassay used for detection and regardless of whether these antibodies emerged following “natural” wild-type HAV infection or appeared following vaccination. Immunogenicity studies with VAQTA® have employed a modified radioimmunoassay with a minimal protective antibody level of ≥10 mIU/mL. Early studies with HAVRIX® set the threshold of protection between 20 and 33 mIU/mL using an enzyme-linked immunoassay. This threshold has been cut to 15 mIU/mL in recent years.

Low levels of anti-HAV IgM antibodies may be detectable by a conventional assay for a few weeks in ~20% of recipients of HAV vaccines. Consequently, anti-HAV IgM antibody assays cannot be used to reliably distinguish between acute hepatitis A and anti-HAV response to vaccination.
3.2 Passive prophylaxis with immune globulin

Since the late 1940s administration of human immune serum globulin (Ig) has been considered as an efficient means of pre- and post-exposure prophylaxis against hepatitis A virus infection. Immune globulin is prepared by ethanol fractionation from pooled human plasma screened for hepatitis B and C, as well as for human immune deficiency virus (HIV). Historically, Ig contained very high concentrations of anti-HAV antibodies. However, in recent years, low titres of anti-HAV antibodies have been observed in plasma donors of Ig in the western hemisphere. Immune globulin is administered through intramuscular injection. The protective efficacy of Ig against HAV infection is well documented. The duration of protection is, however, limited to 12–20 weeks following administration of 0.02 and 0.06mL/kg weight respectively. Pre-exposure prophylaxis is achieved within hours of injection and is 80–90% effective when administered as close as possible to exposure and no later than 14 days.

Despite the proven efficacy of Ig, serum concentration of anti-HAV antibodies in Ig recipients for pre- or post-exposure prophylaxis against HAV infection is low and is often below the detection limit of 15–20mIU/mL of commercially available assays. The mechanism of both pre- and post-exposure protection against hepatitis A conferred by Ig is not fully established but it most probably involves neutralization of circulating virus and possibly prevention of uptake of virus through the gut mucosa and by hepatocytes. Evidence for the efficacy of Ig in pre- and post-exposure prevention of liver disease is well documented, provided that Ig is administered within two weeks of the latter. Yet, given the fact that circulating HAV is cloaked in membranes, it is not yet understood how anti-HAV(IgG) binds to HAV during the incubation and early period of infection. It is possible that contact between virus and antibody occurs following post-endocytic neutralization within endosomes or lysosomes after removal of the membrane from the viral capsid.

Administration of Ig is considered very safe but is contraindicated in patients with IgA deficiency who may develop an anaphylactic reaction. Interference with live attenuated vaccines such as those against measles, mumps, rubella (MMR) and varicella requires special caution. Co-administration of Ig with a hepatitis A vaccine may blunt the initial quantitative anti-HAV antibody response after the first vaccine dose. However, this effect, which is similar to the effect of passively-transferred maternal anti-HAV antibodies, is of minor practical significance and apparently does not reduce the long-term immune memory. Furthermore, such vaccinees responded well to the booster dose given 6 months after the primary immunization. Additionally, although administration of Ig is highly efficacious for pre- and post-exposure short-term prophylaxis, the use of immune globulin worldwide is now declining for a number of reasons: 1) plasma pools used for manufacturing of Ig preparations increasingly fail to contain adequate amounts of anti-HAV (IgG), 2) the cost of specific HAV Ig preparations is high, 3) there are limited stocks and therefore limited availability of Ig preparations (at short and even long notice); 4) Ig mediated protection against HAV infection lasts only several months as compared to hepatitis A vaccines; and 5) inactivated hepatitis A vaccines have already been shown to induce very rapid protection against HAV following the first of two recommended doses. It is, as such, indicated for post-exposure prophylaxis.
### 3.3 Active immunization

#### 3.3.1 Pre-exposure prophylaxis

The efficacy of formaldehyde-inactivated hepatitis A vaccines was demonstrated in two pivotal, double-blind randomized control trials conducted in Thailand \(^68\) and the USA \(^69\) in the early 1990s. In Thailand, HAVRIX® and a control hepatitis B vaccine were administered to 40,119 children aged between 1 and 16 years living in an area with high incidence of hepatitis A. HAVRIX® 360 EU/dose was administered intramuscularly at 0, 1 and 12 months. Protective efficacy against clinically and serologically confirmed hepatitis A disease was demonstrated in 94% and 99% of vaccinees after the second and third doses respectively (95% CI=79%–99%) \(^68\). Serologically confirmed hepatitis A through detection of anti-HAV(IgM) antibodies was documented in 38 episodes of illness in the control group, as compared to two cases in vaccinees. A similar, double-blind placebo-controlled trial was conducted in upstate New York, USA, in 1037 children aged 2–16 years, who received two doses of 25 units of VAQTA® or placebo at 0 and at 6–18 months. Vaccine efficacy of 100% was already established following the first dose \(^69\) (95% CI=87.3%) \(^69\).

