Background document for the SAGE April 2022 session on Hepatitis A vaccines

prepared by the SAGE working group on hepatitis A

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Introduction

SAGE secretariat in agreement with SAGE decided to establish in August 2020 a Working Group to prepare a revision of the 2012 Hepatitis A Vaccine Position Paper and examine, in particular, the evidence generated by the one dose use.

The composition of the Working Group, based on an open call for applicants, is the following:

SAGE Members

- Rakesh Aggarwal (Chair of the working group) Jawaharlal Institute of Postgraduate Medical Education and Research, India.
- Shabir Mahdi, University of the Witwatersrand, South Africa

Experts

- Zhijie An, Chinese Center for Disease Control and Prevention, China
- Fuqiang Cui, Peking University, China
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- Jorge Enrique Gonzalez, National Administration for Laboratories and Institutes of Health, Argentina
- Sema Mandal, Public Health England, UK
- Kassiani Mellou, Hellenic Public Health Organization, Greece
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The secretariat included: Olufunmilayo Lesi, Melanie Marti, Shalini Desai, Christoph Steffen (WHO immunization and hepatitis programmes in WHO Headquarters), and colleagues from WHO Regional Offices, Julien Kabore (AFRO), Alba Vilajeliu (PAHO/AMRO) and Tigran Avagyan (WPRO).

The working group met between Sept. 2020 and April 2022 via 16 teleconferences. An external systematic review has been prepared by external contractors, Nick Walsh and Johanna Torres, and support of Stephanie Curtis, to complement the 2012 review with the latest evidence available.

Since the publication of the first WHO hepatitis A vaccine position paper in 2000, and the updated paper in 2012, there have been changes in the epidemiological features of hepatitis A virus (HAV) infection in several countries, increased supply of hepatitis A vaccines, and new evidence on their public health benefits and their potential for long-term protection.

The updated systematic evidence review has focussed specifically on longer term follow up studies (3 to 7 years and > 7 year follow up) including efficacy, effectiveness and safety data of multidose and single dose regimens of inactivated and live attenuated hepatitis A vaccines in children or adults vaccinated during childhood. In addition, population impact, cost effectiveness and economic impact and outcomes of mathematical modelling were assessed.

The evidence generated from the 2012 systematic review which also included adults, and examined short term efficacy, effectiveness, and safety data as well as studies on post exposure prophylaxis has also been considered in this update.

1 Epidemiology of hepatitis A virus infection

Hepatitis A virus (HAV), an RNA virus, causes inflammatory liver disease that may progress to fulminant liver failure. HAV is transmitted primarily via the faecal/oral route through ingestion of contaminated food and water, or through direct contact with an infectious person, for example, contact with a case within a household. The incidence of hepatitis A correlates with socioeconomic indicators, and rates of HAV infection decrease with increasing income and with access to clean water and adequate sanitation.*(1)* There are two main sources of information used to estimate the disease burden of HAV infection: (i) serological surveys estimating the prevalence of past infections, and (ii) reporting systems estimating the morbidity or mortality from acute hepatitis A disease.*(2)* In line with the classification used in in the 2012 Hepatitis A Vaccine Position Paper *(3)*, levels of endemicity have been classified based on seroprevalence 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); and very low (<50% by age 30 years).

Serological prevalence surveys are based on detection of anti-HAV immunoglobulin G (IgG) antibodies. Estimating the seroprevalence by age enables indirect measurement of age-specific incidence rates of infection and is the best way to describe the hepatitis A epidemiological situation through the midpoint of population immunity (AMPI) in a country.*(4)* The seroprevalence by age gives a measurement of the susceptibility of each age group to new infections and is useful to understand the concept of transition, i.e. shifting of risk of infection to older age groups that have not been infected in childhood, and who are at a higher risk of symptomatic and/or severe disease. To estimate the national burden of disease associated with hepatitis A, countries may choose to assess data from vital registration systems, acute disease surveillance, and health information systems capturing fulminant disease and/or causes of liver transplantation. Such information is important to identify individuals and groups at high risk for the disease, requiring prophylactic measures.

In 2019, there were an estimated 159 million acute hepatitis A virus infections, resulting in 39 000 deaths and 2.3 million disability-adjusted life years *(5)*. The burden of disease in 2019 was not equally distributed worldwide. Overall, 66% of acute hepatitis A cases and 97% of hepatitis A deaths occurred in low-income and low-middle-income countries. In absolute numbers, South-East Asia Region of WHO had the greatest number of hepatitis A cases (42 million) and deaths (23 711; 60% of the total number of deaths). In terms of rates, hepatitis A disease incidence was the highest in the African Region (3 714 infections per 100 000 population per year) and hepatitis A-related mortality was the highest in South-East Asia (1.18 deaths per 100 000 population per year).

The Global Burden of Disease Study (GBDS) estimates that hepatitis A cases worldwide increased by around 4% between 2010 and 2019, while hepatitis deaths decreased by 40% in the same interval *(5)*.

Serological prevalence profiles vary geographically.*(1)* In most low-income regions, including sub-Saharan Africa and parts of South Asia, the prevalence of anti-HAV antibodies in the population may exceed 90% by the age of 10 years. In those areas, exposure to HAV usually occurs before the age of 5 years, when most HAV infections are asymptomatic. As a result of infection and consequent induction of lifelong immunity, there are few susceptible adolescents and adults, and hence little symptomatic disease. Outbreaks are rare in these regions. At the same time, in almost all low-income countries, there is now an urban middle-class subpopulation with adolescents and adults who have not been HAV-infected as children and are at a high risk of symptomatic HAV infection later in life.

In high-income regions (Western Europe, Australia, New Zealand, Canada, the United States, Japan, the Republic of Korea, and Singapore) the prevalence of anti-HAV antibody is very low (<50% are immune by age 30 years). In these regions, the high proportion of susceptible individuals among adults could theoretically allow transmission, but there is almost no circulation of the virus, except in particular risk groups, and the risk of acquiring HAV infection is low. HAV infections may occur in individuals or groups at particular high risk of HAV infection, such as unimmunized travellers to areas of high endemicity, men who have sex with men, injection drug users, occasionally in specific subpopulations and, of increasing importance, among the persons experiencing homelessness and persons who are incarcerated. However, foodborne outbreaks do occur, for example following ingestion of shellfish sourced from in sewage-polluted waters, or through contaminated fresh produce, such as vegetables or fruit. On rare occasions, mainly before appropriate donor screening and viral inactivation procedures were introduced, hepatitis A was associated with transfusion of blood and blood products *(6)*.

In most middle-income regions in Asia, Latin America, Eastern Europe, and the Middle East, surveys of anti-HAV antibodies in the population show a mix of intermediate and low prevalence. In these regions, where a substantial proportion of adolescents and adults are susceptible, HAV may circulate, often with regular community-wide outbreaks. HAV infection in adolescents and adults is associated with a higher rate of severe clinical manifestations. Thus, paradoxically, with the transition from high to intermediate endemicity, the average age at infection and hence the incidence of clinically significant hepatitis A increases.

