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Review

Long-term protective effects of hepatitis A vaccines. A systematic review

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ABSTRACT

Objective: Data on duration and long-term protective effects of hepatitis A vaccines (HepA) have not been reviewed using a systematic approach. Our objective is to provide a comprehensive review of evidence on the duration of protection achieved by HepA, which is needed for revising existing vaccine policies. Limitations in data availability and implications for future research in this area are discussed.

Methods: A systematic literature review was conducted including all studies published between 1997 and 2011 reporting on long-term protection of HepA. The outcomes considered were hepatitis A virus (HAV) infection and sero-protection measured by anti-HAV antibodies after follow-up times of over 5 years post-vaccination.

Results: 299 studies were identified from MEDLINE and 51 studies from EMBASE. 13 manuscripts met our inclusion criteria. The maximum observation times and reported persistence levels of sero-protective anti-HAV antibodies was 15 years for live attenuated HepA and 14 years for inactivated HepA. All data were from observational studies and showed that higher number of doses of live attenuated vaccine led to higher seropositivity and GMT, but dosage and schedule did not significantly impact the long-term protection following inactivated vaccine. Few comparisons were made between the two vaccine types indicating highest levels of antibody titers achieved by multiple doses of live attenuated vaccines 7 years post-vaccination.

Conclusion: Available data indicate that both inactivated and live attenuated HepA are capable of providing protection up to 15 years as defined by currently accepted, conservative correlates of protection. Further investigations are needed to continue to monitor the long-term protection afforded by these vaccines. Standardized methods are required for vaccine-follow-up studies including assessment of co-variables potentially affecting long-term protection.

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1. Introduction

Recent estimates indicate a global incidence of hepatitis A of 1.9% with 119 million individuals having been infected with the virus in 2005 [1]. Although hepatitis A is a self-limiting disease of the liver and the virus itself is not cytopathic, its clinical manifestations can be severe leading to an estimated 34,000 deaths in 2005 [1]. Severity of the disease is strongly age-dependent. Among children below five years of age at the time of infection, 80–95% of HAV infections remain asymptomatic whereas in adults, 70–95% of infections result in clinical illness [2,3].

Infection with HAV can induce lifelong immunity, which is indicated by seroprevalence of antibodies against HAV (anti-HAV). In sub-Saharan Africa and other low income regions, almost 100% of older children and adults have acquired immunity. High income regions including Western Europe and North America have generally low anti-HAV endemicity but there were increases observed between 1990 and 2005 [4]. Improvements in water supply and sanitation standards in many parts of the world have led to better child survival and many of these children reach adulthood without having been exposed to hepatitis A virus. Paradoxically, this factor is responsible for increasing HAV-morbidity and -mortality in adult life, when the disease is generally more severe.

Vaccines against the hepatitis A virus have been commercially available since the 1990s and there are two types, inactivated and live attenuated hepatitis A vaccines. The first inactivated Hepatitis A vaccines were produced from a HAV propagated in cell culture, subsequently purified and inactivated by exposure to formalin. Currently, four inactivated monovalent HAV vaccines are commercially available (Havrix[®], Vaqta[®], Avaxim[®], and Epaxal[®]) and include antigen prepared from different strains of the HAV. Inactivated hepatitis A vaccines have proven to be among the most immunogenic, safe and well-tolerated vaccines [5–7].

In order to produce the live attenuated vaccine, the disease producing 'wild type' virus is first modified in the laboratory. This 'attenuated' virus still retains the ability to replicate and stimulate a host immune response but should not cause clinical disease on vaccination. Although live attenuated hepatitis A vaccines are comparably efficacious and immunogenic, there is so far insufficient evidence obtained from trials to comment on their safety effectiveness [5].

WHO vaccine recommendations have not been updated since 2000. They include a call for both vaccination of individuals with an increased risk of contracting HAV infection in low endemic areas and large-scale childhood vaccination in intermediate endemicity countries. Large-scale vaccination is not recommended for highly endemic countries given the high prevalence of anti-HAV indicating previous infection [2]. There are no worldwide recommendations for use of hepatitis A vaccine booster doses after having completed a full vaccination course. This might be related to the lack of observed and reported data on the persistence of anti-HAV antibodies and the quantified duration of protection of hepatitis A vaccines. Several mathematical models have been applied addressing the long-term persistence of detectable antibodies [8–12] and it was estimated that anti-HAV antibodies persist on average for more than 20–25 years [9]. Recently published modeling data indicated a median predicted duration of protection over 50 years using cut-off levels of ≥ 10 mIU/ml and of 45 years using cut-off levels of ≥ 20 mIU/ml [13].

