

Hepatitis A vaccination and its immunological and epidemiological long-term effects – a review of the evidence

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ABSTRACT

Hepatitis A virus (HAV) infections continue to represent a significant disease burden causing approximately 200 million infections, 30 million symptomatic illnesses and 30,000 deaths each year. Effective and safe hepatitis A vaccines have been available since the early 1990s. Initially developed for individual prophylaxis, HAV vaccines are now increasingly used to control hepatitis A in endemic areas. The human enteral HAV is eradicable in principle, however, HAV eradication is currently not being pursued. Inactivated HAV vaccines are safe and, after two doses, elicit seroprotection in healthy children, adolescents, and young adults for an estimated 30–40 years, if not lifelong, with no need for a later second booster. The long-term effects of the single-dose live-attenuated HAV vaccines are less well documented but available data suggest they are safe and provide long-lasting immunity and protection. A universal mass vaccination strategy (UMV) based on two doses of inactivated vaccine is commonly implemented in endemic countries and eliminates clinical hepatitis A disease in toddlers within a few years. Consequently, older age groups also benefit due to the herd protection effects. Single-dose UMV programs have shown promising outcomes but need to be monitored for many more years in order to document an effective immune memory persistence. In non-endemic countries, prevention efforts need to focus on ‘new’ risk groups, such as men having sex with men, prisoners, the homeless, and families visiting friends and relatives in endemic countries. This narrative review presents the current evidence regarding the immunological and epidemiological long-term effects of the hepatitis A vaccination and finally discusses emerging issues and areas for research.

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1. Introduction

Hepatitis A virus (HAV) infections continue to represent a significant disease burden worldwide causing approximately 200 million infections, 30 million symptomatic illnesses and 30,000 deaths per year.^{1,2} Effective and safe hepatitis A vaccines have been available since the early 1990s. Initially developed for individual prophylaxis, these vaccines are now increasingly used to control hepatitis A in endemic areas in the hope to eliminate HAV in the long run. Following brief summaries on the main features and epidemiology of hepatitis A, as well as on the characteristics of the available HAV vaccines, this narrative review presents the immunological and epidemiological long-term effects of the hepatitis A vaccination, mainly based on publications reporting on well-established long-term data, i.e. with follow-up periods of 5–10 years or more. Finally, emerging trends in the epidemiology of hepatitis A and areas in need of more research will be discussed.

1.1. Hepatitis A disease^{3,4}

Hepatitis A is an enteral virus infection caused by the HAV, a single-stranded RNA-virus of the Picornaviridae family. The virus enters through gut cells and arrives to the liver by the

portal vein. Damage to the hepatocytes is caused by the reaction of the immune system and not by the virus itself which is not cytopathic. HAV is mainly transmitted by the fecal-oral route, thus contaminated food and water, person-to-person contact and men having sex with men (MSM), can all transmit this virus. Very rarely infection occurs parenterally via blood products.

The incubation period ranges from 14 up to 50 days. The first unspecific symptoms are malaise, fatigue, anorexia, vomiting, abdominal discomfort and diarrhea. In the case of a more pronounced symptomatic illness – which significantly increases with age (<10%, 50–75%, and ≥85% symptomatic illness at age <5 years, 10–15 years and ≥18 years, respectively)⁵ – dark urine, pale stool, and jaundice can be observed. Disease severity and case-fatality are strongly correlated with age,⁶ the latter ranging from 0.1% in children <15 years of age to 0.3% at 15–39 years of age and rising to 1.8–5.4% above the age of 50 years. The majority of deaths are caused by fulminant hepatic failure (overall incidence of 0.015–0.5%), usually necessitating liver transplantation, which has a fatality rate of ≥30% with and ≥60% without transplantation. There exists only one serotype of the HAV, but the pathogenicity might differ between HAV genotypes or nucleotide

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ABBREVIATIONS: BMI = Body mass index CD4 = T helper cells; CI = Confidence interval; CMI = Cell-mediated immunity; EIA = Enzyme immune assay; FU = Follow-up; GMC = Geometric mean concentration; HAV = Hepatitis A virus; HIV = Human immunodeficiency virus; IgG = Immunoglobulin isotype G; IgM = Immunoglobulin isotype M; MSM = Men who have sex with men; UMV = Universal mass vaccination; US = United States; VFR = Visiting friends and relatives; WHO = World Health Organization

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sequence variants⁷ and/or might differ due to genetic host factors,⁸ both topics, however, are still not fully elucidated.

Infection-induced immunity persists for life. The humoral immune response is mainly directed against the capsid proteins of the non-enveloped 27 nm virus. At first, anti-HAV IgM antibodies appear 5–10 days before the onset of symptoms; their presence is diagnostic for an acute HAV infection and they only persist for 4 to 6 months. Anti-HAV IgG antibodies start rising sharply only during the first weeks of illness and can reach several 100,000 mIU/ml,⁹ with 10–20 mIU/ml being the cutoff for seroprotection.¹⁰ The IgG antibodies possess virus neutralizing activity and protect from re-infection. The acute cell-mediated immune response (CMI) is responsible for the pathogenesis of hepatitis A. Whether cytolytic T-Cells (CD8+) and/or other mechanisms of the CMI are eventually causing the hepatocyte injury and necrosis, is still debated.¹¹

1.2. Hepatitis A epidemiology^{3,4,12}

As a human enteral virus infection, typically associated with poor hygiene and lack of access to clean water,¹³ hepatitis A is – similar to poliomyelitis – theoretically eradicable. Hepatitis A continues to represent a significant worldwide health issue. It was estimated to have caused in 2005 – apart from approximately 200 million subclinical and oligo-symptomatic hepatitis A virus (HAV) infections¹ – 33 million cases of symptomatic illness² and 35,000 deaths.¹ The Global Burden of Disease (GBD) project estimates a much lower figure of 14,900 deaths in 2013, a 40% reduction since 1990.¹⁴ These global evaluations are, however, not directly comparable, as they are based on different data sets and are using different evaluation methods.

In high-endemicity countries, 100% anti-HAV IgG seroprevalence is reached before adulthood, with the majority of children being infected by the age of 5 years. While infants are protected by maternal anti-HAV antibodies,¹⁵ children up to 5 years of age are the main source of infection. Levels of hepatitis A endemicity are defined on the basis of seroprevalence: “high ($\geq 90\%$ by age 10 years); intermediate ($\geq 50\%$ by age 15 years, with $< 90\%$ by age 10 years); low ($\geq 50\%$ by age 30 years, with $< 50\%$ by age 15); and very low ($< 50\%$ by age 30 years).”^{1,16}

Whereas hepatitis A already started to disappear from Northern European and other industrialized countries after the second world war due to high hygiene standards, endemicity levels only started to decrease around the world over the last three decades.¹⁷ Access to clean water and better sanitary conditions are the main reasons for this worldwide ‘spontaneous’ decline.^{16,18} Simultaneously, the disease burden has paradoxically increased in many places: the improvements in hygiene and access to clean water shifted the first HAV contact to older age groups. This trend toward intermediate endemicity means that, although many children are still being infected and are spreading the HAV, many adults remain susceptible and consequently more severe cases can then be observed and hepatitis A infections often occur as outbreaks.

Contrary to the postulated role of natural boosting in maintaining long-term immunity for certain vaccine-preventable infections,¹⁹ there is no proven natural booster phenomenon for hepatitis A in a given population once anti-HAV immunity has been established after natural infection⁹ (section 3.4.1).

2. Hepatitis A vaccines^{1,3,4}

Hepatitis A vaccines have been available since the early 1990s. All based on the single serotype of the HAV, they are either formalin-inactivated or live attenuated. The currently available inactivated HAV vaccines (Table 1) are all adjuvanted with aluminum hydroxide. The inactivated vaccines developed in Europe and in the US were launched internationally in the early 1990s. The Chinese inactivated vaccines were licensed in the early 2000s and are now mainly used in Asia. Live-attenuated HAV vaccines (Table 1) were developed in the early 1990s in China,^{20–22} only in recent years were they licensed in a few other countries (Bangladesh, Guatemala, India, Philippines, Thailand).^{3,23}

Initially developed for individual prophylaxis, HAV vaccines are now increasingly used to control hepatitis A in endemic areas, in the hope to eliminate it in the long run. The indications for use are: (1) Individual prophylaxis for at-risk populations, such as travelers, children in day care, health care and laboratory workers, and MSM; (2) Outbreak control in the case of an emerging epidemic; (3) Population prophylaxis, either as regional mass or targeted vaccination for pediatric

Table 1. Monovalent and hepatitis A antigen containing HAV vaccines brands reported on in the publications reviewed (Tables 2–5).

Trade name	HAV strain	Adjuvant	HAV antigen Dose/Volume (mL) per Injection		Manufacturer (Country)
			Pediatric	Adult	
<i>Inactivated vaccines</i>					
Avaxim	GBM	Aluminum hydroxide	80 U/0.5	160 U/0.5	Sanofi Pasteur (France)
Epaxal ^a	RG-SB	Virosomes	12 IU/0.25	24 IU/0.5	Crucell/Janssen ^b (Switzerland)
Havrix	HM-175	Aluminum hydroxide	720 EU/0.5	1440 EU/1.0	GSK (Belgium)
Healive	TZ84	Aluminum hydroxide	250 U/0.5	500 U/1.0	Sinovac Biotech (China)
Twinrix (+HBsAg)	HM-175	Aluminum hydroxide	360 EU/0.5	720 EU/1.0	GSK (Belgium)
VAQTA	CR-326	Aluminum hydroxide	25 U/0.5	50 U/1.0	MSD (USA)
<i>Live-attenuated vaccines</i>					
Biovac-A	H2	None	6.5log TCID ₅₀ /0.5 mL	6.5 log TCID ₅₀ /1.0 mL	Zhejiang Pukang Biotech (China)
HAVAC	LA-1	None	6.5log TCID ₅₀ /0.5 mL	6.5 log TCID ₅₀ /1.0 mL	Changchun Inst. of Biologic Products (China)

Contents of this table adapted/taken from WHO (2019),³ Lemon et al. (2018),⁴ and Cui et al. (2014),²⁰ ^aFor economic reasons not on the market anymore; ^bFormerly ‘Berna Biotech’ (Swiss Serum & Vaccine Institute)

Abbreviations: HAV: hepatitis A virus; IU: international units; EU: ELISA units; U: antigen units; HBsAg: hepatitis B virus surface antigen; TCID: tissue culture infecting dose

or adolescent populations at risk or as universal mass vaccination (UMV) of children in their second year of life.

2.1. Inactivated vaccines^{1,3,4}

All inactivated HAV vaccines are licensed with an intramuscular two-dose schedule (0/6–12(–18) months) which induces in healthy children and young adults (<40–50 years of age) seroconversion (≥ 20 mIU/mL) in $\geq 95\%$ after the first (priming) dose and in virtually 100% after the second (booster) dose, with maximum responses of 5,000 to 10,000 mIU/mL. Anti-HAV IgG antibody concentrations of ≥ 10 mIU/mL are considered seroprotective (= correlate of protection^{10,24}), although ≥ 20 mIU/mL is the cutoff most widely used for licensing and in clinical studies. The antibodies produced during the first few weeks include a low level of anti-HAV IgM antibodies²⁵ which contribute, however, significantly to the early immune response. It is, therefore, important to note that the clinical development of HAV vaccines was done using total antibody (IgM + IgG) enzyme immunoassays (EIAs). When using anti-HAV IgG only assays, the early immune response 1 month following the priming dose can be missed, especially in immune-compromised subjects.²⁶ Similar to the natural infection, the vaccine-induced immunity comprises, already after the priming dose, a CMI response which establishes immune memory.²⁷

Apart from age which can in subjects aged >40–50 years lower the priming response (first dose) to only 60–70% seroconversion,^{28,29} there are other host factors which can rise or blunt the humoral immune response:³⁰ Female gender increases, and high BMI, HIV infections, or maternal antibodies blunt the response (section 3.3).

No- or low-response to two doses of inactivated HAV vaccines is very rare. Clinical breakthrough infections have been reported in adult travelers (some elderly or HIV positive) after the priming dose (see references 28–34 in Mayorga et al. 2016³¹) or after two doses in two subjects, immunocompromised through HIV infection³² and acute myeloid leukemia,³³ respectively.