For example, in 1988, during a major outbreak in Shanghai, China, more than 300 000 individuals developed symptomatic HAV infection within a short time period. Over 8 000 of them required hospitalization and more than 90% of those hospitalized were aged between 20 and 40 years.*(7)* In some countries in transition, such as the Republic of Korea,*(8)* Argentina,*(9)* and Brazil,*(10)* HAV infection has become a leading cause of fulminant hepatic failure (FHF). In India, HAV was shown to be associated with up to 50% of all cases of FHF in children. The populations in middle-income countries may benefit the most from large-scale HAV vaccination programmes *(11)*. Vaccine effectiveness in paediatric populations at risk of hepatitis A has been demonstrated in several geographic regions worldwide for two-dose *(12-16)* and single dose schedules.*(17-23)*.

2 Virus and pathogenesis

HAV is classified as a hepatovirus of the Picornaviridae family. It has a single-stranded, linear ribonucleic acid (RNA) genome. It is shed in faeces as naked non-enveloped virions but circulates in blood, cloaked in host membranes *(24)*. Quasi-enveloped HAV (eHAV) virions are released from infected cells non-lytically as small extracellular vesicles (EVs), the membranes of which completely envelope and protect the capsid from neutralizing antibodies *(25, 26)*. In terms of their size and density, these eHAV vesicles resemble ‘exosomes’, small EVs that mediate intercellular communication *(27)*.

Only a single serotype of HAV exists. The identification of several different HAV genotypes and sub-genotypes has significantly enhanced the ability to investigate hepatitis A outbreaks and define HAV transmission routes *(28, 29)*.

HAV is resistant to low pH and heat (60 ºC for 60 minutes) as well as to freezing temperatures. The virus can persist in faeces and soil for a prolonged period of time *(29)*.

Following ingestion, the eHAV may penetrate the gut mucosa, replicate in cells of the epithelial crypts, and reach the liver via the portal blood. HAV has a special tropism for hepatocytes, but is

non-cytopathic. HAV infection induces innate and adaptive immune response, which leads to an acute necro-inflammatory process in the liver, that normally resolves spontaneously without chronic sequelae *(24)*.

Since maximal faecal shedding generally precedes the onset of disease, HAV replication by itself does not cause hepatocellular injury. Early studies suggested that liver injury might result from a robust T cell response, as IFN-γ-producing, virus-specific, cytotoxic CD8+ T cells have been identified in peripheral blood and liver of infected humans *(30, 31)*.

Transmission of HAV is associated with extensive shedding of the virus in faeces, as naked virus, particularly towards the end of the incubation period. Extended viraemia roughly parallels, at a lower magnitude, the shedding of naked virus in the faeces *(29)*.

3 Clinical manifestations and etiological diagnosis

The incubation period of acute hepatitis A is usually14–28 (up to 50) days. The clinical outcome is strongly correlated with age: while young children usually have asymptomatic infection, older children and adults commonly experience symptomatic disease *(24, 32, 33)*.

The clinical manifestations are those of acute viral hepatitis, indistinguishable from hepatitis caused by other viruses. Symptoms typically include malaise, fatigue, anorexia, vomiting, abdominal discomfort, diarrhoea and less commonly, fever, headaches, arthralgia and myalgia. Elevated levels of liver enzymes, the appearance of dark urine and sometimes clay-coloured stools and jaundice are characteristic manifestations of acute viral hepatitis.

Ultimately, hepatitis A resolves completely in >99% of the cases, although relapse of symptoms has been reported in 3%–20% of clinical cases *(34, 35)*. In contrast to hepatitis B and C, hepatitis A does not cause chronic liver disease. The estimated case-fatality ratio of hepatitis A varies with age and ranges from 0.1% among children <15 years of age to 0.3% among persons 15–39 years of age, and 2.1% among adults aged ≥40 years *(36)*. Fulminant hepatitis is rare but associated with high mortality. In Argentina, 0.4% of paediatric cases developed fulminant hepatitis, of which 60% were fatal *(37)*. Immunosuppressed patients and patients with chronic liver disease are at increased risk of developing severe or fulminant hepatitis.

Acute hepatitis A infection in pregnant women has been reported to be associated with an increased risk of preterm labour and gestational complications, such as an increase in incidence of birth of Small for Gestational Age infants *(38, 39)*.

Serological testing (IgM anti-HAV) is required to establish the etiological diagnosis of acute hepatitis A. IgM, IgG and IgA anti-HAV antibodies appear shortly before or concurrent with the onset of symptoms *(40)*. Anti-HAV IgM antibodies are detectable in both symptomatic and asymptomatic patients; in symptomatic patients, theseantibodies appear within 5–10 days of symptom onset, or at the early phase of liver enzyme increase, and persist for about 4 months (range 30–420 days). IgG antibody titres rise later and then persist for a long period of time, i.e. for years after infection, or even life-long. Using nucleic acid amplification and sequencing techniques, HAV RNA can be detected in body fluids and faeces.

4 Hepatitis A vaccines

Following the successful propagation of HAV in cell culture in 1979, several hepatitis A vaccines have been developed. Two types of hepatitis A vaccines are currently used worldwide: (a) formaldehyde-inactivated vaccines produced in several countries which are the most commonly used globally, and (b) live attenuated vaccines, which are manufactured in China and are also available in several other countries *(40)*.

All hepatitis A vaccines contain antigens derived from inactivated or attenuated HAV strains grown in cell culture. The nucleotide and amino-acid sequences of these strains are approximately 95% identical.

Antibody levels ranging from 10–33 mIU/ml, using different assays, have been proposed as the threshold for protection from HAV infection in humans *(41)*. Most recent international practice uses either 10 or 20 mIU/mL as the seroprotection threshold *(40)*. However, clinical experience suggests that protection following vaccination may be present even if anti-HAV antibodies are not detectable using standard immunoassays *(42)*. A positive (qualitative) test for total anti-HAV antibodies is considered to signify immunity to hepatitis A *(40)*.

The 2012 vaccine position paper was based on a systematic review that provided a detailed evidence base on the efficacy of the hepatitis A vaccines. The 2021 systematic review and meta-analyses conducted as background for this paper did not identify any additional studies of efficacy in the period 2012 - 2021. Hence, effectiveness and long-term immunogenicity were the main outcomes of interest. Effectiveness was assessed by consideration of hepatitis A clinical disease incidence, as studies examining data on death, hospitalization or other clinical endpoints of interest were not identified. Immunogenicity was assessed through two endpoints: (i) seropositivity of anti-HAV total or IgG antibodies (mIU/ml) (with a threshold of antibodies titres defined by individual study) and (ii) geometric mean concentration of anti-HAV antibodies, measured through different points of time since immunization.

Single and two dose studies results were pooled and subdivided by follow-up duration (as 3-7 years or > 7 years) , as well as by type of vaccine (live attenuated vaccines or inactivated vaccines). No analysis was undertaken by vaccine brand.