In 2003, an expert group published a consensus statement on long-term protection of hepatitis A vaccines, which involved a non-systematic information search [14]. Based on existing data and models (e.g. Iwarson et al. [15] and Landry et al. [16]), the authors concluded that there is no data to support the need for a booster dose in immunocompetent individuals who received a full vaccination course. This conclusion was based on the finding

that long-term protection against hepatitis A infection does not depend on HAV-antibodies but is conferred by immune memory in a way that an anamnestic response can prevent disease in individuals previously vaccinated with inactivated hepatitis A vaccine [10,17].

Although the duration of protection of anti-HAV antibodies may have important implications for human susceptibility and for cost-effectiveness of vaccination, no systematic review on the duration and long-term protective effects of hepatitis A vaccines has been published. In light of this gap, our objective is to provide a comprehensive and reliable review of existing data on the duration of protection afforded by hepatitis A vaccines, which could help revising existing hepatitis A vaccine recommendations. We evaluated studies from 1997 to 2011 on this topic and discuss limitations in data availability and implications for future research in this area.

2. Methods

The key objective of this review was to assess the long-term efficacy of monovalent hepatitis A vaccines. We developed a search strategy that aimed to identify those articles or abstracts that contain a term related to both hepatitis A vaccine (1) and long-term protection (2). We added a third concept to exclude studies that evaluated combined hepatitis A and B vaccines.

We searched several major electronic databases including: Cochrane Library, MEDLINE and EMBASE. The Cochrane Library and MEDLINE search included the years from 1997 to 2011 and was supplemented by an EMBASE search which included the most recent years of publication, 2010 and 2011 (adapted search strategies available from Annex 1 and 2). We included all types of available studies, irrespective of age, sex, and ethnic origin, route of vaccine administration, dosage, schedule, and irrespective of type of intervention (inactivated hepatitis A vaccine and live attenuated hepatitis A vaccine). The search was not restricted to any language. Since hepatitis A vaccines became available in the early 1990s and the goal was to identify long-term protective effects, the MEDLINE search was restricted to articles published after 1996 and citations were included up to 25 July 2011. The primary outcome considered was HAV infection. Secondary outcomes included immune response as measured by the persistence of anti-HAV antibody (% of seropositivity), and differences in immune response measured by Geometric mean titers (GMT) of anti-HAV antibodies in mIU/ml.

The following studies and study types were excluded:

- (1) Studies providing results that were obtained exclusively from mathematical modeling of long-term protection or vaccine impact.
- (2) Studies that assessed hepatitis A vaccine safety and immunogenicity not related to long-term protection, or those assessing protective effects ≤ 60 months after vaccination.¹
- (3) The study objective was not related to long-term impact assessment of HAV vaccine but was
 - (a) the assessment and comparison of diagnostic tests, detection methods, and laboratory profiles
 - (b) the assessment of economic and cost-effectiveness issues around HAV vaccines
 - (c) the assessment of co-administration with other vaccines/formulations safety and efficacy issues of HAV vaccine
 - (d) the assessment of other factors influencing antibody development, including single and multiple dose, variability in schedule, time and type of vaccine administration

¹ Depending on the study, time after hepatitis A vaccination is provided in months after first dose or last dose vaccination with intervals between first and last dose of <12 months.

