The Immunological Basis for Immunization Series

Module 18: Hepatitis A

Immunization, Vaccines and Biologicals

World Health Organization

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WHO Library Cataloguing-in-Publication Data

The immunological basis for immunization series: module 18: hepatitis A.

(Immunological basis for immunization series ; module 18)

1.Hepatitis A - immunology. 2.Hepatovirus - immunology. 3.Hepatitis A vaccines - therapeutic use. 4.Immunization. I.World Health Organization. II.Series.

ISBN 978 92 4 150142 2 (NLM classification: WC 536)

The Department of Immunization, Vaccines and Biologicals thanks the donors whose unspecified financial support has made the production of this document possible.

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Printed in February 2011

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Printed by the WHO Document Production Services, Geneva, Switzerland

Contents

Abbreviations and acronyms ..... *v*
Preface ..... *vii*

1. The hepatitis A virus, the disease and the vaccine **1**
1.1 Hepatitis A virus *1*
1.2 Epidemiology of hepatitis A virus infection *2*
1.3 Acute viral hepatitis A — clinical manifestations *3*
1.4 Hepatitis A vaccines *4*

2. Immune response to "natural" wild-type HAV infection **8**
2.1 Humoral immune response in acute hepatitis A *8*
2.2 Cellular immune response in acute hepatitis A. *10*

3. Immune response to vaccination **11**
3.1 The humoral and cellular immune response to vaccination *11*
3.2 Immunogenicity of hepatitis A vaccines and immune memory *14*

4. Protection against hepatitis A **15**
4.1 Measurement of protection *15*
4.2 Passive prophylaxis with immune globulin *15*
4.3 Active immunization *16*
4.4 Determinants of the immune response to immunization *18*
4.5 Immunization strategies for protection against hepatitis A *21*

5. Safety of hepatitis A vaccines **25**

6. Future prospects of immunization against hepatitis A **27**

7. References **28**

Abbreviations and acronyms

ABLV	Australian bat lyssavirus
ACIP	Advisory Committee on Immunization Practices
ALT	alanine aminotransferase
BMI	body mass index
CDC	Centers for Disease Control (US)
cDNA	complementary DNA
DTaP	diphtheria, tetanus, acellular pertussis vaccine
EIA	enzyme-linked immunoassay
ELISA	enzyme-linked immunosorbent assay
EL.U	ELISA units
EPI	Expanded Programme on Immunization
GIVS	Global Immunization Vision and Strategy
GMC	geometric mean concentration
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
Hib	*Haemophilus influenzae* vaccine
HIV	human immune deficiency virus
HLA	histocompatibility leukocyte antigen
Ig	immunoglobulin
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-infecting dose
WHO	World Health Organization

Preface

This module is part of the series *The Immunological Basis for Immunization*, which was initially developed in 1993 as a set of eight modules focusing on the vaccines included in the Expanded Programme on Immunization (EPI)[1]. In addition to a general immunology module, each of the seven other modules covered one of the vaccines recommended as part of the EPI programme — diphtheria, measles, pertussis, polio, tetanus, tuberculosis and yellow fever. The modules have become some of the most widely used documents in the field of immunization.

With the development of the Global Immunization Vision and Strategy (GIVS) (2005–2015) (http://www.who.int/vaccines-documents/DocsPDF05/GIVS_Final_EN.pdf) and the expansion of immunization programmes in general, as well as the large accumulation of new knowledge since 1993, the decision was taken to update and extend this series.

The main purpose of the modules — which are published as separate disease/vaccine-specific modules — is to give immunization managers and vaccination professionals a brief and easily-understood overview of the scientific basis of vaccination, and also of the immunological basis for the World Health Organization (WHO) recommendations on vaccine use that, since 1998, have been published in the *Vaccine Position Papers* (http://www.who.int/immunization/documents/positionpapers_intro/en/index.html).

WHO would like to thank all the people who were involved in the development of the initial *Immunological Basis for Immunization* series, as well as those involved in its updating, and the development of new modules.

[1] This programme was established in 1974 with the main aim of providing immunization for children in developing countries.

1. The hepatitis A virus, the disease and the vaccine

1.1 Hepatitis A virus

The hepatitis A virus (HAV) has been infecting humans for centuries. The first distinction between HAV and non-HAV viruses involved in clinical hepatitis was originally made in the 1940s[1]. HAV was first identified in 1973 through electron microscopy[2]. Today, it is classified as hepatovirus of the *Picorna viridae* family. HAV is a 27–32 nm, non-enveloped, icosahedral positive single-stranded linear ribonucleic acid (RNA) virus with a ~7.5 kb genome[3, 4]. 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. HAV is resistant to low pH and heat (60° C for 60 minutes) as well as to freezing temperatures but becomes inactivated at 81° C for 10 minutes[5, 6]. The virus may persist in faeces and soil for a prolonged period[5, 7]. Infection usually occurs through ingestion of HAV contaminated food or fluid(s) which penetrate the gut mucosa where HAV apparently starts to replicate in intestinal epithelial crypt cells, reaching the liver via the portal blood. HAV has a special tropism for liver cells, but is non-cytopathic. HAV entry into hepatocytes is mediated most probably through a surrogate putative mucin-like glycoprotein receptor. Another hypothesis suggests that HAV enters the liver cell as a virus-IgA complex through the asialoglycoprotein receptor[8]. The virus replicates in the liver and is then shed into the bile and faeces and to a lesser degree into the bloodstream.

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. This large polyprotein is divided into three regions; the P_1 region encoding for the structural proteins VP_1, VP_2, and VP_3, and the P_2 and P_3 regions encoding for the non-structural proteins involved in viral replication. HAV RNA can be detected in body fluids and faeces, 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[3, 4]. There are seven known HAV genotypes, defined by sequence of the VP1/P2a junction region of a global collection of viruses. Genotypes are defined by a sequence variability of ~15% in these regions while subgenotypes differ by 7.0-7.5%. Four genotypes, namely I, II, III and VII, were identified in infected humans, while genotypes IV, V and VI have been found in infected non-human primates. All HAV genotypes share a common serotype, irrespective of their origin, and whether they derive from wild-type or attenuated strains. The identification of the various HAV genotypes and subgenotypes has significantly enhanced the ability to investigate the molecular epidemiology of hepatitis A outbreaks and particularly its transmission routes[3].

1.2 Epidemiology of hepatitis A virus infection

The number of reported cases of acute hepatitis A worldwide annually varies significantly, with an assumed underreporting rate of at least 80%[9-13]. Since most data on prevalence of HAV infection were derived more then a decade ago, the WHO has recently initiated a reassessment of the global burden of disease (GBD) for hepatitis A. As a first step, the WHO reviewed 637 eligible reports out of 2,932 papers pooled into 21 GBD regions as described in a systematic review (www.who.int/vaccines-documents/). The results of this review are now being evaluated in preparation of a model for a more accurate assessment of the GBD. Preliminary results suggest a global increase from 117 million infections in 1990 to 121 million infections in 2005. According to this assessment, an increase of incidence was observed in age groups 2-14 years and in >30 years old. Death increased from 30,283 in 1990 to 35,245 in 2005[14].

Traditionally, the global spread of HAV infection can be assessed through monitoring overall and age-specific prevalence which also enables indirect measurement of incidence rates. Overall prevalence has been classified into high (>50% of population), intermediate (15-50%) and low levels of endemicity (<15%), based on detection of anti-HAV immunoglobulin G (IgG) antibodies in selected populations[15]. High endemicity of HAV infection is found in countries with poor sanitary and socioeconomic conditions, where infection typically occurs before the age of five 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 segments of the middle-class population. In such countries, the paediatric population may escape HAV infection in early childhood. As a result, older children and young adults become susceptible to HAV infection during outbreaks or following person to person contact. HAV infection in these populations is associated with a higher rate of 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.

An epidemiological shift from high to intermediate endemicity of HAV is now being observed worldwide[16]. As a result, more adults in such areas of transition escape exposure to HAV in early childhood but become susceptible to infection during outbreaks. This transitional endemicity often results in a paradoxical increase in disease incidence rates and severity despite the presence of improved socioeconomic and sanitary conditions. An example for the potential consequences of such a shift in endemicity was clearly demonstrated during the massive outbreak of hepatitis A in Shanghai in 1988 where over 300,000 individuals contracted HAV infection within a short period[17].

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 the disease as recently reported in Korea[18]. Furthermore, in countries in transition, pockets of intermediate endemicity may exist within the same areas of high endemicity. Finally, despite the observed low attack rates of clinical hepatitis, especially in areas of high 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 Korea[19], Argentina[20, 21] and Brazil[22].

Nowadays, a new classification is emerging regarding endemicity of HAV worldwide based on reported incidence of confirmed acute HAV cases. Thus, endemicity to HAV may also be classified as very low, with an estimated incidence of 5 cases/10^5; low, 5–15 cases/10^5; intermediate, 15–150 cases/10^5 and high > 150 cases/10^5. HAV infection is mainly spread through the faecal/oral route as well as through contaminated water and food. Shellfish are able to ingest and concentrate HAV, and as a result become a reservoir for the spread of the virus. Transmission occurs mainly through common source outbreaks (i.e. food and water borne) as well as person-to-person contact. It is very rarely transmitted through blood products or iatrogenic medical procedures. Epidemiological risk groups include: populations of low socioeconomic status living under crowded conditions; household contacts of infected individuals; children visiting day-care centres and kindergartens; international travellers from countries with low endemicity to areas with intermediate or high endemicity; men who have sex with men (MSM); intravenous drug users; patients with chronic liver disease; food handlers; caretakers of non-human primates and patients with blood-clotting disorders. Despite the recognition of routes of transmission and defined risk groups, the source of HAV infection remains unidentified in >50% of cases[23].

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 incubation period of acute HAV usually lasts between 14–28 days and up to 50 days. Symptoms include malaise, fatigue, anorexia, vomiting, abdominal discomfort, diarrhoea and less commonly, fever, headaches, arthralgia and myalgia. Five clinical patterns are recognized: 1) asymptomatic HAV infection, often present in children under the age of 5 years; 2) symptomatic HAV infection with the appearance of dark urine and sometimes clay-coloured stools, often accompanied or followed by jaundice; 3) cholestatic hepatitis characterized by pruritus, prolonged elevation of alkaline phosphates, gamma glutamyl transpeptidase, bilirubinemia and weight loss; 4) relapsing hepatitis A infection manifested by reappearance of the clinical, biochemical and virologic markers of acute hepatitis A after initial resolution; 5) fulminant hepatitis, frequently resolved spontaneously but which occasionally may require liver transplantation.