The analysis found that hepatitis A vaccines are effective in preventing hepatitis A clinical disease and HAV infection, as well as on conferring long-term seroprotection, regardless of type of vaccine (live attenuated or inactivated). It was also found that two-dose schedules consistently result in higher mean GMCs over time, compared to single-dose schemes.

Based on WHO UNICEF joint report form (2020 data), around 20 countries have implemented universal childhood vaccination programmes across 4 WHO regions (AMR, AMR, EUR and WPR), and 8 countries mainly in the Americas have implemented 1 dose inactivated vaccine programmes.

4.1 Inactivated hepatitis A vaccines

4.1.1 Administration, manufacturers' stipulated schedules and storage of inactivated hepatitis A vaccines

Inactivated HAV vaccines are prepared by propagation of HAV in human fibroblasts, purification of virions from cell lysates and inactivation using formaldehyde. Most of the available inactivated vaccines are adjuvanted by adsorption to aluminium hydroxide. Inactivated hepatitis A vaccines

are currently available in single-dose presentations and most are formulated without preservative.

The biological activity of inactivated hepatitis A vaccines is measured either by an *in vivo* relative potency assay or by an *in vitro* immunochemical determination of antigen content with acceptance criteria validated against the *in vivo* test. For each vaccine, an acceptable unit specification is established based on levels shown to be efficacious in clinical trials. A WHO international reference vaccine was established in 1999. Vaccines developed before the international reference preparation became available, use a unit specification established based on their respective in-house reference, and therefore biological activity expressed in these units may not be comparable across vaccines. WHO has provided recommendations for production and quality control of inactivated hepatitis A vaccines *(43)*.

For children, several manufacturers provide a half-volume presentation of the vaccine with the same antigen concentration as the adult formulation. Inactivated hepatitis A vaccines should be refrigerated at 2–8 °C; the vaccines should not be frozen. When stored at the recommended temperature, the shelf-life for inactivated hepatitis A vaccines ranges between 24 and 36 months, as specified by the manufacturers. The main inactivated vaccines used at the global level are listed in the table 1 below.

Table 1: Main monovalent inactivated hepatitis A vaccines used on the global market

Trade Name	Vaccine Strain	Adjuvant	Paediatric Dose	Adult Dose	no. of doses according to label	Manufacturer	WHO Pre-qualified?
HAVRIX	HM-175	**Aluminum Hydroxide**	**720 EU** (12M-18Y)	**1440 EU** (≥ 19Y)	**2 (0, 6-12M**	**GlaxoSmithKline**	**Yes (2003)**
Healive	TZ-84	**Aluminum Hydroxide**	**250 U** (12M-15Y)	**500 U** (≥16Y)	**2 (0, 6-12M**	**Sinovac Biotech**	**Yes (2017)**
AVAXIM	GBM	**Aluminum Hydroxide**	**80 IU** (12M-15Y)	**160 IU** (≥ 16Y)	**2 (0, 6-36M)**	**Sanofi Pasteur**	**No**
VAQTA	CR-236	**Aluminum Hydroxide**	**25U** (12M-18Y)	**50 U** (≥ 19Y)	**2 (0-6-18M)**	**Merck Vaccines**	**No**
Weisariuian	Lv-8	**Aluminum Hydroxide**	**320 EU**	**640 EU**	**2**	**Inst Med Biology, Chinese Acad Med Sci**	**No**
Veraxim	YN-5	**Aluminum Hydroxide**	**800 EU**	**1600 EU**	**2**	**Shanghai Wison**	**No**
Aimmugen	KRM-003	**None**	**0.5 µg**	**0.5 µg**	**3 (0, 2-4W, 6M)**	**KMB Biologics, Inc.**	**No**
Algavac	LBA-86	**Aluminum Hydroxide**	**25 U**	**50 U**	**2 (0, 6-12M**	**Vector-BiAlgam**	**No**
EPAXAL*	RG-SB	**Virosome**	**24 U**	**24U**	**2**	**Crucell**	**No**

* Manufacturing of EPAXAL was discontinued in 2014. Note: Not comprehensive; vaccines may be marketed under other trade names.

Combined vaccines that include hepatitis A and B, or hepatitis A and typhoid have been developed, mainly intended for use in adult travellers *(44)*. All inactivated hepatitis A vaccines are interchangeable, including combinations containing hepatitis A vaccine *(45, 46)*, see table 2 and 3 below.

Table 2: Main combination vaccines inactivated hepatitis A – Typhoid vaccines used on the global market

Trade Name	Vaccine Strain	Formulation	Paediatric Dose	Adult Dose	no. of doses	Manufacturer	WHO Pre-qualified?

					according to label		
Hepatyrix	Hepatitis A (inactivated) and S, typhi polysaccharide adsorbed	**1440 EU (HM 175)**	**-**	**1 ml IM (15 y and above)**	**One or two***	**GlaxoSmithKline**	**No**
Vivaxim, ViATIM and Tyavax	Hepatitis A (inactivated) and S, typhi polysaccharide adsorbed	**160IU (GBM)**	**-**	**1 ml IM (16 y and above)**	**One or two***	**Sanofi Pasteur**	**No**

* May be administered 6-12 months after single monovalent Hepatitis A vaccine dose as a booster. May also be given as a primary dose for Hep A, followed by either administering a monovalent inactivated booster dose at 6-12 months or, if ongoing typhoid protection is needed, a second dose of the combination vaccine given at 36 months.

Table 3: Main combination vaccines inactivated hepatitis A – Hepatitis B vaccines used on the global market

Trade Name	Vaccine Strain	Adjuvant	Paediatric Dose (HepA component)	Adult Dose (HepA component)	no. of doses according to label	Manufacturer	WHO Pre-qualified?
Twinrix/ Ambirix	Hepatitis A (inactivated) and HBsAg (recombinant)	**Aluminum Hydroxide**	**360 EU** (12M-15Y)	**720 EU (HM 175)** (≥ 16Y)	**3 (0, 1M, 6M)**	**GlaxoSmith Kline**	**No**

Inactivated hepatitis A vaccines are licensed for use in persons ≥12 months of age. This reduces the potential of interference by pre-existing maternal antibodies, whether transferred through placenta or breast feeding, with the vaccine's activity *(47, 48)*. According to the manufacturers, a complete vaccination schedule consists of 2 doses administered into the deltoid muscle. The interval between the first (primary) dose and second (booster) dose is commonly 6–12 months; however, it is flexible and can be extended to 18–36 months, depending on the vaccine type *(40)*. Hepatitis A vaccine doses do not need to be repeated if the interval between doses is exceeded. Hepatitis A vaccines can be administered simultaneously with vaccines against diphtheria, tetanus, pertussis (DTP), polio (oral and inactivated), Haemophilus influenzae type b (Hib), measles, mumps, rubella, typhoid (oral and intramuscular), hepatitis B, cholera, Japanese encephalitis, rabies and yellow fever, without biologically significant interference in the immunogenicity, reactogenicity or safety of the individual vaccines *(40, 49, 50)*.