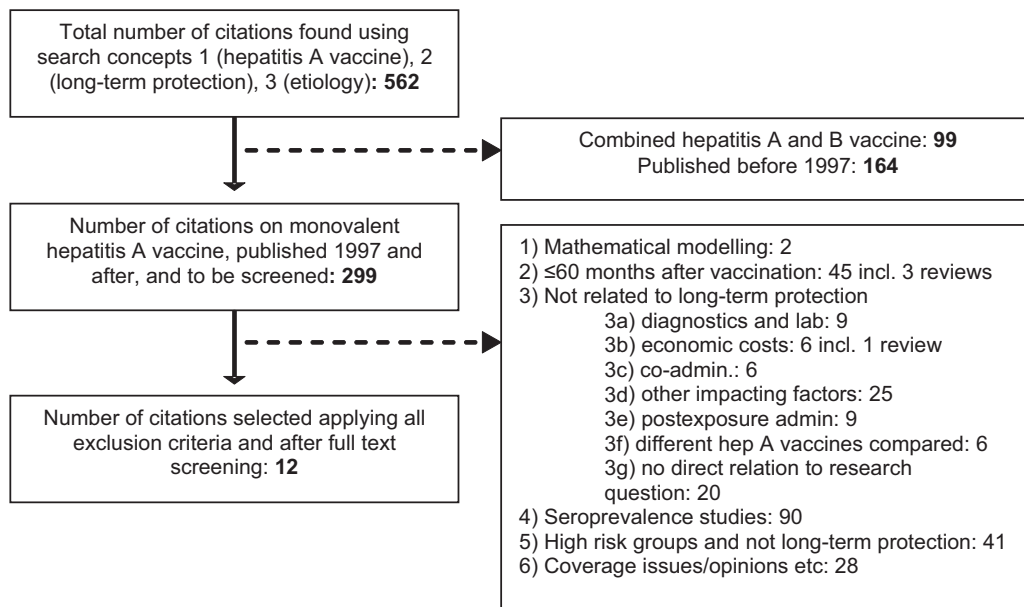


Fig. 1. Trial flow MEDLINE electronic search.

- (e) outbreak investigations and postexposure administration
- (f) the comparison of different hepatitis A vaccines in terms of immunogenicity/interchangeability/tolerability
- (g) other studies not or indirectly related to hepatitis A vaccine
- (4) Study types were seroprevalence studies, studies on country-specific epidemiology, (sub-) population surveys on incidence and prevalence of HAV infection and prevalence of anti-HAV antibody.
- (5) The study focused on immune response, immunogenicity, safety or efficacy of HAV vaccine (not long-term protection) among particular high risk groups, mainly patients with liver disease or HIV-AIDS.
- (6) Opinions, letters, comments, reports, and expert reviews on HAV vaccine recommendations, outcomes, coverage and others.

We selected potentially eligible articles using a two stage process. First, title and abstracts from all citations identified by MEDLINE and EMBASE databases were screened. The second screening involved retrieving the full text of those citations not excluded in the first step while applying the specific criteria related to study type and objective. Translations were obtained for non-English citations, which were considered to be relevant, based on title and abstract screening. We then extracted the following data: number of participants, study location, intervention and comparison characteristics (vaccine type, vaccine schedule, number of

doses, length of follow up) and the outcome of interest (HAV infection, anti-HAV antibody persistence, GMT/GMC).

3. Results

From 1997 to 2011, 299 potentially relevant citations (Annex 3, Fig. 1) were identified from MEDLINE out of which 53 were published in other languages than English, mainly in Chinese (21 articles). Other languages used were Russian (8), Spanish (6), French (5), German (4), Polish (2), and Korean (2). Each of the following languages provided one citation: Portuguese, Romanian, Hebrew, Czech, and Croatian. After title and abstract screening, full text was obtained for 33 English citations and 5 Chinese citations.

The EMBASE search resulted in 51 citations from 2010 and 2011 (Annex 4). Out of these, 10 citations were duplicates in EMBASE and 12 were identified by the two data bases for the respective years. There were 27 citations excluded based on the criteria specified in the method section. 11 of them were seroprevalence studies (Fig. 2). After title and abstract screening, full text was obtained for two citations uniquely identified by EMBASE, one of which met the inclusion criteria (Fig. 2).

Overall, the majority of studies (101 citations) obtained using the search strategy were observational seroprevalence studies of anti-HAV or immunogenicity studies assessing the efficacy of hepatitis A vaccines up to a few months after initial and/or booster vaccination. A number of investigations were available evaluating the protective effects of hepatitis A vaccines up to 48 month/4

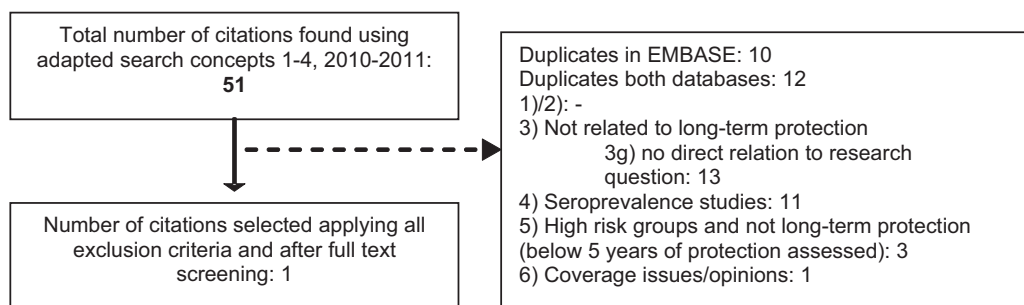


Fig. 2. Supplementary EMBASE electronic search, 2010–2011.

years (e.g. [18]) and 60 months/5 years after vaccine administration [19–22].