Extra-hepatic manifestations of acute hepatitis A may occur, and include skin involvement, pancreatitis, neuritis, carditis, glomerulonephritis, pneumonitis, haemolysis (especially in patients with glucose-6 phosphate dehydrogenase syndrome) and aplastic anaemia. Other manifestations occur in a minority of patients including prolonged fatigue, right upper quadrant discomfort, fat intolerance and indigestion, weight loss, emotional instability and prolonged indirect bilirubinaemia. Acute HAV infection resolves spontaneously in > 99% of infected individuals. Relapsing hepatitis A with subsequent complete resolution has been reported in 3-20% of patients with clinical hepatitis[24]. Fulminant hepatitis is rare, with a wide range of estimated rates up to 1:10,000 or more in immunocompetent individuals. Yet recent reports from South-America and Korea have raised concern that the current incidence of fulminant hepatitis A may be rising[19, 21, 22]. Immune-suppressed patients, and patients with chronic liver disease, are at an increased risk of developing severe or fulminant hepatitis.

Mortality in fulminant hepatitis is rare. Following the massive outbreak of hepatitis A in Shanghai, there were 47 deaths among >300,000 infected patients. Fatality in HBsAg+ patients reached 0.05% as compared to 0.015% in non HBV carriers[17]. In Western countries reports suggest a case-fatality ratio in age groups <40 years of ~0.3%–0.6%. In age groups > 50 years and older, case-fatality may rise to 1.8-5.4%. (These data reported from the US and UK were obtained prior to introduction of liver transplantation for HAV associated liver failure) [25-31].

1.4 Hepatitis A vaccines

1.4.1 Monovalent and combined hepatitis A vaccines

Following the successful propagation of HAV in culture in 1979[32], several hepatitis A vaccines containing attenuated HAV have been developed, tested initially in non-human primates, and then in clinical trials in humans. Two types of HAV vaccines are currently used worldwide. a) Formaldehyde inactivated hepatitis A virus vaccines are used in most countries[33-37] b) Live attenuated vaccines are manufactured and mainly used in China[38-41] and sporadically in India in the private sector[42].

Formaldehyde inactivated vaccines include the monovalent HAVRIX®[33], VAQTA®[34], EPAXAL®[36], AVAXIM®[35], and two other inactivated vaccines which are available in China – TZ 84 HEALIVE® and Lv-8 Weisairuian[37, 43] (Table 1a and 1b).

Table 1a: Monovalent hepatitis A vaccines with attenuated, formaldehyde inactivated hepatitis A virus, available worldwide

Trade name	Attenuated HAV strain	Adjuvant	HAV antigen dose/injection		Manufacturers	Reference
			Paediatric	Adult		
HAVRIX®	HM-5	Alum hydroxide	720 EU	1440 EU	GSK	33
VAQTA®	CR-326	Alum hydroxide	25 U	50 U	MSD	34
AVAXIM®	GBM	Alum hydroxide	80 U	160 U	Sanofi Pasteur	35
EPAXAL®	RG-SB	Virosome	12 U	24 U	Crucell	36

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 flexible however and under certain circumstances can be extended to 18-36 months.

In China, two live attenuated hepatitis A vaccines are available containing the H2 and L-A-1 strains[39, 40, 41] using a single dose immunization schedule. Both these vaccines as well as the two formaldehyde inactivated vaccines, administered in two doses, were tested in clinical trials and integrated into EPI in 2008 (Table 1a and 1b) [39, 41].

In addition to monovalent HAV vaccines, formaldehyde inactivated combination vaccines have been developed in Europe including TWINRIX® and AMBIRIX® (hepatitis A and B)[44-49], VIATIM®/VIVAXIM® and HEPATYRIX® (hepatitis A and typhoid)[50].

Table 1b: Monovalent hepatitis A vaccines available in China*

Trade name	Attenuated HAV strain	Adjuvant	HAV antigen dose/injection		Manufacturers	Reference
			Paediatric	Adult		
Healive®	TZ84	Alum hydroxide	250 U	500 U	Sinovac Biotech Limited, Beijing	Inactivated;DDS**
Weisairuian	Lv-8	Alum hydroxide	320 EU	640 EU	Institute of Medical Biology of the Chinese Academy of Medical Sciences; Kunming	Inactivated DDS**
Weisairuiji	H2	None	6.5lg TCID50	6.5lg TCID50	Institute of Medical Biology of the Chinese Academy of Medical Sciences; Kunming	Live attenuated Freeze dried SDS***
NA	H2	None	6.5lg TCID50	6.5lg TCID50	Zhejiang Pukang Biotechnology Company Limited, Zhejiang Academy of Medical Sciences, Hangzhou	Live attenuated Freeze dried for SDS***
NA	L-A-1	None	6.5lg TCID50	6.5lg TCID50	Changchun Institute of Biological Products. & Changchun Changsheng Life Sciences Limited	Live attenuated Freeze dried for SDS***
HAVAC	L-A-1	None	6.5lg TCID50	6.5lg TCID50	Changchun Institute of Biological Products	Live attenuated Freeze dried for SDS***

* Information provided to the WHO office in Beijing by the China Centers for Disease Control and Prevention http://www.who.int/wer/2010/wer8530/en/index.html

** DDS-double dose schedule

***SD-single dose schedule

NA-Information not available

1.4.2 Attenuated hepatitis A virus strains

All HAV vaccines contain HAV antigens derived from cell cultures of attenuated hepatitis A virus strains (Table 1a and 1b). HAV has been adapted to grow in human and non-human 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 are associated with a number of mutations generated through serial passage of wild-type HAV. Cultured cells persistently infected with HAV produce relatively low amounts of viral antigen[3, 4]. 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 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[51]. 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 sequence of the virus are about 95% identical among 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

Biologic 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[3, 4, 52, 53]. The inactivated antigen immune reactivity and dose is 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 (EIA) 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 is 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, a second inactivated HAV vaccine manufactured in China, contains 320 and 640 EU for paediatric and adult formulation respectively (Table 1b). Two live freeze-dried HAV vaccines manufactured in China contain a 6.5^7 tissue culture-infecting dose ($TCID_{50}$) derived from the H_2 and LA1 attenuated HAV strains.

Hepatitis A virus vaccines should be refrigerated at 2–8 ºC, and freezing should be avoided since it will affect immunogenicity. The shelf-life for formaldehyde inactivated hepatitis A vaccines manufactured in the Western hemisphere ranges between 24-36 months, depending on manufacturer and when stored 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 does not differ from that reported for these vaccines when stored at 2–8 ºC[27, 54]. Finally, shipment of HAVRIX® and VAQTA® at room temperature (which should be avoided) does not significantly affect the immunogenicity of these vaccines[27].

2. Immune response to "natural" wild-type HAV infection

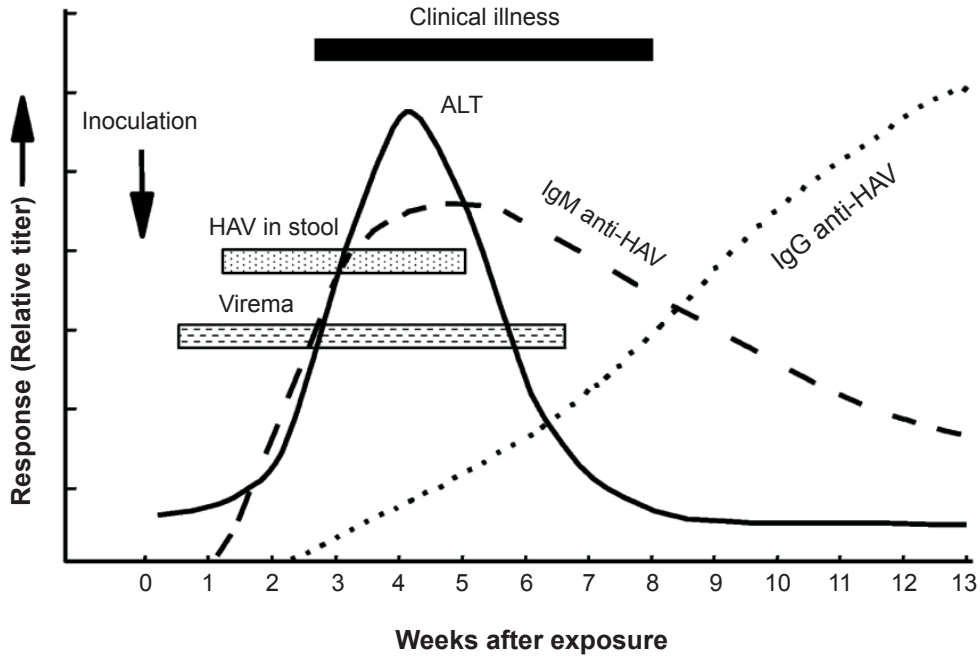
The mechanism of hepatic cell injury induced by HAV is not fully understood, but all available evidence suggests that it is immune mediated. The immune response to wild-type HAV infection involves the cellular, humoral and innate limbs of the immune system.

2.1 Humoral immune response in acute hepatitis A

HAV infection generates a humoral immune response directed mainly against structural HAV proteins. Diagnosis of acute hepatitis A is established through detection of IgM anti-HAV antibodies. Post-infection and post-vaccination immunity is established through detection of total anti-HAV antibodies[3, 52, 53]. Presence of total anti-HAV antibodies in the absence of IgM anti-HAV antibodies signifies immunity against HAV and exclusion of acute HAV infection. Commercially-available EIAs are used for detection of IgM anti-HAV antibodies (mainly 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[55]. 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 a period of about four months (range 30–420 days) (Figure 1)[24, 56, 57]. 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 six months, and occasionally even longer[24, 55, 56, 58]. False positive IgM anti-HAV might rarely be present >1 year post-infection or in patients with hyperglobulinaemia[53, 58].

Figure 1: Virologic, immunologic and biochemical events during the course of experimental hepatitis A virus infection in chimpanzees inoculated intravenously with human HAV, strain HLD2. ALT, alanine aminotransferase



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Total anti-HAV antibodies, often referred to as IgG anti-HAV, are usually detectable at the onset of symptoms, and their titre rises slowly parallel to the decrease in titre of anti-HAV IgM antibodies (Figure 1). 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[3, 59]. 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[60].

Qualitative assays for total anti-HAV antibodies are used for prevalence studies, and may be used for assessment of immunity pending and following vaccination. However, this method does not enable a distinction 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[52, 61]. The inability to distinguish clearly between these two situations led to an attempt to develop an antibody assay against non-structural proteins of the P_2 and P_3 regions of the HAV genome, for differentiation of the humoral immune response against replicating virus from the response to a killed-inactivated HAV vaccine[62, 63]. However at present, these tests remain a research tool only.

There are also 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 a research tool, include the radioimmunofocus inhibition assay (RIFIT) HAVARNA, and radioimmuno-precipitation assay[52].

The role of secretory immunity in hepatitis A remains unclear. Anti-HAV IgA antibodies have been detected in the saliva and faeces of experimentally infected animals and humans[62, 63].