4.1.2 Immunogenicity, efficacy, and effectiveness of inactivated hepatitis A vaccines

4.1.2.1 Standard two-dose immunization

All inactivated hepatitis A vaccines approved by stringent regulatory authorities are highly immunogenic and generally produce comparable immune responses *(19, 51)*. The efficacy of these vaccines was first studied in the early 1990s in a large double-blind randomized controlled trial of children 1 to 16 years conducted in Thailand *(52)* in high-incidence communities, which demonstrated protective efficacy of 94% (95% CI: 79%–99%) after 2 doses; cumulative efficacy following the booster (third) dose at 12 months was 95% (95% CI: 82%–99%). Given such high efficacy, most recent studies have been limited to real-world effectiveness analyses.

The effectiveness of inactivated hepatitis A vaccines has been demonstrated in a wide range of single and two-dose studies in a variety of contexts. Standard two-dose studies have consistently

been shown to be highly effective in preventing new HAV infections and to result in strong, durable immune responses when anti-HAVAb titre is used as a proxy for immunity status *(53-65)*.

Approved vaccines are so effective that clinical trials with longer term follow-up (from 3 – 25 years post primary vaccine course) have failed to consistently demonstrate new cases of clinically apparent HAV infections among vaccinated individuals, regardless of vaccine type (live vs attenuated) or schedule (one vs 2 doses) and natural exposure to HAV by participants during follow-up. Indeed, while subclinical cases have been detected, it has been only through an acute marked elevation in anti-HAV antibody titres through routine clinical trial follow up.

The population-level impact of hepatitis A inactivated vaccines has now been widely demonstrated. The first studies were in areas of Native American and Alaska Native communities *(66, 67)*. Vaccination of the majority of children, and in some cases adolescents and young adults, resulted in a rapid decline in disease incidence. With ongoing routine vaccination of children, reductions in disease incidence in these communities have been sustained over the long term *(68-70)*.

In larger, more heterogeneous communities with lower but consistently elevated hepatitis A rates, accumulating evidence from a number of countries indicates that sustained routine hepatitis A vaccination of children with both one and 2 doses can markedly reduce hepatitis A incidence over time.

The impact on hepatitis incidence in two-dose studies of inactivated HAV vaccine in a variety of contexts (Australia, China, Israel, Panama and the United States) demonstrates a reduction in incidence in all age groups of 76% to 98% *(12-15, 71)*. The largest decrease was in a nation-wide cohort in Israel *(14)*, and the least was reported in Zhejiang province, China *(19, 21, 22)*. In studies that report incidence by age group, the largest decreases were pronounced in children <10 years old. Countries or regions with higher endemicity see larger reductions following universal vaccine introduction.

For grading of the scientific evidence for efficacy of inactivated hepatitis A vaccines (2 doses), see Grading Tables (Annexe 1).

Nevertheless, there are remaining limitations on data interpretation for impact analyses of both types of vaccines. Firstly, despite an ostensible decline observed in reported hepatitis A disease incidence estimates following routine vaccination, very few studies have rigorously either assessed or reported confounders, such as concomitant improvements in sanitation and associated infrastructure, as well as changes in accuracy and completeness of notifications in national surveillance systems that may have followed the introduction of the immunization. Secondly, data on age-specific vaccine coverage rates during the scale up of universal vaccination programmes are lacking in most reports. Finally, the impact of natural boosting through environmental exposure for vaccinated individuals is difficult to quantify. All three factors may have biased to some extent the estimates on effectiveness, impact and immunogenicity in some individual studies and thus limited the possibility to accurately estimate vaccine impact in the systematic review.

Despite such limitations, in key jurisdictions, impact of expanded HAV vaccine programming has been clearly visible. For example, in Argentina, Vizzotti et al. examined the occurrence of fulminant hepatic failure and liver transplantation cases notified from 2002 through to 2011, i.e. during and after the introduction of universal single-dose childhood vaccination in 2005. Hepatitis A had been the leading cause of fulminant hepatic failure and liver transplantation in children in the assessed pre vaccination period (between 2002 and 2004). However, in the post-vaccination period, not a single case of liver failure or transplantation was observed, demonstrating the impact

of vaccination on these critical outcomes *(72)*.

4.1.2.2 Single-dose immunization

Limited evidence regarding single dose immunization for hepatitis A was available at the time of preparation of the 2012 WHO position paper. Only two trials were considered, one from Nicaragua and the other from national use of a single-dose schedule of hepatitis A vaccine in Argentina *(53, 73)*. The SAGE concluded that national programmes may consider a single-dose schedule, although additional evidence of long-term immunogenicity was needed *(3, 74)*. Following this, there has been an expansion of single dose national programmes and further epidemiologic data are available to support the use of such programmes.

For grading of the scientific evidence for efficacy of inactivated hepatitis A vaccines (1 dose), see Grading Tables Annexe 3.

A 2012 review found that protective anti-HAV antibody levels after a single dose of inactivated hepatitis A vaccine can persist for almost 11 years, and its titre increases or reappears after booster vaccination among studies assessing long-term protection up to 10.67 years after a 1-dose vaccination *(75)*.

A Nicaraguan study among 105 children vaccinated in 2005 with a single dose of virosomal vaccine (Epaxal) identified no cases of clinically apparent disease and vaccine effectiveness of 98.3% (95% confidence interval, 87.9–99.8) at 7.5 years. Boosting with HAVRIX elicited an average 29.7-fold increase of anti-HAV levels *(61)*. Argentina includes a single-dose inactivated hepatitis A vaccine in their national immunization schedule at 12 months *(72)*. In that context, a long-term follow up study of 247 children vaccinated with a single dose inactivated HAV vaccine did not identify any clinically apparent HAV disease through 10 years *(54)*. Seroprotection at 10 years was 100%. Also, in Argentina, an additional follow-up of 1119 children at a mean of 9.7 years (range 9-11.3 years) reported that 87.6% individuals had anti-HAV IgG ≥ 10 mIU/mL. and anti-HAV GMC was 28.0 mIU/mL (95% CI: 26.8-29.3 mIU/mL) *(76)*.

The impact of single-dose hepatitis A inactivated vaccine programmes has been increasingly demonstrated across the globe including in Argentina, Brazil, Italy and Russia *(17, 18, 20, 23)*. The reported incidence of hepatitis A decreased in all age groups by 80%-99%. The smallest decrease was documented in Brazil, while the largest decrease in HAV incidence following a population-based programme occurred in Tyva province in Russia *(23)*.

4.1.2.3 Efficacy and effectiveness of post exposure prophylaxis

Post exposure prophylaxis by hepatitis A inactivated vaccine (one dose)

The effectiveness of post-exposure prophylaxis is the greatest when it is administered soon after exposure; thus, HAV vaccine should be administered as soon as possible, and within 2 weeks of exposure, to achieve the best possible protection against symptomatic infection.