Protective efficacies of 95–100% have, for three of the inactivated HAV vaccines, been proven in placebo-controlled trials in epidemic³⁴ or endemic^{35,36} settings. Herd immunity was documented early on as an important secondary effect within the scope of UMV, as recorded in Israel³⁷ (section 4.2).

During more than 20 years of use and a cumulative experience of several hundred million doses, the safety of inactivated HAV vaccines has never been an issue. Although there is some short-term reactogenicity, vaccine-related serious adverse events have been extremely rare. The combined hepatitis A & B vaccines (Table 1) are, regarding safety and anti-HAV immunogenicity, very similar to the monovalent HAV vaccines.

2.2. Live-attenuated vaccines^{1,3,4,20–23}

The information on live-attenuated HAV vaccines is rather limited, partly due to the Chinese language barrier. These vaccines are administered subcutaneously and are used in a single-dose schedule. Whereas vaccinees rarely present with systemic adverse events, such as fever, rash and elevated liver

transaminases, it has been reported that over half of subjects, who were apparently infected orally by excreted vaccine viruses, presented with a mild ‘HAV infection.’²⁰ However, no serious adverse events and no reversion to virulence have been reported. Following vaccination, antibody levels of only a few hundred mIU/mL’s are reached and seroconversion is 10–20% lower and protective efficacy at 90–95% is somewhat inferior compared to inactivated HAV vaccines. Although live-attenuated HAV vaccines seem to prevent asymptomatic HAV infections even less effectively than overt hepatitis A,³⁸ the use in UMV programs in China has shown these vaccines to be efficacious in eliminating hepatitis A, to a large extent due to herd immunity effects.²² During the first month after vaccination, a quarter of vaccinees excrete HAV in the stool;^{39,40} the isolated HAV strains were genetically stable.⁴⁰ The vaccine efficacy was in a large population study shown to persist at 95% during several years, despite seroconversion rates falling to 80% within a couple of years.²¹

3. Immunological long-term effects of vaccination

A systematic review on the long-term protective effects of hepatitis A vaccines concluded in 2012 that both inactivated and live-attenuated vaccines are able to provide real-time seroprotection for up to 15 years; however, in future follow-up studies any co-variables potentially affecting long-term protection should also be assessed.⁴¹ Meanwhile, more data have been published on the duration of the seroprotection, the immune memory persistence, the influence of vaccine-independent co-variables, such as maternal antibodies, sex, age, BMI, and HIV infection, and the assumed ‘natural boosting’ phenomenon through circulating HAV.

3.1 Persistence of humoral immune response

Only data from long-term studies with ≥ 10 years of follow-up for 2- or 3-dose immunization regimens, including long-term studies reporting mathematical modeling estimations and data of ≥ 5 -year follow-up single-dose studies, are presented here. Furthermore, only the newest publication data are used from long-term projects with multiple consecutive publications.

3.1.1. Two (or three) doses of inactivated HAV vaccines

Real-time seroprotection following immunization with two doses (or three doses with lower antigen content than currently licensed) of inactivated monovalent HAV vaccines, or of a HAV antigen containing combined hepatitis A + B vaccine, has been investigated over ≥ 10 years in children (incl. infants & toddlers),^{42–53} adolescents^{54,55} and adults^{56–60} (Table 2). These studies show quite consistently that healthy adults, as well as children and adolescents, will, following standard immunization schedules (0/6–12 months), be real-time seroprotected for up to 15–20 years in 95–100% of vaccinees, while mathematical modeling estimations extend this period up to 30–40 years in 84–97% of subjects.^{43–45,50,56,59,60} Of note is the observation by Chappuis et al.⁵⁶: the validation of the modeling estimates, based on the 15-year real-time data with the 20-year follow-up results, revealed antibody levels higher than predicted, i.e. between the 15 and 20-year visits a further slowing of the antibody decline was

Table 2. Long-term immunogenicity after 2 or 3 doses of inactivated HAV vaccines: real-time follow-up (≥10 years) and modeling estimates.

Author (Publication Year)	N Subjects ^a (age) ^b	Vaccine	Immun. schedule (months)	Follow-up period	Seroprotection cutoff	Seroprotection rate	GMC (mIU/mL)	Modeling estimates ^c (years projected, seroprotection rate)
<i>Children</i>								
Bian (2010) ⁴²	110 (2-3y)	Havrix 720	0, 6	10 years	20 mIU/mL	99.1%	61.6	nd
Espul (2020) ⁴³	51 (11–23 m)	Avaxim 80	0, 6	10 years	3 mIU/mL	100%	352.2	After 30 years: 85% with ≥3mIU/mL
Lopez (2015) ⁴⁴	30 (1–4y)	Avaxim 80	0, 6	14–15 years	20 mIU/mL	100%	253.0	After 20/25/30 years: 95.8%/95.8%/87.5% with ≥20mIU/mL
Plumb(2017) ⁴⁵	17 (3–6y)	Havrix 360	0, 1, 2	20 years ^d	20 mIU/mL	76.5%	60.0	After 25/30 years: ≥95%/93% with ≥20mIU/mL
	18 (3–6y)	Havrix 360	0, 1, 6	20 years ^d	20 mIU/mL	94.4%	110.0	
	17 (3–6y)	Havrix 360	0, 1, 12	20 years ^d	20 mIU/mL	94.1%	184.0	
Racznik (2013) ⁴⁷	5 (3–6y)	Havrix 720	0, 6–12	10 years	20 mIU/mL	100%	160.0	nd
	8 (3–6y)	Havrix 720	0, 6–12	12 years	20 mIU/mL	100%	298.0	
	5 (3–6y)	Havrix 720	0, 6–12	14 years	20 mIU/mL	100%	80.0	
Sintusek (2018) ⁴⁹	40 (1–6y)	Inactivated HepA vacc.	2 doses	13–18 years	Not indicated	97.5%	–	nd
Spradling (2016) ⁵⁰	20 (6 m) – mAb ^e	Havrix 720	0, 6	15 years	20 mIU/mL	75%	49.0	Overall 64% seropositive 30 years after 2nd dose
	18 (6 m) + mAb	Havrix 720	0, 6	15 years	20 mIU/mL	61%	27.0	
	17 (12 m) – mAb	Havrix 720	0, 6	15 years	20 mIU/mL	100%	78.0	
	9 (12 m) + mAb	Havrix 720	0, 6	15 years	20 mIU/mL	67%	35.0	
	19 (15 m) – mAb	Havrix 720	0, 6	15 years	20 mIU/mL	100%	58.0	
	12 (15 m) + mAb	Havrix 720	0, 6	15 years	20 mIU/mL	67%	50.0	
Mosites (2020) ⁵³	13 (6 m) – mAb ^e	Havrix 720	0, 6	20 years	20 mIU/mL	62%	29.0	Overall 55.3%/49.8%/45.7% seropositive 25/30/35 years after 2nd dose
	10 (6 m) + mAb	Havrix 720	0, 6	20 years	20 mIU/mL	30%	17.0	
	15 (12 m) – mAb	Havrix 720	0, 6	20 years	20 mIU/mL	87%	37.0	
	8 (12 m) + mAb	Havrix 720	0, 6	20 years	20 mIU/mL	50%	11.0	
	19 (15 m) – mAb	Havrix 720	0, 6	20 years	20 mIU/mL	84%	54.0	
	10 (15 m) + mAb	Havrix 720	0, 6	20 years	20 mIU/mL	70%	32.0	
Van Damme (2011) ⁵¹	120 (1–11y)	Twimrix	0, 6	10 years	15 mIU/mL	100%	601.6	nd
Wang (2020) ⁵²	217 (3.6–4y)	Healive	0, 6	11 years	20 mIU/mL	100%	166.2	After 30 years 64.6% with ≥20mIU/mL
	73 (3.6–4y)	Havrix jun.	0, 6	11 years	20 mIU/mL	100%	117.1	After 30 years 59.8% with ≥20mIU/mL
<i>Adolescents</i>								
Beran (2016) ⁵⁴	74 (12–15y)	Twimrix	0, 6	15 years	15 mIU/mL	100%	387.5	nd
	88 (12–15y)	Twimrix jun	0, 1, 6	15 years	15 mIU/mL	100%	299.4	nd
Diaz-Mitoma (2008) ⁵⁵	22 (6–15y)	Twimrix jun	0, 1, 6	10 years	15 mIU/mL	100%	680.0	nd
<i>Adults</i>								
Chappuis (2017) ⁵⁶	94 (15–39y)	Epaxal	0, 12	20 years	10 mIU/mL	100%	226.6	For ≥41.5 years 95% with ≥10mIU/mL
	48 (20–70y)	Havrix 720	0, 1, 12	5 years	20 mIU/mL	98.9%	503.0	For ≥33.0 years 95% with ≥20mIU/mL
	7 (20–70y)	Havrix 720	0, 1, 12	10 years	20 mIU/mL	100%	250.0	For 21 years GMC remains ≥20mIU/mL ^f
Rendi-Wagner (2007) ⁵⁸	813 (~53y) ^g	Havrix 720	0, 1, 6–12	10 years	20 mIU/mL	97.9%	406.1	nd
Theeten (2015) ⁵⁹	36 (17–40y)	Havrix 1440	0, 6–12	20 years	15 mIU/mL	94.4%	312.0	After 30/40 years: ≥95%/≥90% of subjects with ≥15 mIU/mL
	86 (17–40y)	Havrix 1440	0, 12	20 years	15 mIU/mL	98.8%	317.0	
Van Damme (2017) ⁶⁰	18 (18–21y) ^h	Twimrix	0, 1, 6	20 years	15 mIU/mL	100%	511.9	After 40 years: ≥97% of subjects with ≥15 mIU/mL
	25 (18–41y) ^h	Twimrix	0, 1, 6	20 years	15 mIU/mL	96%	229.3	

^aN = number of subjects at end of follow-up; ^bAge at vaccination; y = years, m = months; ^cModels used in the studies listed: piecewise linear model [Espul (2020)⁴³], log-linear model [Hammit (2008)⁵⁷], mixed effects models [Lopez (2015)⁴⁴], fractional polynomial regression [Plumb (2017)⁴⁵, Mosites (2020)⁵³], random effects model [Spradling (2016)⁵⁰], linear mixed model [Wang (2020)⁵², Chappuis (2017)⁵⁶, Theeten (2015)⁵⁹, Van Damme (2017)⁶⁰]; ^dMosites (2018)⁴⁶ after 22 years of follow-up 16/16/14 subjects were seroprotected in 75%/94%/93% and had GMCs of 46/122/138 mIU/mL (no new modeling estimates); ^e maternal antibodies; ^f Estimate based on N = 127 → N = 7 (years 0 → 10) adult population; ^g Age at follow-up; ^h two separate phase IV studies with identical follow-up

Abbreviations: GMC: geometric mean concentrations; nd: not done

observed, especially when compared to the earlier analysis (9–11-year visit) of the same study population.⁶¹ This trend should be further observed and confirmed with the few follow-up studies still underway. From the data currently available one can now conclude that healthy children, adolescents, and young adults are, after a complete vaccination course, most likely protected for life and do not need a late second booster.⁶²

A range of mainly pediatric studies with shorter follow-up periods of 5 to <10 years document in the majority 100% seroprotection during their real-time follow-up,^{55,63–67} while some report slightly lower rates of 96–99%.^{68–70} Three publications provide, in addition, model-based predictions: using linear-mixed models long-term seroprotection was calculated to last for two different vaccine doses a median 25.1 and 28.3 years in 1–17-year-old Belgian children (≥ 10 mIU/mL, 5.5 year FU),⁶⁷ a median 18.7–19.1 years in Israeli and Beduin toddlers 12–15 months of age (≥ 10 mIU/mL, 7.5 year FU)⁶⁸ and 13.1 and 9.7 years in 85% and 89% of 1–8-year-old Chinese children (≥ 20 mIU/mL, 5 year FU) vaccinated with Healive and Havrix Junior, respectively.⁷⁰ According to 6.5-year follow-up data in 1.5–6.5-year-old Nicaraguan children vaccinated at 0/15 months³⁶ seroprotection (≥ 10 mIU/mL) was estimated to last in $\geq 95\%$ of vaccinees for 16.2 years.⁶⁶ A fifth, older study reports for 1–7-year-old Taiwanese children (≥ 20 mIU/mL, 5 year FU) a considerably longer seroprotection of 24.5 years, calculated, however, for geometric mean concentration (GMC) changes over time and using a rather crude linear regression model.⁶⁵

