Human Vaccines & Immunotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

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

Christian Herzog , Koen Van Herck & Pierre Van Damme

To cite this article: Christian Herzog , Koen Van Herck & Pierre Van Damme (2020): Hepatitis A vaccination and its immunological and epidemiological long-term effects – a review of the evidence, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2020.1819742

To link to this article: https://doi.org/10.1080/21645515.2020.1819742

© 2020 The Author(s). Published with license by Taylor & Francis Group, LLC.

Published online: 16 Dec 2020.

Submit your article to this journal

Article views: 277

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=khvi20

HUMAN VACCINES & IMMUNOTHERAPEUTICS
https://doi.org/10.1080/21645515.2020.1819742

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

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

Christian Herzog[a,b], Koen Van Herck[c,d], and Pierre Van Damme[c]

[a]Department of Medicine, Swiss Tropical and Public Health Institute, Basel, Switzerland; [b] University of Basel, Basel, Switzerland; [c] Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium; [d] Department of Public Health, Ghent University, Ghent, Belgium

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.

ARTICLE HISTORY
Received 3 June 2020
Revised 16 August 2020
Accepted 1 September 2020

KEYWORDS
Hepatitis A; vaccination; immune response; immune memory; epidemiology; long-term follow-up

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

CONTACT Christian Herzog herzog.ch47@gmail.com Swiss Tropical and Public Health Institute, Basel CH-4051, Switzerland

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

© 2020 The Author(s). Published with license by Taylor & Francis Group, LLC.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

sequence variants[7] 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) infections[1] – 33 million cases of symptomatic illness[2] 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 (≥90% by age 10 years); intermediate (≥50% by age 15 years, with <90% by age 10 years); low (≥50% by age 30 years, with <50% by age 15); and very low (<50% by age 30 years)."[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 infection[9] (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).

			HAV antigen Dose/Volume (mL) per Injection		
Trade name	HAV strain	Adjuvant	Pediatric	Adult	Manufacturer (Country)
Inactivated vaccines					
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)
Live-attenuated vaccines					
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] [a]For economic reasons not on the market anymore; [b]Formerly '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 ≥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 ≥10mIU/mL are considered seroprotective (= correlate of protection[10,24]), although ≥20mIU/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 antibodies[25] 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. 2016[31]) or after two doses in two subjects, immunocompromised through HIV infection[32] 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 epidemic[34] or endemic[35,36] settings. Herd immunity was documented early on as an important secondary effect within the scope of UMV, as recorded in Israel[37] (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)
Children								
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	
Raczniak (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)	Twinrix	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
Adolescents								
Beran (2016)[54]	74 (12–15y)	Twinrix	0, 6	15 years	15 mIU/mL	100%	387.5	nd
	88 (12–15y)	Twinrix jun	0, 1, 6	15 years	15 mIU/mL	100%	299.4	nd
Diaz-Mitoma (2008)[55]	22 (6–15y)	Twinrix jun	0, 1, 6	10 years	15 mIU/mL	100%	680.0	nd
Adults								
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
					20 mIU/mL	98.9%		For ≥33.0 years 95% with ≥20mIU/mL
Hammitt (2008)[57]	48 (20–70y)	Havrix 720	0, 1, 12	5 years	20 mIU/mL	98%	503.0	For 21 years GMC remains ≥20mIU/mL[f]
	7 (20–70y)	Havrix 720	0, 1, 12	10 years	20 mIU/mL	100%	250.0	
Rendi-Wagner (2007)[58]	813 (~53y)[g]	Havrix 720	0, 1, 6–12	10 years	10 mIU/mL	97.9%	406.1	nd
Theeten (2015)[59]	36 (17–40y)	Havrix 1440	0, 6	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]	Twinrix	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]	Twinrix	0, 1, 6	20 years	15 mIU/mL	96%	229.3	

[a]N = number of subjects at end of follow-up; [b]Age at vaccination: y = years, m = months; [c] Models used in the studies listed: piecewise linear model [Espul (2020)[43]], log-linear model [Hammitt (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]]; [d] Mosites (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,[5563–67] 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 months[36] seroprotection (≥10 mIU/mL) was estimated to last in ≥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 Israel[68] 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-vaccination[72] 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 stimulable 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	Seropro-tection cutoff	Seropro-tection rate	GMC (mIU/mL)	Booster dose	Booster effect
Espul (2020)[43]	318 (11–23)	Avaxim 80 190 (11–23)	5 years	10 mIU/mL 10 years	99.7% 3 mIU/mL[c]	122.5 100%	Individual cases 78.2	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 ≥3mIU/mL
Mayorga (2016)[31]	104 (31–65)	Epaxal	7.5 years	10 mIU/mL	95.2%	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 2nd dose between year 1 and 5: GMC 45.8 → 911.4 mIU/mL

[a]N = number of subjects at end of follow-up; [b] Age at vaccination; [c] Change of test system and cutoff for >5 – 10 year follow-up; [d]Espul (2017);[81] [e] HAV 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 capacity[88] 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 'anamnestic 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 years[81] 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 HAV[59] 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 Fcg 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 live,[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 days[15] 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	Seropro-tection cutoff	Seropro-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 2nd 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	–

[a]N = number of subjects at end of follow-up; [b] Age at vaccination; [c] Including n = 13 subjects turning seroneg. (and boosted) at years 1 and 3; [d] GMC of n = 87 (6 yrs)/n = 106 (10 yrs) still anti-HAV positive subjects and not having received booster; [e] GMC of n = 29 still anti-HAV positive subjects; [f] 7 years after 0/12 months (priming + booster) immunization; [g] 1 month after booster dose (month 13 of study); [h] not 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 months[96] 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 seroresponse 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 years[56] 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 years[68] 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 years[92] 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/m^2) at primary vaccination correlated in one study after 4 years with a trend for lower seropositivity[92] 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/µL at baseline,[119] a long duration of the HIV infection,[118] and one additional dose of HAV vaccine[120] 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 assay[122] 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" phenomenons 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 (≥5,000–10,000 mIU/mL) from past HAV infection are not boostable (see documented breakthrough infection [subject ID 237] in Mayorga et al. 2016[31] 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 → 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 trial[36] 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-year[127] 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 (≥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 endemic[129] and 4.1% vs 6.7% in an outbreak[38] 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] Alone 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 countries[135] and seem to start in some West African countries as well.[136] In large countries like India,[133] China,[22] Brazil,[137] and Mexico[138] important differences in endemicity levels still exist between regions within the country itself.

This epidemiological transition to lower endemicity with ensuing higher disease burden[4] 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 States[139] and China[20] 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[t]
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% ↓) 25 → 2.5[d] (90% ↓)	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% 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, Jiaojiang 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
		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 Bejing only

(*Continued*)

Table 5. (Continued).

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
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	Shandong province
Guo (2020)[154]	2008	18 months	Single-dose Live-atten.	82.2%/98.4% (2008/2018)	2008 vs 2018	–	Absolute No of HAV cases reported: 4576 → 237 (94.8% ↓)	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[l] 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 UMV start in Israel born military recruits: 35.3% vs 71.5% (born prior vs born after UMV 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 UMV 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)°	1992–1998 vs 1999–2005	8.15 → 1.4° (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 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
Martinez (2015)[166]	1998	12 years	Three-dose inactivated (Twinrix jun)	–	1991–1998 vs 2000–2012	1.53 → 1.27[p] (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%[q]	2005 vs 2010	88.7 → 2.7 (96.9% ↓)	–	
UNITED STATES								
Wasley (2005)[168]	1999[r]	≥ 2 yrs (children)	Two-dose inactivated	50% (2003)[s]	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[r]	≥ 2 yrs (children)	Two-dose inactivated	30.0% (2004)[s]	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[t]	–
Vogt (2008)[169]	1999[r] 2006	2–12 yrs 1–2 yrs	Two-dose inactivated	–	1990–1995 vs 2000–2004	~90–120/10^6 → 20–40/10^6	Mortality: 0.38 → $0.26/10^6$ (32% ↓)	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[r] 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[r] 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[r] 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[r] 2006	2–12 years 1–2 year	Two-dose inactivated	–	1999 vs 2011	6.0 → 0.4 (93.3% ↓)	Hosp. admission[v]: 7.3% → 24.5% Age at admission: 36 → 45 years Age at death[w]: 48 → 76.2 years	Role of liverrelated 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 a[e] decrease 2014 → 2016; [f] H2-strain: Mao (1997),[150] Zhuang (2005);[86] strain not indicated: Sun (2018),[22] Zhang (2014) [publication in Chinese];[151] [g] Mass vaccination started in 1992; [h] No age indicated (publication in Chinese); [i]L-HepA = live-attenuated, I-HepA = inactivated HAV vaccines; [j] Following integration of HAV vaccination program into EPI in 2008; [k] 1st and 2nd vaccine dose; [l] Seropositivity: ≥100 mIU/mL = likely from infection, <100 mIU/mL = residual maternal anti-HAV antibodies; [m] Vaccination coverage 2003–2010; [n] Vaccination coverage 2001–2002; [o] mean incidence for age group 12–18 years; [p] only outbreak-associated cases; [q] Vaccination coverage 1st dose of target children born in 2007; [r]1999–2005: only children living in 17 States with high hepatitis A rates; [s] Children aged 24–35 months in vaccinating States; [t] mUSD = million US dollars; [u] for children 24–35 months of age; [v] Rate (%) of hepatitis A cases hospitalized; [w]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; UMV: 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, Tunesia) 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 mortality[169] or in hospitalizations[139,157,164,173,174] and health-care costs.[139,145] Similar data were reported for regional UMVs 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/adolescents[153] 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 cases[151] 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] Uruguay[167] and Italy (Puglia region)[162] achieved >90% declines in disease incidence. The single-dose programs in Argentina[77] and Brazil[149] 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 memory[178] (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 Greece[156] – 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 Israel[160] and Australia[147] for inactivated, and for China[22] 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 effects[180] 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] China[153] (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 antibodies[4] (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 loosing 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 UMVs, 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 vaccination[184] 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 America[206] and North America[207] 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-born 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 ≥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 Union[215] 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 enteral 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.