Another smaller-scale randomized, placebo-controlled, double-blind trial of a single dose of EPAXAL®, a virosome formulated, aluminium-free inactivated HAV vaccine, was conducted in Nicaragua \(^71\). Two hundred and seventy-four children (age range 1.5–6 years) received vaccine or placebo injections, and 239 children, seronegative for hepatitis A, were included in the primary efficacy analysis. HAV infection was diagnosed through positive anti-HAV IgM in four children in the vaccine group and 22 children in the placebo group. The vaccine was 100% efficacious by week 6. For the entire study period, primary efficacy analysis was 84.6% (95% CI,54.7–96.1%) and 71.6% (95% CI, 40.5–87.6%) by intent to treat analysis.

All HAV vaccines manufactured in the western hemisphere are highly immunogenic and of comparable efficacy. HAV vaccines of different brand names are interchangeable as shown for HAVRIX®, AVAXIM®, EPAXAL® and VAQTA® \(^163\–165\).

In 2007, China introduced universal vaccination for 18-month-old toddlers. Half of the children received two intramuscular doses of formaldehyde-inactivated vaccines and half received one subcutaneous dose of a live attenuated vaccine. Follow-up evaluation revealed seroconversion rates of 83–91% in recipients of live attenuated vaccines. Protective efficacy was documented in 90–95% and 95–100% in recipients of live attenuated and formaldehyde-inactivated vaccines respectively \(^77\).

#### 3.3.2 Post-exposure prophylaxis

Clinical trials of hepatitis A vaccines in the early 1990s provided unequivocal proof that pre-exposure prophylaxis of hepatitis A is effective and safe. Preliminary evidence obtained in a number of clinical trials suggested already that post-exposure immunization against hepatitis A may also have effectiveness similar to that of Ig, provided that immunization is started within two weeks of exposure.
Support for this assumption was initially obtained from the hepatitis A efficacy trial conducted in the USA where the VAQTA® vaccine was administered during an HAV outbreak and no new cases of acute hepatitis were identified from day 17 onwards after vaccination 69. There was a similar experience in Slovakia where an outbreak of hepatitis A was interrupted by vaccination with HAVRIX® 166. Later, a limited randomized controlled trial in Italy revealed a 79% protective efficacy of post-exposure immunization in household contacts of acute hepatitis A cases (95% CI=7%–95%) 167. In Israel, as in Slovakia, prompt intervention with an active vaccine in a community outbreak of hepatitis A led to effective control of an epidemic within two weeks of starting the intervention, in contrast to the relatively poor performance of Ig 168. Intervention in a major outbreak of hepatitis A in Ukraine led to a 41-fold drop in incidence of infection following a single-dose injection of AVAXIM® 169.

A pivotal support for establishing the effectiveness of post-exposure prophylaxis with an inactivated HAV vaccine has been reported from Kazakhstan 156. In this controlled clinical trial, 1090 household and day-care contacts (aged 2–40 years) of index cases with acute hepatitis were randomized to receive hepatitis A vaccine or Ig. Transmission of HAV, confirmed by anti-HAV IgM, occurred in 4.4% and 3.3% of the study groups respectively (RR 1.35; 95% CI=0.70–2.67). Following a recent update by the United States Advisory Committee on Immunization Practices (ACIP), post-exposure immunization with an active HAV vaccine is now gaining accelerated momentum worldwide 170. However, success of intervention in community outbreaks and epidemics through active vaccination requires a close public health surveillance and intervention system and, most importantly, compliance of the community where the intervention takes place. An example of failure of such an intervention occurred in the 1990s where first-dose coverage of vaccine was only 20–45% with little impact on herd immunity and incidence 171.

