Hepatitis A childhood and adolescent vaccination: a systematic review of the effectiveness, immunogenicity, impact, safety and cost effectiveness of pediatric vaccines

Final report to the World Health Organization Strategic Advisory Group of Experts on Immunization Working Group on hepatitis A vaccines

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Nick Walsh
MD PhD MPH BSc(Med)hons FAFPHM FAChAM
Department of Epidemiology and Preventive Medicine
Monash University, Australia
nick.walsh@monash.edu

Johanna Torres
MD MScIH Specialist in Pediatrics
Doctoral researcher in Epidemiology
Helmholtz Centre for Infection Research
Brunswick, Germany
Johanna.Torres@helmholtz-hzi.de

Stephanie Curtis
MPhil (Applied Epidemiology), MPH, BA, DipPM
Department of Infectious Diseases,
Alfred Hospital and Monash University
stephanie.curtis@monash.edu

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Abbreviations

Ab	antibodies
CEA	cost-effectiveness analysis
CI	confidence interval
GMC	Geometric Mean Concentration (mUI/ml)
ICER	Incremental cost-effectiveness ratio
HAV	hepatitis A virus
HBV	hepatitis B virus
LTFU	long-term follow-up
MD	mean difference
MSM	men who ave sex with men
PAHO	Pan American Health Organization
PWID	people who injected drugs
qRCT	quasi randomised controlled trials
RCT	randomized controlled trials
RR	Risk Ratio
USA	United States of America
WHO	World Health Organization

1 Summary of findings

1.1 EFFECT OF HAV VACCINE SCHEDULES ON EFFECTIVENESS

No efficacy trials were identified during the 2012 – 2021 included time period. Hence, effectiveness was the main outcome of interest. Effectiveness was assessed by consideration of HAV clinical disease incidence, as well as immunogenicity by seroprotection (as defined by the individual study) and geometric mean concentration in included observational studies.

Single and two dose study results were pooled and stratified by ≤ 7 years or > 7 years of follow up as well as by type of vaccine (live attenuated vaccines or inactivated vaccines). No analysis was undertaken by the vaccine manufacturer. The maximum length of follow up was 25 years.

We did not assess the impact of vaccination on HAV circulation in water and soil.

The analysis found that hepatitis A vaccines are effective in preventing HAV clinical disease and confer seroprotection, regardless of type of vaccine (live attenuated or inactivated); further that hepatitis A vaccines confer long –term protection against hepatitis A related disease, including seroprotection.

1.2 EFFECT OF HAV VACCINE SCHEDULES ON IMPACT

The mean hepatitis A incidence decreased in all studies after the introduction of general population vaccination programs (‘post vaccination’). In single dose studies, the hepatitis A incidence in all age groups decreased by 59% to 99%. In two dose studies, the incidence in all age groups decreased by 76% to 98%. In studies that reported incidence by age group, the largest decreases were found among children aged <10 years old.

The impact of HAV vaccination on population seroprevalence was complex to assess given seroprevalence in the population across ages is dependent on endemicity and vaccination rates. There were limited nation-wide studies investigating seroprevalence pre and post universal vaccination. There were no clear trends in seroprevalence by age group.

There were no studies that investigated impact on outcomes in at-risk populations (i.e. liver transplantation liver failure), nor impact on change in HAV circulating serotypes.

1.3 EFFECT OF HAV VACCINE SCHEDULES ON COST EFFECTIVENESS

A consistent finding was that single dose vaccine schedules were more cost effective than 2 dose schedules, even when some reduced efficacy was factored into the single dose analysis. Indeed, single dose schedules were cost saving in a number of studies, compared to two dose schedules being just cost effective.

Higher endemicity, lower cost of vaccine and longer seroprotection assumptions resulted in improved cost effectiveness. Assumptions of coverage varied.

One study of the cost effectiveness of catch-up vaccines (USA) could not demonstrate clear cost effectiveness, apart from in specific late childhood age groups.

1.4 EFFECT OF HAV VACCINE SCHEDULES ON ADVERSE EVENTS

Studies analyzed adverse events following vaccination among healthy children and adolescents. Very few studies examined adverse events of long-term occurrence (over many months to years), and the majority of publications have only short follow-up periods of observation. Incidence of adverse events for both live and inactivated vaccines when administered individually was substantially low across all studies. Mild inflammatory local site reactions were the most frequent.

One included systematic review (Irving, Holden, Yang, & Pope, 2012) examined published literature on vaccine safety and adverse events in the period until 2011. Meta-analysis did not identify any adverse events of note, although data from live vaccines was limited.

1.5 CERTAINTY OF EVIDENCE

All analyses of evidence over the inclusion period January 2012 to February 2021 were graded as very low certainty. Loss to follow up and uncontrolled confounders were consistent limitations across the data.

1.6 GAPS IN THE EVIDENCE

The major gap in evidence was the lack of direct comparisons of single vs two dose HAV vaccine regimens over the long-term (> 7 years). Data with direct comparisons was limited to one series of studies in one country (Espul et al., 2020).

Most studies focused on clinical disease in terms of effectiveness and impact evaluation. Other relevant outcomes to accurately determine HAV burden of disease and vaccination impact, such as death and hospitalizations rates, were not assessed in the studies reviewed.

Overall methodology of most studies did not allow identification of natural infection following vaccine administration. Therefore, it was not possible to estimate to what extent observed effectiveness and immunogenicity were influenced by the boosting effect of natural infection.

We found only two studies assessing cellular immunogenicity over long-term following immunization (Mayorga et al., 2016; Urueña et al., 2021), whereas most studies included in our review focused on humoral immunity only. There was some evidence through booster challenges (providing a second or third dose long after – years – the first and measuring immunogenicity) of the preservation of immune memory over long periods of time following initial single (or two dose) vaccination; however these studies were small scale (Chen et al., 2018; Urueña et al., 2021).

We did not identify manuscripts focused on evaluating safety profile of HAV vaccines when administered in combination with vaccines targeting other viruses or microorganisms.

1.7 IMPLICATIONS OF FINDINGS

In this analysis, no difference was found between one and two dose schedules in terms of clinical case incidence and seroprotection. There was a reduction in the GMC in single-dose regimens. Booster studies of individuals receiving one dose and followed long-term showed strong responses from anamnestic immune memory even in HAV seronegative individuals vaccinated up to 17 years prior. The impact of single dose programs is marked on HAV epidemiology. CEA studies show one and two doses are both cost effective, but single doses are often cost saving. Over the next 5 to 10 years it appears there will be additional data available including from (1) these same studies with longer follow up and (2) more population impact data from countries having implemented single dose regimens. Analysis and interpretation are limited by small studies, very low certainty of evidence and limited long-term data.

2 Background

2.1 INTRODUCTION

Hepatitis A (HAV) is an enterically transmitted ribonucleic acid virus that causes acute infection resulting in inflammatory liver disease which can be severe (fulminant) in some cases. It is endemic to many low- and middle-income countries, though sporadic outbreaks occur across all countries. Socioeconomic development and improved sanitation have resulted in epidemiological transitioning from high- to intermediate endemicity in many middle-income regions and countries, leading to a shift in the susceptible populations for infection and disease. Consequently, there is a need to further consider population based systematic immunization programs within such communities.

HAV vaccination is the mainstay of HAV prevention. In 2012, the World Health Organization (WHO) issued a position paper on vaccination with the following key recommendations:

(a) that HAV vaccination should be part of a comprehensive plan for the prevention and control of viral hepatitis, including measures to improve hygiene and sanitation and measures for outbreak control;
(b) that HAV vaccination be integrated into the national immunization schedule for children aged ≥ 1 year if indicated on the basis of incidence of acute hepatitis A, change in the endemicity from high to intermediate, and consideration of cost-effectiveness;
(c) that HAV vaccination be not recommended in highly endemic settings where a high level of immunity is present; and
(d) that HAV vaccination in low endemic settings be recommended for high risk groups including travellers to endemic regions, lifelong recipients of blood products, men who have sex with men (MSM), people who inject drugs (PWID) and those working with non-human primates.

The 2012 WHO position paper (WHO, 2012) concluded that national immunization programmes may consider inclusion of single-dose inactivated HAVs in immunization schedules but noted that until further evidence was made available, the 2-dose regimen was preferred for individuals at risk of infection. Given the expansion of single dose programs in many countries over the past decade, there is increasing evidence of the impact of single infant vaccine programs to reduce the population burden of HAV and confer immunity to those immunized.

Building on the systematic review that contributed to the 2012 WHO position paper, later published, this systematic review seeks to primarily address this evidence gap on the impact of single-dose inactive vaccines and long-term protection conferred through this approach. In addition, the systematic review examines the effectiveness, immunogenicity, impact, safety and cost effectiveness of paediatric HAVs and cost-effectiveness of such strategies within routine infant, childhood or adolescent immunization programs.

3 Methods

3.1 POPULATION, INTERVENTION, COMPARISONS, OUTCOMES, STUDY DESIGN (PICOS)

3.1.1 Population

The population was infants and children aged between 0 and 17 years old. Adults in whom outcomes of interest were evaluated and who belong to a population in whom a hepatitis A childhood vaccination program has been implemented as either universal or non-universal (targeted to specific population groups).

3.1.2 Intervention

Either of the following as both single-dose or multiple-dose:

I. Live attenuated vaccines
II. Inactivated vaccines (monovalent or combination vaccine), both with either one or two doses.

3.1.3 Comparisons

Any of the following:

III. Inactivated vaccine
IV. Live vaccine
V. No vaccine
VI. Placebo
VII. Same vaccine type examining a different immunization scheme (e.g. 1 vs 2 doses)

3.1.4 Outcomes

There were four key outcomes: effectiveness, impact, safety and cost-effectiveness.

1 Effectiveness

- Disease incidence
- Seroprotection & GMC:
    1. Anti-HAV total or IgG antibodies above threshold of seropositivity following vaccination.
    2. Proportion of individuals with a positive serological test showing anti-HAV total or IgG antibodies titers above universally accepted seroprotection thresholds (10UI/ml or 20UI/ml)
    3. Anti-HAV total or IgG antibodies titers or concentrations measured up to the maximum follow-up time after immunization
- Modeling studies will also be considered through descriptive analysis

2 Impact

- Seroprevalence of anti-HAV antibodies before and after introduction of vaccination program
- Disease incidence before and after introduction of vaccine

- Modelling studies will also be considered through descriptive analysis

3 Safety

- Occurring after administration of HAV: local or systemic; serious vs non-serious
- HAV clinical disease, non-fatal complications and mortality.

4 Cost-effectiveness

- Incremental cost-effectiveness ratio (ICER)
- Cost / Quality-adjusted life year (QALY)

3.1.5 Study design

- Observational studies: cross-sectional studies, cohort studies, retrospective case control analysis, case cohort studies, time series analysis, ecological studies.
- Experimental studies: randomized controlled trials (RCT), quasi-randomised controlled trials (qRCT), community trials, field trials
- Systematic reviews
- Cost-effectiveness studies, modeling analyses.

3.1.6 Duration of follow-up

We were interested in long-term outcomes of HAV vaccination, specifically with single dose vaccine schedules in paediatric populations. Given the large number of studies of the short-term efficacy and effectiveness of HAV vaccine, we excluded studies of less than 3 years follow up. The longest study follow was 25 years, therefore duration of follow up was from 3 – 25 years. Analysis was split at year 7 so effectiveness was compared between 3 – 7 years follow up and 7 – 25 years follow up.

3.1.7 PICO question

The search strategy was undertaken to address the following PICO questions in the period 2012 to February 2021.

Table 1. Primary outcomes

Questions	PICO formulation
1. **Are hepatitis A vaccines safe (a) and effective (b) to prevent clinical disease and transmission of infection, to confer seroprotection?**	- Population: children and/or adolescents (aged between 0 and 17 years old) living in communities where a universal or targeted hepatitis A immunization program/strategy has been implemented. - Intervention: any of the following: (i) Live attenuated vaccines (one or two doses) (ii) Inactivated vaccines (one or two doses) - Comparator *: any of the following: (i) inactivated vaccine (ii) live vaccine (ii) no vaccine (iii) placebo (iv) same vaccine type examining a different immunization scheme (e.g. 1 vs 2 doses) - Outcome: (ii) Direct, indirect effectiveness for the prevention of infection (defined as evidence of HAV seropositivity presumably following infection), clinical hepatitis A disease, non-fatal complications, and death. (i) Adverse events occurring after administration of hepatitis A vaccine: local or systemic; serious vs non-serious (iii) Anti-HAV IgG antibodies above threshold of seropositivity following vaccination.