Out of the 13 studies that met our inclusion criteria, 8 reported on inactivated hepatitis A vaccines and 5 reported on live attenuated vaccine. Two of these studies compared the two vaccine types. Potential study limitations including loss to follow-up and sample size are addressed in the discussion section and additionally highlighted in Tables 1 and 2.

3.1. Inactivated hepatitis A vaccine

Studies using the inactivated hepatitis A vaccines HAVRIX, EPAXAL, and VAQTA were mainly conducted in high income and low anti-HAV prevalence countries (apart from Argentina [23] and China [27]) and were observational follow-up studies of cohorts from randomized vaccine trials. All studies reported secondary outcomes such as seropositivity rates and GMC/GMT of anti-HAV antibodies. The two studies with the longest follow-up times were done in children, one in Argentina [23] and the other one in the US [24]. Byrd et al. [24] found protective GMC to persist for 14 years after the last vaccine dose, independent of schedule. The study among Argentinean children also reported protective GMC of 390.91 mIU/ml (95% CI: 282.2–499.5; range: 36–1860 mIU/ml) up to year 10 after the second/booster dose [23]. A study conducted in Switzerland among adults which reported a similar long duration of protection revealed protective levels of HAV IgG antibodies (GMC 526 mIU/ml; 95% CI: 439–630 mIU/ml) up to 11 years after the second vaccine dose [13].

Studies meeting the inclusion criteria but reporting shorter intervals of protection (between 5.5 years and 6 years after last vaccine dose) did not only compare GMC over time but included comparisons with a different inactivated hepatitis A vaccines, [25] different vaccine schedules [9], and different dosages (180, 360, 720 EI.U) [11]. It appeared that none of these variables impacted significantly on the long-term protective levels of inactivated hepatitis A vaccine. Van Herck and Van Damme [9] concluded that GMT levels 5.5 years post-booster dose were not affected by the schedule (0–6 or 0–12 month) in which HAVRIX was administered. The only available study comparing different dosage of inactivated hepatitis A vaccine regarding long-term protective GMT [11] did not find statistically significant differences in GMT up to year 6 post-booster vaccination between three different dosage groups (180, 360, 720 EI.U). However, higher dosage resulted in higher observed GMT. The study that compared two inactivated hepatitis A vaccines and their interchangeability reported that long-term protection as measured by GMT was similar in all four vaccine groups studied [25].

An investigation compared long-term protection of hepatitis A vaccine between HIV infected individuals and historically HIV-uninfected adults and reported similarly long follow-up times as the studies done in healthy adults. In this study, Crum-Cianflone et al. [26] found protective levels of HAV IgG antibodies of GMC 64 mIU/ml in HIV-infected individuals up to 6–10 years post second dose vaccination with VAQTA or HAVRIX. There was no significant difference in sero-response in a comparison between HIV-uninfected and HIV-infected persons, however, a lower proportion of sero-responders and lower GMC responses was observed among HIV-infected persons [26].

Inactivated hepatitis A vaccine was also the primary intervention in one study that compared the two hepatitis A vaccine types (inactivated and live attenuated) regarding their long term protection in children [27]. The observation time in the group vaccinated with live attenuated hepatitis A vaccine was only 3.6 years, whereas recipients of inactivated hepatitis A vaccine were followed-up for ten years. No significant differences in long-term protective anti-HAV titers were seen between the two vaccine types, but

conclusions drawn from this direct comparison are limited due to different follow-up periods.

3.2. Live attenuated hepatitis A vaccines

All studies assessing duration of protection from live attenuated hepatitis A vaccines were conducted among children in China and were observational follow-up studies of cohorts from randomized vaccine trials. Two publications by Zhuang et al. [28,29] reported on the primary outcome measure incident hepatitis A cases in addition to presenting secondary outcomes including seropositivity rates and GMC/GMT [28,29]. One of these publications reports the longest follow-up time and found protective GMT levels of 128 mIU/ml up to 15 years post-vaccination [29]. No hepatitis case had occurred after the 15 years [29]. Results that were published earlier from the same study [28] showed a GMT of 145 mIU/ml at year 10 after vaccination with live attenuated hepatitis A vaccine.