Acknowledgments

We thank Robert Canavan for proofreading our article.

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 Biotecch/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.

References

1. World Health Organization. WHO position paper on hepatitis A vaccines – June 2012. Wkly Epid Rec. 2012;87:261–76.
2. Rein DB, Stevens G, Flaxman A, Wittenborn JS, Timothy N, Wiktor SZ, Wiersma ST. P703 THE GLOBAL BURDEN OF HEPATITIS A VIRUS IN 1990 AND 2005. J Hepatol. 2014;60(1): S303. doi:10.1016/S0168-8278(14)60865-5.
3. World Health Organization, Shouval D, Van Damme P. WHO immunological basis for immunization series: module 18: hepatitis A (update 2019)2019; [accessed 2020 Mar 12]. https://apps.who.int/iris/bitstream/handle/10665/326501/97892516327-eng.pdf?sequence=1&isAllowed=y.
4. Lemon SM, Ott JJ, Van Damme P, Shouval D. Type A viral hepatitis: A summary and update on the molecular virology, epidemiology, pathogenesis and prevention. J Hepatol. 2018;68 (1):167–84. doi:10.1016/j.jhep.2017.08.034.
5. Armstrong GL, Bell BP. Hepatitis A virus infections in the United States: model-based estimates and implications for childhood immunization. Pediatrics. 2002;109(5):839–45. doi:10.1542/peds.109.5.839.
6. Chen C-M, Chen SCC, Yang H-Y, Yang S-T, Wang C-M. Hospitalization and mortality due to hepatitis A in Taiwan: a 15-year nationwide cohort study. J Viral Hepat. 2016;23 (11):940–45. doi:10.1111/jvh.12564.
7. Vaughan G, Goncalves Rossi LM, Forbi JC, de-Paula VS, Purdy MA, Xia G, Khudyakov YE. Hepatitis A virus: host interactions, molecular epidemiology and evolution. Infect Genet Evol. 2014;21:227–43. doi:10.1016/j.meegid.2013.10.023.
8. Long D, Fix OK, Deng X, Seielstad M, Lauring AS. Whole genome sequencing to identify host genetic risk factors for severe outcomes of hepatitis A virus infection. J Med Virol. 2014;86(10):1661–68. doi:10.1002/jmv.24007.
9. Mayorga Perez O, Brinkhof MWG, Egger M, Frösner G, Herzog C, Zwahlen M. Decreasing risk of hepatitis A infection in León, Nicaragua: evidence from cross-sectional and longitudinal seroepidemiology studies. PLoS ONE. 2014;9(2):e87643. doi:10.1371/journal.pone.0087643.
10. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2006;55(RR–7):1–23.
11. Walker CM. Adaptive immune responses in hepatitis A virus and hepatitis E virus infections. Cold Spring Harb Perspect Med. 2019;9 (9):a033472. doi:10.1101/cshperspect.a033472.
12. Franco E, Meleleo C, Serino L, Sorbara D, Zaratti L. Hepatitis A: epidemiology and prevention in developing countries. World J Hepatol. 2012;4:68–73.
13. Jacobsen KH, Koopman JS. The effects of socioeconomic development on worldwide hepatitis A virus seroprevalence patterns. Int J Epidemiol. 2005;34(3):600–09. doi:10.1093/ije/dyi062.
14. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the global burden of disease study 2013. The Lancet. 2015;385 (9963):117–71. doi:10.1016/S0140-6736(14)61682-2.
15. Brinkhof MWG, Mayorga O, Bock J, Heininger U, Herzog C. Kinetics of maternally acquired anti-hepatitis A antibodies: prediction of waning based on maternal or cord blood antibody levels. Vaccine. 2013;31(11):1490–95. doi:10.1016/j.vaccine.2013.01.011.
16. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28(41):6653–57. doi:10.1016/j.vaccine.2010.08.037.
17. Jacobsen K. The global prevalence of hepatitis A virus infection and susceptibility: a systematic review. 2009. [accessed 2020 Mar 12] http://apps.who.int/iris/bitstream/handle/10665/70180/WHO_IVB_10.01_eng.pdf;jsessionid=E90CC2AAACC8621E9AD4518215D72976?sequence=.
18. Jacobsen KH, Koopman JS. Declining hepatitis A seroprevalence: a global review and analysis. Epidemiol Infect. 2004;132 (6):1005–22. doi:10.1017/S0950268804002857.
19. Pichichero ME. Booster vaccinations: can immunologic memory outpace disease pathogenesis? Pediatrics. 2009;124(6):1633–41. doi:10.1542/peds.2008-3645.
20. Cui F, Liang X, Wang F, Zheng H, Hutin YJ, Yang W. Development, production, and postmarketing surveillance of hepatitis A vaccines in China. J Epidemiol. 2014;24(3):169–77. doi:10.2188/jea.JE20130022.
21. Xu Z-Y, Wang X-Y. Live attenuated hepatitis A vaccines developed in China. Hum Vaccin Immunother. 2014;10(3):659–66. doi:10.4161/hv.27124.
22. Sun X, Wang F, Zheng H, Miao N, Yuan Q, Cui F, Yin Z, Zhang G, Levine H. The impact of expanded program on immunization with live attenuated and inactivated Hepatitis A vaccines in China,