Do hepatitis A vaccines confer long –term protection against Hep A related disease (a) or seroprotection (b)? ** 2.	- Population: children and/or adolescents (aged between 0 and 17 years old) living in communities where a universal or targeted hepatitis A immunization program/strategy has been implemented. Adults who have been exposed to hepatitis A vaccination during their childhood, and in whom outcomes of interest are evaluated. - Intervention: any of the following: (i) Live attenuated vaccines (one or two doses) (ii) Inactivated vaccines (one or two doses) - Comparator *: any of the following: (i) inactivated vaccine (ii) live vaccine (ii) no vaccine (iii) placebo (iv) same vaccine type examining a different immunization scheme (e.g 1 vs 2 doses) - Outcome: (i) HAV clinical disease, non-fatal complications and mortality. (ii) Proportion of individuals with a positive serological test showing anti-HAV IgG antibodies titers above universally accepted seroprotection thresholds (10UI/ml or 20UI/ml) (iii) Anti-HAV IgG antibodies titers or concentrations measured up to the maximum follow-up time after immunization

* In observational studies, a comparator might not be available.
** For the purpose of this systematic review, long-term seroprotection will be defined as any evidence (clinical or non-clinical) of vaccine immunogenicity, which may be examined at least 4 years after the introduction of the hepatitis A vaccination program/strategy being assessed.

Table 2. Secondary outcomes

Questions	PICO
3. Are hepatitis A vaccines efficacious to prevent clinical disease and clinical complications? **4. What is the impact of universal childhood/adolescent hepatitis A vaccination programs on population level disease incidence, seroprevalence of anti-HAV antibodies, viral circulation and outbreaks occurrence over time?** **5. Are universal childhood/adolescent hepatitis A immunization programs cost-effective?** **6. Do hepatitis A vaccines confer protection in terms of cellular immunity?**	- Population: children and/or adolescents (aged between 0 and 17 years old) living in communities where a universal or targeted hepatitis A immunization program/strategy has been implemented. Adults exposed to hepatitis A vaccine during their childhood, in whom vaccine impact is examined. - Intervention: any of the following: (i) Live attenuated vaccines (one or two doses) (ii) Inactivated vaccines (one or two doses) - Comparator *: any of the following: (i) inactivated vaccine (ii) live vaccine (ii) no vaccine (iii) placebo (iv) same vaccine type examining a different immunization scheme (e.g 1 vs 2 doses) - Outcomes for efficacy: (i) hepatitis A disease (ii) Mortality (iii) Non-fatal complications of hepatitis A disease - Outcomes for impact: (i) Seroprevalence of anti-HAV antibodies before and after introduction of vaccination program (ii) Disease incidence before and after introduction of vaccine (iv) Occurrence of hepatitis A outbreaks within a community exposed to a universal childhood/adolescent immunization program (v) Change in HAV circulating serotypes - Outcomes for cost-effectiveness: - Outcomes for cellular immunogenicity: (i) Vaccine-driven cellular immunity, evidenced as the proportion of sensitized T cells in the trial subjects, at maximum follow-up time.

3.1.8 Exclusion criteria

- Non-human studies

- Study designs: historical controlled studies, acceptability studies, narrative reviews, case series, case reports, experts consensus, research protocols, newspaper articles or other forms of popular media. Additionally:
- Immunization targeting adults only (individuals aged 18 years old or older)
- Research performed only in the context of an outbreak investigation
- Secondary prophylaxis (immunization after exposure to individuals infected)

3.2 SEARCH METHODS FOR IDENTIFICATION OF STUDIES

3.2.1 Electronic searches

The search strategy was undertaken to address the following PICO questions in the period January 1, 2012 and February 9, 2021. The search was carried out in Medline (PubMed), the Cochrane Library, Scopus, Virtual Health Library and Scielo.

Table 3. Search terms in electronic databases

Database	Search terms
PubMed	#1 Vaccination [MeSH Terms] #2 immunization [MeSH Terms] #3 (Vaccines, Attenuated [MeSH Terms]) OR (Vaccines, Inactivated [MeSH Terms]) #4 vaccin*[ti/ab] OR immuni*[ti/ab] OR inoculat*[ti/ab] #5 (#1 OR #2 OR #3 OR #4) #6 (hepatitis A[MeSH Terms]) OR (hepatitis A vaccines[MeSH Terms]) #7 ("hepatitis-A"[Title/Abstract]) OR ("hep A"[Title/Abstract]) #8 (#6 OR #7) #9 (hepatitis B NOT (hepatitis B AND hepatitis A)) #10 (#8 NOT #9) #11 (#5 AND #10) #12 Animals NOT (Animals AND Humans) #13 (#11 NOT 12) #14 ("randomized controlled trial"):pt OR ("controlled clinical trial"):pt OR (randomized):ti,ab OR (placebo):ti,ab OR (randomly):ti,ab #15 (trial):ti,ab OR (groups):ti,ab OR (random*):ti,ab OR (cohort*):ti,ab #16 (case AND control*):ti,ab OR (case AND series):ti,ab OR ("case-control study"):MeSH Terms OR ("systematic review"):pt OR ("cohort studies"):MeSH Term #17 MeSH descriptor:[Epidemiologic Methods] explode all trees #18 (#14 OR #15 OR #16 OR #17) #19 (#13 AND #18) #20 (2012/01/01 [Date – Publication]: 3000) #21 (#19 AND #20)

Cochrane *	#1 MeSH descriptor: [Vaccination] explode all trees #2 MeSH descriptor: [Immunization] explode all trees #3 (vaccine* AND (attenuated OR inactivated)):ti,ab,kw #4 (vaccin* OR immuni* OR inoculat*):ti,ab,kw #5 (#1 OR #2 OR #3 OR #4) #6 MeSH descriptor: [hepatitis A] explode all trees #7 (hepatitis-A OR hep A):ti,ab,kw #8 (#6 OR #7) #9 (hepatitis B NOT (hepatitis B AND hepatitis A)) #10 (#8 NOT #9) #11 (#5 AND #10) #12 Animals NOT (Animals AND Humans) #13 (#11 NOT 12) #14 ("randomized controlled trial"):pt OR ("controlled clinical trial"):pt OR (randomized):ti,ab,kw OR (placebo):ti,ab,kw OR (randomly):ti,ab,kw #15 (trial):ti,ab,kw OR (groups):ti,ab,kw OR (random*):ti,ab,kw OR (cohort*):ti,ab,kw OR ("cohort studies"):pt #16 (case AND control*):ti,ab,kw OR (case AND series):ti,ab,kw OR ("case-control study"):pt OR ("systematic review"):pt #17 MeSH descriptor:[Epidemiologic Methods] explode all trees #18 (#14 OR #15 OR #16 OR #17) #19 (#13 AND #18) with Cochrane Library publication date from Jan 2012 to Jan 2021 * Results from Cochrane Library included both Embase and PubMed citations.

Scopus	#1 TITLE-ABS-KEY (vaccination) OR TITLE-ABS-KEY (immunization) OR TITLE-ABS-KEY (vaccin*) OR TITLE-ABS-KEY (immuni*) OR TITLE-ABS-KEY (inoculat*) #2 TITLE-ABS-KEY (vaccine* AND (attenuated OR inactivated)) #3 (#1 OR #2) #4 (TITLE-ABS-KEY ("hepatitis A") OR TITLE-ABS-KEY ("hep A") OR TITLE-ABS-KEY ("hepatitis-A") OR TITLE-ABS-KEY ("hepatitis A vaccines")) #5 (ALL ("hepatitis B") AND NOT ALL ("hepatitis B" AND "hepatitis A")) #6 (#4 AND NOT #5) #7 (#3 AND #6) #8 (ALL (animals) AND NOT ALL (animals AND humans)) #9 (#7 AND NOT #8) #10 (TITLE-ABS-KEY ("randomized controlled trial") OR TITLE-ABS-KEY ("controlled clinical trial") OR TITLE-ABS-KEY (randomized) OR TITLE-ABS-KEY (placebo) OR TITLE-ABS-KEY (randomly) OR TITLE-ABS-KEY (trial) OR TITLE-ABS-KEY (groups) OR TITLE-ABS-KEY (random*) OR TITLE-ABS-KEY (cohort*) OR TITLE-ABS-KEY ("cohort study") OR TITLE-ABS-KEY (case AND control*) OR TITLE-ABS-KEY (case AND series) OR TITLE-ABS-KEY ("case control study") OR TITLE-ABS-KEY ("systematic review") OR TITLE-ABS-KEY ("epidemiologic methods")) #11 (#9 AND #10) #12 (#11 AND PUBYEAR > 2011) #13 (#12 AND NOT INDEX(medline))

VHL	#1 (tw:vaccination OR tw:immunization OR tw: vaccines AND (Attenuated OR Inactivated) OR tw:vaccin* OR tw:immuni* OR tw:inoculat*) #2 (tw:"hepatitis A" OR tw:"hepatitis A Vaccines" OR tw:"hepatitis-A" OR tw:“hep-A”) AND NOT (“hepatitis B” AND NOT (“hepatitis B” AND “hepatitis A”)) #3 (#1 AND #2) #4 Restricted to publication date between 2012 and 2020 #5 Restricted to all databases excluding Medline Final search strategy: tw:((tw:(vaccination OR immunization OR (vaccine* AND (attenuated OR inactivated)) OR vacci* OR immuni* OR inoculat*)) AND (tw:(("hepatitis A" OR "hepatitis A Vaccines" OR "hepatitis-A" OR “hep-a”) NOT (“hepatitis b” NOT (“hepatitis b” AND “hepatitis a”))))) AND (db:("LILACS" OR "IBECS" OR "BINACIS" OR "BDENF" OR "BRISA" OR "CUMED" OR "SES-SP" OR "WHOLIS" OR "ARGMSAL" OR "DECS")) AND (year_cluster:[2012 TO 2020])

* All searches were updated at each database, until February 02, 2021.

3.2.2 Searching other resources

We conducted additional searches for eligible, both published and unpublished studies applying the following methods:

- Identification of relevant studies mentioned or presented in the meetings of the SAGE Working Group on HAV
- Search of on-line registries for ongoing studies
- Examination of websites of public health agencies or governmental institutions in countries with existing hepatitis A vaccination policies, to address queries on ongoing or finished studies they might have conducted in connection to the outcomes of interest of this systematic review
- Exploration of systems for information on grey literature
- Research on completed studies that have not been published yet and were carried out in countries of residence of some of the members of the Working Group
- Reaching out to specific authors of included or other studies for further information and data
- Direct contact with WHO and PAHO Country Offices by authors and working group members (experts or secretariat)

3.3 DATA COLLECTION AND ANALYSIS

3.3.1 Selection of studies

Two reviewers independently performed the screening of titles, abstracts and subsequently full-texts, applying the stablished eligibility criteria. Disagreements were resolved by discussion between both reviewers until reaching a consensus. Where there was no agreement, a third reviewer was invited.

During the screening and selection process, studies assessing vaccination effects on adult population and high-risk adult/pediatric population groups were identified. Nonetheless, we did not apply specific search strategies addressed to such groups; therefore, evidence collected from such populations were only circumstantial and not systematic.

3.3.2 Search, deduplication and integration of results

Search terms were entered in the required format in each database (see detailed search terms in Annex 1). All publications between January 1, 2012 and February 09, 2021 were included. Results were imported into Endnote (a reference manager), merged and further deduplicated. The merged Endnote file was then imported into Covidence, a software tool for systematic literature review. A further deduplication was performed in Covidence. Although search terms were in English, we did not restrict results by language. Search and importation of retrieved publications was performed by one reviewer only.

3.3.3 Data extraction and management

Data was extracted by two reviewers into a standardized table in Microsoft Excel which included all outcomes and study characteristics of interest. Before the start of the data extraction, the reviewers discussed relevant items for data extraction to minimize the risk of misinterpretation, omission and inaccuracy.

3.3.4 Assessment of risk of bias in included studies

One reviewer independently assessed the risk of bias for each individual primary study on single-dose and multiple-dose schedules of hepatitis A vaccination. Results of the assessment were cross checked by a second reviewer. If any disagreement between both reviewers existed, it was solved through consensus. Assessment was made for longitudinal, cohort and randomized studies. Cross-sectional studies were not considered in evaluation of risk of bias. For observational studies we used the Cochrane Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I). Most clinical trials included were followed by longitudinal studies aimed at examining long-term vaccine immunogenicity. Since our assessment was focused on results from prospective observation following randomization and assignment of intervention, publications on follow-up phases derived from randomized trials were evaluated through ROBINS-I instead of ROB-2 (Revised Cochrane risk of bias tool for randomized trials). For each study, a ROBINS-I template was fulfilled. Results of assessment for all studies were summarized and tabulated.