Two other studies compared the long-term protective effects of live attenuated hepatitis A vaccines by number of doses administered [30,31]. Both investigations found significant differences between the single and multiple dose groups with higher GMC in groups receiving multiple doses of live attenuated hepatitis A vaccine 8 years post-vaccination. Sero-conversion rates also differed between the two dose groups in the two studies: Those children having received more than one dose of the vaccine had higher seropositivity at year 8 (100% versus 71–75% [30]; 98% versus 71.6% [31]) indicating higher levels of sero-protection achieved by increasing number of live attenuated vaccine doses.

One study included a multi-dimensional comparison of live attenuated hepatitis A vaccine. The vaccine was compared according to different schedules and also with inactivated hepatitis A vaccine. Overall, Liu et al. [32] found significant differences in antibody GMC between both vaccine types and between different schedules: children vaccinated using a 0–6–12 month schedule with live attenuated vaccine had significantly higher GMC than those vaccinated with a 0–6 month schedule of this vaccine and those vaccinated with inactivated hepatitis A vaccine 7 years post-vaccination.

4. Discussion

This systematic review found evidence for 15 years of sero-protection against HAV-infection conferred by live attenuated hepatitis A vaccines and 14 years of seroprotection against HAV-infection achieved by inactivated hepatitis A vaccines [24]. Different vaccine schedules were assessed [9,24] but do not appear to make significant differences in outcomes. The percentage of participants who maintained protective levels of antibodies varied by schedule and indicated that a longer interval between the second and last dose of inactivated hepatitis A vaccine administration achieves a higher percentage (100%) at 14 years post-vaccination using a three dose regimen [24]. While different dosages of the inactivated vaccine did not produce significantly different GMC, [11] an increasing number of doses of live attenuated vaccine revealed significantly higher GMC and a higher percentage of sero-protection was observed 8 years post vaccination [30,31]. This finding may have implications for the protective efficacy and future use of live attenuated vaccines, however, GMC obtained from a one dose administration of the live attenuated vaccine were still sufficiently high to protect against HAV infection after 8 years.

The duration of protection found from this review is partly in line with the previous consensus group statement [14]. Increasing evidence supporting immune memory and anamnestic response in relation to HAV makes it likely that protection lasts longer than the observed 15 years. Additionally, results from mathematical

Table 1
Studies assessing long-term protection (≥ 60 months/5 years) of live attenuated hepatitis A vaccines.

Author	Design	Country	Population	Intervention	Comparison	Outcome ^a	Comment
Liu et al. [32]	Observational follow-up study; based on randomized vaccine trial.	China	211 children; randomly assigned to dose and vaccine.	Live attenuated hepatitis A vaccine. Group A: 0–6–12 month schedule. Group B: 0–6 month schedule. Inactivated hepatitis A vaccine; Group C: 0–6 month schedule.	Between different follow-up times. Between inactivated and live attenuated hepatitis A vaccine. Between different schedules.	7 years after vaccination: Group A: 100% seropositivity GMC 336.8 mIU/ml (95% CI 223.5–507.5) Group B: 100% seropositivity GMC 84.6 mIU/ml (95% CI 66.4–107.8) Group C: 100% seropositivity GMC: 174.1 mIU/ml (95% CI 123.3–245.7)	<u>Significant difference in GMC, in descending order for the A, C, B group.</u> Highest GMC was 2938.1 mIU/ml, found in group C, and it was 1315.6 mIU/ml and 1586 mIU/ml in group A and B respectively.
Liu et al. [30] Chinese	Observational follow-up study; based on randomized vaccine trial.	China	Group A (three doses, 0–2–6 month schedule): 42 children Group B (single dose): 110 age range 1–7 years.	Live attenuated hepatitis A vaccine (H2 strain).	Between different follow-up times. Between different number of doses.	8 years after vaccination: Group A: 100% seropositivity; GMC: 918.2–480.6 mIU/ml Group B: 71–75% seropositivity; GMC: 80–89 mIU/ml	<u>Significant difference between single and booster dose recipients.</u>
Wang et al. [31]	Observational follow-up study; based on clinical trial.	China	Group A (single dose): 85 children; age range 11–12. Group B (booster dose): 53 children; 48 followed up throughout.	Live attenuated hepatitis A vaccine.	Between different follow-up times. Between different numbers of doses.	8 years after vaccination: Group A: 71.6% seropositivity; GMC: 89.0 mIU/ml (95% CI: 69.7–113.6) Group B (booster dose): 98% seropositivity; GMC: 262.8 mIU/ml (95% CI: 188.0–367.5)	<u>Statistical significant difference between single and booster dose recipients in terms of anti-HAV antibody titers.</u> Loss to follow up not fully explained.
Zhuang et al. [28]	Observational follow-up study; based on two trial sites.	China	220 children (124 boys, 96 girls), age range 1–3 years. 155 followed-up throughout.	Live attenuated Hepatitis A vaccine; single dose.	Between different follow-up times.	10 years after vaccination: No hepatitis A case. 80.2% seropositivity; GMT: 145 mIU/ml.	CI not indicated. Additional evaluation of vaccine impact on hepatitis A incidence.
Zhuang et al. [29]	Observational follow-up study.	China	220 children (124 boys, 96 girls), age range 1–3 years.	Live attenuated hepatitis A vaccine; single dose.	Between different follow-up times.	15 years after vaccination: No hepatitis A case. 81.3% seropositivity; GMT: 128 mIU/ml	