2004–2016. Vaccine. 2018;36(10):1279–84. doi:10.1016/j.vaccine.2018.01.043.
23. Rao S, Mao JS, Motlekar S, Fangcheng Z, Kadhe G. A review of immunogenicity and tolerability of live attenuated Hepatitis A vaccine in children. Hum Vaccin Immunother. 2016;12:3160–65.
24. Plotkin SA. Complex correlates of protection after vaccination. Clin Infect Dis. 2013;56(10):1458–65. doi:10.1093/cid/cit048.
25. Shouval D, Ashur Y, Adler R, Lewis JA, Armstrong ME, Davide JP, McGuire B, Kuter B, Brown L, Miller W, et al. Single and booster dose responses to an inactivated hepatitis A virus vaccine: comparison with immune serum globulin prophylaxis. Vaccine. 1993;11 (Suppl 1):S9–14. doi:10.1016/0264-410X(93)90151-M.
26. Askling HH, Rombo L, van Vollenhoven R, Hallén I, Å T, Nordin M, Herzog C, Kantele A. Hepatitis A vaccine for immunosuppressed patients with rheumatoid arthritis: a prospective, open-label, multi-centre study. Travel Med Infect Dis. 2014;12 (2):134–42. doi:10.1016/j.tmaid.2014.01.005.
27. Melgaço JG, Morgado LN, Santiago MA, deOliveira JM, Lewis-Ximenez LL, Hasselmann B, Gonçalves Cruz O, Alves Pinto M, Lamarca Vitril C. A single dose of inactivated hepatitis A vaccine promotes HAV-specific memory cellular response similar to that induced by a natural infection. Vaccine. 2015;33:3813–20.
28. D'Acremont V, Herzog C, Genton B. Immunogenicity and safety of a virosomal hepatitis A vaccine (Epaxal) in the elderly. J Travel Med. 2006;13(2):78–83. doi:10.1111/j.1708-8305.2006.00001.x.
29. Genton B, D'Acremont V, Furrer H-J, Hatz C, Louis L. Hepatitis A vaccines and the elderly. Travel Med Infect Dis. 2006;4 (6):303–12. doi:10.1016/j.tmaid.2005.10.002.
30. Zimmermann P, Curtis N. Factors that influence the immune response to vaccination. Clin Microbiol Rev. 2019;32:e00084–18.
31. Mayorga O, Bühler S, Jaeger VK, Bally S, Hatz C, Frösner G, Protzer U, Van Damme P, Egger M, Herzog C. Single-dose hepatitis A immunization: 7.5-year observational pilot study in Nicaraguan children to assess protective effectiveness and humoral immune memory response. J Infect Dis. 2016;214(10):1498–506.
32. Fritzsche C, Loebermann M, Reisinger EC. A case of acute hepatitis A infection in an HIV-positive patient despite complete hepatitis A vaccination. Infection. 2018;46(4):565–67. doi:10.1007/s15010-018-1129-1.
33. Vestergaard HT, Harritshøj LH, Midgley SE, Ullum H, Kampmann P. Transfusion transmission of hepatitis A virus with fecal shedding in a previously hepatitis A vaccinated recipient. J Infect Chemother. 2018;24(9):766–68. doi:10.1016/j.jiac.2018.01.020.
34. Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, Miller W, Shouval D, Wiens B, Calandra G, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. N Engl J Med. 1992;327(7):453–57. doi:10.1056/NEJM199208133270702.
35. Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik CA, Suntyakorn S, Suknuntapong T, Safary A, Tang DB, et al. Protection against hepatitis A by an inactivated vaccine. JAMA. 1994;271(17):1328–34. doi:10.1001/jama.1994.03510410040030.
36. Mayorga Pérez O, Herzog C, Zellmeyer M, Loáisiga A, Frösner G, Egger M. Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. J Infect Dis. 2003;188(5):671–77. doi:10.1086/377309.
37. Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of toddlers. JAMA. 2005;294(2):202–10. doi:10.1001/jama.294.2.202.
38. Zhao YL. H2 strain attenuated live hepatitis A vaccines: protective efficacy in a hepatitis A outbreak. World J Gastroenterol. 2000;6 (6):829. doi:10.3748/wjg.v6.i6.829.
39. Ma F, Yang J, Kang G, Sun Q, Lu P, Zhao Y, Wang Z, Luo J, Wang Z. Comparison of the safety and immunogenicity of live attenuated and inactivated hepatitis A vaccine in healthy Chinese children aged 18 months to 16 years: results from a randomized, parallel controlled, phase IV study. Clin Microbiol Infect. 2016;22 (9):811.e9–811.e15. doi:10.1016/j.cmi.2016.06.004.
40. Wang X, Pan Y, Chen J, Luo J, Xi J, Ye C, Zhao Y, Qiu L, Weng S, Hong S, et al. The excretion rate and stability of HAAg in human fecal samples after live attenuated hepatitis A vaccination. J Med Virol. 2020; Online ahead of print. doi:10.1002/jmv.25747.
41. Ott JJ, Irving G, Wiersma ST. Long-term protective effects of hepatitis A vaccines. A Systematic Review Vaccine. 2012;31:3–11.
42. Bian G-L, Ma R, Dong H-J, Ni H-X, Hu F-J, Chen Y-R, Chen JQ, Zhou SY, Lin YX, Xu GZ. Long-term clinical observation of the immunogenicity of inactivated hepatitis A vaccine in children. Vaccine. 2010;28(30):4798–801.
43. Espul C, Cuello H, Lo Castro I, Bravo C, Thollot Y, Voznica J, Vigne C, Coudeville L. Statistical modeling alongside observational data predicts long-term immunogenicity of one dose and two doses of pediatric hepatitis A vaccine in the Mendoza province of Argentina. Vaccine. 2020;38(7):1715–22. doi:10.1016/j.vaccine.2019.12.049.
44. López EL, Contrini MM, Mistchenko A, Kieffer A, Baggaley RF, Di Tanna GL, Desai K, Rasuli A, Armoni J. Modeling the long-term persistence of hepatitis A antibody after a two-dose vaccination schedule in Argentinean children. Pediatr Infect Dis J. 2015;34 (4):417–25. doi:10.1097/INF.0000000000000605.
45. Plumb ID, Bulkow LR, Bruce MG, Hennessy TW, Morris J, Rudolph K, Spradling P, Snowball M, McMahon BJ. Persistence of antibody to Hepatitis A virus 20 years after receipt of Hepatitis A vaccine in Alaska. J Viral Hepat. 2017;24(7):608–12. doi:10.1111/jvh.12676.
46. Mosites E, Gounder P, Snowball M, Morris J, Spradling P, Nelson N, Bulkow L, Bruce M, McMahon B. Hepatitis A vaccine immune response 22 years after vaccination. J Med Virol. 2018;90 (8):1418–22. doi:10.1002/jmv.25197.
47. Raczniak GA, Thomas TK, Bulkow LR, Negus SE, Zanis CL, Bruce MG, Spradling PR, Teshale EH, McMahon BJ. Duration of protection against hepatitis A for the current two-dose vaccine compared to a three-dose vaccine schedule in children. Vaccine. 2013;31(17):2152–55. doi:10.1016/j.vaccine.2013.02.048.
48. Sharapov UM, Bulkow LR, Negus SE, Spradling PR, Homan C, Drobeniuc J, Bruce M, Kamili S, Hu DJ, McMahon BJ, et al. Persistence of hepatitis A vaccine induced seropositivity in infants and young children by maternal antibody status: 10-year follow-up. Hepatology. 2012;56(2):516–22. doi:10.1002/hep.25687.
49. Sintusek P, Sa-nguanmoo P, Posuwan N, Jaroonvanichkul V, Vorayingyong A, Poovorawan Y. Changes in hepatitis A virus (HAV) seroprevalence in medical students in Bangkok, Thailand, from 1981 to 2016. BMC Res Notes. 2018;11(1):379. doi:10.1186/s13104-018-3733-7.
50. Spradling PR, Bulkow LR, Negus SE, Homan C, Bruce MG, McMahon BJ. Persistence of seropositivity among persons vaccinated for hepatitis A during infancy by maternal antibody status: 15-year follow-up. Hepatology. 2016;63:703–11.
51. Van Damme P, Kafeja F, Van der Wielen M, Leyssen M, Jacquet J-M. Long-term immunogenicity and immune memory after two doses of the adult formulation of a combined hepatitis A and B vaccine in children 1 to 11 years of age. Pediatr Infect Dis J. 2011;30(8):703–05. doi:10.1097/INF.0b013e3182138296.
52. Wang Y, Qi Y, Xu W, Hu Y, Wang L, Yu Y, Jiang Z, Xia J, Zeng G, Wang Y, et al. Immunogenicity persistence in children of hepatitis A vaccines Healive® and Havrix®: 11 years follow-up and long-term prediction. Hum Vaccin Immunother. Online ahead of print, 2020;1–6. doi:10.1080/21645515.2020.1715687.
53. Mosites E, Seeman S, Negus S, Homan C, Morris J, Nelson NP, Spradling PR, Bruce M, McMahon B. Immunogenicity of the hepatitis A vaccine 20 years after infant immunization. Vaccine. 2020;38(32):4940–43. doi:10.1016/j.vaccine.2020.05.069.
54. Beran J, Van der Meeren O, Leyssen M, D'silva P. Immunity to hepatitis A and B persists for at least 15 years after immunisation of adolescents with a combined hepatitis A and B vaccine. Vaccine. 2016;34(24):2686–91. doi:10.1016/j.vaccine.2016.04.033.
55. Diaz-Mitoma F, Law B, Subramanya A, Hoet B. Long-term antibody persistence induced by a combined hepatitis A and B vaccine in children and adolescents. Vaccine. 2008;26(14):1759–63. doi:10.1016/j.vaccine.2008.01.014.