2.2 Cellular immune response in acute hepatitis A.

Infection with HAV leads to a cellular immune response which is involved in the immunopathogenesis of HAV infection and the induction of hepatocyte injury[64-72]. Despite the proven tropism of HAV for liver cells, the virus is not cytopathic, and liver cell injury occurs through activation of HAV multispecific cytolytic T-cells[71]. Inflammatory cell infiltrates isolated from liver biopsies of patients with hepatitis A contain CD_8 positive T-cells which can specifically lyse hepatitis A virus-infected target cells in a histocompatibility leukocyte antigen (HLA) class I restricted manner[64]. Although there is only limited information on involvement of the innate immune system in HAV infection, there is evidence that secretion of interferon gamma by activated T-cells may facilitate the expression of HLA class 1 determinants on the surface of infected liver cells. Cytolytic T-cell epitopes residing on the structural protein of HAV may be involved in cytolysis of HAV infected hepatocytes[68, 69, 71]. Little is known about the role of T-helper cells in mounting an immune response to HAV. One putative CD_4 T-cell helper lymphocyte epitope was identified on the VP3 102–121 sequence[66]. 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[67]. Finally, impaired function of CD4+/CD25+ regulatory T-cells has been linked to the frequent resolution of acute hepatitis A with spontaneous recovery[70].

3. Immune response to vaccination

Formaldehyde inactivated hepatitis A vaccines are highly immunogenic and safe, providing rapid, protective immunity to hepatitis A after a complete vaccination schedule of two doses. 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 vaccine type. Based on clinical data and mathematical modelling, protection against HAV is estimated to last for decades, and possibly a lifetime[73-75].

3.1 The humoral and cellular immune response to vaccination

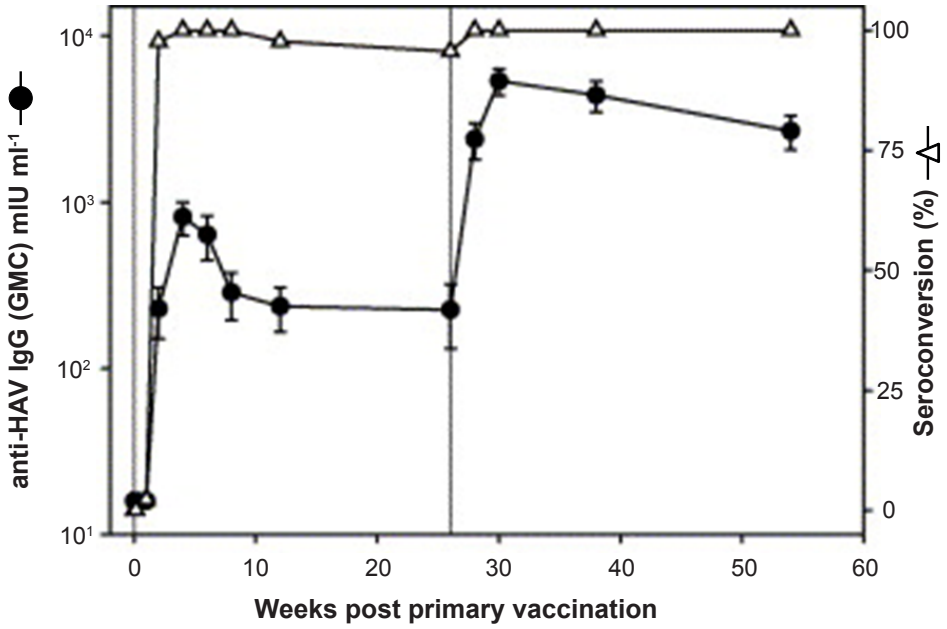
Infection with live, wild-type HAV involves virus replication in liver cells, and is associated with an active cellular and humoral immune response against the virus which induces hepatocellular injury[52, 64-70]. By contrast, viral replication does not occur after immunization with a killed HAV vaccine, and protection against HAV is primarily antibody-based[52, 76, 77]. 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[60, 76, 77]. 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 six years, and may be boosted to revive the immune memory[78-82].

3.1.1 The humoral response

Many studies have documented the rapid and effective humoral immune response to inactivated hepatitis A vaccines[35, 52, 73, 76-86].

One example of careful prospective evaluation of the immune response to HAV was reported in 45 healthy vaccinees (mean age 28.4 years, 23 females) who received 1440 EU of HAVRIX® at 0 and 6 months[78] (Figure 2a). 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®[76] in a small scale comparative randomized trial between HAVRIX® and VAQTA®[77] with AVAXIM®[35], EPAXAL®[36] and HEALIVE®[37].

Figure 2a: Seroconversion rate (open triangles) and serum anti-HAV IgG responses expressed as geometric mean concentration (filled circles) in 45 adults receiving 1440 EU HAVRIX® at 0 and 26 weeks (vertical reference lines). Error bars indicate 95% confidence interval



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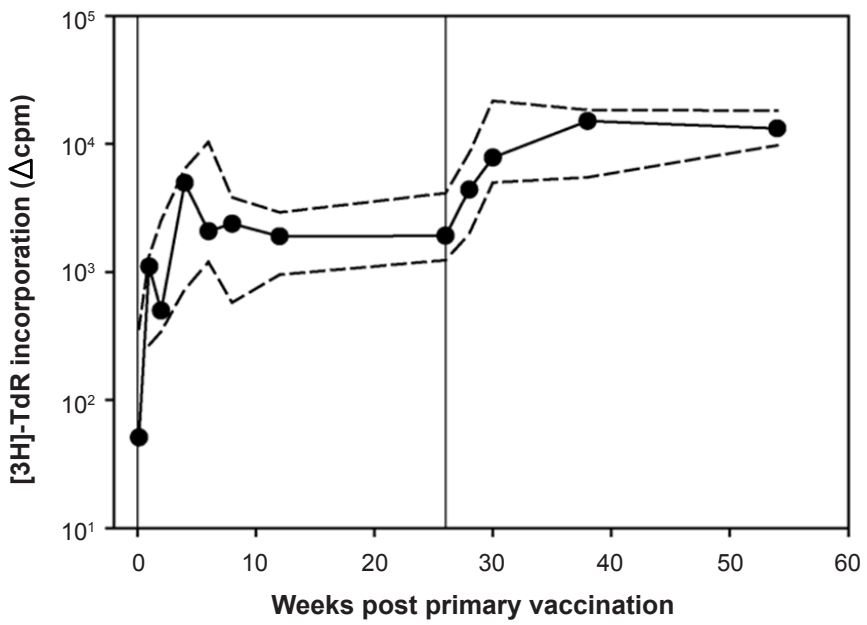
Information available in English on the humoral immune response to the live attenuated HAV vaccines manufactured in China is limited. In one study, one month after a single-dose injection, 81% of 102 vaccinees had detectable anti-HAV (IgG) antibodies (GMC 56 mIU/ml) rising to a peak of 95% (GMC 131 mIU/ml) 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)[41]. Other studies are available in the Chinese literature which have not been made available in English.

3.1.2 The cellular response

Few studies have examined the cellular response to inactivated HAV vaccines[78-82]. Interferon gamma secretion as evidence for an HAV-specific proliferative T-cell response was documented in three studies[78-80]. 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[78] (Figure 2b). A 60% decline of 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[82].

Recently, Garner-Spitzer and co-workers have documented a direct correlation between concentration of cytokines IL-2, interferon gamma and IL-10 with anti-HAV antibody levels before and after booster vaccination[81]. These results provide evidence for the role of cytokines and T-helper cells in induction of protective immunity against hepatitis A through vaccination. Information on the cellular immune response in recipients of the live-attenuated HAV vaccine is yet unavailable.

Figure 2b: 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 Δcpm, upper and lower lines represent the upper and lower quartile ranges



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In 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 and rising to 100% by week 4. A 60%–80% decline in T- and B-cell responses within 24 weeks is reversed through a booster dose at week 24, which leads to a significant rise in cellular and humoral immune reactivity.

3.2 Immunogenicity of hepatitis A vaccines and immune memory

The duration of protective immunity following wild-type HAV infection is thought to be lifelong[59, 75]. In a similar manner, primary immunization with the first dose of inactivated hepatitis A vaccines provides the basis for long-term immunity, probably for decades[11, 74, 80], while non-response to immunization is extremely rare[81]. Hepatitis A vaccines are 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 6-36 months for AVAXIM® 160U . The interval between the priming vaccination and the second dose is flexible. This is of particular importance for vaccinees that missed their second dose, for example, 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 2a).

In China, the live attenuated vaccine is used in a one dose schedule. Persistence of anti-HAV (IgG) antibodies was documented after 15 years in 72-88% of subjects immunized with the H2 live attenuated HAV vaccine[39].

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[83]. A specific gamma interferon-mediated T-cell immune response could be documented in human vaccinees within 1.5–6 years after the completion of the original vaccine series[80]. In this study, a booster dose was given to 36 subjects six 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®[61]. Similar results of long-term persistence were recorded in 98% of Argentinean children, 10 years after immunization with a two dose vaccine schedule[87]. 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[11, 84-86, 88]. 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[88]. Furthermore, administration of a booster dose up to 72 months after the first vaccine dose led to a 32–100 fold rise in anti-HAV IgG antibodies. Thus, there is to date, ample evidence to conclude that immune memory against hepatitis A, established through vaccination, will persist for decades in immunocompetent individuals. Finally, the excellent record of immunogenicity of hepatitis A vaccines in children has led to the evaluation of an experimental single-dose immunization strategy in the routine childhood immunization programme in Argentina[89].

4. Protection against hepatitis A

4.1 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 immuno assays[27]. 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 10–33mIU/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[52, 84]. Immunogenicity studies with VAQTA® have employed a modified radioimmunoassay with a minimal protective antibody level of ≥10 mIU/ml[76, 85]. Early studies with HAVRIX® set the threshold of protection between 20–33 mIU/ml using an enzyme-linked immunoassay[86]. This threshold has been cut to 15 mIU/ml in recent years[90] and recent assays use an even lower cut-off level of 10 mIU/ml.

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[76]. Therefore, anti-HAV IgM antibody assays cannot be used for reliable distinction between acute hepatitis A and anti-HAV response to vaccination.

4.2 Passive prophylaxis with immune globulin

Since the late 1940s administration of human immune serum globulin (Ig) has been considered as an efficient means for pre- and post-exposure prophylaxis against hepatitis A virus infection[60, 91, 92]. Immune globulin is prepared by Ethanol fractionation from pooled human plasma[93] 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, a declining prevalence of anti-HAV antibodies has been observed in plasma donors in the Western hemisphere[94, 95]. Immune globulin is administered through intramuscular injection. The protective efficacy of Ig against HAV infection is well documented[60, 96, 97]. 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[60].