The limited response in the toddlers from Israel⁶⁸ might have been caused in part by inhibiting maternal antibodies which were still detected at low levels (11–151 mIU/mL) in 10% of them at enrollment.⁷¹ Interestingly, the finding by Van Herck et al., assessing the antibody persistence in 1 to 17-year-old Belgian children after 5.5 years, was that the younger children (<8 years) achieved lower GMC's and that their antibody levels declined faster.⁶⁷ Longer follow-ups of these pediatric studies are needed. The dynamics of the antibody decline changes over time and seem to continuously slowdown further or nearly stabilize, as shown in children (originally aged 3–6 years) between 10 and 17 years post-vaccination⁷² and in young adults between 15 and 20 years after vaccination.⁵⁶

3.1.2. Single dose of inactivated HAV vaccines

Pediatric studies investigating prospectively the efficacy of single-dose immunization with inactivated HAV vaccines were started in the early-mid 2000s.⁷³ One was aware that already the first dose of HAV vaccine establishes in adults a stimutable memory immune response.^{74–76} Argentina was the first country to introduce single-dose UMV in toddlers in 2005.⁷⁷ Immunogenicity data for inactivated HAV vaccines (all in young children) have currently reached 10 years of follow-up evaluations in a first study,⁴³ and the single-dose results are looking promising, with seroprotection rates of 100% (10 year follow-up),⁴³ 95.2% (7.5 years),³¹ 97.4% (6.3–9.2 years),⁷⁸ 92.9% (4 years),⁷⁹ and 85.9% (5 years)⁸⁰ (Table 3). Statistical modeling with 10 years of follow-up data resulted in a 30-year seroprotection (≥ 3 mIU/mL) for 89% of children after single-dose vaccination.⁴³ Successful boosting after loss of measurable antibodies has been documented^{31,43,80,81} (Table 3).

Table 3. Long-term immunogenicity after single dose of inactivated HAV vaccine in children: 4–10 years real-time follow-up and booster effect.

Author (Publication Year)	N Subjects ^a (age: months) ^b	Vaccine	Follow-up period	Seroprotection cutoff	Seroprotection rate	GMC (mIU/mL)	Booster dose	Booster effect
Espul (2020) ⁴³	318 (11–23)	Avaxim 80	5 years	10 mIU/mL	99.7%	122.5	Individual cases	Booster given to 6 non-responders at year 1 and to n = 1/1/1 children (<10mIU/mL) at years 3,4,5; all with strong booster response ^d . Modeling estimate: At 30 years 89% with ≥ 3 mIU/mL
Mayorga (2016) ³¹	190 (11–23) 104 (31–65)	Epaxal	10 years 7.5 years	3 mIU/mL ^c 10 mIU/mL	100% 95.2%	78.2 81.0	For all at 7.5 years	Boosting elicited 29.7-fold increase of anti-HAV levels, incl. 4 children with <10mIU/mL
Urueña (2016) ⁷⁸	1088 (11–18)	Various HAV vaccines ^e	7.7 years (6.3–9.2)	10 mIU/mL	97.4%	170.5	Individual cases	Children with <10mIU/mL at end of FU offered booster, no post-booster anti-HAV antibodies measured
Vizzotti (2015) ⁷⁹	1139 (13–22)	Various HAV vaccines ^e	4 years	10 mIU/mL	92.9%	97.9	Individual cases	Children with <10mIU/mL at end of FU offered booster, no post-booster anti-HAV antibodies measured
Zhang (2017) ⁸⁰	85 (18–60)	Healive	5 years	20 mIU/mL	85.9%	76.3	Individual cases	12 children received a 2 nd dose between year 1 and 5: GMC 45.8 → 911.4 mIU/mL

^aN = number of subjects at end of follow-up; ^bAge at vaccination; ^cChange of test system and cutoff for >5 – 10 year follow-up; ^dEspul (2017);⁸¹ ^eHAV vaccines used for UMV in Argentina: Avaxim 80, Virohep A Junior (Epaxal Junior), Havrix 720

Abbreviations: GMC: geometric mean concentrations; FU: Follow-up; HAV: hepatitis A virus; UMV: universal mass vaccination.

3.1.3. Live-attenuated HAV vaccines

Up to 17 years of follow-up data have been published for single-dose live-attenuated HAV vaccines with somewhat lower seroprotection rates compared to inactivated HAV vaccines: 87.6% (10 years follow-up),⁸² 62.0% (17 years),⁸³ 97.3% (5 years),⁸⁴ 71.8% (8 years),⁸⁵ 90.7% (5 years)⁸⁰ and 80.2/81.3% (10/15 years)^{86,87} (Table 4). Although live-attenuated HAV vaccines show a somewhat 'weaker' immunogenicity compared to inactivated vaccines, their single-dose humoral immune response can be boosted easily at 1 year,⁸⁵ as well as, in cases of loss of measurable antibodies, after 17 years of follow-up.⁸³ For the live-attenuated single-dose vaccines no mathematical long-term seroprotection estimates have, to our knowledge, been published so far.

3.2. Immune memory persistence

It has recently been shown that a single dose of inactivated HAV vaccine promotes HAV-specific cellular memory immune responses similar to natural infection, and that the HAV-specific T-cell immunity induced by the primary vaccination persists independently of the circulating antibody levels achieved.²⁷ Thus, the antibody memory recall responses do not only reflect residual B-cell and plasma cell response capacity⁸⁸ but also indicate that the first vaccine dose elicits an efficient priming of the immune system via an early proliferative T-cell response. Hence, after the first (priming) dose of a two-dose inactivated HAV vaccine, the second (booster) dose always uses this cell-mediated immune memory to produce in all age groups within 10–14 days a rapid humoral antibody booster response, with an at least 20–30-fold increase of antibody levels.^{28,89} This response applies after booster intervals of 6, 12, or 18 months, as licensed for each particular vaccine.^{1,73} The terms 'anamnesic response' and 'immune memory persistence', for which to our knowledge no practically relevant criteria have been defined, are generally used when the booster interval exceeds 2–3 years. By then some of the primed vaccinees start to lack measurable anti-HAV antibodies. Following the second (booster) dose, antibodies will increase ≥ 20 -fold or reappear and rise quickly to high levels (usually ≥ 1000 mIU/mL), even after many years.⁷³

Immune memory following HAV vaccination was initially documented in the early 2000s among adult travelers receiving their booster (second dose) 4–8 years too late.^{74–76} Such intact humoral immune memory responses, even in the case of loss of any measurable anti-HAV antibodies, have in the meantime been documented for young healthy children after 1 to 5 years⁸¹ and after 7.5 years,³¹ as well as in 20 to 73 years old healthy adult travelers after an interval of up to nearly 11 years.⁹⁰ Strong immune memory responses have also been reported for healthy young adults who had lost measurable antibodies 20 years following a two-dose immunization with either a monovalent HAV⁵⁹ or a combined HAV + HBV vaccine.⁶⁰ Furthermore, 12 years after a two-dose vaccination with an inactivated HAV vaccine, a rapid and strong anamnestic antibody response after vaccine re-exposure was documented in 30 of 31 adults as indirect evidence of immune memory.⁹¹

Humoral and cell-mediated immune memory responses have also been shown 17 years after a single dose of live-

attenuated vaccine in study participants (healthy children) who had lost measurable antibodies: upon a booster dose 11 of 13 (84.6%) vaccinees seroconverted and the reactivation elicited robust memory B- and T-cell responses in all subjects (Table 4).⁸³

For the elderly (≥ 50 –60 years of age) very little long-term data have been published regarding immune memory. In the study investigating the memory response following booster intervals of up to 10.7 years in 130 adult travelers aged 20–73 years, pre-booster seroprotection rates were lower in the older (≥ 50) than in the younger (< 50) age group (47% versus 63% at ≥ 10 mIU/ml). Nevertheless, both age groups achieved 100% post-booster seroprotection, there were no significant differences in post-booster anti-HAV GMCs and the booster intervals did not influence the memory response in either of the two age groups.⁹⁰ Furthermore, in adults aged over 40 years (mean 59.0) immune memory was documented 4 years after two doses of a combined hepatitis A and B vaccine in seronegative subjects upon an additional booster dose.⁹²

For immunocompromised patients, long-term immune memory data exist only for HIV-infected patients. During a large outbreak intervention in an HIV-positive population of MSM, it was shown that re-vaccination with an inactivated HAV vaccine in 75 subjects whose anti-HAV antibodies had waned completely after a median interval of 6.2 years resulted in 88% of subjects in seroconversion 4 weeks after the first revaccination dose and in 98.7% following a second dose.⁹³ In another study, 6 of 29 HIV-positive children had lost HAV seropositivity 7 years after vaccination with an inactivated HAV vaccine; upon revaccination (2 doses), 83.3% (5/6) seroconverted after the first dose.⁹⁴

3.3. Vaccine-independent co-variables and persistence of immunity

Numerous co-variables can enhance or diminish the immune response of vaccines, as reported in a recent literature review on host intrinsic, perinatal, extrinsic, behavioral, nutritional, environmental, vaccine-related and administration-related factors.³⁰ Long-term data exist for few of these over 40 factors. In the case of hepatitis A vaccination, to our knowledge, only maternal antibodies, sex, age, BMI, and HIV infection have been investigated regarding long-term effects.

3.3.1. Maternal antibodies

Impairment of vaccine immunogenicity by maternal antibodies has been documented in neonates and infants for live vaccines, subunit vaccines, and inactivated vaccines, whereby the maternal antibodies seem to inhibit the B-cell responses through a cross-link between the B-cell receptor with the antibody Fc γ RIIB receptor by a vaccine-antibody complex.⁹⁵

Routine vaccination of young children is an effective strategy to control hepatitis A.¹ Timing is critical, as high levels of passively acquired maternal HAV antibodies, which protect the child in an endemic setting during most of the first year of life,¹⁵ may strongly impede the anti-HAV antibody response when the two-dose^{89,96,97} or three-dose^{98,99} immunization is started before the age of 12 months. Maternal HAV antibodies have a serum half-life of ~ 40 days¹⁵ and, as longitudinal studies

Table 4. Long-term immunogenicity after single dose of live-attenuated HAV vaccine in children: 5–17 years real-time follow-up and booster effect.

Author (Publication Year)	N Subjects ^a (age in years) ^b	Vaccine	Follow-up	Sero-protection cutoff	Sero-pro-tection rate	GMC (mIU/mL)	Booster dose	Booster effect
Bhave (2015) ⁸²	112 (1–12)	Biovac-A	6 years	20 mIU/mL	77.7%	66.6 ^d	Variable (individual cases)	Booster given to 4 non-responders at year 1 and to 9 children (<20mIU/mL) at year 3 (booster response not reported)
	121 (1–12)	Biovac-A	10 years	20 mIU/mL	87.6% ^c	100.5 ^d		
Chen (2018) ⁸³	47 (3/7)	Biovac-A	17 years	20 mIU/mL	62.0%	64.8 ^e	N = 31 (year 17)	N = 18 seropositive: GMC 67.6 → 1832.1; N = 11 of 13 seronegative (84.6%) serocon-verted: GMC 8.0 → 661.3 mIU/mL; all n = 31 with robust memory B- and T-cell response
Mitra (2015) ⁸⁴	111 (1–12)	Biovac-A	5 years	20 mIU/mL	97.3%	127.1	nd	–
Wang (2007) ⁸⁵	85 (1–12)	Biovac-A	8 years	20/30 mIU/mL	71.8%	89.0	nd	–
	49 (1–12)	Biovac-A	8 years ^f	20/30 mIU/mL	98.0% ^f	262.8 ^f	N = 47	Booster at month 12 → 100% seropos. ^g , GMC: 106.9 mIU/mL → 3133.5 mIU/mL ^g
Zhang (2017) ⁸⁰	97 (1.5–5)	Biovac-A	5 years	20 mIU/mL	90.7%	66.8	Individual cases	21 children received a 2 nd dose between year 1 and 5: GMC 39.0 → 955.1 mIU/mL
Zhuang (2005) ⁸⁶	155 (1–3)	Biovac-A	10 years	20 mIU/mL	80.2%	145.0	nd	–
Zhuang (2010) ⁸⁷	n.i. ^h	Biovac-A	15 years	20 mIU/mL	81.3%	128.0	nd	–