High efficacy of post-exposure prophylaxis with inactivated hepatitis A vaccines is well documented. In 1991, a double-blind, placebo-controlled trial was conducted during a hepatitis A outbreak in upstate New York, USA *(77)*. This trial involved 1037 children 2–16 years of age, who received 1 dose of inactivated hepatitis A vaccine, or placebo. In the placebo group, 25 cases of confirmed hepatitis A occurred, whereas in the vaccine group, no new cases were identified from day 17 after vaccination. In Israel, a community-wide outbreak of hepatitis A in a socioeconomically deprived setting was completely interrupted within a few weeks following 1 dose of inactivated hepatitis A vaccine administered to >90% of the paediatric population *(33)*.

High efficacy of post-exposure prophylaxis with an inactivated HAV vaccine was also reported from Kazakhstan *(78)*, where 1090 household and day-care contacts (2–40 years of age) of index cases with acute hepatitis were randomized to receive hepatitis A vaccine or passive prophylaxis with immune globulin. Symptomatic infection with hepatitis A virus, occurred in 4.4% of vaccinated contacts and in 3.3% of contacts receiving immune globulin, (RR 1.35; 95% CI=0.70–2.67).

Response to HAV vaccine within 2 weeks diminishes with age. However, data are limited on the use of HAV vaccine for post-exposure prophylaxis among persons aged >40 years, particularly in discrete age groups *(79)*. A systematic review, including studies using inactivated vaccines (HAVRIX or VAQTA), found no articles that provided explicit estimates of efficacy or effectiveness of HAV vaccine among adults >40 years of age against disease endpoints *(80)*. However, ten articles included hepatitis A vaccine serologic data among persons aged >40 years *(80)*. One reanalysis of a randomized clinical trial included data stratified by age groups and found seroconversion at 15 days post-vaccination of 74% in adults 40–49 years (n = 125; GMT of 26.09 mIU/mL), 54% in adults 50–59 years (n = 37; GMT of 12.80 mIU/mL), and 30% in adults ≥60 years (n = 10; GMT of 1.62 mIU/mL) *(81, 82)*. Other, mostly observational studies, also suggested lower post-HAV vaccination antibody titres and a longer time to seroconversion among persons >40 years compared to persons ≤40 years of age *(80)*. For grading of the scientific evidence for efficacy of inactivated hepatitis A vaccines in post-exposure prophylaxis (2012 systematic review), see Grading Tables Annexes 5 and 6.

Passive prophylaxis with immune globulin

Immune globulin (Ig) provides protection against hepatitis A through passive transfer of antibody *(40, 78)*. Prophylaxis is achieved within hours of injection and is 80%–90% effective when administered within 14 days of exposure. Based on a global study, Ig manufactured from plasma donors with declining herd immunity to HAV yielded low anti-HAV Ig potencies *(83)*. This prompted an increase in the dose of Ig in the U.S *(84)* to 0.1 ml/kg if protection was desired for up to 1 month and 0.2 ml/kg for up to 2 months.

The use of Ig worldwide is now declining because of insufficient concentrations of anti-HAV IgG in non-specific Ig preparations, the high cost of specific HAV IgG preparations, the limited duration of protection following passive IgG prophylaxis, and because hepatitis A vaccines induce rapid and long-lasting protection against HAV after the first dose *(77, 85)*. A randomized controlled trial showed no significant difference in protection against symptomatic and asymptomatic HAV infection when either an IgG preparation or a hepatitis A vaccine was administered to contacts of confirmed cases of hepatitis A aged ≤40 years within 14 days of exposure *(78)*. However, the response to vaccine may be diminished among older adults *(80)*. Ig in addition to vaccine may be considered for this population for post-exposure prophylaxis, when feasible.

For grading of the scientific evidence post exposure prophylaxis of HAV vaccines and Ig see Grading Tables Annexe 5 and 6.

4.1.3 Duration of protection of inactivated hepatitis A vaccines by dose schedule

4.1.3.1 Duration of protection for two- or-more dose schedules

Protection in multi-dose studies against clinically apparent infection persists for up to 25 years in adults who received inactivated vaccine as children with a three-dose schedule *(63)*. In this study,

mean GMC at 25 years was 91.5 mIU/mL among the 43 of the original 144 individuals that could be followed, with 81% having antibody titres ≥20mIU/mL. This schedule has been shown to be equivalent to the current two-dose schedule *(86)*. Long-term studies of the two dose schedules for 7.5 years (Israel) and 10–14 years (Argentina) showed 100% protection against clinical disease and seroprotection ranging between 97–100% *(54, 59, 60)*. A 15-year follow-up study of HAV vaccinated children of HAV Ab positive and negative mothers in Alaska found 100% seroprotection (defined as an anti-HAV antibodies titre ≥20 mIU/mL) for children of maternal anti-HAV-negative compared to 67% for children of maternal anti-HAV-positive, respectively. In adults, persistence of the vaccine-induced immune response following primary two-dose immunization with inactivated hepatitis A has been shown to persist for up to 15 years *(87)*. Anti-HAV seropositivity persisted until at least ages 20 years among three groups of Alaska Native children for whom a 2-dose inactivated HepA vaccination series was initiated at ages 6–21 months *(88)*.

Mathematical modelling and anti-HAV kinetic studies based on long term follow-up data in empiric paediatric studies suggests that detectable antibodies are estimated to persist for as much as 60 years for the two-dose schedules *(54, 89, 90)*. As protection following natural infection is lifelong, protection from the vaccine against clinically apparent disease may also be lifelong .

For grading of the scientific evidence for long term protection of inactivated hepatitis A vaccines (2 doses), see Grading Tables Annexe 7.

For Evidence to recommendation table comparing two doses schedule vs no vaccination, see Annexe 13.

4.1.3.2 Duration of protection for one-dose schedules

Studies of longevity of immune response for single-dose schedules have demonstrated persistence of seroprotection for up to 12 years for inactivated preparations *(54, 91)*. Persistent B and T cell immune memory has been demonstrated at 12 years for inactivated preparations *(92)* even when individuals have lost seroprotection over time. In a sub-analysis of a larger Argentinian study *(76)* of the children who had received a single-dose HAV vaccine 12 years before and were negative for seroprotection (mean GMC 0.7 mIU/mL), 96% reached seroprotection following a booster, and HAV-specific memory CD4+ and CD8+ T-cells were observed in 14/26 (54%) and 7/26 (26.9%) respectively, showing that the presence of memory T-cells was independent of the level or presence of detectable anti-HAV antibodies *(76)*. These results demonstrate the existence of long-term anamnestic immune response to primary single-dose vaccination with inactivated preparations.

Detectable antibodies are estimated to persist up to 30 years with single-dose schedules based on mathematical modelling and on anti-HAV kinetic studies *(54)*. Modelling data comparing single to two dose schedules of inactivated hepatitis A vaccine has confirmed the maintenance of high levels of seroprotection at 20 and 30 years postvaccination, irrespective of the dosing schedule and despite the continued linear decline in antibody level; natural boosting had limited impact conferring only an additional 5% protection *(54)*.