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[76] and is often below the detection limit of 15–20mIU/ml of commercially available assays[98]. The mechanism of protection against hepatitis A conferred by Ig is not fully established, but most probably involves neutralization of circulating virus and possibly prevention of uptake of virus through the gut mucosa and by hepatocytes.

Administration of Ig is considered very safe, but is contraindicated in patients with IgA deficiency that may develop an anaphylactic reaction to Ig. Interference with live-attenuated vaccines such as measles, mumps, rubella (MMR) and varicella requires special caution. However co-administration of Ig with a hepatitis A vaccine may blunt the initial Quantitative anti-HAV antibody response after the first vaccine dose[99, 100]. 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 respond well to the booster dose given 6 months after the primary immunization. Finally, although administration of Ig for pre- and post-exposure short-term prophylaxis is highly efficacious, the use of immune globulin worldwide is now declining for a number of reasons: 1) non-specific Ig preparations increasingly fail to contain adequate amounts of anti-HAV (IgG)[94, 95, 101, 102]; 2) cost of specific HAV Ig preparation is high[101, 103]; 3) duration of Ig mediated protection against HAV infection lasts only several months as compared to Hepatitis A vaccines[60], 4) hepatitis A vaccines have already been shown to induce very rapid protection against HAV following the first out of two recommended doses[34, 76].

4.3 Active immunization

4.3.1 Efficacy

4.3.1.1 Pre-exposure prophylaxis

The efficacy of formaldehyde inactivated hepatitis A vaccines was demonstrated in two pivotal, double-blind randomized control trials conducted in Thailand[33] and the United States of America[34] in the early 1990s. In Thailand, HAVRIX® and a control hepatitis B vaccine were administered to 40 119 children between one and 16 years of age living in an area with high incidence of hepatitis A. HAVRIX® 360 EU/dose was administered intramuscularly at 0, 1 and 12 months. Protective clinical efficacy against clinical hepatitis A, (confirmed by a total anti-HAV titre above 20 mIU/ml), was demonstrated in 94% and 99% of seronegative vaccinees after the second and third dose respectively (95% CI=79%–99%)[33]. A similar, double-blind placebo-controlled trial was conducted in upstate New York in 1037 children, 2–16 years old, 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[34] (95% CI=87.3%)[34]*.

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[36]. 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 (protective efficacy after the first dose (by intention to treat analysis), 84.6%; 95% CI=54.7%–96.1%) and 100% by week 6.

* CI denotes a one-sided confidence interval, lower bound.

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®[104-106] .

4.3.1.2 Post-exposure prophylaxis

Clinical trials of hepatitis A vaccines in the early 1990s have provided unequivocal proof that pre-exposure prophylaxis of hepatitis A is effective and safe. Preliminary evidence obtained in a number of clinical trials suggested that post-exposure immunization against hepatitis A may also have similar effectiveness as 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[34]. A similar experience in Slovakia saw an outbreak of hepatitis A interrupted by vaccination with HAVRIX®[107]. Later, a limited controlled randomized trial in Italy revealed a 79% protective efficacy of post-exposure immunization in household contacts of acute hepatitis A cases (95% CI=7%–95%)[108]. 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[109]. Intervention in a major outbreak of hepatitis A in the Ukraine lead to a 41 fold drop in incidence of infection following a single dose injection of AVAXIM® [110].

A pivotal support for establishing the effectiveness of post exposure-prophylaxis with an inactivated HAV vaccine has recently been reported from Kazakhstan[97]. In this controlled clinical trial, 1090 household and day-care contacts (2–40 years old) 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 US Advisory Committee on Immunization Practices (ACIP), post-exposure immunization with an active HAV vaccine is now gaining an accelerated momentum worldwide[111]. 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 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[112].

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[103].

4.4 Determinants of the immune response to immunization

4.4.1 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[113, 114]. This may have special implications for older individuals who require protection against vaccine-preventable infections, i.e. international travellers from countries with very low and low endemicity for HAV, to countries with intermediate and high endemicity[115-117]. This population is at risk for contracting HAV infection which is associated with an increased morbidity, higher hospitalization rates and higher mortality, as compared to younger individuals below the age of 50 years[118]. Data on seroprotection rates in vaccinees older than 45 years are limited[115-119]; however, one uncontrolled study using EPAXAL® given in two doses, 12 months apart, revealed a blunted seroconversion rate of 65% after the first dose, in comparison to 100% in the younger control group. However, this difference in immunogenicity of the first dose was abolished by the booster dose leading to 97% and 100% seroprotection rates respectively[120]. Similar results were obtained in other studies[115, 116]. Thus, HAV susceptible vaccinees over the age of 45–50 years may require two vaccine doses, preferably four weeks apart, and prior to departure on travel to endemic areas.

Gender: As observed with other vaccines, anti-HAV antibody levels were reported to be higher in female vaccinees following a primary and booster injection, as compared to males[119]. However, in view of the excellent protective antibody levels induced by HAV vaccines, this difference in gender response has no practical consequences[119-121].

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)[117]. A booster dose is expected to minimize the effect of greater body weight 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[122].

4.4.2 Passively-acquired maternal anti-HAV antibodies

Concentration of anti-HAV antibody levels in babies born to seropositive mothers who acquired HAV through natural infection remain high during the first six months post-partum but decay significantly by 12 months of age[123]. 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 post-partum[123-127]. Although depression of the quantitative humoral immune response to vaccination may reach 30%–90% compared to naive newborns, this effect of passively-transferred maternal anti-HAV antibodies does not increase the risk for acquiring HAV infection. In such vaccinated babies, 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 booster vaccination given within 1–6 years of birth[123]. Furthermore, although paediatric HAV vaccines are licensed only for babies ≥12 months old, 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[123-126].

4.4.3 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[99, 100]. However, interference from passively-transferred anti-HAV antibodies with the humoral immune response to vaccination is of minor immunologic consequence, since it does not affect vaccine-induced protective immunity, and response to booster vaccination is excellent.

4.4.4 Immune suppression

4.4.4.1 Human immunodeficiency virus (HIV)

HIV type 1 and 2 infected patients, including intravenous drug users, men who have sex with men (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[128]. Human immunodeficiency virus patients with HAV co-infection developed protracted hepatitis A viraemia with slow clinical resolution compared to non-HIV patients with a normal CD_4 cell count[122, 129-134]. Vaccination against hepatitis A does not affect HIV viral load, can be given to patients who receive anti-viral treatment, is safe, and, in general, almost as immunogenic in HIV children and adults with a CD_4 count >300/mm^3 and HIV viral load <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[133]. However, antibody levels achieved after the first and second vaccine dose may be lower compared to healthy subjects, and sometimes a third vaccine dose is warranted (especially in patients with a high HIV viral load and a CD_4 count < 300 cells/mm) preferably after suppression of viraemia and restitution of the CD_4 cell count[134]. Seroprotection should be confirmed in such patients[122, 134]. Data on duration of protection following HAV immunization in HIV patients are still lacking.

4.4.4.2 Solid organ and stem-cell transplantation

In general, immune-suppressed patients who underwent organ transplantation have a blunted immune response to hepatitis A vaccines[135-138]. As shown for renal transplant patients, only 72% of 39 patients developed protective antibody levels[135]. Furthermore, kidney and liver transplant patients may lose their protection over time as shown also in haematopoeitic stem-cell transplant patients, and especially in those with graft versus host disease[135-138].

4.4.5 Chronic liver disease

The fatality rate of HAV infection in patients with chronic liver disease is 23–58 folds higher as compared to previously healthy infected adults as was shown in two studies in patients with HCV and HBV[139, 140]. Immunization against HAV of children and adults with compensated chronic liver disease who do not receive immunosuppressive therapy, is safe, and leads in general to similar seroprotection rates as in healthy subjects. However, anti-HAV antibody levels are blunted, and geometric mean concentration (GMC) levels are inversely proportional to degree of liver failure[141-145]. In one study conducted in 89 seronegative children between 1–16 years old, seroconversion rates following immunization with the first 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[144]. A booster dose given at month 6 led, however, to 97% and 100% seroconversion rates respectively, thus abolishing 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.

4.4.6 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 <18 years and in adults, inactivated HAV vaccines can be administered simultaneously with diphtheria, tetanus, acellular pertussis (DTaP), polio (oral and inactivated), *Haemophilus influenzae* (Hib), MMR typhoid (oral and intramuscular), hepatitis B, cholera, Japanese encephalitis, rabies and yellow fever vaccines[44, 106, 146-151]. It is recommended that injections should be given at different sites.

In addition, a number of combination vaccines that include hepatitis A and B (TWINRIX® and AMBIRIX®) [45-49] or hepatitis A and typhoid polysaccharide (HEPATRIX®, VIATIM® and VIVAXIM®) have been developed[50, 152-155.]

TWINRIX® contains 720EU of HAV antigen and 20µg of HBsAg per dose, is formulated with aluminium phosphate and aluminium hydroxide, and is given in three doses at 0, 1 and 6-month intervals in adults >18 years old. 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.

Combination vaccines against typhoid and hepatitis A are intended for adult travellers[152-155]. A combined vaccine VIATIM®)/VIVAXIM®) is given as a priming dose day 0 followed by a booster dose of hepatitis A vaccine at month 6 and up to three years. Protective antibody levels against hepatitis A at three years are comparable to those obtained following immunization with the monovalent vaccines with hypo-responsiveness reported for the typhoid vaccine[152].

4.4.7 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 was documented for VAQTA®, EPAXAL®, AVAXIM® and HAVRIX®, as well as for AVAXIM® and VAQTA® following combined immunization against HAV and typhoid [104, 105, 156, 157].

4.5 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 15 years[12, 27, 35, 73, 158, 159]. As more information became available on the extraordinary immunogenicity, effectiveness and safety of hepatitis A vaccines, immunization strategies have shifted from vaccination of individuals belonging to specific risk groups, to mass vaccination campaigns, and then to universal vaccination, which is, however, still restricted to a limited number of countries[23, 27, 73, 160-162.]