Altogether, the use of hepatitis A vaccines instead of Ig for post-exposure prophylaxis has a number of advantages, including induction of long-term protection against HAV, ease of administration and acceptance at a similar cost per dose 162.
4. Determinants of the immune response to immunization

4.1 Risk groups and risk factors

4.1.1 Age, gender, weight and smoking

*Age:* The physiology of the humoral, innate and cellular immune system in older age is often altered, leading to impaired immune responses. This may have special implications for vaccination of older individuals who require protection against vaccine-preventable infections – i.e. international travellers from countries with low or very low endemicity for HAV to countries with intermediate and high endemicity. This population is at risk of contracting HAV infection which is associated with increased morbidity, a higher proportion of hospitalization and higher mortality, as compared to younger persons below the age of 50 years. Data on seroprotection rates in vaccinees older than 45 years are limited; however, one uncontrolled study using EPAXAL® given in two doses, 12 months apart, revealed a blunted seroconversion rate of 65% after the first dose, compared to 100% in the younger control group. However, this difference in immunogenicity of the first dose disappeared after administration of the booster dose leading to 97% and 100% seroprotection rates respectively. Similar results were obtained in other studies. Thus, it has been suggested that HAV-susceptible individuals over the age of 45–50 years may require two vaccine doses, preferably four weeks apart, prior to departure on travel to endemic areas. However, a recent retrospective analysis does not support the introduction of such a strategy.

*Gender:* As observed with other vaccines, anti-HAV antibody levels were reported to be higher in female vaccinees following a primary and booster injection, when compared to males. However, in view of the excellent protective antibody levels induced by HAV vaccines, this difference in gender response has no practical consequences.

*Weight:* Limited data suggest that better seroprotection rates after a first dose of 25U of VAQTA® were significantly associated with lower body weight and body mass index (BMI). A booster dose is expected to minimize the effect of overweight on the immunogenicity of HAV vaccines.

*Smoking:* Results of a single study in HIV patients who received two or three doses of HAVRIX® 1440 EU at 0 and 24 weeks – or at 0, 4 and 24 weeks – revealed that absence of smoking was an independent predictor of response to vaccination.
4.1.2 Passively-acquired maternal anti-HAV antibodies

The concentration of anti-HAV antibody levels in babies born to seropositive mothers who acquired HAV through natural infection remains high during the first six months postpartum but declines significantly by 12 months of age 183. Newborns and young infants born to anti-HAV-positive mothers have a blunted humoral immune response to hepatitis A vaccination which may last for six months or more postpartum 183−187. Although depression of the quantitative humoral immune response to vaccination may reach 30–90% compared to naïve newborns, this effect of passively-transferred maternal anti-HAV antibodies does not increase the risk for acquiring HAV infection. In such vaccinated babies, vaccine-induced anti-HAV IgG titres are still far above the required protective levels. Evidence that this effect is of negligible immunological significance is derived from the observation that such babies still develop an excellent anamnestic immune response to a booster vaccination given within 1–6 years of birth 183. Furthermore, although paediatric HAV vaccines are licensed only for babies from 12 months of age, HAV immunization of 6–12-month-old children has been shown to be safe and sufficiently immunogenic even in the presence of passively transferred maternal antibodies 183−186.

4.1.3 Passively-acquired anti-HAV antibodies with immune globulin

As also observed in newborns to seropositive mothers, immunogenicity of HAV vaccines is suppressed, although to a lesser extent, following concurrent passive and active immunization with Ig and vaccine respectively 158,159. However, interference from passively-transferred anti-HAV antibodies with the humoral immune response to vaccination is of minor immunological consequence since it does not affect vaccine-induced protective immunity and response to booster vaccination is excellent. In an increasing number of countries worldwide passive Ig are no longer commercially available.

4.1.4 Immune suppression

4.1.4.1 Human immunodeficiency virus (HIV)

Patients infected with HIV types 1 or 2, including intravenous drug users, MSM and recipients of multiple blood transfusions (i.e. patients with haemophilia) are at increased risk for contracting HAV, HBV and HCV infection. A relatively high (5.8%) incidence of HAV has been reported in HIV patients in France, a country of low HAV endemicity 188. Human immunodeficiency virus patients with HAV coinfection developed protracted hepatitis A viraemia with slow clinical resolution compared to non-HIV patients with a normal CD4 cell count. Furthermore, seroconversion following vaccination may be blunted, leading to a decline in anti-HAV(IgG) antibodies 182,189−194. However, vaccination against hepatitis A does not affect HIV viral load, can be given to patients who receive antiviral treatment, is safe and, in general, is almost as immunogenic in HIV-infected children and adults with a CD4 count greater than 300/mm³ and an HIV viral load lower than 1000 copies/mL, as in non–HIV subjects. Protection was achieved in up to 100% of children and in 69–83% of adults with HIV using the standard two-dose regimen at a 0 and 24-week interval between vaccine injections 193. However, antibody levels achieved after the first and second vaccine dose may be lower compared to those in healthy subjects, and sometimes a third vaccine dose is warranted (especially in patients with a high HIV viral load and a CD4 count below 300 cells/mm) preferably after suppression of viraemia and restitution of the CD4 cell count 191.
(See the review of performance of HAV vaccines in the era of highly active antiretroviral therapy (HAART) 195.) Seroprotection should be confirmed using a conventional immunoassay for detection of anti-HAV(IgG) antibodies in such patients 182,194. Data on long-term protection following HAV immunization in HIV patients are still lacking.