56. Chappuis F, Farinelli T, Deckx H, Sarnecki M, Go O, Salzgeber Y, Stals C. Immunogenicity and estimation of antibody persistence following vaccination with an inactivated virosomal hepatitis A vaccine in adults: A 20-year follow-up study. Vaccine. 2017;35 (10):1448–54. doi:10.1016/j.vaccine.2017.01.031.
57. Hammitt LL, Bulkow L, Hennessy TW, Zanis C, Snowball M, Williams JL, Bell B, McMahon B. Persistence of antibody to hepatitis A virus 10 years after vaccination among children and adults. J Infect Dis. 2008;198(12):1776–82. doi:10.1086/593335.
58. Rendi-Wagner P, Korinek M, Winkler B, Kundi M, Kollaritsch H, Wiedermann U. Persistence of seroprotection 10 years after primary hepatitis A vaccination in an unselected study population. Vaccine. 2007;25:927–31.
59. Theeten H, Van Herck K, Van der Meeren O, Crasta P, Van Damme P, Hens N. Long-term antibody persistence after vaccination with a 2-dose Havrix (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions. Vaccine. 2015;33(42):5723–27. doi:10.1016/j.vaccine.2015.07.008.
60. Van Damme P, Leroux-Roels G, Suryakiran P, Folschweiller N, Van der Meeren O. Persistence of antibodies 20 y after vaccination with a combined hepatitis A and B vaccine. Hum Vaccin Immunother. 2017;13(5):972–80. doi:10.1080/21645515.2016.1274473.
61. Bovier PA, Bock J, Ebengo TF, Frösner G, Glaus J, Herzog C, Loutan L. Predicted 30-year protection after vaccination with an aluminum-free virosomal hepatitis A vaccine. J Med Virol. 2010;82 (10):1629–34. doi:10.1002/jmv.21883.
62. Van Damme P, Banatvala J, Fay O, Iwarson S, McMahon B, Van Herck K, Shouval D, Bonanni P, Connor B, Cooksley G, et al. Hepatitis A booster vaccination: is there a need? Lancet. 2003;362 (9389):1065–71. doi:10.1016/S0140-6736(03)14418-2.
63. Burgess MA, McIntyre PB, Hellard M, Ruff TA, Lefevre I, Bock HL. Antibody persistence six years after two doses of combined hepatitis A and B vaccine. Vaccine. 2010;28(10):2222–26. doi:10.1016/j.vaccine.2009.12.053.
64. Chan CY, Lee SD, Yu MI, Wang YJ, Chang FY, Lo KJ. Long-term follow-up of hepatitis A vaccination in children. Vaccine. 1999;17 (4):369–72. doi:10.1016/S0264-410X(98)00200-X.
65. Fan PC, Chang MH, Lee PI, Safary A, Lee CY. Follow-up immunogenicity of an inactivated hepatitis A virus vaccine in healthy children: results after 5 years. Vaccine. 1998;16(2–3):232–35. doi:10.1016/S0264-410X(97)00179-5.
66. Mayorga O, Bock J, Egger M, Frösner G, Ibanez R, Herzog C. Long-term immunogenicity of a virosomal, aluminium-free hepatitis A vaccine in Nicaraguan children. Poster presented at: 43th ICAAC; 2003 Sept 14–17; Chicago.
67. Van Herck K, Hens A, de Coster I, Vertruyen A, Tolboom J, Sarnecki M, Van Damme P. Long-term antibody persistence in children after vaccination with the pediatric formulation of an aluminum-free virosomal hepatitis A vaccine. Pediatr Infect Dis J. 2015;34(4):e85–91.
68. Dagan R, Ashkenazi S, Livni G, Go O, Bagchi P, Sarnecki M. Long-term Serologic follow-up of children vaccinated with a pediatric formulation of virosomal hepatitis A vaccine administered with routine childhood vaccines at 12–15 months of age. Pediatr Infect Dis J. 2016;35(7):e220–8. doi:10.1097/INF.0000000000001176.
69. Gilca V, Dionne M, Boulianne N, Murphy D, de Serres G. Long-term immunogenicity of two pediatric doses of combined hepatitis A and B or monovalent hepatitis B vaccine in 8 to 10-year-old children and the effect of a challenge dose given seven years later. Pediatr Infect Dis J. 2009;28:916–18.
70. Yu C, Song Y, Qi Y, Li C, Jiang Z, Li C, Zhang W, Wang L, Xia J. Comparison of immunogenicity and persistence between inactivated hepatitis A vaccine Healive® and Havrix® among children: A 5-year follow-up study. Hum Vaccin Immunother. 2016;12 (10):2595–602. doi:10.1080/21645515.2016.1197450.
71. Dagan R, Amir J, Livni G, Greenberg D, Abu-Abed J, Guy L, Ashkenazi S, Froesner G, Tewald F, Schaetzl HM, et al. Concomitant administration of a virosome-adjuvanted hepatitis a vaccine with routine childhood vaccines at age twelve to fifteen months: a randomized controlled trial. Pediatr Infect Dis J. 2007;26 (9):787–93. doi:10.1097/INF.0b013e318060acbd.
72. Raczniak GA, Bulkow LR, Bruce MG, Zanis CL, Baum RL, Snowball MM, Byrd KK, Sharapov UM, Hennessy TW, McMahon BJ, et al. Long-term immunogenicity of hepatitis A virus vaccine in Alaska 17 years after initial childhood series. J Infect Dis. 2013;207(3):493–96. doi:10.1093/infdis/jis710.
73. Ott JJ, Wiersma ST. Single-dose administration of inactivated hepatitis A vaccination in the context of hepatitis A vaccine recommendations. Int J Infect Dis. 2013;17(11):e939–44. doi:10.1016/j.ijid.2013.04.012.
74. Landry P, Tremblay S, Darioli R, Genton B. Inactivated hepatitis A vaccine booster given ≥24 months after the primary dose. Vaccine. 2000;19(4–5):399–402. doi:10.1016/S0264-410X(00)00188-2.
75. Beck BR, Hatz C, Brönnimann R, Herzog C. Successful booster antibody response up to 54 months after single primary vaccination with virosome-formulated, aluminum-free hepatitis A vaccine. Clin Infect Dis. 2003;37(9):e126–8. doi:10.1086/378890.
76. Iwarson S, Lindh M, Widerström L. Excellent booster response 4 to 8 years after a single primary dose of an inactivated hepatitis A vaccine. J Travel Med. 2004;11(2):120–21. doi:10.2310/7060.2004.17079.
77. Vizzotti C, González J, Gentile A, Rearte A, Ramonet M, Cañero-Velasco MC, Pérez Carrega ME, Urueña A, Diosque M. Impact of the single-dose immunization strategy against hepatitis A in Argentina. Pediatr Infect Dis J. 2014;33(1):84–88. doi:10.1097/INF.0000000000000042.
78. Urueña A, González JE, Rearte A, Pérez Carrega ME, Calli R, Pagani MF, Uboldi A, Vicentín R, Caglio P, Cañero-Velasco MC, et al. Single-dose universal hepatitis A immunization in one-year-old children in Argentina: high prevalence of protective antibodies up to 9 years after vaccination. Pediatr Infect Dis J. 2016;35 (12):1339–42. doi:10.1097/INF.0000000000001322.
79. Vizzotti C, González J, Rearte A, Urueña A, Pérez Carrega M, Calli R, Gentile A, Uboldi A, Ramonet M, Canero-Velasco M, et al. Single-dose universal hepatitis A immunization in Argentina: low viral circulation and high persistence of protective antibodies up to 4 years. J Pediatric Infect Dis Soc. 2015;4(4):e62–7. doi:10.1093/jpids/piu068.
80. Zhang Z, Zhu X, Hu Y, Liang M, Sun J, Song Y, Yang Q, Ji H, Zeng G, Song L, et al. Five-year antibody persistence in children after one dose of inactivated or live attenuated hepatitis A vaccine. Hum Vaccin Immunother. 2017;13(6):1314–19. doi:10.1080/21645515.2016.1278329.
81. Espul C, Benedetti L, Linares M, Cuello H, Lo Castro I, Thollot Y, Rasuli A. Seven-year follow-up of the immune response after one or 2 doses of inactivated hepatitis A vaccine given at 1 year of age in the Mendoza Province of Argentina. Hum Vaccin Immunother. 2017;13(11):2707–12. doi:10.1080/21645515.2017.1358326.
82. Bhave S, Sapru A, Bavdekar A, Kapatkar V, Mane A. Long-term immunogenicity of single dose of live attenuated hepatitis A vaccine in Indian children. Indian Pediatr. 2015;52(8):687–90. doi:10.1007/s13312-015-0697-8.
83. Chen Y, Zhou C-L, Zhang X-J, Hao Z-Y, Zhang Y-H, Wang S-M, Ma J-C, Zhao G, Qiu C, Zhao Y-L, et al. Immune memory at 17-years of follow-up of a single dose of live attenuated hepatitis A vaccine. Vaccine. 2018;36(1):114–21. doi:10.1016/j.vaccine.2017.11.036.
84. Mitra M, Shah N, Faridi M, Ghosh A, Sankaranarayanan VS, Aggarwal A, Chatterjee S, Bhattacharyya N, Kadhe G, Vishnoi G, et al. Long term follow-up study to evaluate immunogenicity and safety of a single dose of live attenuated hepatitis A vaccine in children. Hum Vaccin Immunother. 2015;11(5):1147–52. doi:10.4161/21645515.2014.979646.
85. Wang X-Y, Xu Z-Y, Ma J-C, von Seidlein L, Zhang Y, Hao Z-Y, Han OP, Zhang YL, Tian MY, Ouyang PY, et al. Long-term immunogenicity after single and booster dose of a live attenuated hepatitis A vaccine: results from 8-year follow-up. Vaccine. 2007;25(3):446–49.
86. Zhuang F-C, Qian W, Mao Z-A, Gong Y-P, Jiang Q, Jiang L-M, Chen NL, Chai SA, Mao JS. Persistent efficacy of live attenuated