^aN = number of subjects at end of follow-up; ^bAge at vaccination; ^cIncluding n = 13 subjects turning seroneg. (and boosted) at years 1 and 3; ^dGMC of n = 87 (6 yrs)/n = 106 (10 yrs) still anti-HAV positive subjects and not having received booster; ^eGMC of n = 29 still anti-HAV positive subjects; ^f7 years after 0/12 months (priming + booster) immunization; ^g1 month after booster dose (month 13 of study); ^hnot indicated (Engl. Abstract only)

Abbreviations: GMC: geometric mean concentrations; nd: not done

have shown, will in a third of children persist up to 12 months and beyond,^{15,100,101} depending on the average anti-HAV antibody levels in a given maternal population. Most studies have nevertheless shown that all infants and 12–15-month-old children primed in the presence of maternal anti-HAV antibodies demonstrated following the weak primary response a good antibody response when receiving their second dose 6 months^{89,97,102} or 12 months⁹⁶ later. An anamnestic booster response after very early basic vaccination at age 2, 4, and 6 months was documented upon an extra booster dose at 1 year.⁹⁹ In view of these facts, it is now recommended that young children in endemic areas should preferably not be vaccinated against HAV before 12 months of age.^{1,3}

While the negative effect of the maternal HAV antibodies on the short-term immune response is well documented, there have only been three studies published on possible long-term effects. In Turkey, 43 anti-HAV positive infants vaccinated at age 2, 4, and 6 months showed an anamnestic booster response at age 4 years, even those 10 children who had lost measurable antibodies.¹⁰³ US infants, originally vaccinated at 2, 4, and 6 months of age and born to anti-HAV positive mothers had after 6 years still significantly lower antibody concentrations than the children born to anti-HAV negative mothers; only 4 of 17 (24%) versus 21 of 31 (68%), respectively, were still seroprotected (≥ 33 mIU/mL); however, an anamnestic sero-response upon boosting occurred in almost all children whose antibodies had waned (4 of 6 [67%] versus 5 of 5 [100%]).¹⁰⁴ Negative long-term effects were also reported following a 15-year follow-up of Alaskan infants vaccinated with a two-dose (0/6 months) regimen, starting at 6, 12, or 15 months of age (Groups 1, 2, 3). Whereas seropositivity persisted for 10 years between 90% and 100%, regardless of the original presence of maternal antibodies,⁴⁸ the follow-up at 15 years showed a different picture: seroprotection (≥ 20 mIU/mL) had decreased to 75% and 61% in subjects with vaccination start at 6 months and born without or with maternal anti-HAV antibodies, respectively, and to 67% among maternal anti-HAV-positive subjects who initiated vaccination at ages 12 or 15 months. Those vaccinated at 12 or 15 months of age without maternal anti-HAV antibodies remained 100% seroprotected.⁵⁰ This unexpected late and pronounced decrease of seropositivity suggests that being exposed to maternal antibodies had a kind of 'silent' blunting effect even in the older infants and toddlers, with vaccinations starting at 12 (group 2) and 15 (group 3) months. At baseline only the 6 months old infants (group 1) had sizable maternal anti-HAV antibody levels (baseline mIU/mL GMC's (95% CI) for Gr 1: 295.0 (184–473); Gr 2: 18.7 (15.5–22.7); Gr 3: 15.6 (8.8–16.3) and seropositivity (≥ 10 mIU/mL) rates of 94%, 15%, and 3%, respectively.⁸⁹ It seems that maternal antibodies are still effective inhibitors at concentrations below the detection level. Either that or one could hypothesize that maternal anti-HAV antibodies somehow downregulate the neonatal, or even fetal immune system, with respect to the response against HAV antigens. Mathematical modeling indicated that anti-HAV seropositivity should persist in 84% among all those still seropositive at age 15–16 years for 30 years after the second dose.⁵⁰ At the 20-year follow-up (Table 2) the proportion of seroprotected (≥ 20 mIU/mL) subjects was estimated to drop to 50% by 14.2 years after

the second dose for group 1, 26.9 years for group 2, and 23.8 years for group 3, irrespective of the maternal antibody status.⁵³

Vaccine-derived maternal HAV antibodies present during the first year of life should be no problem: the long-term follow-up of the Alaskan children showed that the immune response in infants vaccinated at the age of 6 months and born to mothers with vaccine-induced immunity did, during the 15-year follow-up, not differ from those infants born to anti-HAV negative mothers.^{48,50}

The effect of maternal antibodies on CMI responses to HAV vaccines has to our knowledge not been investigated. The few existing human studies on measles, mumps, and tetanus show that, despite humoral blunting by the passively acquired maternal antibodies, the vaccine-induced cellular responses are largely not affected and that a robust CMI response persists.¹⁰⁵

We found no published data on the short- or long-term influence of maternal antibodies on the immune response of live attenuated HAV vaccines.

3.3.2. Sex, age, and BMI

Sex. Upon immunization with inactivated HAV vaccines, females respond with up to 2–3x higher anti-HAV antibody levels than males after the priming and after the booster dose. This applies to young adults,^{28,74,106,107} the elderly,^{28,92,108,109} and also to children (1–7 years)^{50,65,68} and adolescents (11–17 years).⁶⁷ This sex difference persists throughout real-time follow-up for up to 10–11 years^{58,61} or even 20 years⁵⁶ in young healthy adults. Even up to 11 years after a first priming dose, females still had 3x higher pre-booster antibody levels than males with a 74% versus 41% higher residual seroprotection rate.⁹⁰ When looking at predicted durations of seroprotection in adults, the sex difference begins to disappear after some 10 years, because the originally much lower antibodies in males are declining slower than in females.⁶¹ Based on 10- and 20-year real-time data of the same study population, both sexes are estimated to perform equally well with predicted median seroprotection (≥ 10 mIU/mL) durations of 51–52 years (females) versus 54–55 years (males)⁶¹ and 77.5 years versus 73.7 years,⁵⁶ respectively. In female infants and toddlers, aged 6–15 months at the time of vaccination, higher GMCs persisted in two prospective studies for 7.5 years⁶⁸ and 15 years,⁵⁰ respectively. Young girls aged 1 to 7 years had higher GMCs than boys during 5 years of follow-up.⁶⁵ Higher antibody levels were found in 11–17 year old females throughout a 5.5 year follow-up and approximately 25–40% lower median predicted seroprotection durations in male as compared to female adolescents.⁶⁷

Age. As for the majority of vaccines, young age (infants and children <8 years)^{67,72} and older age (≥ 50 years)^{28,29,108,110} are associated with lower anti-HAV antibody responses following immunization with inactivated HAV vaccines. In two studies on long-term effects, an age of ≥ 61 years and an age of ≥ 50 years correlated with a lower antibody response after 4 years⁹² and 10 years,⁵⁸ respectively. In a booster interval study in travelers, pre-booster seroprotection (≥ 10 mIU/ml) rates were after 9–128 months 47% for the ≥ 50 year and 63% for the < 50 year old subjects.⁹⁰ There exists no data on predicted long-term seroprotection in the elderly. To our knowledge, the

only pediatric study investigating the long-term effect of age, shows that GMCs were generally lower in the 1–7 years than in those between 8 and 17 years old and antibodies decreased more rapidly in the younger than in the older children.⁶⁷

BMI. The serologic anti-HAV response correlates in adults positively with lower weight and lower BMI.¹¹¹ Data on duration of anti-HAV seroprotection is scanty: being overweight (BMI ≥ 25 –30 kg/m²) at primary vaccination correlated in one study after 4 years with a trend for lower seropositivity⁹² and was in another study a significant risk for seronegativity (<10 mIU/mL) at the 10-year follow-up.⁵⁸

Apart from one Indian study of a live-attenuated HAV vaccine in 18 to 60 months old children, where the youngest age group (18–24 months) responded with higher antibody levels than the older children,¹¹² we found no other published data on the short- or long-term influence of age, sex, or BMI on the immune response of live-attenuated HAV vaccines.

3.3.3. HIV infection

Hepatitis A vaccination of HIV-infected subjects results in lower, delayed, and often failing humoral immune responses, largely depending on the CD4 T helper cell count and the viral load at the time of vaccination; seroconversion rates ranging from 48.5% to 93.9% are reported in the literature.^{113,114} Primary vaccination failures are, therefore, to be expected.^{32,115,116} Interestingly, there has recently a HAV breakthrough infection been reported in a 29-year-old HIV patient, 7 years after full HAV vaccination which he had received 3 years prior to HIV infection,¹¹⁶ however, it is not known whether he was originally a vaccine responder. In the few prospective studies on HIV-infected subjects successfully vaccinated (all with inactivated HAV vaccine) the seroprotection persisted for 7 years in 79% of 29 adolescents,⁹⁴ for 6–10 years in 85% of 116 adults,¹¹⁷ for 3.7 years in 85% of 52 adults,¹¹⁸ and for 5 years in 75.5% of 49 adults.¹¹⁹ Comparing three-dose (0–1–6 month) and two-dose (0–6 month) schedules of HAV vaccination, a slightly higher seroprotection rate of 94% versus 88% was found after 5 years in 155 and 95 adults, respectively.¹²⁰ Higher post-vaccination antibody levels,^{94,118} low HIV RNA levels^{117,118} or CD4-counts of >200 cells/ μ L at baseline,¹¹⁹ a long duration of the HIV infection,¹¹⁸ and one additional dose of HAV vaccine¹²⁰ were the main factors associated with slower antibody waning after HAV immunization.

3.4. Natural boosting through circulating HAV?

Do circulating HAV particles (i.e., enveloped virus – eHAV) boost preexisting immunity and, thus, are in an endemic setting responsible for the persistence of antibodies or prolong the protective efficacy of vaccines?⁷³ Although this might be true for certain vaccine preventable infections,¹⁹ the situation is not so clear for hepatitis A.

3.4.1. Infection-induced immunity

Reactivation of infection-induced immune memory upon HAV encounters was in 1982 reported from Costa Rica, to our knowledge the only published data of this kind: during

a prospective hepatitis A surveillance of households, exposed adults – who had lost measurable antibodies – seroconverted, but only 1 of the 36 (3%) exposed presented with an anti-HAV IgM positive infection.¹²¹ This could be interpreted as immune memory reactivation in the other 35 subjects. However, the anti-HAV test used all along in this prospective study was a rather insensitive, qualitative immune adherence hemagglutination assay¹²² which might have missed pre-exposure antibody levels. With the current, much more specific and more sensitive anti-HAV antibody test systems, no serological “natural booster” phenomena have been detected for hepatitis A. Otherwise, constantly high anti-HAV IgG antibody levels would be observed in endemic settings due to the continuous HAV exposure during the people’s lifetimes. On the contrary, a constant fall in antibody levels has been documented, as, e.g., in an age-stratified, cross-sectional serosurvey in Nicaragua from 12 to 16 years of age onwards.⁹ Infection-induced immunity is not boostable in healthy, immunocompetent subjects: during hepatitis A infection (silent or acute) not only high levels of humoral antibody are generated (up to several 100,000 mIU/mL),⁹ but also a CMI response with HAV-specific memory lymphocyte (CD45RO+) is elicited.²⁷ One can suppose that a cell and antibody-mediated local gut immunity, together with the high systemic anti-HAV IgG barrier, will thus inhibit ‘natural boosting’ upon further wild HAV encounters. In vaccine studies, it has been shown that preexisting high anti-HAV levels ($\geq 5,000$ – $10,000$ mIU/mL) from past HAV infection are not boostable (see documented breakthrough infection [subject ID 237] in Mayorga et al. 2016³¹ and Berna Biotech, unpublished data on file), indicating that infection-induced immunity effectively neutralizes even parenterally administered HAV antigen.