4.1.4.2 Solid organ and stem-cell transplantation

In general, immune-suppressed patients who underwent organ transplantation have a blunted immune response to hepatitis A vaccines 196–199. As shown in renal transplant patients, only 72% of 39 patients developed protective antibody levels 196. Furthermore, kidney and liver transplant patients may lose their protection over time, as shown also in haematopoietic stem-cell transplant patients, and especially in those with graft versus host disease 196–199.

4.1.5 Chronic liver disease

The case fatality of HAV infection in patients with chronic liver disease is 23–58-fold higher compared to that is previously healthy infected adults, as was shown in two studies in patients with HCV and HBV 200,201. Doubts have been raised regarding the cost-effectiveness of HAV immunization in patients with chronic HCV infection 50. Yet immunization is a simple and safe procedure which can prevent hepatic decompensation. Immunization against HAV of children and adults with compensated chronic liver disease who do not receive immunosuppressive therapy generally leads to seroprotection rates similar to those of healthy subjects. However, anti-HAV(IgG) antibody levels are lower compared to those of healthy vaccines, and GMC levels are inversely proportional to the degree of liver failure 202–206. In one study conducted in 89 seronegative children between the ages of 1 and 16 years, seroconversion rates following immunization with 720 EU of HAVRIX® reached 76% as compared to 94% in a control group with anti-HAV titres of 107 and 160 IU/mL respectively 206. A booster dose given at month 6 led, however, to 97% and 100% seroconversion rates respectively, compensating for the slower response after the first dose. Overall, seroprotection rates following immunization are lower and decline faster in patients with decompensated liver disease. Criteria for vaccine booster doses have not been established in this population.

4.1.6 Co-administration of hepatitis A vaccines with other childhood or traveller vaccines

Concurrent administration of a number of routine childhood and traveller monovalent and trivalent vaccines with an HAV vaccine does not lead to biologically significant interference in the immunogenicity, reactogenicity and safety of the individual vaccines. As demonstrated in a number of controlled studies conducted among 12–15-month-old infants, in children under 18 years and in adults, inactivated HAV vaccines can be administered simultaneously with vaccines for diphtheria, tetanus, acellular pertussis (DTaP), polio (oral and inactivated), Haemophilus influenza (Hib), MMR, typhoid (oral and intramuscular), hepatitis B, cholera, Japanese encephalitis, rabies and yellow fever 80,168,207–211. It is recommended that injections should be given at different sites.
A number of combination vaccines have been developed that include hepatitis A and B (TWINRIX® and AMBIRIX®) or hepatitis A and typhoid polysaccharide (HEPATRIX®, VIATIM® and VIVAXIM®).

TWINRIX® contains 720EU of HAV antigen and 20 ug of HBsAg per dose, has been formulated with aluminium phosphate and aluminium hydroxide, and is given in three doses at 0, 1 and 6-month intervals in adults over 18 years of age. In Canada and some European countries, a half dose is available for younger ages. AMBIRIX® is a similar 2-dose combined hepatitis A and B vaccine distributed in Europe for 1−15-year-olds. Protective antibody levels against HAV and hepatitis B in recipients of the combination vaccine and the individual monovalent vaccines are comparable and long-lasting.

Combination vaccines against typhoid and hepatitis A are intended for adult travelers. A combined vaccine VIATIM®/VIVAXIM® is given as a priming dose on day 0 followed by a booster dose of hepatitis A vaccine at month 6 and up to 3 years. Protective antibody levels against hepatitis A at 3 years are comparable to those obtained following immunization with the monovalent vaccines, with hypo-responsiveness reported for the typhoid vaccine.