hepatitis A vaccine (H2-strain) after a mass vaccination program. Chin Med J. 2005;118(22):1851–56.
87. Zhuang F-C, Mao Z-A, Jiang L-M, Wu J, Chen Y-Q, Jiang Q,Chen NL, Chai SA, Mao JS. Long-term immunogenicity and effectiveness of live attenuated hepatitis A vaccine (H2-strain) - a study on the result of 15 years' follow up. Zhonghua Liu Xing Bing Xue Za Zhi. 2010;31(12):1332–35.
88. Andraud M, Lejeune O, Musoro JZ, Ogunjimi B, Beutels P, Hens N. Living on three time scales: the dynamics of plasma cell and antibody populations illustrated for hepatitis A virus. PLoS Comput Biol. 2012;8(3):e1002418. doi:10.1371/journal.pcbi.1002418.
89. Bell BP, Negus S, Fiore AE, Plotnik J, Dhotre KB, Williams J, Shapiro CN, McMahon BJ. Immunogenicity of an inactivated hepatitis A vaccine in infants and young children. Pediatr Infect Dis J. 2007;26(2):116–22. doi:10.1097/01.inf.0000253253.85640.cc.
90. Hatz C, van der Ploeg R, Beck BR, Frösner G, Hunt M, Herzog C. Successful memory response following a booster dose with a virosome-formulated hepatitis A vaccine delayed up to 11 years. Clin Vaccine Immunol. 2011;18(5):885–87. doi:10.1128/CVI.00358-10.
91. Van Herck K, Van Damme P, Lievens M, Stoffel M. Hepatitis A vaccine: indirect evidence of immune memory 12 years after the primary course. J Med Virol. 2004;72(2):194–96. doi:10.1002/jmv.10574.
92. Chlibek R, von Sonnenburg F, Van Damme P, Smetana J, Tichy P, Gunapalaiah B, Leyssen M, Jacquet J-M. Antibody persistence and immune memory 4 years post-vaccination with combined hepatitis A and B vaccine in adults aged over 40 years. J Travel Med. 2011;18(2):145–48. doi:10.1111/j.1708-8305.2010.00499.x.
93. Chen G-J, Sun H-Y, Lin K-Y, Cheng A, Huang Y-C, Hsieh S-M, Sheng W-H, Liu W-C, Hung -C-C, Chang S-C, et al. Serological responses to revaccination with hepatitis A virus (HAV) vaccines among HIV-positive individuals whose anti-HAV antibody waned after primary vaccination. Liver Int. 2018;38(7):1198–205. doi:10.1111/liv.13665.
94. de Gouvêa A, de Moraes Pinto MI, Miyamoto M, Machado DM, Duarte Pessoa S and Bononi de Caremo F, Vasconcelos Beltrao S, Menezes Succi RC.. Persistence of hepatitis A virus antibodies after primary immunization and response to revaccination in children and adolescents with perinatal HIV exposure. Revista Paulista De Pediatria (English Edition). 2015;33(2):142–49.
95. Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Front Immunol. 2014;5:446.
96. Usonis V, Bakasénas V, Valentelis R, Katiliene G, Vidzeniene D, Herzog C. Antibody titres after primary and booster vaccination of infants and young children with a virosomal hepatitis A vaccine (Epaxal). Vaccine. 2003;21(31):4588–92. doi:10.1016/S0264-410X(03)00509-7.
97. Stojanov S, Liese JG, Belohradsky BH, Vandermeulen C, Hoppenbrouwers K, Van der Wielen M, Van Damme P, Georges B, Dupuy M, Scemama M, et al. Administration of hepatitis A vaccine at 6 and 12 months of age concomitantly with hexavalent (DTaP–IPV–PRP, T–HBs) combination vaccine. Vaccine. 2007;25(43):7549–58.
98. Letson GW, Shapiro CN, Kuehn D, Gardea C, Welty TK, Krause DS, Lambert SB, Margolis HS. Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants. J Pediatr. 2004;144(3):327–32.
99. Dagan R, Amir J, Mijalovsky A, Kalmanovitch I, Bar-Yochai A, Thoelen S, Safary A, Ashkenazi S. Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. Pediatr Infect Dis J. 2000;19(11):1045–52. doi:10.1097/00006454-200011000-00004.
100. Derya A, Necmi A, Emre A, Akgün Y. Decline of maternal hepatitis A antibodies during the first 2 years of life in infants born in Turkey. Am J Trop Med Hyg. 2005;73(2):457–59. doi:10.4269/ajtmh.2005.73.457.
101. Lieberman JM, S-jC C, Partridge S, Hollister JC, Kaplan KM, Jensen EH, Kuter B, Ward JI. Kinetics of maternal hepatitis A antibody decay in infants: implications for vaccine use. Pediatr Infect Dis J. 2002;21(4):347–48. doi:10.1097/00006454-200204000-00017.
102. Lagos R, Munoz A, Dumas R, Pichon S, Zambrano B, Levine M, Vidor E. Immunological priming of one dose of inactivated hepatitis A vaccine given during the first year of life in presence of maternal antibodies. Vaccine. 2003;21(25–26):3730–33. doi:10.1016/S0264-410X(03)00385-2.
103. Kanra G, Yalcin SS, Kara A, Ozmert E, Yurdakök K. Hepatitis A booster vaccine in children after infant immunization. Pediatr Infect Dis J. 2002;21(8):727–30. doi:10.1097/00006454-200208000-00006.
104. Fiore AE, Shapiro CN, Sabin K, Labonte K, Darling K, Culver D, Bell BP, Margolis HS. Hepatitis A vaccination of infants: effect of maternal antibody status on antibody persistence and response to a booster dose. Pediatr Infect Dis J. 2003;22(4):354–59. doi:10.1097/01.inf.0000059446.52063.b9.
105. Orije MRP, Maertens K, Corbière V, Wanlapakorn N, Van Damme P, Leuridan E, Mascart F. The effect of maternal antibodies on the cellular immune response after infant vaccination: a review. Vaccine. 2020;38(1):20–28. doi:10.1016/j.vaccine.2019.10.025.
106. Bovier PA, Bock J, Loutan L, Farinelli T, Glueck R, Herzog C. Long-term immunogenicity of an inactivated virosome hepatitis A vaccine. J Med Virol. 2002;68(4):489–93. doi:10.1002/jmv.10244.
107. Chen XQ, Bülbül M, de Gast GC, van Loon AM, Nalin DR, van Hattum J. Immunogenicity of two versus three injections of inactivated hepatitis A vaccine in adults. J Hepatol. 1997;26(2):260–64. doi:10.1016/S0168-8278(97)80039-6.
108. Van der Wielen M, Van Damme P, Chlibek R, Smetana J, von Sonnenburg F. Hepatitis A/B vaccination of adults over 40 years old: comparison of three vaccine regimens and effect of influencing factors. Vaccine. 2006;24(26):5509–15. doi:10.1016/j.vaccine.2006.04.016.
109. Höhler T, Groeger-Bicanic G, Hoet B, Stoffel M. Antibody persistence and immune memory elicited by combined hepatitis A and B vaccination in older adults. Vaccine. 2007;25(8):1503–08. doi:10.1016/j.vaccine.2006.10.024.
110. Nelson NP, Murphy TV, McMahon BJ. Hepatitis A vaccination for post-exposure prophylaxis in persons aged 40 years and older. Vaccine. 2014;32(25):2939. doi:10.1016/j.vaccine.2014.01.086.
111. Reuman PD, Kubilis P, Hurni W, Brown L, Nalin D. The effect of age and weight on the response to formalin inactivated, alum-adjuvanted hepatitis A vaccine in healthy adults. Vaccine. 1997;15(10):1157–61. doi:10.1016/S0264-410X(96)00310-6.
112. Faridi MMA, Shah N, Ghosh TK, Sankaranarayanan VS, Arankalle V, Aggarwal A, Sathiyasekaran M, Bhattacharya N, Vasanthi T, Chaterjee S, et al. Immunogenicity and safety of live attenuated hepatitis A vaccine: a multicentric study. Indian Pediatr. 2009;46(1):29–34.
113. Mena G, García-Basteiro AL, Bayas JM. Hepatitis B and A vaccination in HIV-infected adults: a review. Hum Vaccin Immunother. 2015;11(11):2582–98. doi:10.1080/21645515.2015.1055424.
114. Lin K-Y, Chen G-J, Lee Y-L, Huang Y-C, Cheng A, Sun H-Y,Chang SY, Liu CE, Hung CC. Hepatitis A virus infection and hepatitis A vaccination in human immunodeficiency virus-positive patients: a review. World J Gastroenterol. 2017;23(20):3589–606.
115. Mor Z, Lurie Y, Katchman E. A case of hepatitis A vaccination failure in an HIV-positive man who had sex with men in Israel. Int J STD AIDS. 2012;23(7):529–30. doi:10.1258/ijsa.2010.010269.
116. Brennan J, Moore K, Sizemore L, Mathieson SA, Wester C, Dunn JR, Schaffner W, Jones TF. Notes from the field: acute hepatitis A virus infection among previously vaccinated persons with HIV infection - Tennessee, 2018. MMWR. 2019;68(14):328–29.
117. Crum-Cianflone NF, Wilkins K, Lee AW, Grosso A, Landrum ML, Weintrob A, Ganesan A, Maguire J, Klopfer S, Brandt C, et al. Long-term durability of immune responses after hepatitis