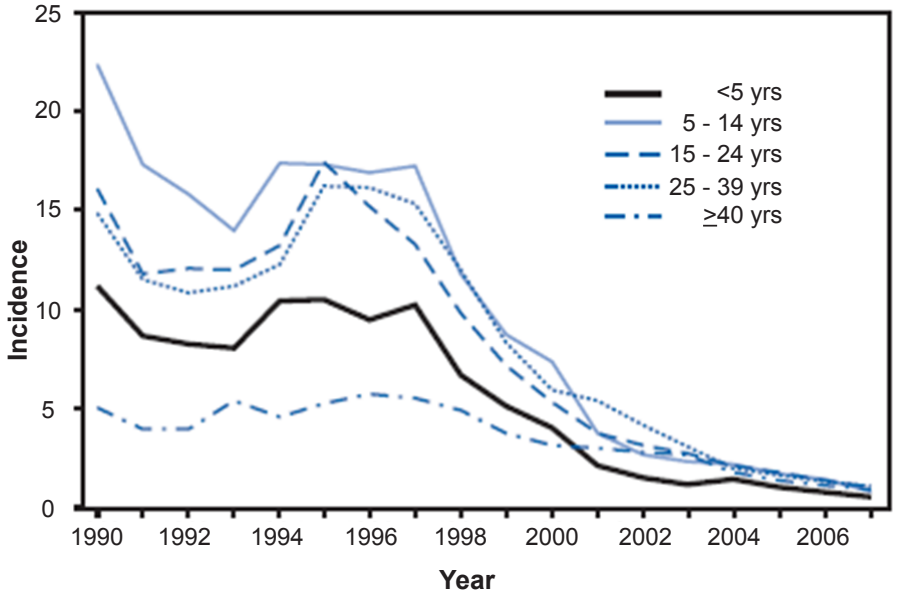
4.5.1 Individual immunization of defined populations at risk

Early strategies for pre-exposure prophylaxis included immunization of defined risk groups for contracting hepatitis A. These included international travellers to areas with intermediate and high endemicity of hepatitis A, MSM, intravenous drug users, patients with chronic liver disease, food handlers, day-care centre staff, caretakers of non-human primates and patients with blood-clotting disorders receiving blood-derived products. Although this policy provided individual protection to vaccinees at risk, it had little practical impact on reduction of disease incidence in the community.

4.5.2. Regional mass vaccination of paediatric subpopulations at risk

The effectiveness of mass vaccination of paediatric populations at risk was demonstrated in a number of geographic regions worldwide. Three demonstration projects conducted in the USA in native Americans in Alaska, in native American Indians 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 unprecedented low rate of 0.1 cases/100 000 at a vaccine coverage rate of 50%–80% in Alaska[161]. As a consequence of these successful projects, the US Advisory Committee on Immunization Practice (ACIP) in 1999 issued a recommendation to introduce universal hepatitis A vaccination into routine childhood vaccination (two doses in children >2 years old and catch-up at the age of 10–12 years) in 17 states in the USA with an annual incidence of >20 cases/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/100 000 to 2.5 cases/100 000, this representing an 88% drop (Figure 3)[23, 162]. Similar projects were introduced in Puglia, Italy in 1997[163], in Catalonia, Spain in 1998[164], and in North Queensland, Australia in 1999[165], leading to a 90%–97% decline in the reported incidence in these regions.

Figure 3: Hepatitis A incidence in the USA by age and year 1990–2007



*** Per 100,000 population**

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The results of these highly successful vaccination projects in selected geographic regions and communities worldwide suggested that mass vaccination of children in communities at risk, is effective, and will lead to herd immunity even under 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.

4.5.3 Universal vaccination of toddlers

In the 1990s, Israel, with a population of ~6 million people, was a country in transition from high to intermediate endemicity. The overall incidence of HAV infection fluctuated between 33 and 70 cases/100 000 during 1992 to 1998, reaching 120 cases/100 000 in 5–9 year old children. 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 vehicle 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 dose 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[161]. Thus, immunization of ~3% of the 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 ~2.5 cases/100 000 (Figure 4 and Table 2).

Figure 4: Annual incidence rates in Israel of reported infectious hepatitis (A, B, C, and non-specified) 1993–2004, and hepatitis A only, 1985–2004

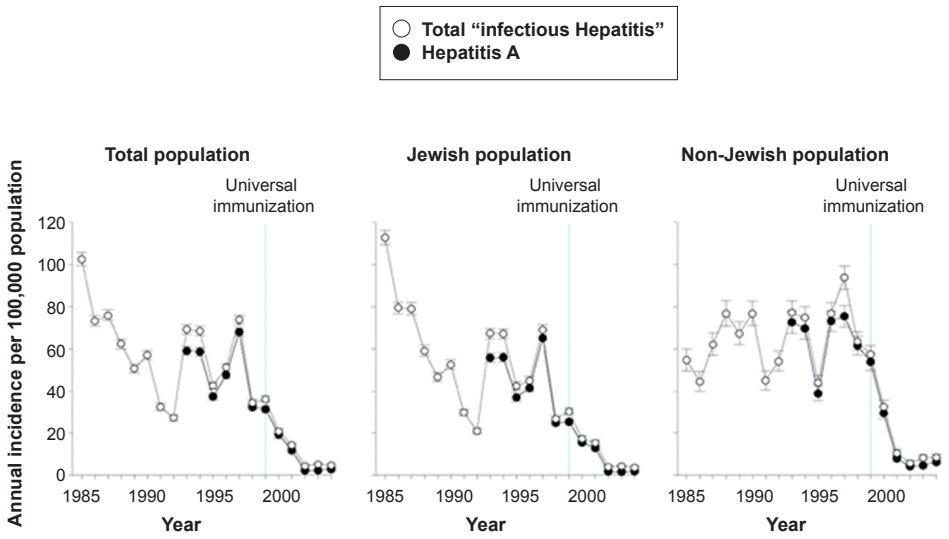

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Table 2: Mean age-specific incidence/100,000 obtained by passive surveillance before and following universal vaccination against HAV in toddlers in Israel. Vaccination started in 1999

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

Adapted, by permission of the publisher, from Dagan et al.160.

4.5.4 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 seroconversion rates in 88% of vaccinees within two weeks of the priming dose and rising to 97%–100% at week 4–6[76, 77, 166, 167]. 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[34, 36, 109]. 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[168, 169]. In 2005, public-health authorities in Argentina began a universal immunization programme in 12-month old babies[89]. Due to 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 70.5–173.8 cases/100 000 between 1995–2004 respectively. So far the results have been excellent. With a vaccination coverage of 95% in 2006, incidence of symptomatic viral hepatitis A in 2007 dropped sharply to ~10 cases/100 000 in all age groups, representing a >80% decrease in incidence. These results also confirmed the experience gained in mass and universal immunization programmes elsewhere that effective immunization of toddlers will lead to widespread herd immunity. It remainsto be seen, however, if 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[169]. Yet, 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 an immunized population, even with a single dose, is quite low.

5. Safety of hepatitis A vaccines

Almost 200 million doses of inactivated hepatitis A vaccines were sold worldwide between 1995 and early 2006. Based on the cumulative experience gained during the past 15 years, the overall safety profile of all formaldehyde-inactivated hepatitis A vaccines administered to children and adults has been excellent, irrespective of manufacturer[27, 35, 127, 158, 170-175]. The following information is quoted from a US Centers for Disease Control (CDC) review[27] :

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.

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, without regard to causality, received by the vaccine manufacturer, included anaphylaxis, Guillain-Barré syndrome, brachial plexus neuropathy, transverse myelitis, multiple sclerosis, encephalopathy and erythema multiform. 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 [33]. 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®[175].

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. However, it will be 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 secondary infection among contacts, so postmarketing surveillance 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 outside China, carefully collected and validated data on safety and efficacy will be valuable. Data of particular interest will be molecular markers of attenuation, the genetic stability of attenuation markers after human passage, the safety of orally ingested vaccine virus, and clinical safety and efficacy as demonstrated in well-conducted and sufficiently large clinical trials (http://www.who.int/wer/2010/wer8530/en/index.html).

6. Future prospects of immunization against hepatitis A

At almost two decades after hepatitis A vaccines 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 expected to last for decades, and possibly for a lifetime in immune competent recipients. 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 become susceptible to HAV infection. Public-health agencies in such countries will have to reassess the need for mass or universal vaccination depending among other factors on the disease burden, available resources and priorities. Meanwhile, recipients of HAV vaccines should be followed with special emphasis on vaccinees who received a single-dose injection or those who are immune compromised and at risk.

7. References

1. MacCallum FO. 1971 International Symposium on Viral Hepatitis. Historical perspectives. Can Med Assoc J 1972;106:Suppl:423-6.
2. Feinstone SM, Kapikian AZ, Purceli RH. Hepatitis A: detection by immune electron microscopy of a viruslike antigen associated with acute illness. Science 1973;182(116):1026-8.
3. Nainan OV, Xia G, Vaughan G, Margolis HS. Diagnosis of hepatitis a virus infection: a molecular approach. Clin Microbiol Rev 2006;19(1):63-79.
4. Martin A, Lemon SM. Hepatitis A virus: from discovery to vaccines. Hepatology 2006;43(2 Suppl 1):S164-72.
5. Siegl G, Weitz M, Kronauer G. Stability of hepatitis A virus. Intervirology 1984;22(4):218-26.
6. Reid TM, Robinson HG. Frozen raspberries and hepatitis A. Epidemiol Infect 1987;98(1):109-12.
7. McCaustland KA, Bond WW, Bradley DW, Ebert JW, Maynard JE. Survival of hepatitis A virus in feces after drying and storage for 1 month. J Clin Microbiol 1982;16(5):957-8.
8. Dotzauer A, Gebhardt U, Bieback K, et al. Hepatitis A virus-specific immunoglobulin A mediates infection of hepatocytes with hepatitis A virus via the asialoglycoprotein receptor. Journal of virology 2000;74(23):10950-7.
9. Armstrong GL, Bell BP. Hepatitis A virus infections in the United States: model-based estimates and implications for childhood immunization. Pediatrics 2002;109(5):839-45.
10. FitzSimons D, Hendrickx G, Vorsters A, Van Damme P. Hepatitis A and E: update on prevention and epidemiology. Vaccine 2010;28(3):583-8.
11. Van Damme P, Van Herck K. A review of the long-term protection after hepatitis A and B vaccination. Travel Med Infect Dis 2007;5(2):79-84.
12. Hendrickx G, Van Herck K, Vorsters A, et al. Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology. J Viral Hepat 2008;15 Suppl 2:1-15.
13. WHO position paper on hepatitis A vaccines. Can Commun Dis Rep 2000;26(5):33-8.
14. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine;28(41):6653-7.
15. Gust ID. Epidemiological patterns of hepatitis A in different parts of the world. Vaccine 1992;10 Suppl 1:S56-8.

16. Jacobsen KH, Koopman JS. Declining hepatitis A seroprevalence: a global review and analysis. Epidemiol Infect 2004;132(6):1005-22.

17. Cooksley WG. What did we learn from the Shanghai hepatitis A epidemic? J Viral Hepat 2000;7 Suppl 1:1-3.

18. Kim YJ, Lee HS. Increasing incidence of hepatitis A in Korean adults. Intervirology 2010;53(1):10-4.

19. Kim JD, Choi JY, Park CH, et al. [Clinical features of patients with fulminant hepatitis A requiring emergency liver transplantation: comparison with acute liver failure due to other causes]. Korean J Hepatol 2010;16(1):19-28.

20. Centeno MA, Bes DF, Sasbon JS. Mortality risk factors of a pediatric population with fulminant hepatic failure undergoing orthotopic liver transplantation in a pediatric intensive care unit. Pediatr Crit Care Med 2002;3(3):227-33.