4.2 Interchangeability of HAV vaccines

HAV vaccines are interchangeable. Crossover immunization from one HAV vaccine brand to another has been shown to be effective and safe in children and adults. Comparative immune reactivity following crossover immunization has been documented for VAQTA®, EPAXAL®, AVAXIM® and HAVRIX® as well as for AVAXIM® and VAQTA® following combined immunization against HAV and typhoid.

4.3 Immunization strategies for protection against hepatitis A

Similar to experience previously gained with other vaccine-preventable infections, immunization strategies against hepatitis A have progressively changed over the past 20 years. As more information has become available on the extraordinary immunogenicity, effectiveness and safety of hepatitis A vaccines, immunization strategies have shifted from the vaccination of persons belonging to specific risk groups to universal vaccination campaigns in specific regions within one country, and then to universal vaccination which is, however, still restricted to a limited number of countries.
4.3.1 Individual immunization of defined populations at risk

Early strategies for pre-exposure prophylaxis included immunization of defined risk groups for contracting hepatitis A (Table 1). These risk groups include international travellers to areas with intermediate and high endemcity of hepatitis A, MSM, people who inject drugs, patients with chronic liver disease, food-handlers, day-care centre staff, caretakers of nonhuman primates, parents of adoptees born in HAV-endemic countries, children of refugees and migrants from HAV-endemic countries, garbage and sewage workers, and patients with blood-clotting disorders receiving blood-derived products. (Homeless persons in the USA have recently been added to these risk groups) 225. Although this policy has provided individual protection to vaccinees at risk, it has had little practical impact on the reduction of disease incidence/burden in low- and very low-endemicity settings, as demostrated by the massive hepatitis A outbreaks among MSM in some European Union countries. A vast majority of National Immunization Technical Advisory Groups in Europe continue to recommend this risk group policy with variable uptake and limited efficacy. The recent outbreaks of hepatitis A in MSM, homeless persons and HIV populations in Asia, Europe and the USA provide examples of the limitations of uptake of the strategy 225−231.

4.3.2 Regional vaccination of paediatric subpopulations at risk

The effectiveness of universal vaccination projects in distinct regions within the same country targeting paediatric populations at higher risk of HAV infection (as compared to neighbouring regions) was demonstrated in a number of regions worldwide. Three demonstration projects conducted in the USA in native Americans in Alaska and in Butte County, California, led to a 94–97% reduction in incidence of reported symptomatic acute hepatitis A within 6–10 years, reaching an unprecedentedly low rate of 0.1 cases per 100 000 at a vaccine coverage of 50–80% in Alaska 224. As a consequence of these successful projects, the United States ACIP in 1999 issued a recommendation to introduce universal hepatitis A vaccination into routine childhood vaccination (two doses in children over 2 years of age and catch-up at 10–12 years) in 17 states of the USA with an annual incidence of over 20 cases per 100 000. Follow-up surveillance revealed that, despite variable first vaccine coverage of 50–80%, a progressive decline in reported incidence of hepatitis A was observed from 21.1 cases per 100 000 to 2.5 cases per 100 000, representing an 88% drop (Figures 4a and 4b) 45,224. Similar projects were introduced in Puglia, Italy, in 1997 232, in Catalonia, Spain, in 1998 233, and in North Queensland, Australia, in 1999 234, leading to a 90–97% decline in the reported incidence in these regions.

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The results of these highly successful vaccination projects in selected geographical regions and communities worldwide suggested that universal vaccination of children in communities at risk is effective and will lead to herd immunity even with moderate coverage. These early projects paved the way for the introduction of universal vaccination against hepatitis A in selected countries with intermediate endemicity in transition and defined patterns of HAV transmission.

4.3.3 Universal vaccination of toddlers

Universal vaccination of babies born in countries of intermediate endemicity of HAV or in areas in transition from high to intermediate endemicity is being gradually introduced in selected regions worldwide.