We explored the possibility of assessing impact studies for risk of bias, but considering the multitude of shortcomings of these data (e.g. reliance on surveillance and notification systems of variable quality, multiple countries or regions, differences in definitions, laboratory quality, variability in vaccine programs and demographics), it was agreed an assessment of risk of bias would not add substantially to interpretation of the quality and outcomes of impact studies.

We considered the following domains on evaluation: bias due to confounding, selection bias, bias derived from classification or deviations of intervention, bias due to missing data, information bias in measurement of outcome and bias in selection of reported results. Overall risk of bias was classified as critical, serious, moderate or low.

3.3.5 Dealing with missing data

If data on specific outcomes or population groups were missing, we attempted to contact study authors to request this data. We did not impute missing outcome data. Where data were missing or losses to follow-up were substantial, we downgraded the certainty of study evidence due to risk of bias according to GRADE criteria for all outcome analyses.

3.3.6 Assessment of heterogeneity

We considered heterogeneity and downgraded the certainty of the evidence according to GRADE criteria due to inconsistency where appropriate (Guyatt 2011b). When pooling of studies was feasible (i.e., at least two studies included), we inspected forest plots visually for potential outlying studies and variability in the estimated effects across studies. Where possible, we assessed statistical heterogeneity using the I2 statistic.

3.3.7 Publication bias

We had planned to use funnel plots to investigate the possible presence of small-study effects for each outcome. However, we could not use this approach due to the limited number of studies per outcome.

3.3.8 Summarising and interpreting results

We used the GRADE approach to interpret findings and create 'Summary of findings' tables following the GRADE handbook. These tables provided outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data. Evidence certainty was downgraded for the following reasons:

- Limitations in study design or execution (risk of bias)
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Publication bias

The different levels of certainty that result from GRADE ratings of the evidence should be interpreted as follows:

- High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low-certainty: we were very uncertain about the estimate.

3.3.9 Sensitivity analysis

For the critical question regarding the long term effectiveness of single dose HAV vaccine schedules in pediatric populations, given the very limited number of single dose studies and outcomes (disease, seroprotection and GMC) identified for inclusion in the meta-analysis, the utility of a sensitivity analysis was limited; however, for this analysis (See SoF table *Single dose HAV vaccine (inactivated)*

compared to 2 dose HAV vaccine (inactivated) for children >7 years follow up) application of a fixed or random effects model did not alter the direction nor heterogeneity of the results. In addition, long term single dose follow-up studies were universally small outside of China and there were no long-term inactivated vaccine trials conducted in China.Also only one single dose study included in the meta-analysis was rated as having a low risk of bias, impeding our ability to explore the impact on the results of only including studies classified as having a low risk of bias.

Sensitivity analysis of the GMC analysis identified the impact of Luo *et al.* 2019 on the outcome of single dose live attenuated (vs 2 dose inactive) vaccine. The mean GMC in this study was an order of magnitude higher than any other study (mean GMC > 5000 mIU/mL) for both arms. Only in one other study's arms – the 2 dose arm of Espul *et. al* 2017, a single vs two dose inactive comparison with 7 year follow-up - was the mean GMC greater than 500 mIU/mL. The higher GMC in Luo *et al.* 2019 is likely due to the natural environmental exposure to HAV in the study geographic area. Given the heavy impact of this substantially higher GMC on the results for this specific analysis, , we excluded Luo *et al.* from analysis of GMC mean difference, while including it in the analyses for other outcomes.

3.3.10 Pooling data and meta-analysis

When pooling was considered feasible, that is addressed similar research questions, populations and and outcome variables, we employed a random-effects meta-analysis since it was assumed that effect size might vary across studies and settings. We used data from the last available follow-up relevant to the 7-year mark. That is, the latest data point prior or at 7 years follow up, for the 3 – < 7 year analysis group, and the latest data point for the ≥7 – 25 year analysis group. Where studies were measured multiple times over the course of the cohort, we took only one data point on either side of the =>7 year mark, as described.

3.3.11 Integration of results with prior systematic review

Three systematic reviews were reviewed and considered for inclusion in the current review. Two of these systematic review (Irving *et al.* 2012 & Ott *et al.* 2012) formed the background to the previous WHO position paper in 2012, providing data continuity between the two position papers:

- Irving, G. J., Holden, J., Yang, R. & Pope, D. 2012. Hepatitis A immunisation in persons not previously exposed to hepatitis A. Cochrane Database Syst Rev, 2012, Cd009051.
- Ott, J. J., Irving, G. & Wiersma, S. T. 2012. Long-term protective effects of hepatitis A vaccines. A systematic review. Vaccine, 31, 3-11.
- Andani, A., van Damme, P., Bunge, E. M., Salgado, F., van Hoorn, R. C. & Hoet, B. 2021. One or two doses of hepatitis A vaccine in universal vaccination programs in children in 2020: A systematic review. Vaccine.

We contacted the authors of the respective publications regarding further details on all of these publications. Reference lists of these identified systematic reviews were checked for relevant articles that might have been overlooked.

On close examination of all the search strategies and data, there was a clear distinction between the methods in Ott 2012 and Irving 2012, which drew most data from adults and the present systematic review which excluded adults, focusing on the paediatric population. Indeed, there was only one additional study that could be identified which fulfilled the present systematic review search strategy, that of Bian *et al.* 2010 (Bian et al., 2010), however since it was a two-dose study only, it was not

included. Early results from both the Argentina series of studies (Espul, Benedetti, Cuello, Houillon, & Rasuli, 2012; Espul et al., 2017; Espul, Benedetti, Linares, Cuello, & Rasuli, 2015; Espul et al., 2020) and the Alaska series of studies (Mosites et al., 2018; Plumb et al., 2017; Raczniak, Bulkow, et al., 2013; Raczniak, Thomas, et al., 2013; Ramaswamy et al., 2020) were present in these previous systematic reviews and the present review.

The Andani et al. 2021 (Andani et al., 2021) systematic review reported on vaccine efficacy and vaccine effectiveness (one and two dose, longevity), Impact of HAV vaccination on other hepatitis A-related outcomes (incidence of disease, hospitalizations and mortality) and population impact. Individual studies were presented and there was no pooling of data. The present review included key studies of importance identified in Andani 2021. We did not consider the impact of vaccination on HAV circulation in water and soil, which was covered in the Andani 2021 review.

4 Results

4.1 DESCRIPTION OF STUDIES

4.1.1 Results of the search

Overall, 70 studies were included (Figure 1). The characteristics of individual studies are presented in the subsequent section of results.

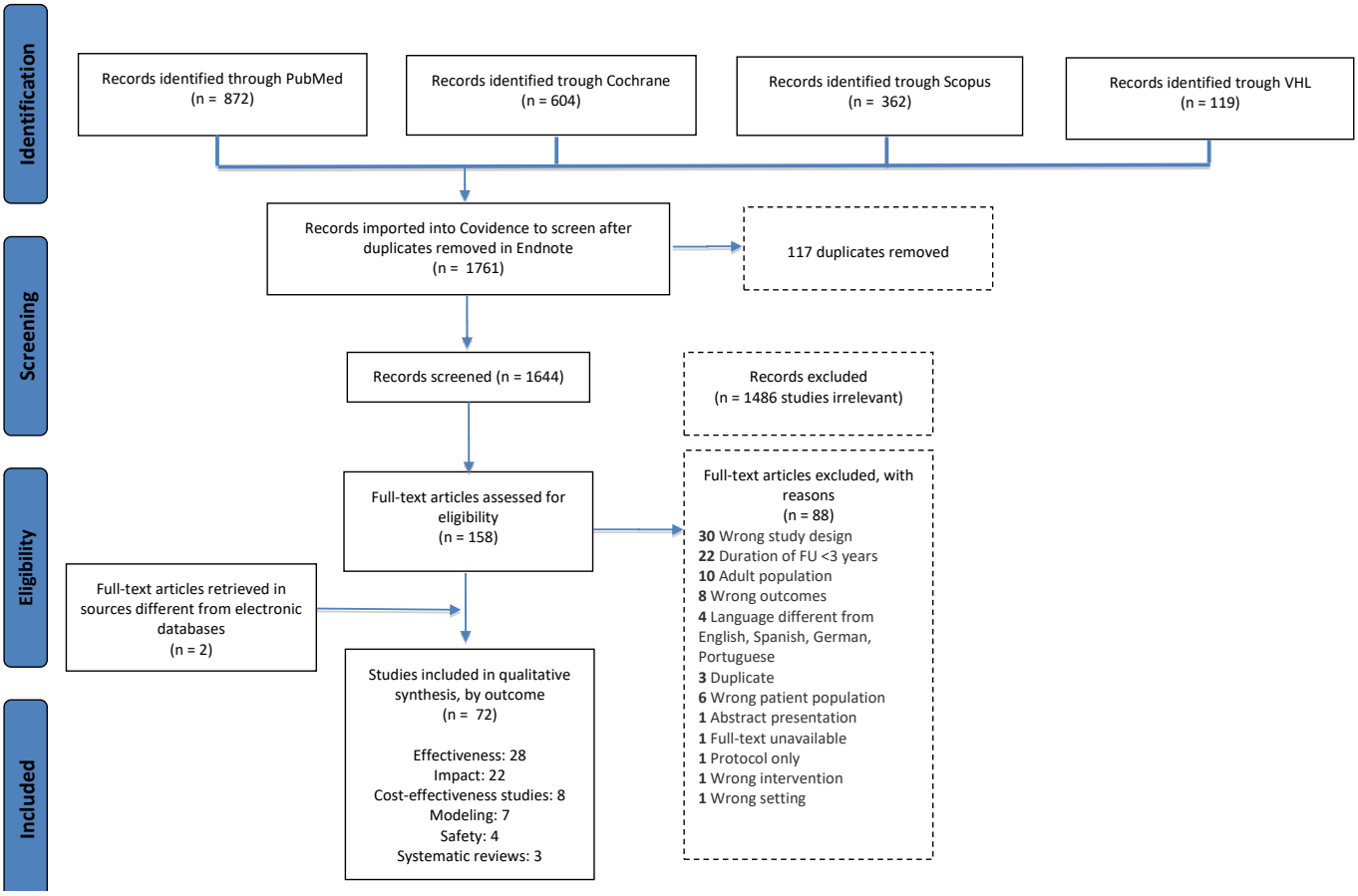

Figure 1 - Study Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

4.2 INCLUDED STUDIES

4.2.1 RCT studies

Table 4. Included studies

Author Year	Participants	Interventions	Follow up duration	Outcomes	Source of funding	Notes
Liu 2013	N=841 Children	1. Single dose inactivated (Healive) 2. Two-doses inactivated (Healive) 3. Single dose live attenuated (3 types of vaccine)	6 months (n=196) 12 12 months (n=422)	GM1C	Sinovac Biotech Co., Ltd	Very short follow-up
Zhang 2017	N=332 Children	1. Single dose inactivated (Biovac) 2. Single dose live attenuated (Healive)	5 years (n=182)	GMC and seropositivity	Sinovac Biotech Co., Ltd	These vaccines are not available on the global market Seroprotection level does not appear to be defined (is 20IU/mL in other Chinese studies)
Yu 2016	N=400 Children 1-8 years	1. Two-doses inactivated (Healive), 0 and 6 months. 2. Two-doses inactivated (Havrix), 0 and 6 months.	5 years (n=309)	GMC and seroprotection	National Natural Science Foundation of China	While seroprotection not universal at 5 years, it was universal at 11 years
Wang 2020			**11 years (n=290)**			

Luo 2019	N=9000 Infants 18 – 36 month (n=3000), Children 3- 16 years old (n=3000), Adults > 16 years (n=3000)	1. Two-doses inactivated (6 months apart) 2. Single dose live attenuated (Both manufactured by the Institute of Medical Biology, Chinese Academy of Medical Sciences, Kunming, China)	3 years (n=559)	GMC and seroconversion	The Jointly Supported Foundation of the National Project in Yunnan Province, the CAMS Initiative for Innovative Medicine, the National Natural Science Foundation of China, and the Natural Science Foundation of Yunnan Province.	Blood samples were collected at 28 days, 1 year, 2 years and 3 years after vaccination. The risk of re-exposure to wild-type HAV or live vaccine virus strain excreted in the field cannot be excluded as possible explanations for the elevation of anti-HAV titers in this study

4.2.2 Cohort studies with LTFU (> 3 years)

Author Year	Participants	Study design	Interventions	Follow up duration	Outcomes	*Notes*
Bhave 2015				10 years (n=108)		Cohort GMT was higher (101) at year 10 than at year 6 (66) In 2010, there were 25 children with anti-HAV titres <20mIU/mL. They were not given any additional dose / doses of live/inactivated HAV vaccine. The serial anti-HAV GMTs of these 25 children as compared to all 98 with single dose of live HAV vaccine is presented. In 2014 and 2019, 23 of these 25 regained seroprotective levels.
Bhave 2021	N=143 Children 1-12 years old	Observational cohort	Single dose live attenuated (Biovac-A)	15 years (n=98)	GMT	
Brito 2018	N=1135 Children 1-2 years	Observational cohort	Single dose inactivated (VaqtaTMPed/Adol, MSD)	236 days (n=252)	Anti-HAV antibody positive	Anti-HAVab with DBS EIA and if negative (18/252) then venous EIA
Chen 2018	N=47 Children 1-12 years old	Observational cohort within an RCT	Participants from longer term study that received single dose of live attenuated (Pukang Biotech) in 1996 – 1999, who received a booster vaccine in this study	17-years (n=47)	B cell and T cell immune memory and GMC	Long follow up and recall responses after a booster suggest that the existence and functions of HAV-specific memory B cells are independent of the status of the serum anti-HAV antibody.