21. Munne MS, Vladimirsky S, Moreiro R, et al. Molecular characterization of hepatitis A virus in children with fulminant hepatic failure in Argentina. Liver Int 2008;28(1):47-53.

22. Santos DC, Martinho JM, Pacheco-Moreira LF, et al. Fulminant hepatitis failure in adults and children from a Public Hospital in Rio de Janeiro, Brazil. Braz J Infect Dis 2009;13(5):323-9.

23. Daniels D, Grytdal S, Wasley A. Surveillance for acute viral hepatitis - United States, 2007. MMWR Surveill Summ 2009;58(3):1-27.

24. Glikson M, Galun E, Oren R, Tur-Kaspa R, Shouval D. Relapsing hepatitis A. Review of 14 cases and literature survey. Medicine (Baltimore) 1992; 71(1):14-23.

25. Krugman S, Giles JP. Viral hepatitis. New light on an old disease. Jama 1970;212(6):1019-29.

26. Lednar WM, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML, Kelley PW. Frequency of illness associated with epidemic hepatitis A virus infections in adults. Am J Epidemiol 1985;122(2):226-33.

27. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2006;55(RR-7):1-23.

28. Tong MJ, el-Farra NS, Grew MI. Clinical manifestations of hepatitis A: recent experience in a community teaching hospital. J Infect Dis 1995; 171 Suppl 1:S15-8.

29. Schiff ER. Atypical clinical manifestations of hepatitis A. Vaccine 1992; 10 Suppl 1:S18-20.

30. Willner IR, Uhl MD, Howard SC, Williams EQ, Riely CA, Waters B. Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. Ann Intern Med 1998;128(2):111-4.

31. Crowcroft NS, Walsh B, Davison KL, Gungabissoon U. Guidelines for the control of hepatitis A virus infection. Commun Dis Public Health 2001;4(3):213-27.

32. Provost PJ, Hilleman MR. Propagation of human hepatitis A virus in cell culture in vitro. Proc Soc Exp Biol Med 1979;160(2):213-21.

33. Innis BL, Snitbhan R, Kunasol P, et al. Protection against hepatitis A by an inactivated vaccine. Jama 1994;271(17):1328-34.

34. Werzberger A, Mensch B, Kuter B, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. The New England journal of medicine 1992;327(7):453-7.

35. Vidor E, Dumas R, Porteret V, Bailleux F, Veitch K. Aventis Pasteur vaccines containing inactivated hepatitis A virus: a compilation of immunogenicity data. Eur J Clin Microbiol Infect Dis 2004;23(4):300-9.

36. Mayorga Perez O, Herzog C, Zellmeyer M, Loaisiga A, Frosner G, Egger M. Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. J Infect Dis 2003;188(5):671-7.

37. Jiang WP, Chen JT, Wang X, et al. Immunogenicity and safety of three consecutive lots of a new preservative-free inactivated hepatitis A vaccine (Healive): a double-blind, randomized and controlled trial. Vaccine 2008;26(18): 2297-301.

38. Mao JS, Dong DX, Zhang HY, et al. Primary study of attenuated live hepatitis A vaccine (H2 strain) in humans. J Infect Dis 1989;159(4):621-4.

39. Mao JS, Chai SA, Xie RY, et al. Further evaluation of the safety and protective efficacy of live attenuated hepatitis A vaccine (H2-strain) in humans. Vaccine 1997;15(9):944-7.

40. Zhao YL, Meng ZD, Xu ZY, et al. H2 strain attenuated live hepatitis A vaccines:protective efficacy in a hepatitis A outbreak. World J Gastroenterol 2000;6(6):829-32.

41. Wang XY, Xu ZY, Ma JC, et al. Long-term immunogenicity after single and booster dose of a live attenuated hepatitis A vaccine: results from 8-year follow-up. Vaccine 2007;25(3):446-9.

42. Faridi MM, Shah N, Ghosh TK, et al. Immunogenicity and safety of live attenuated hepatitis A vaccine: a multicentric study. Indian Pediatr 2009;46(1):29-34.

43. Shen YG, Gu XJ, Zhou JH. Protective effect of inactivated hepatitis A vaccine against the outbreak of hepatitis A in an open rural community. World J Gastroenterol 2008;14(17):2771-5.

44. Ambrosch F, Andre FE, Delem A, et al. Simultaneous vaccination against hepatitis A and B: results of a controlled study. Vaccine 1992;10 Suppl 1:S142-5.

45. Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. Expert review of vaccines 2004;3(3):249-67.

46. Czeschinski PA, Binding N, Witting U. Hepatitis A and hepatitis B vaccinations: immunogenicity of combined vaccine and of simultaneously or separately applied single vaccines. Vaccine 2000;18(11-12):1074-80.

47. Joines RW, Blatter M, Abraham B, et al. A prospective, randomized, comparative US trial of a combination hepatitis A and B vaccine (Twinrix) with corresponding monovalent vaccines (Havrix and Engerix-B) in adults. Vaccine 2001;19(32):4710-9.

48. Van Damme P, Van der Wielen M. Combining hepatitis A and B vaccination in children and adolescents. Vaccine 2001;19(17-19):2407-12.

49. Knoll A, Hottentrager B, Kainz J, Bretschneider B, Jilg W. Immunogenicity of a combined hepatitis A and B vaccine in healthy young adults. Vaccine 2000;18(19):2029-32.

50. Beeching NJ, Clarke PD, Kitchin NR, Pirmohamed J, Veitch K, Weber F. Comparison of two combined vaccines against typhoid fever and hepatitis A in healthy adults. Vaccine 2004;23(1):29-35.

51. Cohen JI, Rosenblum B, Ticehurst JR, Daemer RJ, Feinstone SM, Purcell RH. Complete nucleotide sequence of an attenuated hepatitis A virus: comparison with wild-type virus. Proc Natl Acad Sci U S A 1987; 84(8):2497-501.

52. Lemon SM. Immunologic approaches to assessing the response to inactivated hepatitis A vaccine. J Hepatol 1993;18 Suppl 2:S15-9.

53. Lemon SM. Type A viral hepatitis: epidemiology, diagnosis, and prevention. Clin Chem 1997;43(8 Pt 2):1494-9.

54. Wiedermann G, Ambrosch F, Andre FE, Delem A, D'Hondt E, Safary A. Thermostability of an inactivated hepatitis A vaccine stored at 37 degrees C for one week. Journal of medical virology 1994;44(4):442.

55. Margolis HS, Nainan OV, Krawczynski K, et al. Appearance of immune complexes during experimental hepatitis A infection in chimpanzees. Journal of medical virology 1988;26(3):315-26.

56. Bower WA, Nainan OV, Han X, Margolis HS. Duration of viremia in hepatitis A virus infection. J Infect Dis 2000;182(1):12-7.

57. Liaw YF, Yang CY, Chu CM, Huang MJ. Appearance and persistence of hepatitis A IgM antibody in acute clinical hepatitis A observed in an outbreak. Infection 1986;14(4):156-8.

58. Kao HW, Ashcavai M, Redeker AG. The persistence of hepatitis A IgM antibody after acute clinical hepatitis A. Hepatology 1984;4(5):933-6.

59. Villarejos VM, Gutierrez-Diermissen A, Anderson-Visona K, Rodriguez-Aragones A, Provost PJ, Hilleman MR. Development of immunity against hepatitis A virus by subclinical infection. Proc Soc Exp Biol Med 1976;153(2):205-8.

60. Liu JP, Nikolova D, Fei Y. Immunoglobulins for preventing hepatitis A. Cochrane Database Syst Rev 2009(2):CD004181.

61. Rendi-Wagner P, Korinek M, Winkler B, Kundi M, Kollaritsch H, Wiedermann U. Persistence of seroprotection 10 years after primary hepatitis A vaccination in an unselected study population. Vaccine 2007;25(5):927-31.

62. Kabrane-Lazizi Y, Emerson SU, Herzog C, Purcell RH. Detection of antibodies to HAV 3C proteinase in experimentally infected chimpanzees and in naturally infected children. Vaccine 2001;19(20-22):2878-83.

63. Robertson BH, Jia XY, Tian H, Margolis HS, Summers DF, Ehrenfeld E. Serological approaches to distinguish immune response to hepatitis A vaccine and natural infection. Vaccine 1992;10 Suppl 1:S106-9.

64. Vallbracht A, Maier K, Stierhof YD, Wiedmann KH, Flehmig B, Fleischer B. Liver-derived cytotoxic T cells in hepatitis A virus infection. J Infect Dis 1989;160(2):209-17.

65. Hashimoti E, Kojimahara N, Noguchi S, Taniai M, Ishiguro N, Hayashi N. Immunohistochemical characterization of hepatic lymphocytes in acute hepatitis A, B, and C. J Clin Gastroenterol 1996;23(3):199-202.

66. Sanchez G, Pinto RM, Bosch A. A novel CD4+ T-helper lymphocyte epitope in the VP3 protein of hepatitis A virus. Journal of medical virology 2004;72(4):525-32.

67. Baba M, Fukai K, Hasegawa H, Nakayabu M, Suzuki S. The role of natural killer cells and lymphokine activated killer cells in the pathogenesis of hepatic injury in hepatitis A [corrected]. J Clin Lab Immunol 1992;38(1):1-14.

68. Vallbracht A, Gabriel P, Maier K, et al. Cell-mediated cytotoxicity in hepatitis A virus infection. Hepatology 1986;6(6):1308-14.

69. Kurane I, Binn LN, Bancroft WH, Ennis FA. Human lymphocyte responses to hepatitis A virus-infected cells: interferon production and lysis of infected cells. J Immunol 1985;135(3):2140-4.

70. Perrella A, Vitiello L, Atripaldi L, et al. Impaired function of CD4+/CD25+ T regulatory lymphocytes characterizes the self-limited hepatitis A virus infection. J Gastroenterol Hepatol 2008;23(7 Pt 2):e105-10.

71. Schulte I, Hitziger T, Giugliano S, et al. Characterization of CD8+ T-cell response in acute and resolved hepatitis A virus infection. J Hepatol, Epub Sep 2010 .

72. Wunchmann S,Vallbracht A, Flehmig B, Winokur P, Klinzmann D, Stapleton JT. Cytolytic T-lymphocyte epitopes are present on hepatitis A virus structural proteins.In Viral Hepatitis and Liver Disease. Edts M.Rizzetto, RH Purcell, JL Gerin and G.Verme. Turin: Edizion: Minerva Medica; 1997 pp51-54.

73. Andre FE. Universal mass vaccination against hepatitis A. Curr Top Microbiol Immunol 2006;304:95-114.

74. Van Damme P, Banatvala J, Fay O, et al. Hepatitis A booster vaccination: is there a need? Lancet 2003;362(9389):1065-71.