In the 1990s, Israel, with a population of some 6 million people, was in transition from high to intermediate endemicity. The overall incidence of HAV infection revealed seasonal fluctuations between 33 and 70 cases per 100,000 during 1992–1998, reaching 120 cases per 100,000 in children aged 5–9 years. The decision to introduce universal vaccination to toddlers, irrespective of regional differences in incidence, was based on cost–benefit analysis and long-term surveillance data, suggesting that children were the main source for transmission of HAV in babies and adults alike. The programme, which started in 1999, offers free-of-charge vaccine (HAVRIX® 720 El.U) to 18-month-old babies, with a booster dose at the age of 24 months. At a vaccination coverage of 90% and 85% for the first and second doses respectively, the annual incidence of hepatitis A
dropped sharply within 2–3 years of programme initiation, reaching an overall decline of 95% compared to pre-vaccination rates. Thus, immunization of some 3% of the overall population annually led to a marked decrease in attack rates of HAV infection in all age groups and a shift from a state of HAV intermediate endemicity to very low endemicity with an annual incidence of around 2.5 cases per 100 000 (Figure 5, Figure 6, Table 3). However, despite the successful increase in herd immunity following universal mass vaccination, which has now been documented for more than 15 years (Figure 6), and the control of HAV infection achieved in Israel, occasional outbreaks still occur. Such an outbreak was recorded in 2012–2013 in Tel-Aviv and was associated with the detection of HAV in sewage samples and confirmed by phylogenetic analysis. This occurrence was apparently facilitated, at least in part, through contact between non-immunized susceptible populations and migrant workers from countries or regions that are endemic for HAV.

Table 3. Mean age-specific incidence per 100 000 obtained by passive surveillance before and following universal vaccination against HAV in toddlers in Israel. Vaccination started in 1995

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;1</th>
<th>1–4</th>
<th>5–9</th>
<th>10–14</th>
<th>15–44</th>
<th>45–64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jewish population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993–1998</td>
<td>19.1</td>
<td>105.7</td>
<td>181.2</td>
<td>85.5</td>
<td>30.1</td>
<td>6.8</td>
</tr>
<tr>
<td>2002–2004</td>
<td>4.2</td>
<td>0.5</td>
<td>1.2</td>
<td>2.2</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Incidence reduction (%)</td>
<td>78.1</td>
<td>99.5</td>
<td>99.3</td>
<td>97.4</td>
<td>92.9</td>
<td>89.6</td>
</tr>
<tr>
<td>Non-Jewish population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993–1998</td>
<td>34.2</td>
<td>186.8</td>
<td>224.6</td>
<td>73.7</td>
<td>7</td>
<td>2.7</td>
</tr>
<tr>
<td>2002–2004</td>
<td>2.6</td>
<td>5.9</td>
<td>18.4</td>
<td>8.4</td>
<td>2.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Incidence reduction (%)</td>
<td>92.3</td>
<td>96.8</td>
<td>91.8</td>
<td>88.6</td>
<td>67.9</td>
<td>93.9</td>
</tr>
</tbody>
</table>

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Figure 4b: Follow-up on incidence of HAV infection in the USA


* Rate per 100 000 United States population

Data reproduced by permission of the United States Centers for Disease Control and Prevention data on progress of viral hepatitis elimination United States – National Report 2017
Figure 5: Annual incidence rates in Israel of reported infectious hepatitis (A, B, C and non-specified), 1993–2004, and hepatitis A only, 1985–2004

Reproduced, by permission of Elsevier, from Dagan et al.222
WHO recommends integration of universal vaccination against HAV in national immunization schedules for children aged 1 year and above if justified on the basis of acute HAV incidence, declining endemicity from high to intermediate and cost-effectiveness. A recent survey analysed the impact of universal mass vaccination on incidence of hepatitis A in selected regions worldwide, using two doses of monovalent inactivated hepatitis A vaccines. Data collected from a total of 27 studies conducted in Argentina, China, Greece, Israel, Panama, the United States and Uruguay, revealed a marked decline in the incidence of hepatitis A after introduction of universal vaccination in all surveyed countries (except for Greece where the declining baseline incidence of HAV infection prior to vaccination had a statistical impact on the results). Declines in incidence were observed, irrespective of age at first vaccine dose (12–24 months), vaccine brand or vaccine coverage. The incidence in nonvaccinated age groups also decreased, suggesting herd immunity but also rising susceptibility. Long-term anti-HAV antibody persistence was documented up to 20 years after a 2-dose immunization schedule given 6–12 months apart. A similar short- and intermediate-term impact was observed in Argentina and China using a single-dose immunization schedule with inactivated or live attenuated vaccines respectively. In addition to a marked reduction in the incidence of HAV infection, the introduction of universal mass vaccination in selected countries and regions has had additional indirect effects, including a reduction in age-adjusted mortality, fulminant hepatitis and referral for liver transplantation in Argentina, a decline in hospitalization rates for severe hepatitis A in Greece and a drop in outbreaks of hepatitis A in day-care centres in Israel.
4.3.4 Single-dose immunization