Dagan 2016	N=327 Children 12 – 15 months	Observational cohort within an RCT	1. Epaxal Junior + routine childhood vaccination (RCV) (both day 1) and HAV booster at 6 months 2. Epaxal Junior (day 1) + RCV (day 29) and HAV booster at 6 months 3. Havrix 720 + RCV (Both day 1). and HAV booster at 6 months	15 month (n-157)	GMC and seroprotection	2 doses, study examined impact of different vaccine brand when administered with or without RCV
Espul 2012 **Espul 2015** **Espul 2017** **Espul 2020**	N=546 Children 12 – 23 months	Observational cohort within an RCT	1. Two dose inactivated (Avaxim™ 80 U Pediatric) at 12 and 18 months 2. Single dose inactivated hepatitis A vaccine (Avaxim™ 80 U Pediatric) at 12-23 months.	3 years (n=365) 5 years (n=318) 7 years (n=204) 10 years (n=367)	GMC	Although GMC decreased for the group, some participants increased GMC indicating potential environmental exposure and increasing seroprotection to 100% at years 7 and 10. No clinical cases of acute HAV infection. Mathematical model predicted no difference in GMC between groups at 30 years, with both above 3mIU/mL

Mayorga 2016	N=130 Children 1.7–17 years	Observational cohort	Single dose virosomal (Avaccine Epaxal (Crucell Switzerland) then at year 7.5 a booster dose of (Havrix Junior or Havrix, depending on age)	7.5 years (n=105)	GMC	No adverse events Area of endemic HAV infection and authors had predicted an attack rate of 15% during the study period with a 99% probability
Mitra 2015	N=349 Children 1-12 years	Observational cohort	Single dose live attenuated (Biovac ATM, H2 strain, freeze dried)	5 year (n=111)	Seroconversion and GMC	
Lopez 2015	N=537 Children 1-15 years	Observation cohort	Two dose inactivated (Avaxim® 80U Pediatric, Sanofi Pasteur), 6 months apart	10 years (n=54)	Seropositivity and GMC	A minority of children increased their GMCs by year 15. Children HAV-seropositive prior to vaccination appear to reach higher peak concentrations and have a slower rate of antibody decline post-booster, but the small sample size (n = 6) means trends must be interpreted with caution.
Sharapov 2012	N=197	RCT of 3 different age schedules but	Inactivated HepA vaccine HAVRIX	10 years (n=197)	Seroprotection, GMC and	Vaccinating later (after the first year of life) showed

Spradling 2016	Children 6 – 21 months	treated as Observation cohort (outcomes grouped)	(GlaxoSmithKline Biologicals, Rixensart, Belgium) 1. Two doses at 6 & 12months of age. 2. Two doses at 12 & 18 months of age 3. Two doses at 15 & 21months of age	15 years (n=183)	maternal antibody status	greater long-term protection. Maternal antibody positivity associated with reduced long-term protection (but minimal). There were 43/129 (34%) of children exposed to maternal anti-HAV Ab in the study at 10 years
Raczniak 2012	N=143 Children 3 -6 years	RCT of 3 different age schedules but treated as Observation cohort (outcomes grouped)	Inactivated HepA vaccine HAVRIX (GlaxoSmithKline Biologicals, Rixensart) 3 dose schedules 1. 3 doses at 0, 1, and 2 months 2. 3 doses at 0, 1, and 6 months 3. 3 doses at 0, 1, and 12 months	17 years (n=58)	Seroprotection and GMC	Authors have published that this 3 dose schedule is equivalent to the current 2 doses schedule, hence included in this analysis (Raczniak 2013) Participants in schedule C had a consistently and significantly higher GMC compared to those in schedule A at the 10 year, 14 year, and 22 year time points. At year 2017, authors had concluded that is was likely protection would persist into late adulthood
Plumb 2016				22 years (n=52)		
Mosites 2017				20 years (n=46)		
Ramaswamy 2020[1]				25 years (n=43)		

[1] We include the Alaska series of long-term follow up of a 3 dose series of inactive HAV vaccine randomized to 3 schedules in Indigenous 3- 6 year old Alaskan children (0,1,2; 0,1,6; and 0,1,12 months). The authors have published the 3 doses schedule is equivalent to a 2 dose schedule.(Raczniak, Thomas, et al., 2013) In our analysis we include this RCT as a cohort (3 groups grouped together) in the 2 dose arm.

Urueña 2016	N=1088 Children 12 months of age	Observation cohort – seroprevalence study	Single dose inactivated HAV vaccine	9 years (n=1088)	anti-HAV antibody levels and GMC	Since 2005 and up to 2013, when this study began, more than 6 million doses of HAV vaccine were administered in the country and national vaccine coverage was above 92% during the whole period.
Van Herck 2015	N=271 Children aged 1–17 years	Observation cohort – was RCT but treated as cohort in this analysis	1. Two doses intramuscular (i.m.) (Epaxal® Junior, Epaxal® 2. Two doses (Havrix® Junior) according to a 0/6-month schedule	5.5 years (n=213)	Seroprotection and GMC	mIU/mL) was 25.1 years (95% CI: 22.5–27.3) for Epaxal® Junior, 28.3 years (95% CI: 26.4–31.0) for Epaxal® and 24.5 years (95% CI: 22.1–28.6) for Havrix® Junior Age had a significant influence on anti-HAV antibody decline over the 5.5 years of follow-up and on the predicted duration of antibody persistence with younger subjects showing a faster decay and shorter periods of antibody persistence. This age effect seemed to be independent of gender and vaccine received.

4.2.3 Cohort studies with combined HAV HBV vaccines

Author Year	Participants	Study design	Interventions	Follow up duration	Outcomes	
Beran 2015	N=162 Adolescents 12-15 years	Observation cohort	1. Two doses of combined HAV-HBV (Twinrix, GSK Vaccines, Belgium) 2. Three doses of combined HAV-HBV (Twinrix, GSK Vaccines, Belgium)	15 years (n=162)	Seroprotection and GMC for HAV and HBV	GMC is higher in 2 dose vs 3 dose groups. TwinrixTMAdult; containing 720 EL.U of inactivated HAV antigenand 20 g of HBs antigen.

4.2.4 Cohort studies with LTFU in special populations

Author Year	Participants	Study design	Selection criteria	Interventions	Follow up duration	Outcomes	Notes
Gouvea 2015	N=39 Children	Observation cohort	HIV-infected vs HIV-exposed but non-infected	Two doses inactivated (Havrix), over 6 months	7 years (n=39)	Seropositivity	Study was regarding infants exposed to or infected with HIV only The levels of hepatitis A antibodies in the primary vaccination were the only factor independently associated with maintaining these antibodies for 7 years. The group that lost HAV seropositivity was revaccinated and 83.3% (5/6) responded with antibodies >20 mUI/mL.

Kalyoncu 2012	N=30 Children 7.3 – 18 years	Observation cohort with matched control arm	Children and adolescents, either healthy or with chronic hepatitis C virus	Two doses inactivated (Havrix), over 6 months	8 years (n=30)	Seroprotection	3/30 CHC children had initial evidence of nature HAV immunity so only 22 included in the intervention, whereas 15/50 control (non-CHC) had evidence of natural HAV immunity

4.2.5 Cross sectional studies

Author Year	Participants	Study design	Selection criteria	Interventions	Follow up duration	Outcomes	Notes
Xiaojin 2020	N= 6349 Nationwide	Observational (time separated serosurvey)	Sera of individuals who had participated in a nationwide serological survey in 2014 who had received HepA or HepA-L	1. Single dose of live attenuated HepA (HepA-L) at 18months 2. Two dose inactivated HepA-I at 18 and 24 months	10 years (n=6349)	Seroprevalence	GMC not recorded. Low numbers in long-term groups.
Juliao 20	N=600 Children	Cross sectional	Serosurvey of children who had received either 1 or 2 Havrix doses under the National Immunization Program	1. Single dose inactivated (Havrix) 2. Two-doses inactivated (Havrix)	10 years (n=601) persons)	GMC, seropositivity and seroprevalence	Ecological, province wide, notification data with embedded seroprevalence study

4.2.6 Case control studies

Author Year	Participants	Study design	Selection criteria	Interventions	Follow up duration	Outcomes	Notes
Gallone 2016	N= 1827 Adults (HAV vaccinated as children or adolescents)	Retrospective case control	Adult blood donors in Bari, Italy following initiation of HAV vaccine program in late 1990s targeted to new-borns and adolescents	1. Single dose HAV vaccine for 90% of cohort 2. Two doses of HAV vaccine	13 years (n=207)	Anti-HAV positive	Blood donor population study. Vaccination status checked against official records. Appears to be a maximum of 13 years follow-up but would vary within the group
Vizzotti 2015	N= 1578 Children	Retrospective case control	Children of 4 provinces in Argentina (BsAs, BA province, Tucaman City and Santa Fe)	Single dose inactivated vaccines: 1. strains HM 175 720 EL.U, HAVRIX [GSK Biologicals, Rixensart, Belgium] 2. CR 326 25 U, VAQTA Merck Sharp & Dohme [Whitehouse Station, NJ] 3. GMB 80 U, AVAXIM [Sanofi-Pasteur, Lyon, France]; and RG-SB 4. 12 UI, Virohep-A Junior [NOVARTIS, Buenos Aires, Argentina]	4 years (n=1578)	Seroprotection and GMC	Attendance at kindergarten associated with seroprotection in MVA

4.2.7 Ecological studies

Author Year	Study population	Study design	Interventions	Study period	Outcomes	Notes
Yonghao 2020	Population wide in Henan province, China	Ecological	Single dose of live attenuated HepA (HepA-L) (or two doses of inactivated vaccine (HepA-I), which was charged to the family)	2008 – 2018	Vaccine coverage, HAV case notifications in national notification system, embedded seroprevalence	Ecological, province wide, notification data. Embedded seroprevalence study
Sun 2018	Population wide in China	Ecological	1. Single dose live attenuated (HepA-L) at 18months (115m administered) 2. Two doses live attenuated (HepA-I) at 18 and 24 months	2008 – 2016	Vaccine coverage, HAV case notifications in national notification system, embedded seroprevalence	Ecological, province wide, notification data. Embedded seroprevalence study
Vizzotti 2014	Population wide in Argentina	Ecological	Single dose inactivated vaccines: 1. strains HM 175 720 EL.U, HAVRIX [GSK Biologicals, Rixensart, Belgium] 2. CR 326 25 U, VAQTA Merck Sharp & Dohme [Whitehouse Station, NJ] 3. GMB 80 U, AVAXIM [Sanofi-Pasteur, Lyon, France]; 4. RG-SB 12 UI, Virohep-A Junior [NOVARTIS, Buenos Aires, Argentina]	2000 - 2011	Vaccine coverage, HAV case notifications in national notification system, fulminant hepatic failure and liver transplant	Data from the National Health Surveillance System

4.2.8 Systematic reviews

Author Year	Objective	Search	Selection criteria	Included	Notes
Irving 2012	To determine the clinical protective efficacy, seroprotective efficacy, and safety and harms of hepatitis A vaccination in persons not previously exposed to hepatitis A.	The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, and China National Knowledge Infrastructure (CNKI) up to November 2011.	RCTs comparing HAV vaccine with placebo, no intervention, or appropriate control vaccines in participants of all ages.	11 clinical studies	There was insufficient data to draw conclusions on adverse events for the live attenuated HAV vaccine. Unable to differentiate single vs two vaccine schedules in general analysis, though subanalysis included effectiveness of single dose schedule (just one study). This is a meta-analysis

Ott 2012	To determine evidence on the duration of protection achieved by hepatitis A vaccine	Studies published between 1997 and 2011 in the 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.	Exclusion criteria: (1) Studies providing results that were obtained exclusively from mathematical modeling. (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. (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.	13 clinical studies	There was insufficient data to draw conclusions on adverse events for the live attenuated HAV vaccine. Unable to differentiate single vs two vaccine schedules in general analysis, though subanalysis included effectiveness of single dose schedule (just one study). No meta-analysis

4.3 RISK OF BIAS IN INCLUDED STUDIES

The assessed risk of bias for each included study is detailed in the tables immediately below. Where the same study/cohort has been published multiple times, we consider the multiple publications as one study in the assessment process (e.g., one series from Argentina and one series from Alaska, USA).