A vaccination among HIV-infected adults. J Infect Dis. 2011;203 (12):1815–23. doi:10.1093/infdis/jir180.
118. Kernéis S, Desaint C, Brichler S, Rey D, Belarbi L, Gordien E, Pacanowski J, Lortholary O, Abgrall S, Boëlle P-Y, et al. Long-term persistence of humoral immunity after hepatitis A vaccination in HIV-infected adults. J Acquir Immune Defic Syndr. 2011;57(3):e63–6. doi:10.1097/QAI.0b013e31821fdec3.
119. Jabłonowska E, Kuydowicz J. Durability of response to vaccination against viral hepatitis A in HIV-infected patients: a 5-year observation. Int J STD AIDS. 2014;25(10):745–50. doi:10.1177/0956462413518902.
120. Cheng A, Chang S-Y, Sun H-Y, Tsai M-S, Liu W-C, Su Y-C, Wu P-Y, Hung C-C, Chang S-C. Long-term durability of responses to 2 or 3 doses of hepatitis A vaccination in human immunodeficiency virus-positive adults on antiretroviral therapy. J Infect Dis. 2017;215(4):606–13.
121. Villarejos VM, Serra J, Anderson-Visona K, Mosley JW. Hepatitis A virus infection in households. Am J Epidemiol. 1982;115 (4):577–86. doi:10.1093/oxfordjournals.aje.a113339.
122. Coursaget P, Drucker J, Maupas P, Hibon P, Goudeau A, Bernard D, Sauvage D, Lelord G. Epidemiological and serological study of hepatitis A virus outbreaks in France: a comparison between immunoadherence and radioimmunoassay. J Hyg (Lond). 1981;86(2):155–62. doi:10.1017/S0022172400068868.
123. Werzberger A, Kuter B, Nalin D. Six years' follow-up after hepatitis A vaccination. N Engl J Med. 1998;338(16):1160. doi:10.1056/NEJM199804163381615.
124. Yu C, Mayorga O, Emerson SU, Purcell RH, Herzog C. Antibodies to HAV 3C proteinase in naturally infected and vaccine-protected children: 6½-year follow-up data of a placebo-controlled field trial. Poster presented at: 45th ICAAC; 2005 Sep 21–24; New Orleans.
125. Dagan R, Greenberg D, Weber F. Immunogenicity of an inactivated hepatitis A pediatric vaccine: three-year post-booster follow-up. Vaccine. 2005;23(44):5144–48. doi:10.1016/j.vaccine.2005.06.017.
126. Espul C, Benedetti L, Cuello H, Houillon G, Rasuli A. Persistence of immunity from 1 year of age after one or two doses of hepatitis A vaccine given to children in Argentina. Hepat Med. 2012;4:53–60. doi:10.2147/HMER.S33847.
127. Espul C, Benedetti L, Linares M, Cuello H, Rasuli A. Five-year follow-up of immune response after one or two doses of inactivated hepatitis A vaccine given at 1 year of age in the Mendoza Province of Argentina. J Viral Hepat. 2015;22(4):453–58. doi:10.1111/jvh.12317.
128. López EL, Contrini MM, Mistchenko A, Debbag R. Long-term immunity after two doses of inactivated hepatitis A vaccine, in Argentinean children. Pediatr Infect Dis J. 2010;29:568–70.
129. Xu Z, Wang X, Li R, Meng Z, Zhang Y, Gong J, Ma J, Li Y, Zhao Y, Li Y, et al. Immunogenicity and efficacy of two live attenuated hepatitis A vaccines (H(2) strains and LA-1 strains). Zhonghua Yi Xue Za Zhi. 2002;82(10):678–81.
130. Böttiger M, Christenson B, Grillner L. Hepatitis A immunity in the Swedish population. A study of the prevalence of markers in the Swedish population. Scand J Infect Dis. 1997;29(2):99–102. doi:10.3109/00365549709035867.
131. Melnick JL. History and epidemiology of hepatitis A virus. J Infect Dis. 1995;171(Suppl. 1):S2–8. doi:10.1093/infdis/171.Supplement_1.S2.
132. Carrillo-Santisteve P, Tavoschi L, Severi E, Bonfigli S, Edelstein M, Byström E, Lopalco P, Alfonsi V, Chilbek R, Dominguez A, et al. Seroprevalence and susceptibility to hepatitis A in the European union and European economic area: a systematic review. Lancet Infect Dis. 2017;17(10):e306–e319. doi:10.1016/S1473-3099(17)30392-4.
133. Gripenberg M, Aloysia D'Cor N, L'Azou M, Marsh G, Druelles S, Nealon J. Changing sero-epidemiology of hepatitis A in Asia Pacific countries: A systematic review. Int J Infect Dis. 2018;68:13–17. doi:10.1016/j.ijid.2017.12.021.
134. Tanaka J. Hepatitis A shifting epidemiology in Latin America. Vaccine. 2000;18(Suppl 1):S57–60. doi:10.1016/S0264-410X(99)00466-1.
135. Koroglu M, Jacobsen KH, Demiray T, Ozbek A, Erkorkmaz U, Altindis M. Socioeconomic indicators are strong predictors of hepatitis A seroprevalence rates in the Middle East and North Africa. J Infect Public Health. 2017;10(5):513–17. doi:10.1016/j.jiph.2016.09.020.
136. Jacobsen KH. Hepatitis A virus in West Africa: is an epidemiological transition beginning? Niger Med J. 2014;55(4):279–84. doi:10.4103/0300-1652.137185.
137. Ximenes RAdA, Martelli CMT, Amaku M, Sartori AMC, de Soárez PC, Novaes HMD, Pereira LMMB, Moreira RC, Figueiredo GM, de Azevedo RS, et al. Modelling the force of infection for hepatitis A in an urban population-based survey: a comparison of transmission patterns in Brazilian macro-regions. PLoS ONE. 2014;9(5):e94622. doi:10.1371/journal.pone.0094622.
138. López-Gatell H, García-García L, Echániz-Avilés G, Cruz-Hervert P, Olamendi-Portugal M, Castañeda-Desales D, Sanchez-Alemán MÁ, Romero-Martínez M, DeAntonio R, Cervantes-Apolinar MY, et al. Hepatitis A seroprevalence in adolescents and young adults in Mexico: a 2012 national health and nutrition survey analysis. Vaccine. 2018;36(52):8094–99. doi:10.1016/j.vaccine.2018.10.037.
139. Zhou F, Shefer A, Weinbaum C, McCauley M, Kong Y. Impact of hepatitis A vaccination on health care utilization in the United States, 1996–2004. Vaccine. 2007;25(18):3581–87. doi:10.1016/j.vaccine.2007.01.081.
140. Hendrickx G, Van Herck K, Vorsters A, Wiersma S, Shapiro C, Andrus JK, Ropero AM, Shouval D, Ward W, Van Damme P, et al. Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology. J Viral Hepat. 2008;15 (Suppl 2):1–15. doi:10.1111/j.1365-2893.2008.01022.x.
141. Stuurman AL, Marano C, Bunge EM, de Moerlooze L, Shouval D. Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines - A systematic review. Hum Vaccin Immunother. 2017;13(3):724–36. doi:10.1080/21645515.2016.1242539.
142. Suwantika AA, Beutels P, Postma MJ. Cost-effectiveness of hepatitis A vaccination in Indonesia. Hum Vaccin Immunother. 2014;10(8):2342–49. doi:10.4161/hv.29353.
143. Cervio G, Trentadue J, D'Agostino D, Luque C, Giorgi M, Armoni J, Debbag R. Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program. Hepat Med. 2011;3:99–106. doi:10.2147/HMER.S22309.
144. Blanco Fernández MD, Torres C, Riviello-López G, Poma HR, Rajal VB, Nates S, Cisterna DM, Campos RH, Mbayed VA. Analysis of the circulation of hepatitis A virus in Argentina since vaccine introduction. Clin Microbiol Infect. 2012;18(12):E548–51. doi:10.1111/1469-0691.12034.
145. Vizzotti C, Pippo T, Urueña A, Altuna J, Palópoli G, Hernández ML, Artola MF, Fernández H, Orellano P, Cañero-Velasco MC, et al. Economic analysis of the single-dose immunization strategy against hepatitis A in Argentina. Vaccine. 2015;33 (Suppl 1):A227–32. doi:10.1016/j.vaccine.2014.12.077.
146. Hanna JN, Hills SL, Humphreys JL. Impact of hepatitis A vaccination of Indigenous children on notifications of hepatitis A in north Queensland. Med J Aust. 2004;181(9):482–85. doi:10.5694/j.1326-5377.2004.tb06404.x.
147. Thompson C, Dey A, Fearnley E, Polkinghorne B, Beard F. Impact of the national targeted Hepatitis A immunisation program in Australia: 2000–2014. Vaccine. 2017;35(1):170–76. doi:10.1016/j.vaccine.2016.11.002.
148. Fisenka EG, Germanovich FA, Glinskaya IN, Lyabis OI, Rasuli AM. Effectiveness of universal hepatitis A immunization of children in Minsk City, Belarus: four-year follow-up. J Viral Hepat. 2008;15 (Suppl 2):57–61. doi:10.1111/j.1365-2893.2008.01031.x.