Cumulative experience using hepatitis A vaccines, irrespective of the manufacturer, has confirmed the unprecedented high immunogenicity of these vaccines, as manifested by anti-HAV(IgG) seroconversion rates in 88% of vaccinees within two weeks of the priming dose and rising to 97–100% at weeks 4–6. Furthermore, results from clinical trials in the USA, and intervention during HAV outbreaks in several other countries, suggest that a single HAV dose may be sufficient to prime the immune response and interrupt the spread in communities at risk. Moreover, international travellers who received one priming dose of an HAV vaccine, either as a monovalent vaccine or in combination with a typhoid vaccine, and had a booster dose given 4–8 years later, developed a robust anamnestic response against HAV. In 2005, public health authorities in Argentina began a universal immunization programme in 12-month-old babies. Because of economic constraints, a decision was made to use a single-dose vaccine schedule. This decision was based on a prediction that an encounter of vaccinees with wild-type HAV after a single dose would result in an anamnestic immune response. The original incidence of reported HAV in Argentina fluctuated between 70.5 and 173.8 cases per 100 000 between 1995 and 2004. So far the results of this strategy have been excellent. At a vaccination coverage of 95% in 2006, incidence of symptomatic viral hepatitis A dropped sharply in 2007 to around 10 cases per 100 000 in all age groups, representing a more than 80% decrease in incidence. The experience gained in Argentina, using a single vaccine dose strategy, is gaining momentum worldwide. Consequently, the short- and intermediate-term effectiveness of such a policy, using a formaldehyde-inactivated or live attenuated vaccine has been documented in Nicaragua, Korea, China, and India, including persistence of vaccine-acquired immune memory against HAV. It remains to be seen, however, whether a single-dose immunization policy will indeed provide long-term protection against HAV or whether a booster dose will after all be required, as predicted by some. In view of the high immunogenicity of HAV vaccines, and given the rapid impact already observed in Argentina, the probability for acquiring natural infection in a immunized population, even with a single dose, is quite low.

4.3.5 Hepatitis A outbreaks and vaccine supply

Between June 2016 and July 2017, 16 European countries reported 1500 cases of confirmed acute HAV infection and 2660 cases of probable or suspected infection. Outbreaks of hepatitis A in MSM have been documented in several countries both within and outside Europe. An outbreak also occurred among homeless persons in the USA. In parallel, between 2016 and 2017, a shortage in supply of inactivated HAV vaccine occurred in Europe and the USA, apparently as a result of manufacturing issues and increase in demand. Consequently, public health authorities in the European Union and the USA had to redefine priorities regarding indication for pre- and post-exposure prophylaxis. Several options were considered and some implemented, including pre-vaccination screening for anti-HAV(IgG) in MSM and homeless persons, use of a paediatric HAV formulation for immunization of adults, vaccination with a single-dose strategy, and redefining the risk for travellers to previously-reported endemic HAV regions with improving sanitary and socioeconomic conditions. The follow-up to the impact of these measures is pending.

5. Safety of hepatitis A vaccines

On the basis of the cumulative experience gained from using hundreds of million doses over the past 20 years, the overall safety profile of all formaldehyde-inactivated hepatitis A vaccines administered to children and adults has been excellent, irrespective of manufacturer \(^{55,70,187,220,252−257}\). The following information is quoted from a review by the United States Centers for Disease Control and Prevention (CDC) \(^{55}\):

**Reactogenicity:** Local reactions, including soreness or tenderness at injection site, were reported in pre-licensure clinical trials in 56\% (N=50 000) and 53\% (N=10 000) of adult recipients of HAVRIX® and VAQTA® respectively, while in children these figures were at a range of 15\% and 17\%. Headaches were reported in 14\% to 16\% of adults for both vaccines respectively, and in 4\% of children receiving HAVRIX® in whom ~8\% had feeding problems.

Mild injection site reactions have been reported with all inactivated hepatitis A vaccines. Symptoms are transient, more commonly reported in adults, and usually occur following the first dose. The rate of injection site reactions varies depending on the specific study. The most frequently reported local adverse events have included injection site soreness (14−27\% in children, up to 43−56\% in adults) and induration at the injection site (4\%) with lower rates of injection site erythema and pain noted after booster doses in 9\% of children and up to 24\% of adults.