3.4.2. Inactivated vaccine-induced immunity

It is debatable if the immunity induced with inactivated HAV vaccines can ‘silently’ be boosted through circulating HAV, prolonging this way the persistence or raising the level of anti-HAV antibodies. Investigations of the CMI, in single-dose-vaccinated young adults, suggest that central memory cells are activated by the HAV antigen and that these cells activate effector cells *in vivo* and would thus prevent infection upon subsequent HAV exposure; furthermore, the cellular response observed in vaccinated subjects was similar to the CMI activation observed in patients with acute infection.²⁷

Although frequently quoted, the so-called ‘natural boosting’ of vaccine-induced immunity is certainly not a common phenomenon, if it exists at all. Suggestive data in the literature have, in our opinion, been presented in four publications for only a few cases in studies carried out in Nicaragua, Alaska and the US:

- (1) During a placebo-controlled field trial in Nicaragua 10 of 124 children enrolled into the vaccine group showed, during 15 months of follow-up after the first dose, substantial rises in total anti-HAV antibodies, labeled as ‘natural booster’ reactions.³⁶ Two children were vaccinated in the incubation period and at the beginning of clinical illness, respectively; the eight other children, after having responded normally to the priming dose

(70–405 mIU/mL), presented between months 3 and 15 with an on average 20.2-fold rise (range: 2.1–75.8) of antibody levels (all consecutive 3-monthly sera tested in parallel) without any clinical symptoms, liver enzyme elevations or rises in anti-HAV IgM antibodies (Berna Biotech, unpublished data on file).

- (2) A probable silent breakthrough infection – rather than a ‘natural booster’ reaction – was reported from Nicaragua in an 11-year-old low-responder girl participating in a longitudinal single-dose HAV vaccine effectiveness study. After a low primary response (27 mIU/mL) the child lost measurable anti-HAV antibodies during year 1 and eventually seroconverted ‘silently’ between year 5 and 7 of the serological follow-up ($<10 \rightarrow 7106$ mIU/mL, anti-HAV IgM negative).³¹ Any diagnostic rise in anti-HAV IgM (lasting 3–6 months only) was most likely missed in the 2-year gap between the last two follow-up visits.
- (3) In a long-term immunogenicity study performed in Alaska, two of 197 infants and young children had four-fold or higher anti-HAV increases between subsequent time points that might be attributed to natural boosting; the authors concluded that there was no evidence that natural boosting contributed to the persistence of seroprotective GMCs among study participants during the 10 years of follow-up.⁴⁸
- (4) In a US hepatitis A vaccine field trial three cases with considerable antibody increases were noted (peaks ranging from 2050 to 29,931 mIU/mL) following a case contact of 6 to 74 days after the 1st dose, suggesting – according to the authors – a booster effect after contact with the wild virus.¹²³ With the relatively short interval from the 1st dose it is, however, more likely that this was – at least in the ‘day 6 case’ – due to vaccination into the incubation period, resulting in a mitigated infection-induced immune response, as it was also seen in a Nicaragua field trial³⁶ in 6 of 50 children closely followed-up serologically.¹²⁴

The above described, rare subclinical ‘breakthrough boosters’^{31,36,48,123} and the immune response of subjects vaccinated during the incubation period^{123,124} are quite different from the three published and widely quoted accounts of antibody increases labeled “natural boosters.” In the first study, the antibody level in 1 of 93 children barely doubled in the second year of a 5-year follow-up.⁶⁴ In the second study, clinically insignificant 1.4-fold to moderate 3.4-fold rises in antibody levels were reported between some of the yearly visits in 17 of 142 children during a 3-year post-booster follow-up and were interpreted as “natural boosting”;¹²⁵ the follow-up serum samples were not tested in parallel at the end of the study (R. Dagan, personal communication). In the third study,^{43,126,127} natural boosters were reported with yearly varying rates in up to one-third of Argentinian children during the 3-year,¹²⁶ during the 3- to 5-year¹²⁷ and finally at the 10-year follow-up,⁴³ in single- and 2-dose vaccinated children. The antibodies rose in the subjects concerned by only 80%–100% and the consecutive serum samples were not tested in parallel (C. Espul, personal communication). The level of positive variations ($\geq 25\%$ increases) tended to decrease from Year 2 to Year 10, and there was no trend toward a relationship with hepatitis A cases in

household members.⁴³ Likewise, it was in another study from Argentina reported that one-third of children from a long-term immunogenicity study had documented close contact (household, school, neighbors) with acute HA cases after immunization, but no significant difference was found between anti-HAV antibody levels in children reporting exposure and those reporting no contact with HA patients during 10 years.¹²⁸

All these reported “natural booster” cases are in our opinion wrongly labeled, as the very modest changes were most likely not genuine. In our experience, when testing consecutive serum samples not in parallel, i.e. not using the same enzyme immunoassay test kit lot in the same test run, this can easily result in up to 50%–100% variations in anti-HAV antibody levels (Berna Biotech, unpublished data on file). Overall, true booster events through HAV exposure must be very rare in healthy, successfully vaccinated subjects and may – if not well documented – wrongly be labeled so.

In a different context “natural boosting” was recently reported from Taiwan in a large prospective immunogenicity trial with inactivated HAV vaccines in HIV-infected young adults (all MSM). Of the 295 primary responders, 26 met the criteria for a silent HAV infection during the 5-year study period. This was based on ≥ 2 -fold and for 6 months sustained secondary asymptomatic antibody rises.¹²⁰ Three of these subjects had slight rises in bilirubin and/or liver enzymes; as anti-HAV IgM was not measured, it is not possible to say whether these 3 or more of the 26 “natural boosters” were in fact secondary vaccine failures.

3.4.3. Live-attenuated vaccine-induced immunity

For both Chinese live-attenuated HAV vaccine strains, H2 and LA-1, it is known that they provide a durable ~95% protective efficacy, even so, the vaccine-induced measurable seroprotection rate declines to 80% or less in a couple of years.²¹ During large field trials in the late 1990s with both the H2 and LA-1 vaccine strains, it was observed that vaccinees had rates of anti-HAV IgM positive subclinical infections on similar scales to the unvaccinated control groups (2.3–3.1% vs 3.6–4.2% in an endemic¹²⁹ and 4.1% vs 6.7% in an outbreak³⁸ setting), while the protection against clinical hepatitis A was 95%. Furthermore, the LA-1 strain only provided a low level of protection and the H2 strain none whatsoever against subsequent subclinical infections.^{21,129} The Chinese investigators postulate that these subclinical infections serve as natural boosters for the vaccinees and could explain the sustained protective efficacy despite the relatively rapid waning anti-HAV antibodies.²¹ In an immunogenicity study with a live attenuated vaccine, silent anti-HAV IgG antibody increases above 10,000 mIU/mL (all anti-HAV IgM negative) were noted during 1 to 8 years of follow-up in 14/102 (13.7%) single-dose and in 1/53 (1.9%) two-dose (0/12 months) vaccinated, 1–12-year-old children, a finding which was labeled “natural boosting.”⁸⁵

4. Long-term effects of vaccination on HAV epidemiology

The endemicity of hepatitis A correlates with the socio-economic level and hygiene standard in a given population.¹³ Along with improving living conditions,

clinical hepatitis A – then still called infectious jaundice – started to decline after the second world war in most industrialized countries/areas in Europe and North America.^{130,131} Only with the isolation of the HAV in the 1970s and the availability of anti-HAV antibody tests in the early 1980s, this trend could be documented in serosurveys.¹⁷ In today’s 31 countries of the European Union and European Economic Area, HAV circulation has during the past 40 years as a whole been decreasing steadily toward very low endemicity, although differences still exist at national and subnational levels.¹³² Prior to any widespread use of HAV vaccines, transitions from high toward intermediate or low endemicity have in the last 20–25 years also been observed from some Asia Pacific,¹³³ Latin American,^{16,134} and Middle East & North African countries¹³⁵ and seem to start in some West African countries as well.¹³⁶ In large countries like India,¹³³ China,²² Brazil,¹³⁷ and Mexico¹³⁸ important differences in endemicity levels still exist between regions within the country itself.

This epidemiological transition to lower endemicity with ensuing higher disease burden⁴ led some endemic countries to implement UMV with two doses of inactivated HAV vaccine. The first country was Israel in 1999, effectively eliminating hepatitis A within a few years by targeting young children (toddlers), the main source of infection, thereby providing herd immunity protection to older age groups as well.³⁷ The United States,¹³⁹ China,²⁰ and other countries (Australia, Belarus, Italy, Spain) decided in the 1990s to protect, initially, only specific risk groups (toddlers, older children, and teenagers) in certain more affected regions.¹⁴⁰ After a few years of successful regional vaccination campaigns, the United States¹³⁹ and China²⁰ extended their strategies to nationwide UMV of toddlers in the mid-2000s, many other countries subsequently followed suit (section 4.1).

These UMV programs were in almost all settings within a few years successful. There were sharp declines of hepatitis A incidences, even in non-vaccinated age groups, indicating herd immunity effects, while maintaining susceptibility in older age groups.¹⁴¹ High vaccine costs, however, impeded for many years a larger-scale implementation of a two-dose HAV vaccine strategy in most endemic countries in need.^{1,73,142} In 2005 Argentina, therefore, being the first country worldwide, implemented a single-dose UMV strategy trusting that protection from 1 dose would last for at least 5–10 years, this being enough time to eliminate HAV circulation.⁷⁷

Real-time long-term effects of UMVs, with monovalent HAV or HAV containing vaccines, on disease burden and different epidemiological parameters of hepatitis A, are presented for those countries for which findings have been published (Table 5).

4.1. Effect of universal mass vaccination (UMV) on disease burden

According to current WHO data (information taken from the country profiles, last updated 10 December 2019), there are today 12 countries (Bahrain, Greece, Israel, Kazakhstan, Mongolia, Panama, Qatar, South Korea, Saudi Arabia, Turkey,

Table 5. Effect of universal mass vaccination (UMV) programs on incidence of hepatitis A and on other outcome measures.

Country	Author	Start of UMV	Target population (age)	Vaccination Schedule Vaccine type	Vaccination coverage	Years compared/ investigated	Change in Incidence ^a (per 10 ⁵)	Other outcome measures ^a	Comment
ARGENTINA									
	Cervio (2011) ¹⁴³	2005	12 months	Single-dose Inactivated	78.4 → 99.8% (2005 → 2008 countrywide)	1993–2005 vs 2005–2008	–	Fulminant hepatic failures: 54.6% → 27.7% due to HAV; after Nov. 2006 no more cases	Data from 4 pediatric centers in Buenos Aires
	Blanco (2012) ¹⁴⁴	2005	12 months	Single-dose Inactivated	–	2005–2006 vs 2010–2012	–	River samples: HAV positivity 61.7% → 4.2%	Data from 3 selected sites, Buenos Aires area
	Vizzotti (2014) ⁷⁷	2005	12 months	Single-dose Inactivated	96.8% (2006–2011)	2000–2002 vs 2006–2011	66.5 → 7.9 (88.1% ↓)	Fulminant hepatitis/Liver-transplantation due to HAV: No more cases after Feb. 2007	
	Vizzotti (2015) ¹⁴⁵	2005	12 months	Single-dose Inactivated	–	2000–2004 vs 2006–2010	84.2 → 8.9 ^b (89.4% ↓)	HAV-related medical + non-medical costs: 85.1% ↓	Immunization costs: 6.5 → 40.9 mUSD ^c
AUSTRALIA									
	Hanna (2004) ¹⁴⁶	1999	1.5–4 yrs	Two-dose Inactivated	77% (2000)	1996–1999 vs 2000–2003	110 → 4.0 ^c (96.4% ↓)	Herd protection in not targeted, non-indigenous (any age) and indigenous ≥ 5 year old people	North Queensland only, indigenous people
	Thompson (2017) ¹⁴⁷	2005	12–24 month	Two-dose Inactivated	2 doses: 60% (2013) 1 dose: 71% (2013)	2000–2005 vs 2006–2014	8.4 → 0.85 (89.9% ↓)	Substantial herd protection effect among non-indigenous population	Indigenous people in Queensland, South and Western Australia, Northern Territory
BELARUS									
	Fisenka (2008) ¹⁴⁸	2003	6–9 yrs	Two-dose Inactivated	98.6%	2003 → 2006	0.59 → 0.03 (94.1% ↓)	Incidence fold-decrease: - 12 x ↓ for age 1–5 years - 19.7 ↓ for age 6–9 years - 13 x ↓ for age 10–14 years - 4–6 x ↓ in adults	City of Minsk only, change in overall incidence for subjects aged ≤ 14 years
BRAZIL									
	Souto (2019) ¹⁴⁹	2014	15–24 months	Single-dose inactivated	60% → 97%	2014 → 2016 → 2017	3.28 → 0.47 → 0.72 (85.7% ↓, 78.1% ↓)	Incidence decrease by age: - 96.8% ↓ for age <5 years - 97.8% ↓ for age 5–14 years - 85.1% ↓ for age 15–19 years - 73.5% ↓ for age 20–39 years ^e - 48.7% ↓ for age ≥ 60 years	Incidence increase 2016 → 2017 mainly due to males aged 20–39 years (epidemic among MSM)
CHINA									
	Mao (1997) ¹⁵⁰	1991	1–15 yrs	Single-dose Live-atten. ^f	0.0% → 54.0% → 84.8%	1983–1990 vs 1991 → 1995	213.6 → 34.6 → 0.0 (100% ↓)	–	Jiaojing City (Zhejiang province)
	Zhuang (2005) ⁸⁶	(1990) 1992 ^g	1–15 yrs	Single-dose Live-atten. ^f	0% → 91.5%	< 1990 vs 1992 → 2002	267–360 → 5.8 → 0.0 (100% ↓)	–	Shengsi county, Jiaojing city (Zhejiang province)
	Zhang (2014) ¹⁵¹	2001	Children ^h	Single-dose Live-atten. ^f	–	2000 vs 2011	2.89 → 0.12 (95.9% ↓)	Rate of HAV among all viral hepatitis cases: 8.02 → 0.45%	Tianjin city
	Sun (2018) ²²	2008	18 months	Single-dose Live-atten. ^f	98.7%	2004 vs 2016	7.5 → 1.7 (77.4% ↓)	Strong herd immunity effect seen from 2008 → 2016 in both L-HepA ⁱ and I-HepA ⁱ regions	Separate evaluation of L-HepA and I-HepA regions
	Wang (2019) ¹⁵²	1994	18 months	Two-dose Inactivated	99.6%	2004 vs 2016	3.9 → 0.7 (82.3% ↓)	–	–
	Wang (2019) ¹⁵²	1994	18/24 months	Two-dose inactivated	> 99% ^j	1990 → 2017	59.4 → 0.80 (98.6% ↓)	Incidence 2004 → 2017 by age: - 2.52 → 0.06 for age < 10 years - 1.96 → 0.26 for age 10–20 years - 3.27 → 0.91 for age > 20 years	City of Beijing only