149. Souto FJD, de Brito WI, CJF F. Impact of the single-dose universal mass vaccination strategy against hepatitis A in Brazil. Vaccine. 2019;37(6):771–75. doi:10.1016/j.vaccine.2018.12.054.
150. Mao JS, Chai SA, Xie RY, Chen NL, Jiang Q, Zhu XZ, Zhang SY, Huang HY, Mao HW, Bao XN, et al. Further evaluation of the safety and protective efficacy of live attenuated hepatitis A vaccine (H2-strain) in humans. Vaccine. 1997;15(9):944–47. doi:10.1016/S0264-410X(96)00304-0.
151. Zhang Z, Zhu X, Ding Y, Gao Z, Li Y, Shan A, Liu Y, Xia W. Evaluation on the hepatitis A vaccine in preventing hepatitis A infection in Tianjin, from 2000 to 2011]. Zhonghua Liu Xing Bing Xue Za Zhi. 2014;35(10):1127–30.
152. Wang H, Gao P, Chen W, Bai S, Lv M, Ji W, Pang X, Wu J. Changing epidemiological characteristics of Hepatitis A and warning of Anti-HAV immunity in Beijing, China: a comparison of prevalence from 1990 to 2017. Hum Vaccin Immunother. 2019;15(2):420–25. doi:10.1080/21645515.2018.1529128.
153. Yan B-Y, Lv -J-J, Liu J-Y, Feng Y, Wu W-L, A-Q X, Zhang L. Changes in seroprevalence of hepatitis A after the implementation of universal childhood vaccination in Shandong Province, China: a comparison between 2006 and 2014. Int J Infect Dis. 2019;82:129–34. doi:10.1016/j.ijid.2019.03.005.
154. Guo Y, Zhang L, Feng D, Zhao S, Liu Q, Xu J, Lu M, Li J, Zhang Y, Guo W, et al. The impact of universal live attenuated hepatitis A vaccines in Henan, China, 2005–2018. International Journal of Infectious Diseases. 2020;93:163–67. doi:10.1016/j.ijid.2020.02.001.
155. Wang F, Sun X, Wang F, Zheng H, Jia Z, Zhang G, Bi S, Miao N, Zhang S, Cui F, et al. Changing epidemiology of Hepatitis A in China: evidence from three national serological surveys and the national notifiable disease reporting system. Hepatology. (2020); Online ahead of print. doi:10.1002/hep.31429.
156. Mellou K, Sideroglou T, Papaevangelou V, Katsiaflaka A, Bitsolas N, Verykouki E, Triantafillou E, Baka A, Georgakopoulou T, Hadjichristodoulou C, et al. Considerations on the current universal vaccination policy against hepatitis A in Greece after recent outbreaks. PLoS ONE. 2015;10(1):e0116939. doi:10.1371/journal.pone.0116939.
157. Papaevangelou V, Alexopoulou Z, Hadjichristodoulou C, Kourlamba G, Katsioulis A, Theodoridou K, Theodoridou M. Time trends in pediatric hospitalizations for hepatitis A in Greece (1999–2013): assessment of the impact of universal infant immunization in 2008. Hum Vaccin Immunother. 2016;12(7):1852–56.
158. Belmaker I, Dukhan L, Yosef Y, Leventhal A, Dagan R. Elimination of hepatitis A infection outbreaks in day care and school settings in southern Israel after introduction of the national universal toddler hepatitis A immunization program. Pediatr Infect Dis J. 2007;26(1):36–40. doi:10.1097/01.inf.0000247105.45185.13.
159. Barkai G, Belmaker I, Givon-Lavi N, Dagan R. The effect of universal toddlers-only hepatitis A virus vaccination program on seropositivity rate in unvaccinated toddlers: evidence for reduced virus circulation in the community. Pediatr Infect Dis J. 2009;28(5):391–93. doi:10.1097/INF.0b013e318190655c.
160. Levine H, Kopel E, Anis E, Givon-Lavi N, Dagan R. The impact of a national routine immunisation programme initiated in 1999 on Hepatitis A incidence in Israel, 1993 to 2012. Eurosurveillance. 2015;20(7):3–10. doi:10.2807/1560-7917.ES2015.20.7.21040.
161. Galor I, Perry Markovich M, Wolf D, Haber M, Hartal M, Avramovich E. Population seroprotection against hepatitis A virus in Israel 18 years after introduction of inactivated vaccine into the routine childhood vaccination schedule. Vaccine. 2020;38(7):1593–96. doi:10.1016/j.vaccine.2019.12.041.
162. Chironna M, Prato R, Sallustio A, Martinelli D, Tafuri S, Quarto M, Germinario C. Hepatitis A in Puglia (South Italy) after 10 years of universal vaccination: need for strict monitoring and catch-up vaccination. BMC Infect Dis. 2012;12(1):271. doi:10.1186/1471-2334-12-271.
163. Gallone MF, Desiante F, Gallone MS, Barbuti G, Tafuri S, Germinario C. Serosurveillance of hepatitis A in a region which adopted the universal mass vaccination. Med (Baltimore). 2017;96(9):e5884. doi:10.1097/MD.0000000000005884.
164. Estripeaut D, Contreras R, Tinajeros O, Castrejón MM, Shafi F, Ortega-Barria E, DeAntonio R. Impact of Hepatitis A vaccination with a two-dose schedule in Panama: results of epidemiological surveillance and time trend analysis. Vaccine. 2015;33(28):3200–07. doi:10.1016/j.vaccine.2015.04.100.
165. Oviedo M, Pilar Muñoz M, Domínguez A, Borras E, Carmona G. A statistical model to estimate the impact of a hepatitis A vaccination programme. Vaccine. 2008;26(48):6157–64. doi:10.1016/j.vaccine.2008.08.066.
166. Martínez A, Broner S, Sala MR, Manzanares-Laya S, Godoy P, Planas C, Minguell S, Torner N, Jané M, Domínguez A, et al. Changes in the epidemiology of hepatitis A outbreaks 13 years after the introduction of a mass vaccination program. Hum Vaccin Immunother. 2015;11(1):192–97. doi:10.4161/hv.35861.
167. Romero C, Perdomo V, Chamorro F, Assandri E, Pírez M, Montano A. Prevención de hepatitis A mediante vacunación en Uruguay (2005–2010). Rev Méd Urug. 2012;28:115–22.
168. Wasley A, Samandari T, Bell BP. Incidence of hepatitis A in the United States in the era of vaccination. JAMA. 2005;294(2):194–201. doi:10.1001/jama.294.2.194.
169. Vogt TM, Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. J Infect Dis. 2008;197(9):1282–88. doi:10.1086/586899.
170. Singleton RJ, Hess S, Bulkow LR, Castrodale L, Provo G, McMahon BJ. Impact of a statewide childhood vaccine program in controlling hepatitis A virus infections in Alaska. Vaccine. 2010;28(38):6298–304. doi:10.1016/j.vaccine.2010.06.113.
171. Erhart LM, Ernst KC. The changing epidemiology of hepatitis A in Arizona following intensive immunization programs (1988–2007). Vaccine. 2012;30(42):6103–10. doi:10.1016/j.vaccine.2012.07.029.
172. Klevens RM, Denniston MM, Jiles-Chapman RB, Murphy TV. Decreasing immunity to hepatitis A virus infection among US adults: findings from the National Health and Nutrition Examination Survey (NHANES), 1999–2012. Vaccine. 2015;33(46):6192–98. doi:10.1016/j.vaccine.2015.10.009.
173. Collier MG, Tong X, Xu F. Hepatitis A hospitalizations in the United States, 2002–2011. Hepatology. 2015;61(2):481–85. doi:10.1002/hep.27537.
174. Ly KN, Klevens RM. Trends in disease and complications of hepatitis A virus infection in the United States, 1999–2011: a new concern for adults. J Infect Dis. 2015;212(2):176–82. doi:10.1093/infdis/jiu834.
175. World Health Organization. WHO vaccine-preventable diseases: monitoring system. 2019 global summary; 2019 [accessed 2020 Mar 12]. http://apps.who.int/immunization_monitoring/globalsummar.
176. Elam-Evans LD, Yankey D, Singleton JA, Kolasa M. National, state, and selected local area vaccination coverage among children aged 19–35 months - United States, 2013. MMWR. 2014;63:741–48.
177. Dhankhar P, Nwankwo C, Pillsbury M, Lauschke A, Goveia MG, Acosta CJ, Elbasha EH. Public health impact and cost-effectiveness of hepatitis A vaccination in the United States: a disease transmission dynamic modeling approach. Value Health. 2015;18(4):358–67. doi:10.1016/j.jval.2015.02.004.
178. Curran D, de Ridder M, van Effelterre T. The impact of assumptions regarding vaccine-induced immunity on the public health and cost-effectiveness of hepatitis A vaccination: is one dose sufficient? Hum Vaccin Immunother. 2016;12(11):2765–71. doi:10.1080/21645515.2016.1203495.
179. Jayasundara D, Hui BB, Regan DG, Heywood AE, MacIntyre CR, Wood JG. Modelling the decline and future of hepatitis A transmission in Australia. J Viral Hepat. 2019;26:199–207.
180. Armstrong GL, Billah K, Rein DB, Hicks KA, Wirth KE, Bell BP. The economics of routine childhood hepatitis A immunization in the United States: the impact of herd immunity. Pediatrics. 2007;119(1):e22–9. doi:10.1542/peds.2006-1572.
181. Cutts FT, Hanson M. Seroepidemiology: an underused tool for designing and monitoring vaccination programmes in low- and middle-income countries. Trop Med Int Health. 2016;21(9):1086–98. doi:10.1111/tmi.12737.
182. Patterson J, Abdullahi L, Hussey GD, Muloiwa R, Kagina BM. A systematic review of the epidemiology of hepatitis A in Africa. BMC Infect Dis. 2019;19(1):651. doi:10.1186/s12879-019-4235-5.