For grading of the scientific evidence for long term protection of inactivated hepatitis A vaccines comparing one dose versus multiple dose schedules, respectively 3–7-year follow-up and above 7 years follow up, see Grading tables Annexe 9 and Annexe 10.

For grading of the scientific evidence for long term protection comparison of inactivated hepatitis A vaccine (1 dose) vs multiple dose inactivated schedules, respectively 3-7 year and above 7 years

follow up, see Grading tables Annexe 11 and 12.

For Evidence to recommendation table comparing one and two doses schedule see Annexe 14.

4.1.4 Safety of inactivated hepatitis A vaccines

Based on the cumulative global experience gained from the use of several hundred million doses, the overall safety profile of all formaldehyde-inactivated hepatitis A vaccines administered to children (aged 1 to <15 years) and adults has been excellent, irrespective of schedule and manufacturer *(42, 93-95)*.

Large pre-licensure safety studies of two different inactivated hepatitis A vaccines found that among adult recipients, local reactions, including soreness or tenderness at injection site, were reported in 56% and 53%, respectively, whereas in children the respective rates were 15% and 17%. Headache was reported in 14%–16% of adults for both the vaccines, but rarely in children *(42)*.

No vaccine-related, serious adverse events were reported in approximately 40 000 children who participated in a study of safety and efficacy of inactivated hepatitis A vaccine *(52)*. Similarly, in two post-licensure studies, one with 11 273 children and 25 467 adults, and the other with about 2000 vaccinees in different age groups, no serious adverse events occurred that were considered to be associated with administration of the vaccine *(42, 94)*.

A 2012 systematic review *(96)* examined published literature on vaccine safety and adverse events in the period until 2011, and did not identify any adverse events of note.

Regarding more recent evidence, a phase IV, open-label, single-arm trial conducted by Shi et al *(97)* in 2018 examined the safety of an inactivated vaccine licensed in China since 2010 (Avaxim® 80U Paediatric) in a two-dose schedule administered 6 months apart to 355 healthy toddlers, children and adolescents up to 15 years of age. Endpoints were solicited injection site reactions, unsolicited reactions, systemic adverse events and serious adverse events, and maximum time of observation was 30 days after the second dose. Loss to follow-up was 6.5% at the end of that period. There were no serious adverse events. Solicited injection site reactions were present in 17.2% of infants and toddlers and 33.3% of adolescents, and the systematic reactions were observed in 23.1% and 25%, respectively. Unsolicited events occurred only in infants and toddlers, with a prevalence of 6.3%. These results confirmed safety and tolerability of this inactivated vaccine, similar to the prior studies with other vaccines.

For grading of the scientific evidence for safety of inactivated hepatitis A vaccines (2 doses), see Grading tables Annexe 1.

4.2 Live attenuated hepatitis A vaccine

4.2.1 Administration, manufacturers' stipulated schedules and storage of live-attenuated hepatitis A vaccines

Two live attenuated hepatitis A vaccines, based on the viral H2 strain and on the L-A-1-strain, have been licensed in China since 1992 for subcutaneous administration in children aged ≥18 months *(19)*. These live vaccines were attenuated through multiple cell culture passages and subsequently propagated in human diploid embryonic lung fibroblast cells. Their potency is established by tissue culture infective dose (TCID50) assessments. For children, the live attenuated vaccine is scheduled as a single dose of 0.5 ml volume, and 1.0 ml (containing no less than 6.50

lgCCID50 of live HAV) for adults. The dosage formulation was changed from liquid preparation to freeze-dried preparation in Chinese pharmacopeia in 2000 to extend the shelf-life. The freeze-dried live attenuated vaccine should be stored in refrigerator at 2℃-8℃. When stored at the recommended temperature, the shelf-life for live attenuated hepatitis A vaccines is 18-24 months.

Table *4* lists the main live attenuated hepatitis A vaccines used.

Table 4 Main live attenuated vaccines used globally

Trade Name	Attenuated HAV Strain	Formulation/ adjuvant	Paediatric Dose (18 mths - 15 y)	Adult Dose (Age ≥ 16 y)	no. of doses according to label	Manufacturer	WHO Pre-Qualified?
Weisairuiji	**H2**	**Lyophilized, no adjuvant**	**0.5 ml s.c**	**1.0 ml s.c.**	**one**	**Inst Medical Biology, Chinese Acad Medical Sciences**	**No**
HAVAC	**LA-1**	**Lyophilized, no adjuvant**	**1.0 ml s.c.**	**1.0 ml s.c.**	**one**	**Changchun Inst of Biological Products**	**No**

There is limited evidence on safety and immunogenicity from China that live-attenuated HAV can be administered simultaneously with other routine immunization vaccines, including DTP and MMR *(98, 99)*.

4.2.2 Immunogenicity, efficacy, and effectiveness of live-attenuated hepatitis A vaccines

Clinical trials in the 1990s, which were limited to the Chinese context, of the live-attenuated vaccine preparations have demonstrated high efficacy and effectiveness with persistent immunity*(100, 101)*. This was further demonstrated in a 4-year vaccine efficacy study of the H2-based vaccine conducted in children 1–15 years of age at 11 primary schools in Shaoxing County, China, in which no hepatitis A cases were reported during 18 102 cumulative person-years in the vaccination group, while in the control group, 495 cases occurred during 242 168 cumulative person-years (vaccine efficacy 100%). In a large-scale vaccination of children aged 1–15 years in Jiaojiang City, China, the presence of anti-HAV IgG antibodies was documented after 15 years in 72%–88% of the vaccinees *(102)* and was associated with a 32-fold reduction in reported HAV incidence, implying that in most cases, long-term protection against hepatitis A is achieved following 1 dose of this vaccine.

A systematic review in 2012 included 5 trials assessing the live attenuated vaccine (690 690 participants). Subgroup analyses confirmed the clinical effectiveness of live attenuated hepatitis A vaccines (RR 0.07, 95% CI 0.03 to 0.17) to prevent clinically apparent hepatitis A *(96)*.

The impact of mass vaccination strategies using live attenuated vaccines has been demonstrated in several large population impact studies in China, ranging from a 50% to a 84% reduction in all-age hepatitis incidence between before and after universal vaccination with a single dose live attenuated schedule *(19, 21, 22)*.

A national-level analysis by provinces that used single dose live attenuated hepatitis A vaccine at 18 months age (115 million doses administered) or inactivated vaccine at 18 and 24 month age (16 million doses administered) found that coverage in this period increased from 82.4% to 98.4%, while annual reported HAV cases in the national notification system decreased from 7489 in 2007

(4 576 in 2008) to 237 in 2018 – an overall 96.8% decline.*(103)* In those provinces only using the live attenuated preparation, the overall pre-vaccination incidence of hepatitis A was over 6.0/100,000. Shortly after initiation of the Hepatitis A immunization programme in 2008, the incidence declined sharply from 7.5/100 000 in 2004 to 1.7/100 000 in 2016, indicating a 78.0% decline. Since 2012, the incidence has remained stable and declined below 2.0/100 000. Henan province, China, expanded HAV immunization in 2008 using a live attenuated vaccine preparation, demonstrating a 94.8% decrease in case incidence to 2018, which was particularly pronounced among adolescents (98.2%). Considering all HAV case reports the proportion of hepatitis A cases in patients younger than 10 years decreased from 41.6% in 2012 to 3.8% in 2018, with a parallel shift in the majority of new cases occurring among those >40 years (69.2%).