(Continued)

Table 5. (Continued).

Country Author	Start of UMW	Target population (age)	Vaccination Schedule Vaccine type	Vaccination coverage	Years compared/ investigated	Change in Incidence ^a (per 10 ⁵)	Other outcome measures ^a	Comment
Yan (2019) ¹⁵³	2008	18 months 18/24 months	Single-dose live-atten. Two-dose inactivated	> 99% (2014)	2006 vs 2014	-	Seroprevalence change by age: - 30.8% → 77.5% age 1.5–7 years - 35.3% → 66.7% age 8–14 years - 85.7% → 69.2% age 20–29 years - No difference for age ≥ 30 years Absolute No of HAV cases reported: 4576 → 237 (94.8% ↓)	Shandong province
Guo (2020) ¹⁵⁴	2008	18 months	Single-dose Live-atten.	82.2%/98.4% (2008/2018)	2008 vs 2018	-		Henan province
Wang (2020) ¹⁵⁵	2008	18 months 18/24 months	Single-dose live-atten. Two-dose inactivated	94.0% (2014)	1992 vs 2006 vs 2014	>100 → 9.2 → < 5.0	Seroprevalence (selected age groups): - 2–4 years: 55.0 → 52.0 → 88.1% - 20–24 years: 82.9 → 78.6 → 56.8% - 40–44 years: 90.8 → 90.3% → -	Vaccination coverage for age 3 years; morbidity data for age < 10 years
GREECE Mellou (2015) ¹⁵⁶	2008	>12 months	Two-dose inactivated	ca. 80%	1982 → 2013	No significant change	Mean age of HAV cases increased significantly	Confounding epidemics (Roma groups & immigrants)
Papaevangelou (2016) ¹⁵⁷	2008	>12 months	Two-dose inactivated	-	1999–2008 vs 2009–2013	-	Hospitalizations for HAV: 50.5 → 20.8/1000 admissions	Tertiary pediatric hospital in Athens
ISRAEL Belmaker (2007) ¹⁵⁸	1999	18 months	Two-dose inactivated	86.4% (1 st d) ^k 77.3% (2 nd d) ^k	1993 → 2005	73.6 → 0.68 (99.1% ↓)	Since 2001 no HAV cases, out-breaks or postexposure IgG used	Data from Negev area
Barkai (2009) ¹⁵⁹	1999	18 months	Two-dose inactivated	85.5% (1 st d) ^k 74.9% (2 nd d) ^k	1991–1998 vs 2001–2002 vs 2003–2007	-	Seropositivity of non-vaccinated children (aged 16–20 months): 17.2% → 2.0% → 0.0%	Data from Beduin children in Negev
Levine (2015) ¹⁶⁰	1999	18 months	Two-dose inactivated	92% ^m (1 st d) ^k 88% ^m (2 nd d) ^k	1993–1998 vs 2008–2012	50.4 → < 1.0 (> 98% ↓)	Strong herd immunity effect maintained from 2000 → 2012	
Galor (2020) ¹⁶¹	1999	18 months	Two-dose inactivated	90% ⁿ (1 st d) ^k 85% ⁿ (2 nd d) ^k	<1999 vs 2017	-	Seropositivity 18 years after UMW start in Israel born military recruits: 35.3% vs 71.5% (born prior vs born after UMW start)	
ITALY Chironna (2012) ¹⁶²	1998	15–18 months 12 years	Two-dose inactivated	65% (2008) 68% (2008)	1998 vs 2009	14.8 → 0.8 (94.6% ↓)		Puglia region data
Gallone (2017) ¹⁶³	1998	12–24 months 12 years	Two-dose inactivated	64.8% (2008) 67.6% (2008)	2011/2012	-	Susceptibility (sero-neg.) at age 18–26 years: 35.5% 27–35 years: 67.1% 36–45 years: 41.1% 46–55 years: 12.7% 56–65 years: 2.8%	Puglia region data: 13 years after UMW start: young adult blood donors at higher risk
PANAMA Estripeaud (2015) ¹⁶⁴	2007	1–4 years	Two-dose inactivated	64.5% (2008) 66.4% (2009) 40.1% (2010)	2000–2006 vs 2008/09/10	51.1 ^b → 13.1/ 7.9/3.7 ^b (97.8% ↓)	Hospital-based survey: hepatitis A patients aged 0–14 years falling off to zero (2009 → 2011)	
SPAIN Oviedo (2009) ¹⁶⁵	1998	12 years	Three-dose inactivated (Twinrix jun)	91% (2006) ^o	1992–1998 vs 1999–2005	8.15 → 1.4 ^o (98.3% ↓)	Incidence change by age <12 years: 14.6 → 7.6 (48% ↓) 12–18 years: 6.9 → 1.1 (84% ↓) 19–39 years: 8.2 → 5.1 (38% ↓) ≥40 years: 0.9 → 0.6 (33% ↓)	Catalonia data only

(Continued)

Table 5. (Continued).

Country Author	Start of UJM	Target population (age)	Vaccination Schedule Vaccine type	Vaccination coverage	Years compared/ investigated	Change in Incidence ^a (per 10 ⁵)	Other outcome measures ^a	Comment
Martinez (2015) ¹⁶⁶	1998	12 years	Three-dose inactivated (Twinrix jun)	–	1991–1998 vs 2000–2012	1.53 → 1.27 ^b (17.0% ↓)	Hospitalization rate (per 10 ⁶): 0.08 → 0.75 (89.4% ↑)	Catalonia data only; incidence of out-breaks among MSM and immigrants increased
URUGUAY Romero (2012) ¹⁶⁷	2008	15–21 months	Two-dose inactivated	74% ^c	2005 vs 2010	88.7 → 2.7 (96.9% ↓)	–	–
UNITED STATES Wasley (2005) ¹⁶⁸	1999 ^f	≥ 2 yrs (children)	Two-dose inactivated	50% (2003) ^g	1990–1997 vs 2003	21.1 → 2.5 (88.2% ↓)	Incidence: 10.7 → 2.6 (all States) 5.7 → 2.7 (not vaccinating States)	–
Zhou (2007) ¹³⁹	1999 ^f	≥ 2 yrs (children)	Two-dose inactivated	30.0% (2004) ^h	1996/97 vs 2004	–	Hospitalizations: 0.81 → 0.26/10 ⁵ Ambulatory visits: 12.9 → 7.5/10 ⁵ Medical costs: 29.1 → 9.3 mUSD ⁱ Mortality: 0.38 → 0.26/10 ⁶ (32% ↓)	–
Vogt (2008) ¹⁶⁹	1999 ^f 2006	2–12 yrs 1–2 yrs	Two-dose inactivated	–	1990–1995 vs 2000–2004	~90–120/10 ⁶ → 20–40/10 ⁶	–	CDL is important contributing cause of death
Singleton (2010) ¹⁷⁰	1996	2–14 yrs	Two-dose inactivated	72.7% (2003) ^u 65.9% (2006) ^u	1972–1995 vs 2002–2007	60.0 → 0.9 (98.6% ↓)	Vaccination program 2–3x more successful than in US children	State of Alaska
Erhart (2012) ¹⁷¹	1999 ^f 2006	2–12 yrs 1–2 yrs	Two-dose inactivated	–	1994–1995 vs 2006–2007	41 → 2.6 (93.7% ↓)	Rate of international travel associated cases: 6% → 52% Disease burden shift → older age	State of Arizona
Klevens (2015) ¹⁷²	1999 ^f 2006	2–12 yrs 1–2 yrs	Two-dose inactivated	–	1999–2006 vs 2007–2012	–	Seroprevalence (all states) at age 2–11 years: 21.4% → 59.5% 12–19 years: 19.4% → 39.6% 20–29 years: 17.8% → 21.1% 30–39 years: 17.7% → 17.6% 40–49 years: 23.7% → 16.1%	Susceptibility shift toward older age
Collier (2015) ¹⁷³	1999 ^f 2006	2–12 years 1–2 year	Two-dose inactivated	–	2002 vs 2011	–	Hospitalizations: 0.72 → 0.29/10 ⁵ Age of patients: 37.6 → 45.5 years	Liver and other comorbidity important risk factors
Ly (2015) ¹⁷⁴	1999 ^f 2006	2–12 years 1–2 year	Two-dose inactivated	–	1999 vs 2011	6.0 → 0.4 (93.3% ↓)	Hosp. admission: 7.3% → 24.5% Age at admission: 36 → 45 years Age at death ^w : 48 → 76.2 years	Role of liver-related comorbidity in HAV cases increasing

Footnotes: ^a Always countrywide data, unless specified otherwise under 'comment'; ^b Hepatitis A + unspecified hepatitis; ^c indigenous persons; ^d non-indigenous persons ^e decrease 2014 → 2016; ^f H2-strain; Mao (1997); ^g Zhuang (2005); ^h strain not indicated; Sun (2018); ⁱ Zhang (2014) [publication in Chinese]; ^j Mass vaccination started in 1992; ^k No age indicated (publication in Chinese); ^l L-HepA = live-attenuated, I-HepA = inactivated HAV vaccines; ^m Following integration of HAV vaccination program into EPI in 2008; ⁿ 1st and 2nd vaccine dose; ^o Seropositivity: ≥ 100 mIU/mL = likely from infection, < 100 mIU/mL = residual maternal anti-HAV antibodies; ^p Vaccination coverage 2003–2010; ^q Vaccination coverage 2001–2002; ^r mean incidence for age group 12–18 years; ^s only outbreak-associated cases; ^t Vaccination coverage 1st dose of target children born in 2007; ^u 1999–2005: only children living in 17 States with high hepatitis A rates; ^v Children aged 24–35 months in vaccinating States; ^w mUSD = million US dollars; ^x for children 24–35 months of age; ^y rate (%) of hepatitis A cases hospitalized; ^z Age at death among decedents with HAV infection.

Abbreviations: CDL: chronic liver disease; HAV: hepatitis A virus; live-atten.: live-attenuated; MSM: men who have sex with men; UJM: universal mass vaccination; vs: versus.