Overall, no studies were judged as low risk of bias. Eight studies were judged as having a moderate risk of bias (Beran, Van Der Meeren, Leyssen, & D'Silva, 2016; Dagan et al., 2016; Luo et al., 2019; Mayorga et al., 2016; Raczniak, Thomas, et al., 2013; Van Herck et al., 2015; Y. Wang et al., 2020; C. Yu et al., 2016; Zhang et al., 2017) and 7 studies as having serious risk of bias (Bhave et al., 2021; Bhave, Sapru, Bavdekar, Kapatkar, & Mane, 2015; Chen et al., 2018; Espul et al., 2012; Espul et al., 2017; Espul et al., 2015; Espul et al., 2020; Mitra et al., 2015; Plumb et al., 2017; Raczniak, Bulkow, et al., 2013; Ramaswamy et al., 2020; Sharapov et al., 2012; Spradling et al., 2016).

A summary of the judgement is arranged as two tables, the first for single-dose (8 studies) and the second for multiple-dose publications (7 studies), respectively. None of the studies was judged as having a low overall risk of bias. Four out of eight studies on single-dose vaccination were assessed with a moderate risk of bias (Dagan et al., 2016; Luo et al., 2019; Mayorga et al., 2016; Zhang et al., 2017); for the remaining four studies the risk was classified as serious (Bhave et al., 2021; Bhave et al., 2015; Chen et al., 2018; Espul et al., 2012; Espul et al., 2017; Espul et al., 2015; Espul et al., 2020; Mitra et al., 2015). Among studies examining multiple-dose vaccination, five studies were judged as having moderate risk of bias (Beran et al., 2016; Raczniak, Thomas, et al., 2013; Van Herck et al., 2015; Y. Wang et al., 2020; C. Yu et al., 2016), while two studies were judged as high risk (Mosites et al., 2018; Plumb et al., 2017; Raczniak, Bulkow, et al., 2013; Ramaswamy et al., 2020; Sharapov et al., 2012; Spradling et al., 2016).

The high proportions of loss-to-follow up in a substantial number of studies was considered a critical issue and likely source of confounding bias. While this is understandable – perhaps unavoidable – for very long-term cohorts following paediatric immunization, it impacted heavily on the assessment of risk of bias.

Bias derived from selection of participants, application of interventions and selection of reported results was assessed as low in most studies included.

In six studies we classified the risk of bias due to incomplete data as serious or critical (Beran et al., 2016; Espul et al., 2012; Espul et al., 2017; Espul et al., 2015; Espul et al., 2020; Luo et al., 2019; Mosites et al., 2018; Plumb et al., 2017; Raczniak, Bulkow, et al., 2013; Ramaswamy et al., 2020; Sharapov et al., 2012; Spradling et al., 2016), owing to significantly high proportions of loss-to-follow-up. In four studies on single-dose vaccination the overall risk of bias was classified as serious, whereas two studies on multiple-dose schedules had the same assessment.

4.3.1 Selection bias

We assessed most studies as having a low risk of bias in selection of participants. In three studies aimed at evaluating single-dose vaccination (Chen et al., 2018; Espul et al., 2012; Espul et al., 2017; Espul et al., 2015; Espul et al., 2020; Mitra et al., 2015), and two studies on multiple-dose schedules (Raczniak, Thomas, et al., 2013; Sharapov et al., 2012; Spradling et al., 2016) we considered a

moderate risk of bias, given relatively prolonged times elapsed between selection of participants and start of the follow-up period.

4.3.2 Confounding

We assessed all except two studies to have either a critical or serious risk of bias due to potential confounding.

We considered confounding to be bias of critical importance in determining the actual association between the assessed immunization schedule and outcomes observed in both antibodies and anamnestic immunological response following vaccination. Therefore, when the risk of bias of a study in such a domain was deemed as critical, the overall risk of bias was considered as serious or critical. Longitudinal studies with no comparison group and thus a high risk of factors other than vaccination influencing the outcome were considered at critical risk of bias due to confounding. All confounders were expected to be assessed at both inclusion and during follow-up.

The confounding domains determined as relevant were the following:

- Underlying immunological status of study participants
- Nutritional status, having weight, height, and body mass index as proxy
- Sanitation conditions relevant to risk of hepatitis A infection
- Socioeconomic conditions, assessed through household income data and parental educational level
- Place of residence (urban vs rural)
- Natural infection occurring either before or after vaccination
- Age of study participants at both vaccination and at time of measurement of vaccine response
- Co-interventions (administration of booster doses of hepatitis A vaccine)

There was a consistent lack of a comprehensive assessment of exposures apart from vaccination that could have influenced the outcome of long-term immunogenicity (i.e., natural boosting from environmental exposure). To some extent this was due to the study design of most studies (longitudinal follow-up with no comparison groups), absence of reporting of underlying characteristics of study participants and their distribution across study groups that might have been of relevant influence on the outcomes of interest, and lack of analysis plans aimed at controlling for covariables affecting the outcomes, in a time-varying manner.

Among the factors influencing the examined outcomes on immunogenicity, natural infection occurring any time during the follow-up time that might potentially boost antibody response to vaccination was considered of paramount importance in our review. Very few studies examined such possible confounders and those studies that explored natural infection following vaccination did so in only some of the points of time of outcome measurement, and mainly considered infection presenting as clinical disease (although most infections are expected to have been asymptomatic in study participants). Two studies (Dagan et al., 2016; Van Herck et al., 2015) considered age within their statistical analysis as a variable with an effect on the outcomes examined and estimated how age influenced the duration of seroprotection.

4.3.3 Classification of intervention

We assessed the risk of bias for classification of the intervention as low for all studies. We generally found intervention groups were clearly defined. From the methodology of the studies included, we inferred that the information used to define intervention groups was recorded at the start of intervention or shortly after it. We did not consider the possibility that there was a high risk that classification of intervention status could have been affected by preliminary knowledge of the risk of outcome. Nevertheless, in studies where the intervention was retrospectively recorded from previously registered data on vaccination history, accuracy of collected information and potential information bias on exposure could raise concerns.

4.3.4 Deviations from interventions

We considered the risk of bias due to deviations from the intended interventions was low for all studies. In some studies, a booster dose of HAV vaccine was administered throughout the follow-up period. However, this was normally taken into account to controlled for within the statistical analysis and such co-intervention was generally balanced across the main and comparison groups when applicable.

4.3.5 Incomplete outcome data

We assessed six studies as being at serious or critical risk of bias due to missing data on the outcome of interest (Beran et al., 2016; Espul et al., 2012; Espul et al., 2017; Espul et al., 2015; Espul et al., 2020; Luo et al., 2019; Mitra et al., 2015; Mosites et al., 2018; Plumb et al., 2017; Raczniak, Bulkow, et al., 2013; Ramaswamy et al., 2020; Sharapov et al., 2012; Spradling et al., 2016). One study was judged as having a low risk (Chen et al., 2018) and the remaining eight studies were classified at a moderate risk. A high attrition rate was a widespread shortcoming in studies of observational nature with long-term follow-up periods. The main reasons for missing data on the outcome were loss to follow up, migration, withdrawal out of personal reasons and technical errors that impeded blood samples collection or processing.

One study (Mitra et al., 2015) examined the persistence of antibody response up to 5 years following vaccination with a live attenuated hepatitis A vaccine and had loss to follow-up as high as 68.2%. A study examining long-term immunogenicity after administration of one of three different schedules of an hepatitis A inactivated vaccine in Alaskan children (Mosites et al., 2018; Plumb et al., 2017; Raczniak, Bulkow, et al., 2013; Ramaswamy et al., 2020) , with a maximum follow-up time of 25 years, reported loss to follow up of approximately 50% beginning at year 10.

4.3.6 Outcome measurement

We assessed most studies as being at low risk of bias for outcome measurement. We found methods of outcome assessment were comparable across intervention groups in cohort studies and trials, and considered methods of blinding in outcome measurement were appropriate when applicable.

It is of potential concern that some studies utilized different immunological assays to assess antibody response at different points of time during the follow-up period. These assays might have had different methods, accuracy and seropositivity thresholds, making it difficult to assess seropositivity dynamics from one point of measurement to another during the follow-up period. In three studies (Bhave et al., 2021; Bhave et al., 2015; Espul et al., 2012; Espul et al., 2017; Espul et al., 2015; Espul et al., 2020; Y. Wang et al., 2020), changes in serological assays over the follow-up period were required.

6.6.6 Selection of reported result

We generally considered a low risk of bias in selection of reported results (publication bias) for all studies.

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Table 5. Risk of bias assessment of included studies on single-dose hepatitis A vaccination

Author, year	Study type	Bias due to confounding	Bias in selection of participants	Bias in classification of intervention	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcome	Bias in selection of reported result	Overall risk of bias
Bhave et al., 2015	Longitudinal study	Critical	Low	Low	Low	Moderate	Moderate	Low	Serious
Chen et al., 2018	Longitudinal study	Critical	Serious	Low	Low	Low	Low	Low	Serious
Mayorga et al., 2016.	Longitudinal study	Serious	Low	Low	Low	Moderate	Low	Low	Moderate
Mitra et al, 2015.	Longitudinal study	Critical	Serious	Low	Low	Serious	Unclear	Low	Serious
Zhang et al, 2017	Observational study following RCT	Serious	Low	Low	Low	Moderate	Low	Low	Moderate
Espul et al., 2012 – 2020.	Longitudinal study	Critical	Moderate	Low	Low	Serious	Serious	Low	Serious
Dagan et al., 2016.	Longitudinal study	Moderate	low	low	low	moderate	Low	Low	Moderate
Luo et al., 2019	Randomized, double-blind parallel controlled	Serious	Low	Low	Low	Serious	Low	Low	Moderate

	phase IV clinical								

Table 6. Risk of bias assessment of included studies on multiple-dose hepatitis A vaccination

Author, year	Study type	Bias due to confounding	Bias in selection of participants	Bias in classification of intervention	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measurement of outcome	Bias in selection of reported result	Overall risk of bias
Beran et al.,2016.	Longitudinal study	Serious	Low	Low	No information	Serious	Low	Low	Moderate
Yu et al.,2016	RCT followed by cohort study	Serious	Low	Low	Low	Moderate	Low	Low	Moderate
Wang et al., 2020.	Cohort study	Serious	Low	Low	Low	Moderate	Moderate	Low	Moderate
VanHerck et al., 2015.	Cohort study	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Spradling et al., 2016. & Sharapov et al., 2012.	Longitudinal study	Critical	Moderate	Low	Low	Serious	Low	Low	Serious
Mosites et al., 2018	Longitudinal study	Serious	Low	Low	Low	Critical	Low	Low	Serious
Raczniak et al., 2013	Cohort study	Serious	Moderate	Low	Low	Moderate	Low	Low	Moderate

4.4 SYNTHESIS OF RESULTS

4.4.1 Effectiveness (Primary outcome)

No studies of efficacy were identified. Hence, effectiveness was the main outcome of interest. Effectiveness was assessed by consideration of HAV clinical disease incidence, as well as immunogenicity by seroprotection (defined by individual study) and geometric mean concentration in included observational studies.

Single and two dose[2] studies results were pooled and stratified by 3 - 7 years or > 7 years of follow up, as well as by type of vaccine live attenuated vaccines or inactivated vaccines. No analysis was undertaken by the vaccine manufacturer.

We did not assess the impact of vaccination on HAV circulation in water and soil.

The analysis found that hepatitis A vaccines are effective in preventing HAV clinical disease and confer seroprotection, regardless of type of vaccine (live attenuated or inactivated); further that hepatitis A vaccines confer long –term protection against Hep A related disease, including seroprotection.