75. Bovier PA, Bock J, Ebengo TF, et al. Predicted 30-year protection after vaccination with an aluminum-free virosomal hepatitis A vaccine. Journal of medical virology;82(10):1629-34.

76. Shouval D, Ashur Y, Adler R, et al. Single and booster dose responses to an inactivated hepatitis A virus vaccine: comparison with immune serum globulin prophylaxis. Vaccine 1993;11 Suppl 1:S9-14.

77. Ashur Y, Adler R, Rowe M, Shouval D. Comparison of immunogenicity of two hepatitis A vaccines–VAQTA and HAVRIX–in young adults. Vaccine 1999;17(18):2290-6.

78. Schmidtke P, Habermehl P, Knuf M, Meyer CU, Sanger R, Zepp F. Cell mediated and antibody immune response to inactivated hepatitis A vaccine. Vaccine 2005;23(44):5127-32.

79. Cederna JB, Klinzman D, Stapleton JT. Hepatitis A virus-specific humoral and cellular immune responses following immunization with a formalin-inactivated hepatitis A vaccine. Vaccine 1999;18(9-10):892-8.

80. Leroux-Roels G, Desombere I, Van Herck K, Thoelen S, Collard F, Van Damme P. Long-term persistence of cellular immunity towards hepatitis A virus following hepatitis A virus vaccination. In viral Hepatitis and Liver disease Edts HS Margolis, MJ Alter, TJ Liang and JL Dienstag. International Medical Press; 2002 pp41-44.

81. Garner-Spitzer E, Kundi M, Rendi-Wagner P, et al. Correlation between humoral and cellular immune responses and the expression of the hepatitis A receptor HAVcr-1 on T cells after hepatitis A re-vaccination in high and low-responder vaccinees. Vaccine 2009;27(2):197-204.

82. Hayney MS, Buck JM, Muller D. Production of interferon-gamma and interleukin-10 after inactivated hepatitis A immunization. Pharmacotherapy 2003;23(4):431-5.

83. Purcell RH, D'Hondt E, Bradbury R, Emerson SU, Govindarajan S, Binn L. Inactivated hepatitis A vaccine: active and passive immunoprophylaxis in chimpanzees. Vaccine 1992;10 Suppl 1:S148-51.

84. Lemon SM, Binn LN. Serum neutralizing antibody response to hepatitis A virus. J Infect Dis 1983;148(6):1033-9.

85. Nalin DR, Kuter BJ, Brown L, et al. Worldwide experience with the CR326F-derived inactivated hepatitis A virus vaccine in pediatric and adult populations: an overview. J Hepatol 1993;18 Suppl 2:S51-5.

86. Clemens R, Safary A, Hepburn A, Roche C, Stanbury WJ, Andre FE. Clinical experience with an inactivated hepatitis A vaccine. J Infect Dis 1995; 171 Suppl 1:S44-9.

87. Lopez EL, Contrini MM, Mistchenko A, Debbag R. Long-term immunity after two doses of inactivated hepatitis A vaccine, in Argentinean children. The Pediatric infectious disease journal 2010;29(6):568-70.

88. Van Herck K, Van Damme P, Lievens M, Stoffel M. Hepatitis A vaccine: indirect evidence of immune memory 12 years after the primary course. Journal of medical virology 2004;72(2):194-6.

89. Vacchino MN. Incidence of Hepatitis A in Argentina after vaccination. Journal of viral hepatitis 2008;15 Suppl 2:47-50.

90. Nolan T, Bernstein H, Blatter MM, et al. Immunogenicity and safety of an inactivated hepatitis A vaccine administered concomitantly with diphtheria-tetanus-acellular pertussis and haemophilus influenzae type B vaccines to children less than 2 years of age. Pediatrics 2006;118(3):e602-9.

91. Stokes J, Jr., Blanchard M, et al. Methods of protection against homologous serum hepatitis; studies on the protective value of gamma globulin in homologous serum hepatitis Sh virus. J Am Med Assoc 1948;138(5):336-41.

92. Stapleton JT. Passive immunization against hepatitis A. Vaccine 1992; 10 Suppl 1:S45-7.

93. Cohn EJ, Oncley JL, Strong LE, Hughes WL, Armstrong SH. Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation. I. the Characterization of the Protein Fractions of Human Plasma. J Clin Invest 1944;23(4):417-32.

94. Higgins G, Wreghitt TG, Gray JJ, Blagdon J, Taylor CE. Hepatitis A virus antibody in East Anglian blood donors. Lancet 1990;336(8726):1330.

95. Ferguson M, Sands D, Lelie N. Hepatitis A immunoglobulin: an international collaborative study to establish the second international standard. Biologicals 2000;28(4):233-40.

96. Hall WT, Madden DL, Mundon FK, Brandt DE, Clarke NA. Protective effect of immune serum globulin (ISG) against hepatitis A infection in a natural epidemic. Am J Epidemiol 1977;106(1):72-5.

97. Victor JC, Monto AS, Surdina TY, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. The New England journal of medicine 2007;357(17):1685-94.

98. Lemon SM, Murphy PC, Provost PJ, et al. Immunoprecipitation and virus neutralization assays demonstrate qualitative differences between protective antibody responses to inactivated hepatitis A vaccine and passive immunization with immune globulin. J Infect Dis 1997;176(1):9-19.

99. Wagner G, Lavanchy D, Darioli R, et al. Simultaneous active and passive immunization against hepatitis A studied in a population of travellers. Vaccine 1993;11(10):1027-32.

100. Walter EB, Hornick RB, Poland GA, et al. Concurrent administration of inactivated hepatitis A vaccine with immune globulin in healthy adults. Vaccine 1999;17(11-12):1468-73.

101. Howell D, Barbara JA, Brennan M. Hepatitis A virus, blood donors, and immunoglobulin preparations. Lancet 1991;337(8750):1165.

102. Tedder RS, Cameron CH, Barbara JA, Howell D. Viral hepatitis markers in blood donors with history of jaundice. Lancet 1980;1(8168 Pt 1):595-6.

103. Anonychuk AM, Tricco AC, Bauch CT, et al. Cost-effectiveness analyses of hepatitis A vaccine: a systematic review to explore the effect of methodological quality on the economic attractiveness of vaccination strategies. Pharmacoeconomics 2008;26(1):17-32.

104. Soysal A, Gokce I, Pehlivan T, Bakir M. Interchangeability of a hepatitis A vaccine second dose: Avaxim 80 following a first dose of Vaqta 25 or Havrix 720 in children in Turkey. European journal of pediatrics 2007;166(6):533-9.

105. Abarca K, Ibanez I, Perret C, Vial P, Zinsou JA. Immunogenicity, safety, and interchangeability of two inactivated hepatitis A vaccines in Chilean children. Int J Infect Dis 2008;12(3):270-7.

106. Dagan R, Amir J, Livni G, et al. Concomitant administration of a virosome-adjuvanted hepatitis a vaccine with routine childhood vaccines at age twelve to fifteen months: a randomized controlled trial. The Pediatric infectious disease journal 2007;26(9):787-93.

107. Prikazsky V, Olear V, Cernoch A, Safary A, Andre FE. Interruption of an outbreak of hepatitis A in two villages by vaccination. Journal of medical virology 1994;44(4):457-9.

108. Sagliocca L, Amoroso P, Stroffolini T, et al. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial. Lancet 1999;353(9159):1136-9.

109. Zamir C, Rishpon S, Zamir D, Leventhal A, Rimon N, Ben-Porath E. Control of a community-wide outbreak of hepatitis A by mass vaccination with inactivated hepatitis A vaccine. Eur J Clin Microbiol Infect Dis 2001;20(3):185-7.

110. Selnikova O, Moisseeva A, Zadorozhnaja V, Dokachenko A, Kachur N, Gavrik S. Hepatitis A vaccination effectiveness during an outbreak in the Ukraine. Vaccine 2008;26(25):3135-7.

111. Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2007;56(41):1080-4.

112. Craig AS, Sockwell DC, Schaffner W, et al. Use of hepatitis A vaccine in a community-wide outbreak of hepatitis A. Clin Infect Dis 1998;27(3):531-5.

113. Franceschi C, Monti D, Barbieri D, et al. Immunosenescence in humans: deterioration or remodelling? Int Rev Immunol 1995;12(1):57-74.

114. Ben-Yehuda A, Weksler ME. Immune senescence: mechanisms and clinical implications. Cancer Invest 1992;10(6):525-31.

115. Genton B, D'Acremont V, Furrer HJ, Hatz C, Louis L. Hepatitis A vaccines and the elderly. Travel Med Infect Dis 2006;4(6):303-12.

116. Scheifele DW, Bjornson GJ. Evaluation of inactivated hepatitis A vaccine in Canadians 40 years of age or more. Cmaj 1993;148(4):551-5.

117. Reuman PD, Kubilis P, Hurni W, Brown L, Nalin D. The effect of age and weight on the response to formalin inactivated, alum-adjuvanted hepatitis A vaccine in healthy adults. Vaccine 1997;15(10):1157-61.

118. Steffen R, Kane MA, Shapiro CN, Billo N, Schoellhorn KJ, van Damme P. Epidemiology and prevention of hepatitis A in travelers. Jama 1994;272(11):885-9.

119. Holzer BR, Hatz C, Schmidt-Sissolak D, Gluck R, Althaus B, Egger M. Immunogenicity and adverse effects of inactivated virosome versus alum-adsorbed hepatitis A vaccine: a randomized controlled trial. Vaccine 1996;14(10):982-6.

120. D'Acremont V, Herzog C, Genton B. Immunogenicity and safety of a virosomal hepatitis A vaccine (Epaxal) in the elderly. Journal of travel medicine 2006;13(2):78-83.

121. Maiwald H, Jilg W, Bock HL, Loscher T, Sonnenburg F. Long-term persistence of anti-HAV antibodies following active immunization with hepatitis A vaccine. Vaccine 1997;15(4):346-8.

122. Launay O, Grabar S, Gordien E, et al. Immunological efficacy of a three-dose schedule of hepatitis A vaccine in HIV-infected adults: HEPAVAC study. J Acquir Immune Defic Syndr 2008;49(3):272-5.

123. Lieberman JM, Chang SJ, Partridge S, et al. Kinetics of maternal hepatitis A antibody decay in infants: implications for vaccine use. The Pediatric infectious disease journal 2002;21(4):347-8.

124. Usonis V, Bakasenas V, Valentelis R, Katiliene G, Vidzeniene D, Herzog C. Antibody titres after primary and booster vaccination of infants and young children with a virosomal hepatitis A vaccine (Epaxal). Vaccine 2003;21(31):4588-92.

125. Letson GW, Shapiro CN, Kuehn D, et al. Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants. J Pediatr 2004;144(3): 327-32.

126. Dagan R, Amir J, Mijalovsky A, et al. Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. The Pediatric infectious disease journal 2000;19(11):1045-52.