GMC, geometric mean concentrations in mIU/ml.

^a Seropositivity refers to protective anti-HAV seropositivity rate and the percentage of sero-conversion.

Table 2
Studies assessing long-term protection (≥ 60 months/5 years) of inactivated hepatitis A vaccines.

Author	Design	Country	Population	Intervention	Comparison	Outcome ^a	Comment
Bian et al. [27]	Observational follow-up study.	China	Group A (inactivated hepatitis A vaccine): 215 children; average age 2.1 years. 110 followed throughout. Group B (live attenuated hepatitis A vaccine): 206 children; average age 2.3 years. 85 followed throughout.	Inactivated hepatitis A vaccine (HAVRIX); 0–6 month schedule.	Live attenuated hepatitis A vaccine; single dose.	10 years after last dose of inactivated hepatitis A vaccine (group A): No hepatitis A case. 99.09% seropositivity GMC: 61.59 mIU/ml (95% CI: 51.92–73.07) 3.6 years after live attenuated hepatitis A vaccine (group B): 97.65% seropositivity GMC: 67.87 mIU/ml (95% CI: 36.38–86.30)	<u>GMCs were not significant different between vaccine groups.</u> Study also reports on memory response after booster dose.
Bovier et al. [25]	Randomized clinical trial (individuals randomized to intervention group) and followed-up.	Switzerland	118 adults; age range 18–48. 54 adults followed throughout.	Virosomal hepatitis A vaccine (EPAXAL); 0–12 month schedule.	Inactivated hepatitis A vaccine (HAVRIX). Vaccines interchanged	5–6 years after booster dose: EPAXAL/EPAXAL group: GMT: 1321 mIU/ml (95% CI: 704–2482) HAVRIX/HAVRIX group: GMT: 1208 mIU/ml (95% CI: 674–2164) HAVRIX/EPAXAL group: GMT: 859 mIU/ml (95% CI: 457–1612) EPAXAL/HAVRIX group: GMT: 1191 mIU/ml (95% CI: 690–2055)	
Bovier et al. [13]	Observational follow-up study (prospective)	Switzerland	332 adults vaccinated 1992–1995; age range 16–48. 130 agreed to participate in follow-up and 127 followed throughout.	Virosomal hepatitis A vaccine (EPAXAL); 0–12 month schedule.	Between different follow-up times (year 2, 3, 4, 5, 6, 7, 10–12).	9–11 years after second dose/10–12 years after initial dose: GMC: 526 mIU/ml (95% CI: 439–630). Subgroup analysis: GMC females: 741 mIU/ml (95% CI: 590–930) GMC males: 332 mIU/ml (95% CI: 266–414).	Year range derives from different time points of initial vaccination. Study provides additional modeling data.
Byrd et al. [24]	Observational follow-up study (prospective)	USA	144 children (3–6 years). 56 followed throughout.	Inactivated hepatitis A vaccine (HAVRIX). A: 0–1–2 month schedule B: 0–1–6 months C: 0–1–12 months schedule.	Between different follow-up times. Between different schedules.	14 years after last dose: Group A: 86% seropositivity GMC: 131 mIU/ml (95% CI: 65–265) Group B: 100% seropositivity GMC: 227 mIU/ml (95% CI: 144–357) Group C: 100% seropositivity GMC 212 mIU/ml (95% CI: 89–505)	Withdrawals not sign. different from those followed up throughout No stat. sign. differences in anti-HAV levels by vaccination schedule and sex.