The results of the analysis are presented below in the Summary of Findings tables.

Combined HAV/HBV vaccine preparation

One study (Beran, Van Der Meeren, Leyssen, & D'Silva, 2016b) examined long-term effectiveness of the combined HAV HBV vaccine (Twinrix). At 15 years all participants had detectable anti-HAV antibodies, regardless of the regimen (n= 74 for 2 doses; n= 88 for 3 doses), which had been administered at 12-15 years of age. There was no single dose arm.

Special populations

One study (Kalyoncu & Urganci, 2012) examined long-term effectiveness of primary HAV vaccine (inactivated (Havrix), 2 doses). 22 children with chronic HCV infection age 7 – 18 years were vaccinated and followed for 8 years. There was one primary non-responder (1/22 – 4.5%) however at 8 years all individuals, apart from the primary non-responder, had evidence of anti-HAV antibodies.

[2] One 3 dose study was included, as the authors had shown the 3 doses given was in fact equivalent to a standard two dose schedule

4.4.2 Summary Of Findings Tables

Summary of findings:

Single dose HAV vaccine (live attenuated) compared to 2 dose HAV vaccine (inactivated) ⩽ 7 years follow up

Patient or population: children 0 - 17 years
Setting: ⩽ 7 years follow up
Intervention: Single dose HAV vaccine (live attenuated)
Comparison: 2 dose HAV vaccine (inactivated)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 2 dose HAV vaccine (inactivated)	**Risk with Single dose HAV vaccine (live attenuated)**				
hepatitis A disease incidence follow up: range 3 years to 7 years	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 1** (1 to 1)	164 (2 observational studies)	⨁◯◯◯ VERY LOW [1,2,a,b]	
hepatitis A seroprotection (at study cut-off) follow up: range 3 years to 7 years	995 per 1,000	**995 per 1,000** (985 to 1,000)	**RR 1.00** (0.99 to 1.01)	1972 (6 observational studies)	⨁◯◯◯ VERY LOW [1,2,3,4,5,6,a,b,c]	
hepatitis A GMC (anti-HAV ab titre) (GMC) follow up: range 3 years to 7 years	The mean hepatitis A GMC (anti-HAV ab titre) was **288.9** IU/mL	MD **147.6 IU/mL lower** (156.7 lower to 138.5 lower)	-	1342 (5 observational studies)	⨁◯◯◯ VERY LOW [1,2,3,4,6,a,c,d,e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4.4.2.1 Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environments.
b. There are no 2 dose live attenuated studies in children published.
c. The 2 dose group is always an inactive vaccine.
d. There is heterogeneity in effect size, including no direction of effect in one study.
e. Wide confidence intervals are reported.

4.4.2.2 References

1. Mitra, M., Shah, N., Faridi, M., Ghosh, A., Sankaranarayanan, V. S., Aggarwal, A., Chatterjee, S., Bhattacharyya, N., Kadhe, G., Vishnoi, G., Mane, A.. 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.

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6. 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.

Summary of findings:

Single dose HAV vaccine (inactivated) compared to 2 dose HAV vaccine (inactivated) ⩽ 7 years follow up

Patient or population: children 0 - 17 years
Setting: ⩽ 7 years follow up
Intervention: Single dose HAV vaccine (inactivated)
Comparison: 2 dose HAV vaccine (inactivated)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 2 dose HAV vaccine (inactivated)	**Risk with Single dose HAV vaccine (inactivated)**				
hepatitis A disease incidence (Incidence) assessed with: Cases of HAV clinical disease follow up: range 3 years to 7 years	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	257 (1 observational study)	⨁◯◯◯ VERY LOW [1,a,b]	
hepatitis A seroprotection (Seroprotection) assessed with: Anti HAV Ab titre > study cut-off follow up: range 3 years to 7 years	995 per 1,000	**995 per 1,000** (975 to 1,000)	**RR 1.00** (0.98 to 1.02)	1234 (5 observational studies)	⨁◯◯◯ VERY LOW [1,2,3,4,5,a,c]	
Geometric mean concentration (GMC) assessed with: Anti HAV Ab titre IU/mL follow up: range 3 years to 7 years	The mean geometric mean concentration was **288.9** IU/mL	MD **188 IU/mL lower** (196.8 lower to 179.2 lower)	-	928 (4 observational studies)	⨁⨁◯◯ LOW [1,2,3,4,a,c,d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Summary of findings:

Single dose HAV vaccine (inactivated) compared to 2 dose HAV vaccine (inactivated) ⩽ 7 years follow up

Patient or population: children 0 - 17 years
Setting: ⩽ 7 years follow up
Intervention: Single dose HAV vaccine (inactivated)
Comparison: 2 dose HAV vaccine (inactivated)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 2 dose HAV vaccine (inactivated)	**Risk with Single dose HAV vaccine (inactivated)**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4.4.2.3 Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environments.
b. Only one study was identified.
c. Limited publications. Manufacturers recommend two doses.
d. Heterogeneity is difficult to assess. Only one study had 2 arms

4.4.2.4 References

1. 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.

2. Zhang, Z., Zhu, X., Hu, Y., Liang, M., Sun, J., Song, Y., Yang, Q., Ji, H., Zeng, G., Song, L., Chen, J.. Five-year antibody persistence in children after one dose of inactivated or live attenuated hepatitis A vaccine. Hum Vaccin Immunother; 2017.

3. 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.

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5. Luo, J., Wang, X., Ma, F., Kang, G., Ding, Z., Ye, C., Pan, Y., Zhao, Y., Hong, S., Chen, J., Xi, J., Wen, S., Lin, Y., Li, X., Qiu, L., Yang, X., Li, G., Yang, J., Sun, Q.. Long-term immunogenicity and immune persistence of live attenuated and inactivated hepatitis a vaccines: a report on additional observations from a phase IV study. Clin Microbiol Infect; Nov 2019.

Summary of findings:

Single dose HAV vaccine (live attenuated) compared to 2 dose HAV vaccine (inactivated) >7 years follow up

Patient or population: children 0 - 17 years
Setting: >7 years follow up
Intervention: Single dose HAV vaccine (live attenuated)
Comparison: 2 dose HAV vaccine (inactivated)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 2 dose HAV vaccine (inactivated)	**Risk with Single dose HAV vaccine (live attenuated)**				
hepatitis A disease incidence (Incidence) assessed with: Cases of HAV clinical disease follow up: range >7 years to 25 years	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 1** (1 to 1)	149 (2 observational studies)	⨁◯◯◯ VERY LOW [1,2,a,b,c]	
hepatitis A seroprotection (Seroprotection) assessed with: Anti HAV Ab titre > study cut-off follow up: range 7 years to 25 years	980 per 1,000	**980 per 1,000** (950 to 1,000)	**RR 1.00** (0.97 to 1.03)	1026 (7 observational studies)	⨁◯◯◯ VERY LOW [1,2,3,4,5,6,7,a,b,c,d,e]	
Geometric mean concentration (GMC) assessed with: Anti HAV Ab titre IU/mL follow up: range 7 years to 25 years	The mean geometric mean concentration was **145.0** IU/mL	MD **65.4 IU/mL lower** (68 lower to 62.9 lower)	-	774 (7 observational studies)	⨁◯◯◯ VERY LOW [1,2,3,4,5,6,7,a,b,c,e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Summary of findings:

Single dose HAV vaccine (live attenuated) compared to 2 dose HAV vaccine (inactivated) >7 years follow up

Patient or population: children 0 - 17 years
Setting: >7 years follow up
Intervention: Single dose HAV vaccine (live attenuated)
Comparison: 2 dose HAV vaccine (inactivated)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 2 dose HAV vaccine (inactivated)	**Risk with Single dose HAV vaccine (live attenuated)**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4.4.2.5 Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environments.
b. There are no 2 dose live attenuated studies in children published.
c. The vaccine manufacturers recommend two doses.
d. There is variability in the threshold of seroprotection.
e. The heterogeneity in effect size is difficult to assess given limited single dose live attenuated studies.

4.4.2.6 References

1. Bhave, S.,, Sapru, A., Bavdekar, A., Jain, R., Debnath, K., Kapatkar, V.. Long-term Immunogenicity of Single Dose of Live Attenuated hepatitis A Vaccine in Indian Children - Results of 15-year Follow-up.. Indian Pediatr; 2021.

2. 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.

3. Wang, Y., Qi, Y., Xu, W., Hu, Y., Wang, L., Yu, Y., Jiang, Z., Xia, J., Zeng, G., Wang, Y.. Immunogenicity persistence in children of hepatitis A vaccines Healive® and Havrix®: 11 years follow-up and long-term prediction. Hum Vaccin Immunother; 2020.

4. Spradling, P. R., Bulkow, L. R., Negus, S. E., Homan, C., Bruce, M. G., McMahon, B. J.. Persistence of seropositivity among persons vaccinated for hepatitis A during infancy by maternal antibody status: 15-year follow-up. Hepatology (Baltimore, Md.); 2016.

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Summary of findings:

Single dose HAV vaccine (inactivated) compared to 2 dose HAV vaccine (inactivated) for children >7 years follow up

Patient or population: children 0 - 17 years
Setting: >7 years follow up
Intervention: single dose HAV vaccine (inactivated)
Comparison: 2 dose HAV vaccine (inactivated)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 2 dose HAV vaccine (inactivated)	**Risk with single dose HAV vaccine (inactivated)**				
hepatitis A disease incidence (Incidence) assessed with: Cases of HAV clinical disease follow up: range 7 years to 25 years	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 1** (1 to 1)	403 (2 observational studies)	⨁◯◯◯ VERY LOW [1,2,a,b]	
hepatitis A seroprotection (Seroprotection) assessed with: Anti HAV Ab titre > study cut-off follow up: range 7 years to 25 years	962 per 1,000	**962 per 1,000** (933 to 991)	**RR 1.00** (0.97 to 1.03)	1319 (7 observational studies)	⨁◯◯◯ VERY LOW [1,2,3,4,5,6,7,a,c,d]	
Geometric mean concentration (GMC) assessed with: IU/mL follow up: range 7 years to 25 years	The mean geometric mean concentration was **145.0** IU/mL	MD **66.5 IU/mL lower** (68.7 lower to 64.3 lower)	-	1259 (7 observational studies)	⨁◯◯◯ VERY LOW [1,2,3,5,6,7,8,a,c,e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4.4.2.7 Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environments.
b. The outcome of incidence is not clearly defined and there is infrequent follow-up during the study.
c. Heterogeneity is difficult to assess as only one study had two arms.
d. There is variability in the threshold of seroprotection.
e. There are limited publications, and the vaccine manufacturers recommend two doses.

4.4.2.8 References

1. Mayorga, O., Bühler, S., Jaeger, V. K., 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.

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3. Wang, Y., Qi, Y., Xu, W., Hu, Y., Wang, L., Yu, Y., Jiang, Z., Xia, J., Zeng, G., Wang, Y.. Immunogenicity persistence in children of hepatitis A vaccines Healive® and Havrix®: 11 years follow-up and long-term prediction. Hum Vaccin Immunother; 2020.

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5. Lopez, E. L., Contrini, M. M., Mistchenko, A., Kieffer, A., Baggaley, R. F., Di Tanna, G. L., 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; Apr 2015.

6. 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.

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4.4.3 Grade Evidence Profiles

Question: Single dose HAV vaccine (live attenuated) compared to 2 dose HAV vaccine (inactivated) for children 0 - 17 years ⩽ 7 years follow up
Setting: ⩽ 7 years follow up
].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose HAV vaccine (live attenuated)	2 dose HAV vaccine (inactivated)	Relative (95% CI)	Absolute (95% CI)		
hepatitis A disease incidence (follow up: range 3 years to 7 years)												
2	observational studies	very serious [a,b]	serious [b]	not serious	not serious	publication bias strongly suspected [b]	0/111 (0.0%)	0/53 (0.0%)	**RR 1** (1 to 1)	**0 fewer per 1,000** (from 30 fewer to 30 more)	⨁◯◯◯ VERY LOW [1,2]	
hepatitis A seroprotection (at study cut-off) (follow up: range 3 years to 7 years)												
6	observational studies	very serious [a,c]	not serious	not serious	not serious	publication bias strongly suspected [b]	1158/1173 (98.7%)	795/799 (99.5%)	**RR 1.00** (0.99 to 1.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⨁◯◯◯ VERY LOW [1,2,3,4,5,6]	
hepatitis A GMC (anti-HAV ab titre) (follow up: range 3 years to 7 years)												
5	observational studies	very serious [a,c]	serious [d]	not serious	serious [e]	publication bias strongly suspected strong association dose response gradient [c]	703	639	-	MD **147.6 IU/mL lower** (156.7 lower to 138.5 lower)	⨁◯◯◯ VERY LOW [1,2,3,4,6]	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

4.4.3.1 Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environments.
b. There are no 2 dose live attenuated studies in children published.
c. The 2 dose group is always an inactive vaccine.
d. There is heterogeneity in effect size, including no direction of effect in one study.
e. Wide confidence intervals are reported.