For grading of the scientific evidence for efficacy of live attenuated hepatitis A vaccines, see Grading Tables Annexe 2.

4.2.3 Duration of protection of live-attenuated hepatitis A vaccines

Studies of longevity of immune responses following live attenuated vaccines have shown at least 15-17 years of protection, and demonstrated preserved immune memory at that time point *(104, 105)*. A 5-year follow up study in India showed that single dose of a live attenuated vaccine (Biovac-A) was well tolerated and provided long-term immunity in healthy children *(106)*. This was confirmed by another follow-up study demonstrating no cases of clinically apparent disease at 10 and 15 years after administration of Biovac-A in an endemic area *(104)*. Seroprotection in this latter study of 98 individuals followed at 15 years was 95.9% with a mean GMC of 79.6mIU/mL in those with seroprotection. The seroprotection rate was reduced to 86.2% when the 11 subjects who were boosted because of low antibodies titres (<20mIU/ml) were also included in the denominator. A 17-year follow up of 47 children administered (Pukang Biotechnological Co. Hanzhou, China) demonstrated seroprotection of 62% (titre ≥20mIU/mL) with no cases of undetectable titres. GMCs of anti-HAV IgG were 64.8 mIU/mL and 7.6 mIU/mL respectively in the anti-HAV seropositive and seronegative groups. However, persistent B and T cell immune memory were demonstrated in 94% of the 31 individuals receiving a booster at 17 years post primary vaccination, including 13 seronegative at this time point *(105)*.

For grading of the scientific evidence for long term protection of live-attenuated hepatitis A vaccines, see Grading tables Annexe 8.

For grading of the scientific evidence for long term protection comparison of live-attenuated hepatitis A vaccine (1 dose) vs multiple dose inactivated schedules respectively 3-7 year and above 7 years follow up see Grading tables Annexe 11 and 12.

4.2.4 Safety of live attenuated hepatitis A vaccines

Experience during clinical trials and through passive surveillance did not identify any substantial safety concerns related to the Chinese live attenuated hepatitis A vaccines *(40, 101)*. However, as with most other live attenuated vaccines, these vaccines are not recommended for use in pregnant women and in immunocompromised patients.

Although the H2 vaccine strain is known to be shed in the stools of vaccinees, serological studies of non-vaccinated classmates during the school-based clinical trials in China showed no case of seroconversion as a consequence of person-to-person H2 strain transmission *(101)*.

A 2012 systematic review *(96)* examined published literature on vaccine safety and adverse events

in the period until 2011, and did not identify any adverse events of note, although data from live vaccines was limited.

For grading of the scientific evidence for safety of live attenuated hepatitis A vaccines, see Grading tables Annexe 2.

More recent evidence stems from a large review in China evaluating safety of both inactivated (I-HepA) and live attenuated (L-HepA) hepatitis A vaccines licensed in China for healthy children above 14 years old, based on data from a nationwide surveillance system. The annual incidence of adverse events following immunization (AEFI) was 0.5/100 000 for both vaccines. The most common serious AEFIs were anaphylactic shock and febrile convulsion. Non-serious AEFI were reported with incidence estimates of 10.1/100 000 doses for I-HepA and 8.5/100 000 doses for L-HepA. There were no meaningful differences regarding safety between the inactivated and live vaccines *(22)*. In a phase IV multi-centre study in India among 343 healthy children aged 1 to 12 years old, who were followed-up for 5 years after immunization with a single-dose of a live attenuated vaccine, no adverse event was registered over the observation period, demonstrating that the vaccine was safe for children and adolescents *(106)*.

4.3 Groups at high risk of hepatitis A infection

High-risk groups for hepatitis A infection include those who are (a) at increased risk of HAV exposure, as well as those (b) at increased risk of serious clinical outcomes after acquiring the infection. Some countries and institutions have recommended targeted immunization of such high-risk groups, including (a) travellers from low-endemic countries to areas of intermediate or high endemicity, men who have sex with men (MSM), at-risk occupational groups, people who inject drugs, people who experience homelessness, migrants, refugees, incarcerated persons and (b) patients with chronic liver disease or people living with HIV.

HAV outbreaks have been increasingly reported among MSM across Europe, and North America *(107-109)*. A large outbreak in 2016-2017 led to the occurrence of cases in 17 EU countries, in Argentina, Brazil, Chile, Israel, Japan, Canada and USA *(110)*.

Among the people experiencing homelessness, surveillance data indicate increased severity and higher mortality. Since 2016, several hepatitis A outbreaks in multiple states have been reported in the USA among drug users and/or homeless people *(111)*.

Most of the reported foodborne hepatitis A outbreaks have been traced to infected food handlers, as a single infected food handler can transmit the virus to dozens or even hundreds of persons *(112, 113)*. Vaccination of food handlers to prevent common-source food-borne hepatitis A is recommended; however, practical constraints, including staff turnover, may limit its effectiveness *(114)*. The analysis of 2016-2019 data in the USA concluded that the risk for secondary infection from hepatitis A–infected food handlers to food establishment patrons during person-to-person community outbreaks is low (<1.0%). Therefore, vaccination of all food handlers would be ineffective at mitigating the risk for ongoing person-to-person outbreaks *(115)*.

In some countries, vaccination is recommended for displaced children from endemic areas after serological testing, while in other countries all refugee/migrant children are vaccinated without prior serological testing after their arrival. Cost-effectiveness studies on the different immunization strategies are needed.

4.3.1 Use of hepatitis A vaccines in immunocompromised individuals and the elderly

A literature review of 11 studies (921 patients) in immunocompromised individuals reported an

overall serological response rate of 37% at least one month after one vaccine dose, and 82% after two doses *(116)*. Immunosuppressed patients who have undergone organ or haematopoietic stem-cell transplant transplantation (and are receiving immunosuppressive drugs) have a blunted immune response to hepatitis A vaccines and may lose their protection over time *(117, 118)*. Such groups may need special attention, which is beyond the scope of this guidance document.

Vaccination of patients with chronic liver disease is recommended in several countries. Most individuals with compensated chronic liver disease who do not receive immunosuppressive therapy achieve similar seroprotection rates as those in healthy subjects. However, anti-HAV antibody levels following immunization are reduced proportional to the degree of liver failure *(119, 120)*.

A randomized double-blind controlled trial among HIV-infected showed that adult vaccinees with CD4 cell counts of <300 cells/mm3 had a seroconversion rate of 87%, as compared to 100% in subjects with CD4 cell counts of ≥300 cells/mm3 *(121)*.