Table 2 (Continued)

Author	Design	Country	Population	Intervention	Comparison	Outcome ^a	Comment
Crum-Cianflone et al. [26]	Observational follow-up study (prospective)	USA	130 HIV-1 infected adults (median age 31 years, mainly males); vaccinated 1996–2003. 74 adults followed-up throughout.	Inactivated hepatitis A vaccine (VAQTA or HAVRIX); administered 6–18 months apart after HIV diagnosis.	Between different follow-up times. With historical data from HIV-uninfected adults having received 2 doses of VAQTA, 0–6 month schedule.	6–10 years (median time 8.2 years) after second HAV vaccine dose: 74 individuals/85% (95% CI: 75–92%) seropositivity GMC: 64 mIU/ml (95% CI: 2–2066) Subgroup analysis: GMC among 54 individuals with higher CD4 counts (≥ 350 cells/mm ³): 70 (95% CI: 2–2422) GMC among 20 individuals with CD4 counts below 350 cells/mm ³ : 50 (95% CI: 1–1755) GMC among historically HIV-uninfected individuals (descriptive comparison): 684 mIU/ml (95% CI: 564–831).	No vaccine-specific analysis (HAVRIX and VAQTA in one) Study assesses other factors associated with antibody response after HAV vaccination in HIV-infected persons
Lopez et al. [23]	Observational follow-up study; based on randomized vaccine study.	Argentina	111 children vaccinated; mean age 156.06 months. 48 children followed throughout.	Inactivated hepatitis A vaccine (AVAXIM); 0–6 month schedule.	Between different follow-up times.	10 years after second dose: 97.9% seropositivity GMC: 390.91 mIU/ml (95% CI: 282.2–499.5, range: 36–1860 mIU/ml)	
Van Herck, Van Damme	Observational follow-up study; based on randomized vaccine trial.	Belgium	120 (study A)/194 (study B) adults; age range 18–40. 58 (study A)/134 (study B) adults followed throughout.	Inactivated hepatitis A vaccine (HAVRIX); A: 0–6 month schedule B: 0–12 month schedule.	Between different follow-up times. Between different schedules.	5.5 years after second dose: Study A: 100% seropositivity GMT: 522 mIU/ml (95% CI: 398–685) Study B: 99.3% seropositivity GMT: 749 mIU/ml (95% CI: 604–929)	Not assessed if drop-outs were different in the two groups (misclassification). Study provides additional modeling data.
Wiedermann et al. [11]	Observational follow-up study; based on randomized vaccine trial.	Austria	110 adults vaccinated; average age 26.7; range 17–55 years. 59 adults followed throughout.	Inactivated hepatitis A vaccine (candidate); 0–1–2–12 month schedule.	Between different follow-up times (month 1, 4, 6, 18, 24, 36, and 84) after first dose. Between different dosage groups (180, 360, 720 El.U).	6 years after last dose/76 month after last dose: Dosage 180 El.U (28 individuals): GMT: 506 mIU/ml (95% CI: 319–803) Dosage 360 El.U (27 individuals): GMT: 983 mIU/ml (95% CI: 662–1461) Dosage 720 El. U (4 individuals): GMT: 1587 mIU/ml (95% CI: 622–4045)	Drop outs not described.

GMC, geometric mean concentrations in mIU/ml.

^a Seropositivity refers to protective anti-HAV seropositivity rate and the percentage of sero-conversion.

models indicate that protective levels of antibody induced by two doses of inactivated hepatitis A vaccine can last for at least 25 years [9]. Nevertheless, from the observed data, it is not possible to make a statement on life-long protection of HAV vaccines and there might be important considerations regarding schedule and age, particularly for live attenuated vaccines.

This review did not include studies conducted in populations at high risk for HAV infection (e.g. people who live in places with poor sanitation) given that they were all excluded on the basis of short observation times and mainly targeting immunogenicity and safety of the vaccine. We have included one study conducted among HIV-infected adults because of the long follow-up time and the comparison with HIV-non infected individuals that was done in this study [26]. Although sufficiently protective levels persisted until year 6–10 post hepatitis A vaccination, it is not possible to generalize this result to individuals with co-morbidities. Despite the upcoming research on long-term immunologic response to hepatitis A vaccine in HIV-positive individuals [26,33], too few data are available.

The design of the included studies varied with respect to their intervention and comparison groups and makes it difficult to generalize the overall finding to all HAV vaccines and schedules. The interchangeability of inactivated and live attenuated hepatitis A vaccines has been addressed in two studies of which one used different observation periods (3.6 years for live attenuated versus 10 years for inactivated vaccines [27]), which makes the comparison less relevant. Liu et al. [32] found significant differences in GMC between the two vaccine types 7 years post-vaccination and between different schedules of administration of attenuated vaccine. The overall result was that live attenuated vaccine using a 0–6–12 months schedule achieved significantly higher GMC as compared to another schedule with the same vaccine and compared to inactivated hepatitis A vaccine. Although both vaccine types revealed sufficiently high GMC to be protective after 7 years, there may be differences regarding lifelong protective effects. Since this is the only study comparing the two vaccine types regarding their long-term efficacy and since this was done in children only in China, the results cannot be generalized.