4.4.3.2 References

1. Mitra, M., Shah, N., Faridi, M., Ghosh, A., Sankaranarayanan, V. S., Aggarwal, A., Chatterjee, S., Bhattacharyya, N., Kadhe, G., Vishnoi, G., Mane, A.. 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.

2. 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.

3. Zhang, Z., Zhu, X., Hu, Y., Liang, M., Sun, J., Song, Y., Yang, Q., Ji, H., Zeng, G., Song, L., Chen, J.. Five-year antibody persistence in children after one dose of inactivated or live attenuated hepatitis A vaccine. Hum Vaccin Immunother; 2017.

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Question: Single dose HAV vaccine (live) compared to 2 dose HAV vaccine (inactivated) for children 0 - 17 years >7 years follow up
Setting: >7 years follow up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose HAV vaccine (live attenuated)	2 dose HAV vaccine (inactivated)	Relative (95% CI)	Absolute (95% CI)		
Hepatitis A disease incidence (follow-up: range >7 years to 25 years; assessed with: Cases of HAV clinical disease)												
2	observational studies	very serious[a,b]	serious[b]	not serious	not serious	publication bias strongly suspected[b,c]	0/98 (0.0%)	0/51 (0.0%)	**RR 1** (1 to 1)	**0 fewer per 1,000** (from 30 fewer to 30 more)	⨁◯◯◯ Very low[1,2]	
Hepatitis A seroprotection (follow-up: range 7 years to 25 years; assessed with: Anti HAV Ab titre > study cut-off)												
7	observational studies	very serious[a,b]	serious[b]	not serious	serious[d]	publication bias strongly suspected[c]	123/145 (84.8%)	863/881 (98.0%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1,000** (from 29 fewer to 29 more)	⨁◯◯◯ Very low[1,2,3,4,5,6,7,e]	
Geometric mean concentration (follow-up: range 7 years to 25 years; assessed with: Anti HAV Ab titre IU/mL)												
7	observational studies	very serious[a,b]	serious[e]	not serious	not serious	publication bias strongly suspected[b,c]	98	676	-	MD **65.4 IU/mL lower** (68 lower to 62.9 lower)	⨁◯◯◯ Very low[1,2,3,4,5,6,7,e]	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

4.4.3.3 Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environment.
b. There are no 2 dose live attenuated studies in children published.
c. The vaccine manufacturers recommend two doses.
d. There is variability in the threshold of seroprotection.
e. The heterogeneity in effect size difficult to assess given limited single dose live attenuated studies.

4.4.3.4 References

1.Bhave, S.,, Sapru, A., Bavdekar, A., Jain, R., Debnath, K., Kapatkar, V.. Long term Immunogenicity of Single Dose of Live Attenuated Hepatitis A Vaccine in Indian Children - Results of 15-year Follow-up.. Indian Pediatr; 2021.
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4.Spradling, P. R., Bulkow, L. R., Negus, S. E., Homan, C., Bruce, M. G., McMahon, B. J.. Persistence of seropositivity among persons vaccinated for hepatitis A during infancy by maternal antibody status: 15-year follow-up. Hepatology (Baltimore, Md.); 2016.
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Question: Single dose HAV vaccine (inactivated) compared to 2 dose HAV vaccine (inactivated) for children 0 - 17 years ⩽ 7 years follow up
Setting: ⩽ 7 years follow up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose HAV vaccine (inactivated)	2 dose HAV vaccine (inactivated)	Relative (95% CI)	Absolute (95% CI)		
hepatitis A disease incidence (follow up: range 3 years to 7 years; assessed with: Cases of HAV clinical disease)												
1	observational studies	very serious [a,b]	not serious	not serious	not serious	publication bias strongly suspected [b]	0/204 (0.0%)	0/53 (0.0%)	not estimable	**0 fewer per 1,000** (from 30 fewer to 30 more)	⨁◯◯◯ VERY LOW [1]	
hepatitis A seroprotection (follow up: range 3 years to 7 years; assessed with: Anti HAV Ab titre > study cut-off)												
5	observational studies	very serious [a]	not serious	not serious	not serious	publication bias strongly suspected [c]	390/403 (96.8%)	827/831 (99.5%)	**RR 1.00** (0.98 to 1.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)	⨁◯◯◯ VERY LOW [1,2,3,4,5]	
Geometric mean concentration (follow up: range 3 years to 7 years; assessed with: Anti HAV Ab titre IU/mL)												
4	observational studies	very serious [a]	serious [d]	not serious	not serious	publication bias strongly suspected strong association dose response gradient [c]	289	639	-	MD **188 IU/mL lower** (196.8 lower to 179.2 lower)	⨁⨁◯◯ LOW [1,2,3,4]	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

4.4.3.5 Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environments.
b. Only one study was identified.
c. Limited publications. Manufacturers recommend two doses.
d. Heterogeneity is difficult to assess. Only one study had 2 arms

4.4.3.6 References

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Question: Single dose HAV vaccine (inactivated) compared to 2 dose HAV vaccine (inactivated) for children 0 - 17 years >7 years follow up
Setting: >7 years follow up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	single dose HAV vaccine (inactivated)	2 dose HAV vaccine (inactivated)	Relative (95% CI)	Absolute (95% CI)		
hepatitis A disease incidence (follow up: range 7 years to 25 years; assessed with: Cases of HAV clinical disease)												
2	observational studies	very serious [a]	not serious	not serious	serious [b]	none	0/352 (0.0%)	0/51 (0.0%)	**RR 1** (1 to 1)	**0 fewer per 1,000** (from 30 fewer to 30 more)	⨁◯◯◯ VERY LOW [1,2]	
hepatitis A seroprotection (follow up: range 7 years to 25 years; assessed with: Anti HAV Ab titre > study cut-off)												
7	observational studies	very serious [a]	serious [c]	not serious	serious [d]	none	342/343 (99.7%)	939/976 (96.2%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1,000** (from 29 fewer to 29 more)	⨁◯◯◯ VERY LOW [1,2,3,4,5,6,7,c]	
Geometric mean concentration (follow up: range 7 years to 25 years; assessed with: IU/mL)												
7	observational studies	very serious [a]	serious [c]	not serious	not serious	publication bias strongly suspected [e]	348	911	-	MD **66.5 IU/mL lower** (68.7 lower to 64.3 lower)	⨁◯◯◯ VERY LOW [1,2,3,5,6,7,8]	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

4.4.3.7 Explanations

a. There are only non-randomized observational studies. Moderate loss to follow up. No control for natural booster in endemic environments.
b. The outcome of incidence is not clearly defined and there is infrequent follow-up during the study.
c. Heterogeneity is difficult to assess as only one study had two arms.
d. There is variability in the threshold of seroprotection.
e. There are limited publications, and the vaccine manufacturers recommend two doses.

4.4.3.8 References

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4.4.4 Impact (secondary outcome)

4.4.4.1 Impact of vaccination on the incidence of hepatitis A

There were 13 studies reporting the change in incidence of hepatitis A in countries pre and post universal vaccination programs; 8 employing single-dose HAV vaccinations, 5 employing two- dose HAV vaccinations. For single-dose studies, four were from China, and one each from Argentina, Brazil, Italy and Russia. For two-dose studies, there was one study each from Australia, China, Israel, Panama and the United States. The universal vaccination programs included were initiated in 1999 to 2014, and followup was from 1 year to 19 years.

The mean incidence decreased in all studies post vaccination. In single dose studies, the incidence in all age groups decreased by 59% to 99%. The largest decrease was in Tyva province Russia (Mikhailov et al., 2020), and the least in Zhejiang providence China (Z. Wang, Chen, Xie, & Lv, 2016). In two dose studies, the incidence in all age groups decreased by between 76% to 98%. The largest decrease was in a nation-wide cohort in Israel (Levine, Kopel, Anis, Givon-Lavi, & Dagan, 2015), and the least was also reported in Zhejiang providence China (Z. Wang et al., 2016) as part of the same study that compared the one and two dose schedules. In studies that reported incidence by age group, the smallest decrease in incidence was mostly in older age groups, whilst the largest decreases were pronounced in children <10 years old.

Incidence studies utilized notifiable disease data, therefore no studies report anti-HAV IgG antibody levels nor the proportion of individuals with a positive serological test showing anti-HAV IgG antibodies titers were above an accepted seroprotection thresholds at the end of the last follow-up period. Denominator data was not available, as only positive cases were reported.

4.4.4.2 Impact of vaccination on the seroprevalence of hepatitis A

There were 6 studies reporting the changes in seroprevalence of hepatitis A in countries; 3 employing single-dose HAV vaccinations, 3 employing two-dose HAV vaccinations.

In Italy, no pre-universal vaccination seroprevalence was reported, however post single-dose universal vaccination in adult blood donors the seroprevalence was lowest for ages 27-35 (32.9%) and highest for the oldest age reported, 45-65 years (97.2%) (Gallone et al., 2017). In Henan, China, where the single-dose universal vaccination program was implemented (though a 2 dose schedule is available out-of-pocket) no pre-vaccination seroprevalence was reported, however, post-universal vaccination , seroprevalence was lowest in the youngest age group 0-15 years (38.6%), and highest for an older age group, 30-70 years (92.7%) (Guo et al., 2020). This study also reported the number of HAV notified cases pre and post universal vaccination , with a reduction of 30.60% for all ages, and 398.22% for children aged 0-9. Additionally, in Shandong China where a single dose universal vaccination program was implemented (though a 2 dose schedule is available out-of-pocket) province wide seroprevalence increased from 80.6% to 83.5% for all ages, but less for ages 1.5-7 years, from 30.8% to 77.5% (Yan et al, 2019).

In two dose studies, in a hospital cohort in Guri-si South Korean, there was mixed changes in seroprevalence from pre-universal vaccination to post- universal vaccination (Chung et al.). In all ages, the decrease was 2.1%, from 54.7% to 53.6%; older populations tended to have decreases in seroprevalence with the largest decrease of 72% in ages 25-29 years; and those aged 5-9 years had the highest seroprevalence increase, from 16% to 69%, an increase of 331 %. In the United States, national seroprevalence increased 54.1% for ages 60-19 years, from 24.4% to 37.6% in (Kruszon-Moran, Klevens, & McQuillan).

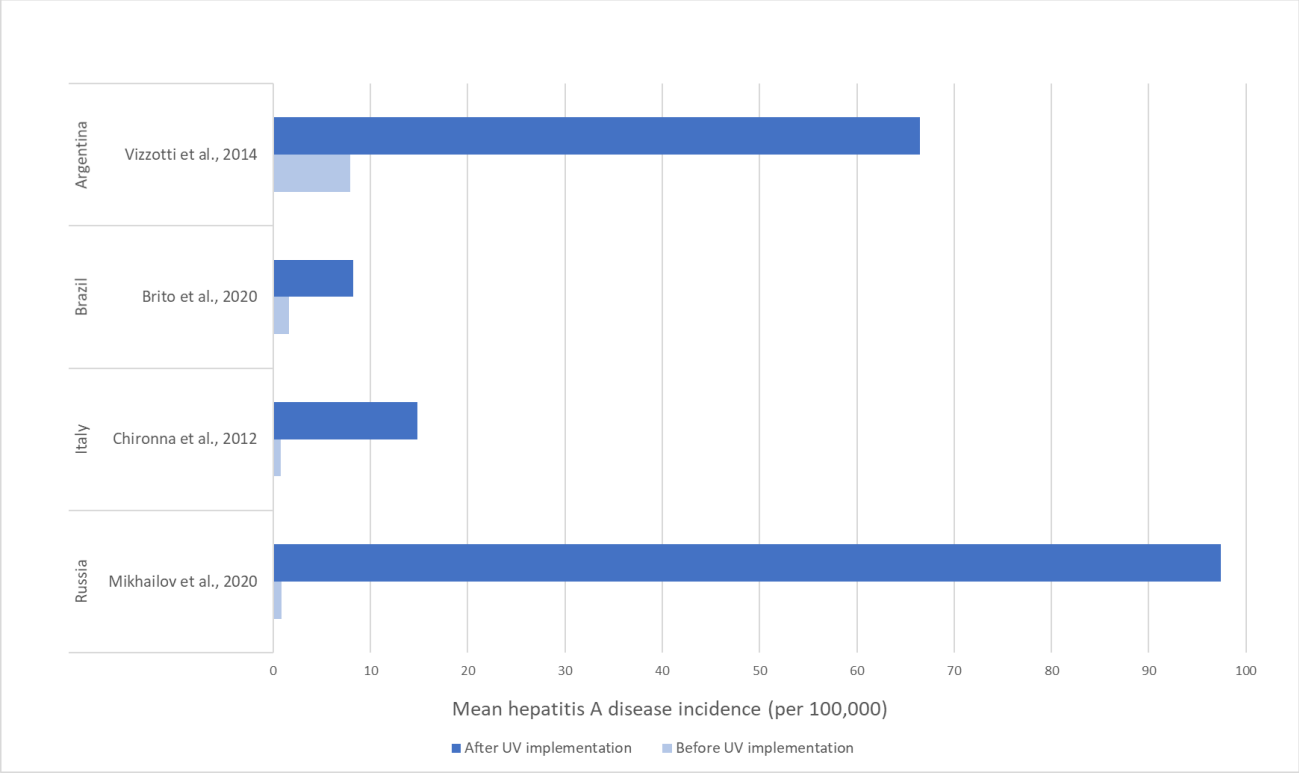

Figure 2 - Mean changes in all-ages hepatitis A incidence before and after the implementation of a post universal vaccination program with single dose Inactivated schedule.