Other studies have also showed that the protective antibody response is associated with a higher CD4/CD8 ratio and having received two doses of standard schedule (compared with patients receiving only one dose of the same schedule) *(122)*.

In HIV-positive individuals, who seroconvert, anti-HAV titres were lower by a factor of 10 as compared to those in HIV-seronegative vaccinees *(123)*. The factors associated with persistent seroprotection are virologic suppression at vaccination, maintained lower levels of HIV viremia, and absence of acute hepatitis C *(122)*. A study published in 2011 showed that most adults with well-controlled HIV infection had durable seropositive responses up to 6–10 years after HAV vaccination *(124)*. Given the lower initial antibody levels, the apparent waning of antibody levels and the increasing life expectancy of HIV-positive individuals, post-vaccination booster doses may be necessary to maintain anti-HAV levels. Still, further studies are needed on the effectiveness of booster HAV vaccination *(125)*. There is limited experience using HAV vaccination as post-exposure prophylaxis in HIV-positive individuals.

Finally, it is well established that severity of disease increases with increasing age. In a study, the first dose of an inactivated hepatitis A vaccine induced adequate antibody responses in 100% of young adults, but in only 65% of individuals aged ≥50 years. However, following the second dose, the corresponding figures were 100% and 97%, respectively *(126)*.

Clinical breakthrough infections have been reported in adult travellers (some elderly or HIV positive) after the priming dose *(61)* or after two doses in two subjects, who were immunocompromised with HIV infection *(127)* and acute myeloid leukaemia, *(128)* respectively.

4.4 Cost-effectiveness and economic impact

Population impact models for universal HAV vaccine programmes are complex, given wide contextual variations in age structures and epidemiological situations; this means that it may be challenging to draw overarching conclusions from these models.

Several health economic studies covering a wide range of contexts including Brazil, Indonesia, Mexico, Jordan, Tunisia and the United States were reviewed *(90, 129-138)*. Key themes in these studies include that universal, primary immunization programs have early and substantial epidemiological impact; that both single-dose and two-dose HAV vaccine schedules are effective at the population level, and that any projected difference between these schedules is determined by assumptions on waning immune protection; that herd immunity is a substantial contributor to

the overall impact of a universal HAV vaccine programme; that universal HAV vaccine programs are more impactful where endemicity is higher; and finally, pros and cons of committing the extra resources necessary to initiate a complete catch-up vaccine programme in the settings of low endemicity are not clear, and their initiation would require a country and context-specific investigation .

Specifically, the Mexican models *(130, 131)* suggest at the population level that universal two-dose strategies have a greater impact on the epidemiology of HAV infection, but only the single-dose strategy is cost-saving. Sensitivity analyses show the profound impact of assumptions on longevity of the immune protection. In the USA, one study examined the impact of a universal childhood vaccination programme (to coverage of 81%) and found that it would result in a substantial reduction in infections and hospital visits (i.e. morbidity and subsequently costs), but would prevent just 228 deaths *(132, 139)*. The study found that herd immunity contributed substantially to accelerating the impact of such a vaccine programme. Another study modelled the epidemiologic impact of population-based catch-up programme for HAV vaccination, and found that it did not have a marked impact, since 752 doses of vaccine would have to be administered to prevent one HAV case *(133)*. An analysis in Tunisia *(129)* reported that while the two-dose regimen appeared to have an epidemiological impact, the single-dose regimen (though with reduced impact) was more attractive because of budgetary reasons. The Jordanian model *(134)*, which indeed used a mathematical model similar to the vaccine study in the USA *(132)* demonstrated that the introduction of a universal vaccine program would have an almost immediate and substantial impact, with a reduction in the HAV incidence from 900 to <1 case/100 000 population over the first 5 years of the programme, thus dramatically changing the epidemiology of HAV in the country. In Indonesia, an assessment of the impact of vaccinating a full calendar year birth cohort on HAV disease in their lifetime showed a 40% further reduction in cases from the two-dose regimen (~453 000) compared to a single dose strategy (~322 000), but again with few additional deaths avoided. *(136)*. Finally, a model of the impact of universal HAV childhood vaccination (vs current policy of targeted vaccination) in Brazil *(135)* showed substantial reductions in morbidity and mortality (around 60%) as well as years of life lost to HAV. In addition, the impact was greater for northern than southern parts of Brazil (prevalence is higher in the former part of the country).

Cost effective and economic impact analyses reviewed included 9 studies examining universal childhood/adolescent hepatitis A vaccination strategies in a range of contexts and countries, including Brazil, Bulgaria, Indonesia, Mexico, Jordan and the United States.*(130-136, 140, 141)*. Methodological quality varied across these studies.

Single dose strategies are consistently more cost effective than 2 dose schedules, even when some reduced efficacy was factored into the single dose analysis. Key themes in economic analyses are that single-dose schedules were demonstrated to be cost saving in a number of cases, compared to two-dose schedules which were shown to be just cost effective. Universal vaccination was more effective than targeted or regional programmes. Higher endemicity, lower cost of vaccine and longer seroprotection assumptions resulted in improved cost effectiveness. Assumptions of coverage varied.

Our literature review also identified a systematic review on the cost-effectiveness of HAV vaccination in middle-income countries between 1998–2013. The review included a quality assessment of studies. *(137)*. It identified nine studies from six countries: Argentina (n=2), Brazil (n=1), Chile (n=2), China (n=1), Egypt (n=1) and Thailand (n=2). The authors suggested that their systematic review indicated that universal hepatitis A vaccination of infants, children and

adolescents in MICs is cost-effective in the intermediate-endemic countries and that most of the studies confirmed that hepatitis A vaccination was cost effective or even cost saving under certain conditions. In sensitivity analysis, the most influential parameters were vaccine price, medical costs, incidence of infection and discount rate. The authors concluded that given the relatively limited financial resources of many low-middle income countries, implementation of a single-dose vaccination could be considered.

While HAV vaccination was generally cost effective, the local context (HIC versus LMICs) had a substantial impact. In one analysis *(140)*, universal vaccination was cost-effective as compared to no vaccination; however, in the USA, the cost-effectiveness fell below the CE threshold of $100 000/QALY gained, whereas in Rio de Janeiro, Brazil it was around 0.5x GDP or highly cost effective. However, results varied across studies, since another analysis that used a dynamic transmission model which incorporated the impact of herd immunity *(132)* demonstrated that a universal paediatric hepatitis A immunization programme in the USA would be cost saving.

In Mexico, a study examined the impact of antibody waning on the cost-effectiveness of single-dose vs two-dose HAV vaccine regimens *(130)*. While assuming high vaccine efficacy initially, the group allowed for waning immunity after two doses at the rate of 0.12% per year for the first 25 years and 0.62% per year thereafter. For 1-schedule dose assumptions were 97% efficacy waning at the rate of 1.62% for 10 years, and then 2.62% thereafter. Based on these assumptions, near and intermediate term cost-effectiveness favoured single-dose regimens, while long-time horizons (50–75 years) showed the two-dose schedule to be relatively more cost effective.

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