United States, Uruguay) using 2-dose UMV and 7 countries actually using (Argentina, Brazil, Chile, Colombia, Paraguay, Turkmenistan) or planning to introduce in 2020 (Honduras) single-dose UMV with inactivated HAV vaccines.¹⁷⁵ China has implemented UMV mainly using single-dose, live-attenuated hepatitis A vaccines.^{20,22,152} Another 10 countries report currently vaccinating only certain risk groups in the entire country (Armenia, Australia, Kuwait, Mexico, Slovenia, Tunisia) or perform UMV only in certain affected regions (Canada, Italy, Russia, Spain).¹⁷⁵

Data on real-time long-term effects of UMV have been published for 12 countries, mainly since the mid-2000s and spans observation periods of 3 to 23 years (Table 5). Only one country (Greece) reported no noticeable change in disease burden. This was a rather unexpected finding and most likely due to confounding epidemics in Roma and immigrant groups.¹⁵⁶ From all other countries, nationwide evaluations indicated pronounced declines in disease incidence (morbidity per 100,000 population/year),^{22,77,145,149,155,160,164,167–169,174} in severe disease, such as acute liver failure,^{77,143} in mortality¹⁶⁹ or in hospitalizations^{139,157,164,173,174} and health-care costs.^{139,145} Similar data were reported for regional UVMs regarding disease incidence,^{86,152,154} outbreak frequency,¹⁵⁸ and regarding hospitalizations.¹⁶⁶ Other epidemiological parameters indicating nationwide or regional success or expected effects of UMV were: herd protection of untargeted age groups^{22,146,147,149,154,160} (section 4.2), a rise in seroprotection rates in targeted children/adolescents¹⁵³ or young adults,¹⁶¹ susceptibility (seronegativity) shift toward older age groups,^{163,172} a disease burden shift toward older age,^{154,156,171–174} international travel becoming a predominant risk factor for HAV transmission,^{171,172} a decline in the rate of infection-induced high anti-HAV levels in non-vaccinated toddlers,¹⁵⁹ a declining rate of HAV among all viral hepatitis cases¹⁵¹ and finally, declining HAV positivity of river water samples.¹⁴⁴

To sustain HAV elimination, a certain vaccination coverage of the pediatric target population should be maintained. The US have defined a two-dose vaccination coverage target of 85%,¹⁷⁶ based on the successful demonstration projects conducted in Alaska among children and young adults in the early 1990s. In these projects, approximately 80% coverage was sufficient to stop epidemics and to lower morbidity to 0.1/100'000 by 2004.¹⁰ Israel, with coverages of 92% and 88% (1st and 2nd dose), maintained the morbidity for over 10 years below 1.0/100'000.¹⁶⁰ Even with only 65–75% coverage, Alaska,¹⁷⁰ Panama,¹⁶⁴ Uruguay¹⁶⁷ and Italy (Puglia region)¹⁶² achieved >90% declines in disease incidence. The single-dose programs in Argentina⁷⁷ and Brazil¹⁴⁹ lowered, with 96.8% and 97% coverage, their national morbidities within 2–3 years by 88.1% and 85.7%, respectively.

There have only been a few modeling studies published so far which use well-founded assumptions (derived from real data) to project the persistence of HAV elimination through UMV in the long-run, i.e. for more than one generation.^{177–179} Using a disease transmission dynamic modeling approach, the impact of universal versus regional vaccination on hepatitis A morbidity and the cost-effectiveness was projected for up to 100 years for

the US: universal vaccination was cost-saving compared with regional vaccination policy; in addition, herd protection effects of the hepatitis A vaccination programs had a significant impact on mortality, morbidity, and cost-effectiveness ratios.¹⁷⁷ Based on Mexican data, the potential impact of HAV vaccine immune memory on the modeled reduction of hepatitis A disease in vaccinated subjects was explored for time periods of up to 75 years: the analysis indicated that routine vaccination of toddlers against hepatitis A virus would be cost-effective in Mexico using a single-dose strategy.¹⁷⁸ With an age-structured hepatitis A transmission model, incorporating demographic changes and fitted to seroprevalence and disease notification data, the decline and future of hepatitis A transmission in Australia was projected for the following 40–50 years: the results suggest that sustained endemic transmission in the general Australian population is no longer possible although risks of sporadic outbreaks remain.¹⁷⁹

For such projections not only vaccination coverage and long-term immunogenicity has to be taken into account, but also the vaccine-induced immune memory¹⁷⁸ (section 3.2), the herd protection effect^{177,180} (section 4.2), and the transmission mode,¹⁷⁹ as well as the shifting of HAV epidemiology, clean water access and hygiene standards.¹³ The WHO advises to regularly assess the impact of hepatitis A UMV's, using information on morbidity and mortality generated by surveillance and study data; in addition, duration of immune protection by 1- and 2-dose schedules should be monitored.¹ Endemic countries should periodically monitor the epidemiology of HAV infection, e.g. through repeated cross-sectional seroepidemiological surveys^{9,181} in order to identify epidemiologic transitions and thus to be able to implement UMV in time.¹⁸² The interpretation of anti-HAV immunity (infection- or vaccine-induced) becomes, however, more and more difficult as the use of HAV vaccines spreads (section 5.3.2).

4.2. Herd immunity through vaccination

Herd immunity plays a vital role in the success story of UMV in young children,¹⁸⁰ leading – with the exception of Greece¹⁵⁶ – in all countries with such programs to noticeable population-wide declines in disease incidences or other epidemiological parameters (Table 5). Prospective (≥5–10 years) real-time age- or population-specific details of herd protection ensuing from the age group of vaccinated, seroprotected young children are available for Israel¹⁶⁰ and Australia¹⁴⁷ for inactivated, and for China²² for live-attenuated HAV vaccines. The herd protection effect, which is assumed to account for more than one-third of the estimated number of cases prevented by vaccination,¹⁸³ maintained in Israel for over 10 years in all age groups very low disease incidences.¹⁶⁰ The vaccination of special population groups, such as the indigenous toddlers in Australia, robustly led, in all age groups, to very low disease incidences in the targeted, as well as in the non-targeted, non-indigenous population.¹⁴⁷ Although live-attenuated HAV vaccines seem to prevent asymptomatic HAV infections even less effectively than overt hepatitis A,³⁸ the use in UMV programs in China has shown these vaccines to be efficacious in eliminating hepatitis A, attributed by the investigators to a large extent to herd immunity effects.²²

4.3. Shifting seroepidemiology

With young children in endemic settings being the main source of infection, access to clean water and improved hygiene leads eventually to reduced transmission of HAV. These sanitary improvements leave increasing numbers of older children, adolescents, and young adults susceptible (seronegative), causing an increase in the average age at infection, and, consequently, a paradoxical increase in morbidity in the older age groups, as well as in further risks of outbreaks. Contrary to this 'natural', socio-economic driven shift in seroprevalence toward older age groups and hence toward intermediate endemicity,¹ the vaccine-induced seropositivity through toddler UMV programs protects not only the young children directly, but protects through herd protection effects¹⁸⁰ simultaneously large parts of all older age groups as well.¹⁶⁰ These UMV effects lead to an, at first glance, "uncoordinated" looking shift in seroprevalence, with seroprotection rates increasing for the young age groups and initially decreasing or leveling off for the adolescents and young adults, while high infection-induced seropositivity remains for the rest of the older adult population. A few reports on serological long-term effects of UMV have shown this seroprevalence pattern for the US,¹⁷² Italy,¹⁶³ China¹⁵³ (see also Table 5) and Israel.¹⁸⁴ Furthermore, a population-based study from Israel typically shows how difficult it is to interpret the serological data 12 years after successful implementation of toddler vaccination, i.e. to differentiate over all age groups between UMV-induced seropositivity, seroprotection due to additional vaccination in the general population and infection-induced pre-existing seroprotection.¹⁸⁴ There is clearly a need for serological tests which can differentiate between vaccine- and infection-induced anti-HAV antibodies⁴ (section 5.3.2).

4.4. Is HAV eradicable?

As a human enteral virus infection with a fecal-oral transmission mode, hepatitis A is – similar to poliomyelitis – theoretically eradicable. The HAV has in the past indeed been considered as a target for eradication. However, international bodies have never made this recommendation primarily because of high cost and uncertain feasibility. In 1998, only a few years after licensing of the first vaccines, experts concluded that eradication of HAV transmission appears to be both biologically and epidemiologically feasible and that the time required to achieve cessation of transmission may be short and they recommended to initiate population-based projects to demonstrate sustained elimination of HAV transmission.¹⁸⁵ These conclusions regarding elimination were proven correct within the ensuing 5–10 years. The topic of eradication was, however, never taken up again and it is not even mentioned in the most recent WHO hepatitis A vaccine position paper of 2012.¹ The most obvious reason being that – apart from the protective effects of access to clean water and improved hygiene – hepatitis A UMV programs are able to achieve in endemic countries near complete cessation of HAV transmission, leading to sustainable morbidities of <1/100,000 (Table 5).

5. Emerging issues and areas for research

5.1. Long-term seroprotection

5.1.1. No need for late second booster

Inactivated HAV vaccines are immunogenic in all age groups. Based on serological long-term follow-up studies (including modeled projections), and based on the documented immune memory, one can conclude that a two-dose HAV vaccination (0/6–18 months) leads in healthy children and young adults (<50 years) to life-long protection and that there is no need for a late booster after 20 or 30 years.⁶² As documented in studies discussed beforehand, an exception might be younger children below 8 years of age who achieve lower GMC's and whose antibody levels decline faster than in the 8 to 17-year old's,⁶⁷ or children vaccinated in infancy (6/12 months), with 25–32% of them losing immunoprotection after 15–20 years.^{50,53} Longer follow-ups of these pediatric studies are still needed.

The single-dose live-attenuated HAV vaccines are somewhat less immunogenic compared to inactivated vaccines, although they seem in UMV programs equally effective in eliminating HAV circulation and overt disease. Nevertheless, more real-time serological follow-up data and monitoring of UMV programs is needed to corroborate the elimination of HAV and to settle the issue of the need for a second, "booster" dose.²²

5.1.2. Extra priming dose for elderly and immunocompromised subjects?

There are insufficient long-term data for the elderly (>50 years) and for immune-compromised (including HIV infection) subjects. This is so for long-term protection after full vaccination and also regarding basic immunization, i.e. whether or not these often weak and slow responding subjects would profit from two primary doses (4 weeks apart),^{29,114} especially when protection is needed speedily prior to traveling. This issue has been contested in a retrospective analysis of pooled study data,¹⁸⁶ even so 20.3% of ≥ 40 year old healthy subjects were two weeks after one dose not seroprotected (≥ 20 mIU/mL). In addition, it should be investigated if following waning of measurable antibodies after >10 years the immune memory is still intact or whether elderly and/or immunocompromised subjects would routinely need a late second booster dose.

5.1.3. Single-dose UMV strategy

Despite the available long-term immunogenicity data and the successful UMV's of toddlers in Argentina and Brazil, single-dose immunization of such young children with inactivated HAV vaccines needs more long-term data, regarding real-time seroprotection and monitoring of the UMV programs for at least 15 years,^{73,141} and more documentation of the immune memory when detectable anti-HAV antibodies have been lost. In long-term immunogenicity studies in progress, the frequency of silent breakthrough infections and the presumed 'natural booster' effects should also be further investigated. Countries pursuing single-dose UMV strategies should not only monitor morbidity and changes in seroprevalence, but also document the herd protection for other age groups.

5.2. Hepatitis A virus

5.2.1. Monitoring HAV circulation

The fecal excretion of HAV starts even before the clinical illness and usually lasts for 1 to 3 months.^{3,187} In the case of relapsing hepatitis A, excretion has been documented for up to 11 months,¹⁸⁸ but so far no chronic carriers have been reported, not even in HIV-infected patients.¹¹⁴ HAV is resistant to low pH, to heat (60°C for 60 minutes) and to freezing temperatures; furthermore, HAV may persist in feces and soil for a prolonged period.³ In water, it can survive for up to 1 year.¹⁸⁹ Monitoring of HAV circulation through environmental sampling is, therefore, important whilst conducting public health interventions.