183. Samandari T, Bell BP, Armstrong GL. Quantifying the impact of hepatitis A immunization in the United States, 1995–2001. Vaccine. 2004;22(31–32):4342–50. doi:10.1016/j.vaccine.2004.04.014.
184. Bassal R, Weil M, Cohen D, Sofer D, Mendelson E, Shohat T. Seroprevalence of hepatitis A twelve years after the implementation of Toddlers' vaccination: a population-based study in Israel. Pediatr Infect Dis J. 2017;36(10):e248–e251. doi:10.1097/INF.0000000000001640.
185. Goodman RA, Foster KL, Trowbridge FL, Figueroa JP. Global disease elimination and eradication as public health strategies. Proceedings of a conference; 1998 Feb 23–25; Atlanta, Georgia, USA.Bull World Health Organ 1998; 76(Suppl 2):5–162.
186. Van der Meeren O, Crasta P, de Ridder M. A retrospective pooled analysis assessing the effect of age on the immunogenicity of Havrix™ in healthy adults. Hum Vaccin Immunother. 2015;11 (7):1729–34. doi:10.1080/21645515.2015.1045167.
187. Tjon GMS, Coutinho RA, Van den Hoek A, Esman S, Wijkmans CJ, Hoebe CJPA, Wolters B, Swaan C, Geskus RB, Dukers N, et al. High and persistent excretion of hepatitis A virus in immunocompetent patients. J Med Virol. 2006;78 (11):1398–405. doi:10.1002/jmv.20711.
188. Inoue K, Yoshiba M, Yotsuyanagi H, Otsuka T, Sekiyama K, Fujita R. Chronic hepatitis A with persistent viral replication. J Med Virol. 1996;50(4):322–24. doi:10.1002/(SICI)1096-9071-(199612)50:4<322::AID-JMV7>3.0.CO;2-A.
189. Biziagos E, Passagot J, Crance JM, Deloince R. Long-term survival of hepatitis A virus and poliovirus type 1 in mineral water. Appl Environ Microbiol. 1988;54(11):2705–10. doi:10.1128/AEM.54.11.2705-2710.1988.
190. Manor Y, Lewis M, Ram D, Daudi N, Mor O, Savion M,Kra-Oz Z, Shemer Avni Y, Sheffer R, Shouval D, et al. Evidence for Hepatitis A virus endemic circulation in Israel despite universal toddlers' vaccination since 1999 and low clinical incidence in all age groups. J Infect Dis. 2017;215(4):574–80.
191. Yanez LA, Lucero NS, Barril PA, MDP D, Tenaglia MM, Spinsanti LI, Nates SV, Isa MB, Ré VE. Evidence of hepatitis A virus circulation in central Argentina: seroprevalence and environmental surveillance. J Clin Virol. 2014;59(1):38–43. doi:10.1016/j.jcv.2013.11.005.
192. Ping LH, Lemon SM. Antigenic structure of human hepatitis A virus defined by analysis of escape mutants selected against murine monoclonal antibodies. J Virol. 1992;66(4):2208–16. doi:10.1128/JVI.66.4.2208-2216.1992.
193. Pérez-Sautu U, Costafreda MI, Caylà J, Tortajada C, Lite J, Bosch A, Pintó RM. Hepatitis A virus vaccine escape variants and potential new serotype emergence. Emerging Infect Dis. 2011;17 (4):734–37. doi:10.3201/eid1704.101169.
194. Sabrià A, Gregori J, Garcia-Cehic D, Guix S, Pumarola T, Manzanares-Laya S, Caylà JA, Bosch A, Quer J, Pintó RM, et al. Evidence for positive selection of hepatitis A virus antigenic variants in vaccinated men-having-sex-with men patients: implications for immunization policies. EBioMedicine. 2019;39:348–57. doi:10.1016/j.ebiom.2018.11.023.
195. Trujillo-Ochoa JL, Viera-Segura O, Fierro NA. Challenges in management of hepatitis A virus epidemiological transition in Mexico. Ann Hepatol. 2019;18(1):14–22. doi:10.5604/01.3001.0012.7857.
196. Mohd Hanafiah K, Jacobsen KH, Wiersma ST. Challenges to mapping the health risk of hepatitis A virus infection. Int J Health Geogr. 2011;10(1):57. doi:10.1186/1476-072X-10-57.
197. Itani T, Jacobsen KH, Nguyen T, Wiktor SZ. A new method for imputing country-level estimates of hepatitis A virus endemicity levels in the Eastern Mediterranean region. Vaccine. 2014;32 (46):6067–74. doi:10.1016/j.vaccine.2014.09.006.
198. Arankalle V, Tiraki D, Kulkarni R, Palkar S, Malshe N, Lalwani S, Mishra A. Age-stratified anti-HAV positivity in Pune, India after two decades: has voluntary vaccination impacted overall exposure to HAV? J Viral Hepat. 2019;26(6):757–60.
199. Jayasundara D, Hui BB, Regan DG, Heywood AE, MacIntyre CR, Wood JG. Quantifying the population effects of vaccination and migration on hepatitis A seroepidemiology in Australia. Vaccine. 2017;35:5228–34.
200. Kabrane-Lazizi Y, Emerson SU, Herzog C, Purcell RH. Detection of antibodies to HAV 3C proteinase in experimentally infected chimpanzees and in naturally infected children. Vaccine. 2001;19 (20–22):2878–83. doi:10.1016/S0264-410X(00)00560-0.
201. Su Q, Guo M, Jia Z, Qiu F, Lu X, Gao Y, Meng Q, Tian R, Bi S, Yi Y, et al. Epitope-based recombinant diagnostic antigen to distinguish natural infection from vaccination with hepatitis A virus vaccines. J Virol Methods. 2016;233:41–45. doi:10.1016/j.jviromet.2016.02.014.
202. Ye C, Luo J, Wang X, Xi J, Pan Y, Chen J, Yang X, Li G, Sun Q, Yang J, et al. Development of a peptide ELISA to discriminate vaccine-induced immunity from natural infection of hepatitis A virus in a phase IV study. Eur J Clin Microbiol Infect Dis. 2017;36(11):2165–70. doi:10.1007/s10096-017-3040-6.
203. Bohm K, Filomena A, Schneiderhan-Marra N, Krause G, Sievers C. Validation of HAV biomarker 2A for differential diagnostic of hepatitis A infected and vaccinated individuals using multiplex serology. Vaccine. 2017;35:5883–89.
204. Herzog C, Mayorga O. Serologic differential diagnosis of hepatitis A virus (HAV) infected and vaccinated individuals: how long persist antibodies to non-structural HAV proteins? Vaccine. 2018;36(27):3883–84. doi:10.1016/j.vaccine.2018.05.015.
205. Werber D, Michaelis K, Hausner M, Sissolak D, Wenzel J, Bitzegeio J, Belting A, Sagebiel D, Faber M. Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017 - linked to other German cities and European countries. Eurosurveillance. 2017; 22(5):pii=30457
206. Mariojoules J, Castro G, Pisano MB, Barbero P, Fantilli A, Borda M, Canna F, Barbás G, Ré V. Hepatitis A outbreak affecting men who have sex with men (MSM) in central Argentina, occurred in July 2017–April 2018, later than the European outbreak. J Clin Virol. 2019;117:49–53. doi:10.1016/j.jcv.2019.05.014.
207. Foster MA, Hofmeister MG, Kupronis BA, Lin Y, Xia G-L, Yin S, Teshale E. Increase in hepatitis A virus infections - United States, 2013–2018. MMWR. 2019;68(18):413–15.
208. Alberts CJ, Boyd A, Bruisten SM, Heijman T, Hogewoning A, van Rooijen M, Siedenburg E, Sonder GJB. Hepatitis A incidence, seroprevalence, and vaccination decision among MSM in Amsterdam, the Netherlands. Vaccine. 2019;37(21):2849–56. doi:10.1016/j.vaccine.2019.03.048.
209. Hu X, Collier MG, Xu F. Hepatitis A Outbreaks in Developed Countries: detection, Control, and Prevention. Foodborne Pathog Dis. 2020;17(3):166–71. doi:10.1089/fpd.2019.2648.
210. Severi E, Verhoef L, Thornton L, Guzman-Herrador BR, Faber M, Sundqvist L, Rimhanen-Finne R, Roque-Afonso AM, Ngui SL, Allerberger F, et al. Large and prolonged food-borne multistate hepatitis A outbreak in Europe associated with consumption of frozen berries, 2013 to 2014. Eurosurveillance. 2015;20(29): pii=21192. doi:10.2807/1560-7917.ES2015.20.29.21192.
211. Enkirch T, Severi E, Vennema H, Thornton L, Dean J, M-L B, Ciccaglione AR, Bruni R, Christova I, Ngui SL, et al. Improving preparedness to respond to cross-border hepatitis A outbreaks in the European union/European economic area: towards comparable sequencing of hepatitis A virus. Euro Surveill. 2019;24(28). doi:10.2807/1560-7917.ES.2019.24.28.1800397.
212. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kang Y. Vaccination coverage among children aged 19–35 months - United States, 2017. MMWR. 2018;67:1123–28.
213. Foster M, Ramachandran S, Myatt K, Donovan D, Bohm S, Fiedler J,Barbeau B, Collins J, Thoroughman D, McDonald E, et al. Hepatitis A virus outbreaks associated with drug use and homelessness — California, Kentucky, Michigan, and Utah, 2017. MMWR. 2018;67(43):1208–10.
214. Yin S, Barker L, Ly KN, Kilmer G, Foster MA, Drobeniuc J, Jiles RB. Susceptibility to hepatitis A virus infection in the United States, 2007–2016. Clin Infect Dis. 2020;14:38.
215. Tavoschi L, Severi E, Carrillo Santisteve P, Lopalco P. HepatitisA in the EU/EEA: the case for scaling up prevention. Vaccine. 2018;36:2501–03.