127. Fiore AE, Shapiro CN, Sabin K, et al. Hepatitis A vaccination of infants: effect of maternal antibody status on antibody persistence and response to a booster dose. The Pediatric infectious disease journal 2003;22(4):354-9.

128. Fonquernie L, Meynard JL, Charrois A, Delamare C, Meyohas MC, Frottier J. Occurrence of acute hepatitis A in patients infected with human immunodeficiency virus. Clin Infect Dis 2001;32(2):297-9.

129. Ida S, Tachikawa N, Nakajima A, et al. Influence of human immunodeficiency virus type 1 infection on acute hepatitis A virus infection. Clin Infect Dis 2002;34(3):379-85.

130. Costa-Mattioli M, Allavena C, Poirier AS, Billaudel S, Raffi F, Ferre V. Prolonged hepatitis A infection in an HIV-1 seropositive patient. Journal of medical virology 2002;68(1):7-11.

131. Ridolfo AL, Rusconi S, Antinori S, Balotta C, Galli M. Persisting HIV-1 replication triggered by acute hepatitis A virus infection. Antivir Ther 2000;5(1):15-7.

132. Wallace MR, Hill HE, Tasker SA, Miller LK. Hepatitis A in human immunodeficiency virus-infected patients. Clin Infect Dis 1998;27(3):651-3.

133. Laurence JC. Hepatitis A and B immunizations of individuals infected with human immunodeficiency virus. Am J Med 2005;118 Suppl 10A:75S-83S.

134. Overton ET, Nurutdinova D, Sungkanuparph S, Seyfried W, Groger RK, Powderly WG. Predictors of immunity after hepatitis A vaccination in HIV-infected persons. J Viral Hepat 2007;14(3):189-93.

135. Gunther M, Stark K, Neuhaus R, Reinke P, Schroder K, Bienzle U. Rapid decline of antibodies after hepatitis A immunization in liver and renal transplant recipients. Transplantation 2001;71(3):477-9.

136. Stark K, Gunther M, Neuhaus R, et al. Immunogenicity and safety of hepatitis A vaccine in liver and renal transplant recipients. J Infect Dis 1999;180(6):2014-7.

137. Arslan M, Wiesner RH, Poterucha JJ, Zein NN. Safety and efficacy of hepatitis A vaccination in liver transplantation recipients. Transplantation 2001;72(2):272-6.

138. Godoi ER, de Souza VA, Cakmak S, Machado AF, Vilas Boas LS, Machado CM. Loss of hepatitis A virus antibodies after bone marrow transplantation. Bone Marrow Transplant 2006;38(1):37-40.

139. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. The New England journal of medicine 1998;338(5):286-90.

140. Pramoolsinsap C, Poovorawan Y, Hirsch P, Busagorn N, Attamasirikul K. Acute, hepatitis-A super-infection in HBV carriers, or chronic liver disease related to HBV or HCV. Annals of tropical medicine and parasitology 1999;93(7):745-51.

141. Smallwood GA, Coloura CT, Martinez E, Stieber AC, Heffron TG. Can patients awaiting liver transplantation elicit an immune response to the hepatitis A vaccine? Transplantation proceedings 2002;34(8):3289-90.

142. Lee SD, Chan CY, Yu MI, et al. Safety and immunogenicity of inactivated hepatitis A vaccine in patients with chronic liver disease. Journal of medical virology 1997;52(2):215-8.

143. Majda-Stanislawska E, Bednarek M, Kuydowicz J. Immunogenicity of inactivated hepatitis A vaccine in children with chronic liver disease. The Pediatric infectious disease journal 2004;23(6):571-4.

144. Ferreira CT, da Silveira TR, Vieira SM, Taniguchi A, Pereira-Lima J. Immunogenicity and safety of hepatitis A vaccine in children with chronic liver disease. Journal of pediatric gastroenterology and nutrition 2003;37(3):258-61.

145. Dumot JA, Barnes DS, Younossi Z, et al. Immunogenicity of hepatitis A vaccine in decompensated liver disease. The American journal of gastroenterology 1999;94(6):1601-4.

146. Gil A, Gonzalez A, Dal-Re R, Calero JR. Interference assessment of yellow fever vaccine with the immune response to a single-dose inactivated hepatitis A vaccine (1440 EL.U.). A controlled study in adults. Vaccine 1996;14(11):1028-30.

147. Guerra FA, Gress J, Werzberger A, et al. Safety, tolerability and immunogenicity of VAQTA given concomitantly versus nonconcomitantly with other pediatric vaccines in healthy 12-month-old children. The Pediatric infectious disease journal 2006;25(10):912-9.

148. Bienzle U, Bock HL, Kruppenbacher JP, Hofmann F, Vogel GE, Clemens R. Immunogenicity of an inactivated hepatitis A vaccine administered according to two different schedules and the interference of other "travellers" vaccines with the immune response. Vaccine 1996;14(6):501-5.

149. Jong EC, Kaplan KM, Eves KA, Taddeo CA, Lakkis HD, Kuter BJ. An open randomized study of inactivated hepatitis A vaccine administered concomitantly with typhoid fever and yellow fever vaccines. Journal of travel medicine 2002;9(2):66-70.

150. Usonis V, Meriste S, Bakasenas V, et al. Immunogenicity and safety of a combined hepatitis A and B vaccine administered concomitantly with either a measles-mumps-rubella or a diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine mixed with a Haemophilus influenzae type b conjugate vaccine in infants aged 12-18 months. Vaccine 2005;23(20):2602-6.

151. Ambrosch F, Fritzell B, Gregor J, et al. Combined vaccination against yellow fever and typhoid fever: a comparative trial. Vaccine 1994;12(7):625-8.

152. Overbosch D, Peyron F, Picot N, et al. Combined typhoid fever and hepatitis A vaccine: comparison of immunogenicity and safety to concomitant monovalent vaccine over 3 years. Journal of travel medicine 2005;12(6):319-26.

153. Beran J, Chlibek R, Weber F. A combined dual-chamber typhoid/hepatitis A vaccine as a booster dose in hepatitis A primed adults. Vaccine 2003;21(32):4650-4.

154. Proell S, Maiwald H, Nothdurft HD, et al. Combined vaccination against hepatitis A, hepatitis B, and typhoid fever: safety, reactogenicity, and immunogenicity. Journal of travel medicine 2002;9(3):122-6.

155. Loebermann M, Kollaritsch H, Ziegler T, et al. A randomized, open-label study of the immunogenicity and reactogenicity of three lots of a combined typhoid fever/hepatitis A vaccine in healthy adults. Clinical therapeutics 2004;26(7):1084-91.

156. Bovier PA, Farinelli T, Loutan L. Interchangeability and tolerability of a virosomal and an aluminum-adsorbed hepatitis A vaccine. Vaccine 2005;23(19):2424-9.

157. Ekwall E, Ulgemo A, Watson M, Boisnard F, Thomas S, Goullet F. Interchangeability of Hepatitis A boosters, Avaxim and Vaqta, in healthy adults following a primary dose of the combined typhoid/Hepatitis A vaccine Viatim. Vaccine 2006;24(20):4450-7.

158. Werzberger A, Mensch B, Nalin DR, Kuter BJ. Effectiveness of hepatitis A vaccine in a former frequently affected community: 9 years' followup after the Monroe field trial of VAQTA. Vaccine 2002;20(13-14):1699-701.

159. Bovier PA. Epaxal: a virosomal vaccine to prevent hepatitis A infection. Expert review of vaccines 2008;7(8):1141-50.

160. Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of toddlers. Jama 2005;294(2):202-10.

161. Bialek SR, Thoroughman DA, Hu D, et al. Hepatitis A incidence and hepatitis A vaccination among American Indians and Alaska Natives, 1990-2001. American journal of public health 2004;94(6):996-1001.

162. Wasley A, Samandari T, Bell BP. Incidence of hepatitis A in the United States in the era of vaccination. Jama 2005;294(2):194-201.

163. Lopalco PL, Salleras L, Barbuti S, et al. Hepatitis A and B in children and adolescents–what can we learn from Puglia (Italy) and Catalonia (Spain)? Vaccine 2000;19(4-5):470-4.

164. Dominguez A, Salleras L, Carmona G, Batalla J. Effectiveness of a mass hepatitis A vaccination program in preadolescents. Vaccine 2003; 21(7-8):698-701.

165. Hanna JN, Hills SL, Humphreys JL. Impact of hepatitis A vaccination of Indigenous children on notifications of hepatitis A in north Queensland. The Medical journal of Australia 2004;181(9):482-5.

166. Van Damme P, Mathei C, Thoelen S, Meheus A, Safary A, Andre FE. Single dose inactivated hepatitis A vaccine: rationale and clinical assessment of the safety and immunogenicity. Journal of medical virology 1994;44(4):435-41.

167. Beck BR, Hatz C, Bronnimann R, Herzog C. Successful booster antibody response up to 54 months after single primary vaccination with virosome-formulated, aluminum-free hepatitis A vaccine. Clin Infect Dis 2003;37(9):e126-8.

168. Iwarson S, Lindh M, Widerstrom L. Excellent booster response 4-6 y after a single primary dose of an inactivated hepatitis A vaccine. Scandinavian journal of infectious diseases 2002;34(2):110-1.

169. Ellis A, Ruttimann RW, Jacobs RJ, Meyerhoff AS, Innis BL. Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted. Revista panamericana de salud publica = Pan American journal of public health 2007;21(6):345-56.

170. Van Der Wielen M, Vertruyen A, Froesner G, et al. Immunogenicity and safety of a pediatric dose of a virosome-adjuvanted hepatitis A vaccine: a controlled trial in children aged 1-16 years. The Pediatric infectious disease journal 2007;26(8):705-10.

171. Niu MT, Salive M, Krueger C, Ellenberg SS. Two-year review of hepatitis A vaccine safety: data from the Vaccine Adverse Event Reporting System (VAERS). Clin Infect Dis 1998;26(6):1475-6.

172. Riedemann S, Reinhardt G, Frosner GG, et al. Placebo-controlled efficacy study of hepatitis A vaccine in Valdivia, Chile. Vaccine 1992;10 Suppl 1:S152-5.

173. Ellerbeck EF, Lewis JA, Nalin D, et al. Safety profile and immunogenicity of an inactivated vaccine derived from an attenuated strain of hepatitis A. Vaccine 1992;10(10):668-72.

174. Demicheli V, Tiberti D. The effectiveness and safety of hepatitis A vaccine: a systematic review. Vaccine 2003;21(19-20):2242-5.

175. Black S, Shinefield H, Hansen J, Lewis E, Su L, Coplan P. A post-licensure evaluation of the safety of inactivated hepatitis A vaccine (VAQTA, Merck) in children and adults. Vaccine 2004;22(5-6):766-72.

The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization,Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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ISBN 978 92 4 150142 2