Evidence for endemic HAV circulation was found in Israel despite universal toddler vaccinations since 1999 and low clinical incidence in all age groups: during an outbreak investigation in 2012–2013, there were 16 of 27 (59.2%) sewage samples from Tel-Aviv, 4 of 14 (28.6%) samples throughout Israel and 6 of 6 (100%) samples from Gaza found to contain HAV.¹⁹⁰ Argentina started a successful UMV in 2005, lowering within 5 years the morbidity by nearly 90%,^{77,145} and the HAV positivity of river samples from the Buenos Aires area decreased from 2005–2006 to 2010–2012 by 93.2% (Table 5).¹⁴⁴ However, in the city of Córdoba environmental monitoring revealed in 2009–2010 the presence of HAV still in 20.8% and 16.1% of wastewater and river samples, respectively; that poses a risk for outbreaks among the increasing subpopulation of susceptible adults.¹⁹¹ In countries attempting to eliminate HAV via U MVs, regular monitoring of wastewater could help the health authorities to identify high HAV circulation in areas with possibly under-vaccinated populations.

5.2.2. Emergence of escape mutants

Already in the late 1980s and early 1990s, prior to the licensing of hepatitis A vaccines, researchers used in vitro-induced neutralization escape mutants derived from the HM175 vaccine strain to investigate the immunodominant neutralization sites in the antigenic structure of the HAV capsid proteins.¹⁹² Two decades later HAV antigenic variants were isolated in Spain that were thought to have escaped the protective effect of available vaccines; these HAV variants were isolated mostly from MSM in connection with the 2008–2009 HAV epidemic among MSM.¹⁹³ The same Spanish research group performed deep-sequencing analysis on HAV strains isolated from vaccinated ($n = 5$) and non-vaccinated ($n = 8$) patients during the large 2016–2018 epidemic among MSM. They found a higher diversity in epitope-coding regions of the vaccinated group (all subjects sub-optimally vaccinated and three, in addition, HIV infected) and concluded that the data suggested positive selection of antigenic variants in some vaccinated patients.¹⁹⁴ The circulation of such antigenic variants may increase in MSM groups and further expand to the general population, and thus may eventually become a public health threat. To avoid possible selections of such escape variants, measures have to be taken to assure complete two-dose vaccination in the MSM populations and possibly administer booster doses to vaccinees with low anti-HAV antibodies, the investigators suggested.¹⁹⁴ These vaccines escape HAV variants have so far only been

reported from Spain and this needs to be corroborated by other similar investigations. Until the quoted observation receives further confirmation, the public health risks associated with the emergence of such mutants remain speculative.

5.3. Epidemiology and public health

5.3.1. Monitoring the HAV epidemiology

HAV endemic countries should closely monitor epidemiology and disease burden of hepatitis A in order to allow timely identification of transition toward intermediate endemicity and introduction of preventive strategies.^{1,195} Priority should be given to collecting HAV seroprevalence data and regularly assessing the hepatitis A control strategies in order to prevent future disease outbreaks, as it was recently postulated for Africa.¹⁸² The WHO, in addition, recommends acute disease surveillance (including registration of fulminant hepatic failure cases and/or causes of liver transplantation) and cost-effectiveness analyses of relevant immunization strategies.¹

For future serosurveys to be comparable across place and time, it has been proposed to use the ‘age at midpoint of population immunogenicity or susceptibility’ as standard indicators for the level of hepatitis A endemicity within countries or a world region; they are defined as the age at which half of the population in a particular age group does or does not have anti-HAV IgG antibodies, indicating past exposure or no past exposure to the virus.^{196,197} A very high endemicity is defined as an age at the midpoint of immunity of <5 years; high, of 5–14 years; intermediate, of 15–34 years; and low, of ≥ 35 years.¹⁹⁶ Standardized surveillance with these parameters would facilitate future decisions about hepatitis A vaccination policy in a given region.¹⁹⁷

5.3.2. Infection- versus vaccine-induced anti-HAV antibodies

With the introduction of HAV vaccination, it becomes increasingly difficult to interpret seroprevalence data generated with today’s standard anti-HAV antibody assays because the results are a mixture of naturally acquired immunity and vaccine-induced antibody data. This difficulty is exemplified by three recent long-term reports, one from India on the age-stratified anti-HAV positivity after two decades of voluntary vaccination,¹⁹⁸ one from Israel on the seroprevalence of hepatitis A twelve years after the implementation of the universal toddler vaccination¹⁸⁴ and a third one from Australia on the quantification of the population effects of vaccination and migration on hepatitis A seroepidemiology.¹⁹⁹ In all three publications, the interpretation of the data is based on assumptions regarding the relative contribution of HAV infection and vaccination, with some conclusions remaining unavoidably imprecise and theoretical. A serologic test differentiating between HAV infected and vaccinated individuals would help to interpret serosurveys, especially in countries in transition to intermediate endemicity and/or partial vaccination coverage.^{4,198}

In the 1990s, pilot antibody tests using as an antigen the non-structural HAV 3 C proteinase, an antigen presented to the human immune system only during active virus replication, demonstrated that one can theoretically distinguish between antibodies acquired

in response to active HAV infection and those induced by immunization.²⁰⁰ The potential value of such a diagnostic tool was then not further investigated. Interest in this topic reemerged recently and several publications on tests using recombinant antigens^{201–203} claim to be able to discriminate between natural infection and antibodies induced by live-attenuated or inactivated vaccines,^{201,202} or to distinguish between natural infection and immunity induced by inactivated vaccines.²⁰³ The aforementioned three studies were made with sera collections containing mainly onetime samples only. In an earlier prospective study, two-thirds of children followed-up yearly for 6.5 years after acute HAV infection, had at the end lost their anti 3 C HAV proteinase antibodies.¹²⁴ Whereas infection-acquired anti-capsid HAV IgG antibodies persist for life, antibodies against non-structural HAV proteins might – until proven otherwise – not persist long enough in a given population to allow reliable assessments of long-term changes in seroprevalence of infection-induced versus vaccine-induced immunity; the persistence of antibodies against non-structural HAV antigens needs to be investigated in well-designed long-term studies.²⁰⁴

5.3.3. Newly emerging epidemics

The current changes in global HAV epidemiology implicate potentials for outbreaks and shifts in vulnerable populations.⁴ Apart from the outbreak risks in those endemic countries undergoing transition from high to intermediate endemicity, there are in industrialized countries, in connection with international travel and globalization, new risks emerging.

In recent years there have in Europe,²⁰⁵ Asia,¹¹⁴ Latin America²⁰⁶ and North America²⁰⁷ large HAV outbreaks among MSMs been reported, with epidemiological investigations showing transmission between countries and even continents.^{205,206} These outbreaks can only be controlled by educative public health interventions and eventually achieving high vaccination coverage among MSM.²⁰⁸

The globalization of the food industry causes for its consumers, in recent years, with increasing frequency, food-borne hepatitis A outbreaks.²⁰⁹ As an example, the large epidemic in Europe in 2013 was transmitted by frozen fruits imported from an endemic country.²¹⁰ These inadvertent ‘hepatitis A imports’ – often in parallel to several countries^{210,211} – are difficult to control, unless HAV is eliminated to a large extent in the currently still endemic countries. The HAV outbreaks associated with imported food in developed countries requires new approaches and tools for early detection and control. For public health preparedness, surveillance data on HAV infection should be monitored and viral sequencing data should be collected and shared.²⁰⁹ In response to known outbreaks, public notifications, product recalls, and mass vaccination campaigns are important strategies.²⁰⁹

The US introduced in 2006 nationwide hepatitis A UMV for all children aged 12–24 months. Vaccination rates in 2017, however, still did not reach the $\geq 85\%$ target of 2 doses,¹⁷⁶ with 59.7% for two and 86.0% for one dose among children aged 19–35 months, and with even lower rates of 35.7% and 63.3%, respectively, e.g. for underprivileged, uninsured population groups.²¹² Under these

circumstances the herd protection effect does not function properly and not only sections of the pediatric population are left unprotected, but younger adults as well, resulting in the US in recent years in outbreaks among MSM,²⁰⁷ prisoners, homeless people and intravenous drug users.²¹³ During 2007–2016, approximately three-fourths of U.S.-born adults aged ≥ 20 years remained HAV susceptible.²¹⁴

Prevention strategies for hepatitis A matching the changing epidemiology have in non-endemic countries not received the necessary attention in recent years. Therefore, public health experts advocate to urgently scale up hepatitis A prevention in the European Union²¹⁵ and in the US,^{207,214} with special focus on the susceptible risk groups.

6. Conclusions

Inactivated HAV vaccines are safe and provide healthy children, adolescents, and young adults (<40–50 years) after two doses (6–18 months apart) with solid immune memory and seroprotection for ≥ 30 –40 years, if not lifelong. Thus, in healthy subjects, there is no need for a late, second booster. To allow modeling of long-term estimates for young children and the elderly, the real-time duration of seroprotection needs in these age groups yet to be documented for a total of at least 10–15 years.

Two-dose UMV. Countrywide systematic introduction of a two-dose UMV in young children (toddlers) leads, when sustained on a high coverage level (≥ 85 –90%), within a few years to elimination of clinical disease in all groups thanks to the herd protection effect and to an ensuing very low levels of wild virus circulation.

Single-dose usage of inactivated HAV vaccines. The duration of individual long-term protection and immune memory after a single dose of an inactivated hepatitis A vaccine is not fully established yet and more follow-up data are needed from ongoing, pediatric single-dose immunogenicity studies. The first single-dose UMV programs in young children have made a good start in lowering the hepatitis A disease burden, but need to be monitored for many more years.

Elderly and immunocompromised subjects. For elderly healthy travelers, immunocompromised patients, and HIV-infected subjects there exist no good long-term seroprotection data after inactivated HAV vaccination, a knowledge gap which needs urgently to be closed. It should also be investigated whether these subjects with their usually slow and weak primary immune response would not profit from a second priming dose.

Live-attenuated HAV vaccines. The situation for the single-dose, live-attenuated HAV vaccines is not so clear-cut yet, but the available data points to equal safety, good protective efficacy, and long-term seroprotection in young and older children, whereby the need for a late booster dose (after 20–30 years) is not yet settled.

Natural booster. The frequently quoted phenomenon of ‘natural boosting’ of anti-HAV antibodies, through wild HAV encounters as a mechanism sustaining or even enhancing vaccine-induced immunity, is not based on many facts. The few well-documented cases are rather related to primary vaccine failures.

Eradication of HAV. Similar to the polioviruses, the human enteric hepatitis A virus is basically eradicable. Because of the excellent efficacy of the HAV vaccines, eliminating within a few years of UMV the disease burden of hepatitis A in a given population, the issue of HAV eradication is currently not pursued as an option.

Monitoring of HAV circulation. In spite of successful UMV programs, regular monitoring of HAV presence in waste and surface waters is still necessary for some time in order to detect early enough potential outbreak risks from pockets of HAV excreting population groups.

Infection-induced antibodies. In order to be able to analyze the immune status of a population in transition from infection- to vaccine-induced immunity, the current ‘indifferent’ anti-HAV antibody tests have to be supplemented by new test systems which can identify infection-induced antibodies.

Escape mutants. Variants of HAVs escaping neutralization have not only be produced under laboratory conditions, but there are first indications that variants escaping the protective effects of vaccines could emerge in under-vaccinated and at the same time heavily infected and immunocompromised populations, such as MSM. This issue has to be monitored very carefully.

New ‘emerging’ epidemics. In non-endemic countries prevention efforts need to focus on the ‘new’ risk groups, such as MSM, prisoners, homeless subjects and families visiting friends and relatives (VFRs) in endemic countries. Whether strict application of food hygiene helps to prevent epidemics ensuing from imported HAV contaminated food is doubtful as long as HAV circulates freely in the countries of origin.

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Disclosure of potential conflicts of interest

C. Herzog was from 1994 to 2011 employed by Berna Biotech/Crucell (formerly Swiss Serum and Vaccine Institute) as Medical Director/Chief Medical Advisor. K. Van Herck conducted clinical trials and undertook modeling for which the University of Ghent obtains research grants from Glaxo SmithKline and other companies. P. Van Damme acted as chief and principal investigator for Berna Biotech/Crucell and Glaxo Smith Kline vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers. All authors declare no conflicts of interest.

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