4.1. Limitations of the studies

The quality of the available studies was often affected by study design and reporting of loss to follow-up and only one study randomized individuals to the intervention group [25]. Although some studies randomized participants to different dosage or schedule at the time of primary vaccination, all studies were nonrandomized and observational in their design of long-term antibody persistence. This resulted in high loss-to-follow up with increasing follow-up times and a relatively low number of individuals agreeing on participation after having received the required vaccine. Overall, the drop out rate exceeded 50% at maximum follow-up in the majority of cases. Given the nature of study design, it was also not possible to rule out whether natural exposure to HAV can act or acted as a natural booster among the study participants followed up for many years. This question is however, crucial to be addressed in future research. Not all studies reported confidence intervals around the observed GMT/GMC and few indicated the range of GMT/GMC.

4.2. Limitations of this review

General bias potentially affecting systematic reviews using electronic databases can occur from late indexing of research and under-representation of literature from developing countries in

electronic databases [34]. Most of the studies found on long-term protective effects of hepatitis A vaccine were conducted in high-income countries and in China. There were not much data published and available from other world regions, particularly from low income countries.

We restricted this review to studies on monovalent hepatitis A vaccines, which have been licensed for individuals aged ≥ 1 year. Studies on combination vaccine containing hepatitis A and B vaccines were excluded since these vaccines have only been licensed for use in children aged 1 year and older in a few countries and the majority of them are licensed for adults (aged ≥ 18 years). Nevertheless, combination vaccines are increasingly used and long-term protective effects should be evaluated specifically for these products.

4.3. Future research needs and conclusions

The data found from our systematic review supports the need further investigations evaluating antibody levels beyond 15 years post-vaccination with inactivated and live attenuated hepatitis A vaccines, as well as the interplay between detectable antibody levels and memory responses to HAV. This is particularly relevant for individuals with other chronic infections such as HIV and for understanding the pathogenesis of HAV-related fulminant liver failure.

Several factors can impact the long-term protection of vaccines in general and hepatitis A vaccine in particular. Differences between males and females have been shown in regard to both absolute GMCs and their change with time. Females were more likely to have higher GMCs than males but declines in GMCs were more moderate in males later after vaccine administration, resulting in a slightly lower estimated duration of protection in females [13]. Reporting of sex- and age-specific anti-HAV antibody persistence was less common across the studies but differences should be assessed routinely and be accompanied by statistical analysis. Since all studies on long-term protection of live attenuated hepatitis A vaccine were done in children, it is important to obtain data from adult cohorts as well.

There is a need for a clear understanding of “protective levels” when discussing surrogates of protection. The lower limit of anti-HAV antibody titer requirement to prevent HAV infection is not standardized and some studies on inactivated HAV vaccine use a anti-HAV antibody titer of 10 mIU/ml as lower cut-off [11–13,25,26] instead of the 20 mIU/ml. Currently, available studies on this subject are of experimental nature [35] or done in vitro [36] and more clinical and applied research is encouraged on this issue. Furthermore, assays for anti-HAV are not standardized, which may impact on comparability.

The cost-utility and the impact of herd immunity are two other subjects that need to be investigated further in the context of long-term protection from hepatitis A vaccines. Cost-effectiveness of hepatitis A vaccines depends on several factors including on country-specific endemicity levels, herd immunity, vaccine coverage and within country variations and studies focusing on amounts of costs saved need to be seen in context of estimated health consequences [37,38].

With respect to inactivated hepatitis A vaccines, which are recommended to be administered using a two-dose schedule, research should be stimulated to a closer look at the number of doses really needed to achieve long-term protection against hepatitis A infection since protection may be largely conferred by the first dose of the vaccine. Single or flexible dose administration of inactivated hepatitis A vaccines might be an option for some countries and a review of existing data on this topic is important as well as an incentive to directly compare single and full dose administration in relation to long-term protection.

Contributions

JJO designed and carried out the systematic review, reviewed all literature, wrote the manuscript, and interpreted the data. GI contributed to writing the manuscript and interpreting the study data. STW supervised the review and contributed to writing the manuscript.

Conflict of interest

None declared.

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Appendix A. Supplementary data

The following are the supplementary data to this article:

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2012.04.104>.

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