**Systemic adverse events:** Mild systemic adverse events have been reported after all inactivated hepatitis A vaccines and, like local reactions, may be less frequent after booster doses. Symptoms have included headache (4\% in children, up to 16\% in adults), malaise (7\%), anorexia, feeding problems (8\%) and fatigue, fever, diarrhoea and vomiting occurring in less than 5\% of vaccine recipients. Symptoms usually resolved within 48 hours.\(^1\)

**Serious Adverse Events (SAE):** An estimated 1.3 million persons in Asia and Europe were vaccinated with HAVRIX® before the vaccine’s licensure in the United States in 1995. Reports of serious adverse events received by the vaccine manufacturer, included anaphylaxis, Guillain-Barré syndrome, brachial plexus neuropathy, transverse myelitis, multiple sclerosis, encephalopathy and erythema multiforme. The majority of these events occurred among adults, and approximately one third occurred among persons concurrently receiving other vaccines. For serious adverse events for which background incidence data can be estimated (e.g. Guillain-Barré syndrome and brachial plexus neuropathy), rates for vaccine recipients were no higher than would be expected for an unvaccinated population.

No vaccine-related serious adverse events were reported for approximately 40,000 children who were administered the 360EL.U. dose of HAVRIX® in the protective efficacy study (26). In a post-licensure study of 11,417 children and 25,023 adults who were administered VAQTA®, no serious adverse events occurred that were considered to be associated with administration of vaccine. A published post-licensure evaluation of safety among 2000 child and adult recipients identified no serious adverse events associated with VAQTA® 257.

According to information received from the China Centers for Disease Control, between 1992–2007, 60 million doses of mainly live attenuated HAV vaccines were administered in China. Since 2005, 8 million doses are distributed annually to 18-month-old toddlers and older children. With respect to the Chinese inactivated and live attenuated hepatitis A vaccines, experience during clinical trials and through passive surveillance did not identify any substantial safety issues 77. It will be however essential to conduct rigorous high-quality postmarketing surveillance in selected communities to measure and monitor safety and adverse reactions. Studies of children vaccinated with live vaccines have shown shedding of the vaccine virus and possibly secondary, albeit “silent” infection among contacts. Thus, post-marketing surveillance is essential and may provide a context in which to conduct specific studies to examine the outcome of secondary infection and virus circulation if it occurs. In view of the volume of use of live hepatitis A vaccines in China and their potential usefulness in other countries, carefully collected and validated data on safety and efficacy will be valuable. Data of particular interest will be follow-up of molecular markers of attenuation, the genetic stability of attenuation markers after human passage, as well as further follow-up and information on clinical safety and efficacy to be demonstrated in well-conducted and sufficiently large clinical trials.8

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5.1 Monovalent hepatitis A vaccine

No severe adverse events have been causally linked to hepatitis A vaccines. In pre-licensure clinical studies involving more than 60,000 persons vaccinated, no serious adverse reactions were definitively attributed to hepatitis A vaccine. Post-licensure AEFI reports after vaccination of an estimated 1.3 million persons included anaphylaxis, Guillain-Barré syndrome, brachial plexus neuropathy, transverse myelitis, multiple sclerosis, and erythema multiforme but none of those events could be conclusively linked to vaccine administration. Most of these events occurred among adults, and approximately one third have occurred among persons concurrently receiving other vaccines. For adverse events for which background incidence data are available (e.g. Guillain-Barré syndrome and brachial plexus neuropathy) the rates among vaccine recipients are not higher than would be expected for an unvaccinated population.
6. Conclusions

After almost two decades since hepatitis A vaccines first became available, it can be stated without reservation that these vaccines are among the most immunogenic, safe and well-tolerated vaccines ever produced. Two doses of a hepatitis A vaccine will generate a long-lasting protective cellular and humoral immune response in children and adults which is expected to last for decades, and possibly for a lifetime in immune-competent recipients. Short-term and intermediate-term protective immunity against HAV has also been documented following injection of a single vaccine dose. In view of the many countries which are currently in transition from high to intermediate endemicity, it can be expected that large cohorts of young adults and children worldwide will remain susceptible to HAV infection transmitted via unsafe food products, travel or person-to-person contact. Public health agencies in such countries will have to strengthen surveillance and reassess the need for universal vaccination depending, among other factors, on the disease burden, available resources and health priorities. Meanwhile, duration of immune memory against HAV in recipients of HAV vaccines should be followed with special emphasis on vaccinees who received a single-dose injection (using live attenuated or inactivated HAV vaccines) and those who are immunocompromised and at risk.

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