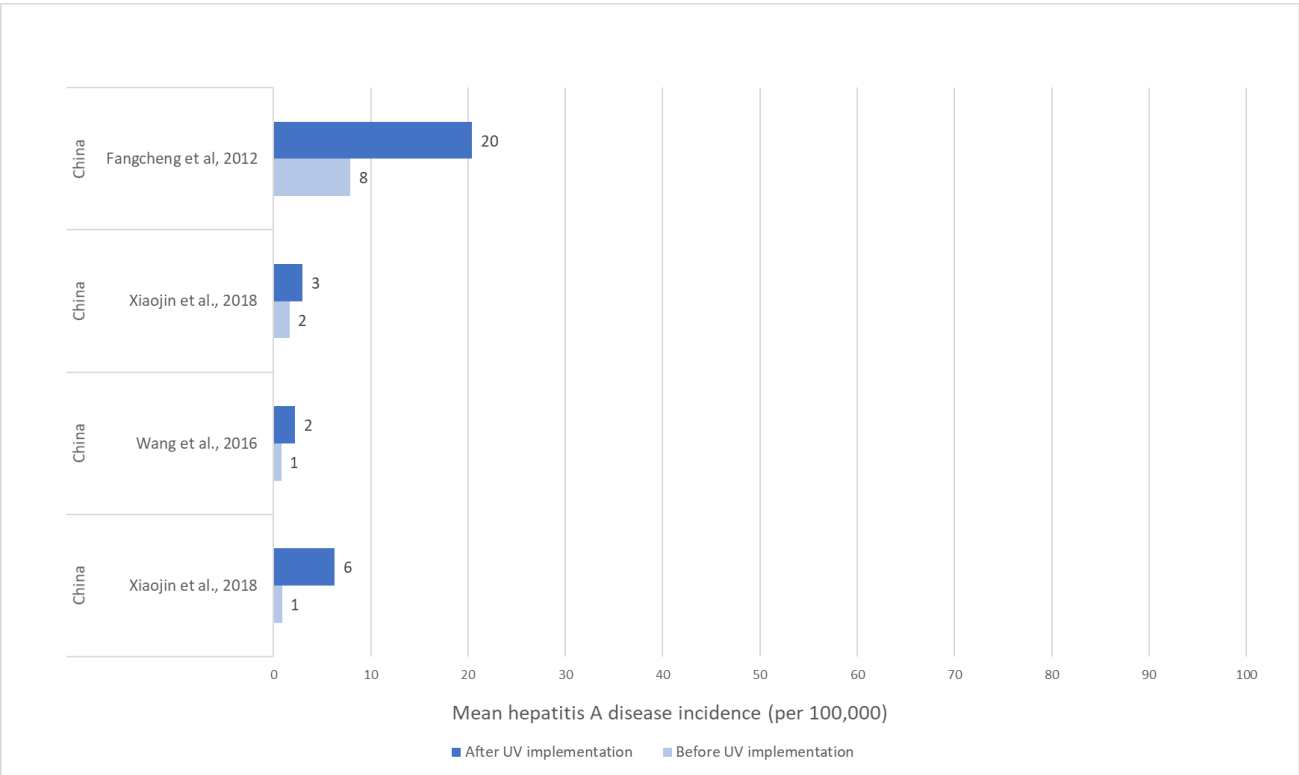

Figure 3 - Mean changes in all-ages hepatitis incidence before and after the implementation of a

universal vaccination program with a single dose live attenuated schedule.

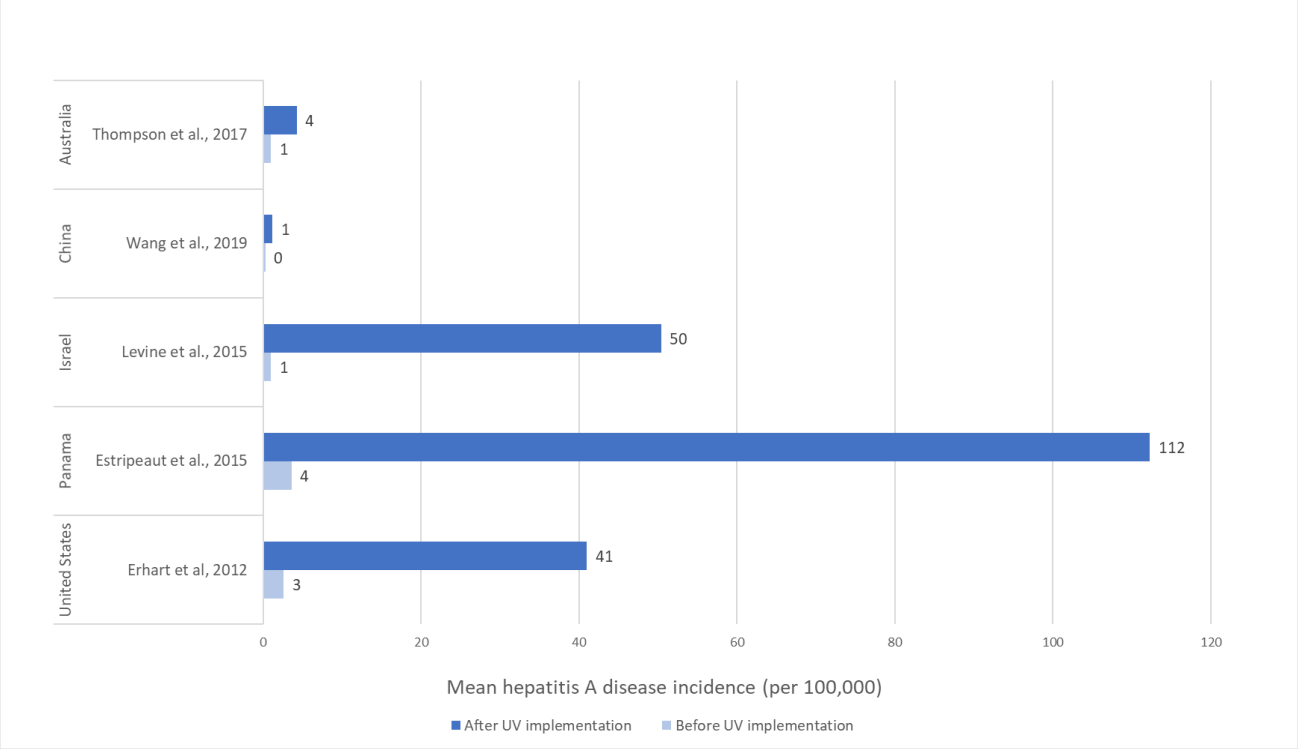

Figure 4 - Mean changes in all-ages hepatitis A incidence before and after the implementation of a

universal vaccination program with a two-dose schedule

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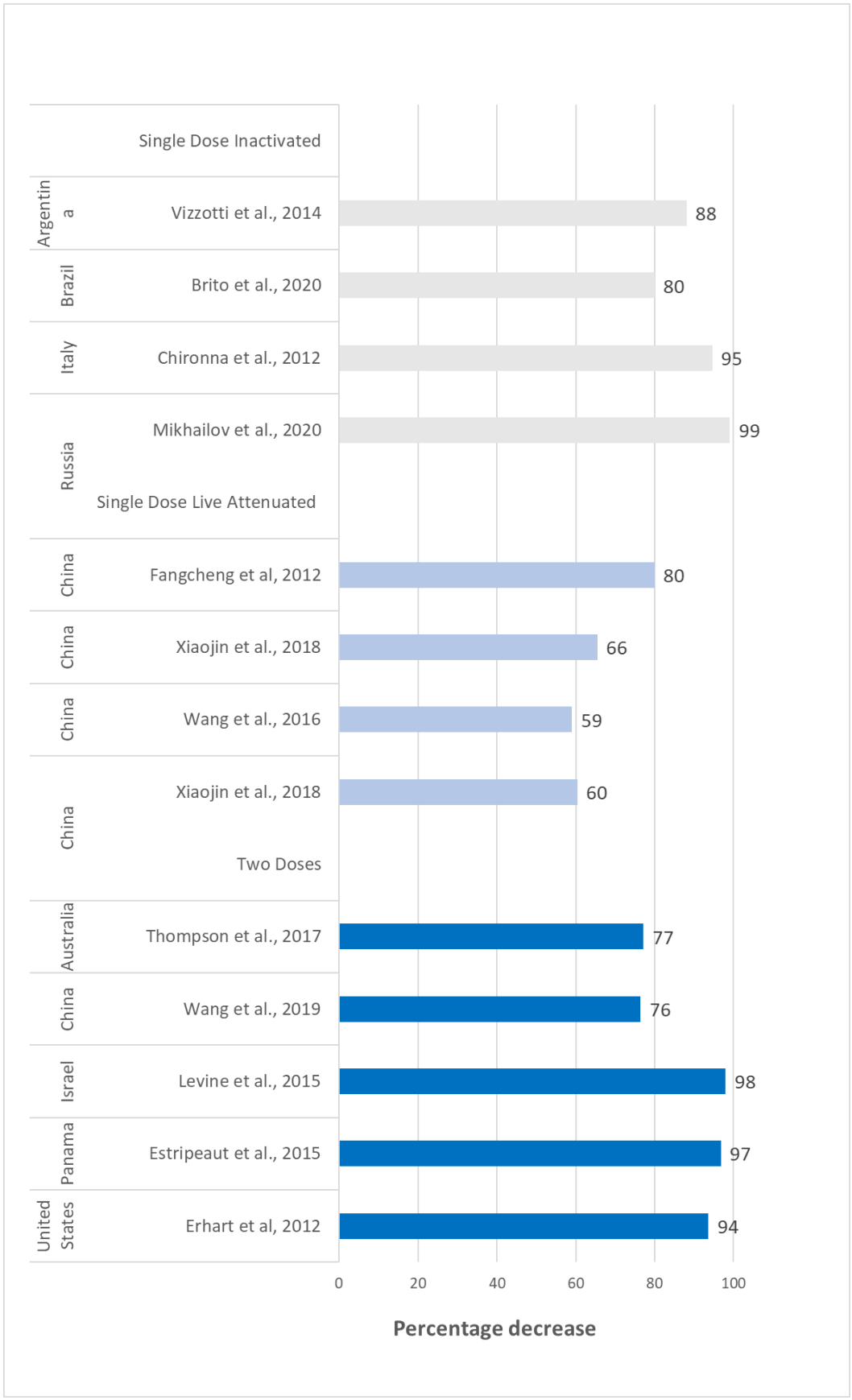

Figure 5 - Percentage decrease of hepatitis A incidence after the implementation of universal vaccination program, by type of vaccine administered

Table 7. Summary of vaccine impact on disease incidence

Study	Country	Year of vaccination start	Vaccine	Study period	Follow up duration	Age	Mean hepatitis A disease incidence (per 100,000)		% Decrease
							Before universal vaccination	After universal vaccination	
One dose									
Vizzotti et al. 2014	Argentina	2005	Inactivated (strains HM 175 720 EL.U, HAVRIX [GSK	2000–2011	12 years		2000–2002	2006–2011	
						All ages	66.5	7.9	88.12
						0–4	162.2	15.5	90.44
						5–9	245.2	26.6	89.15
						10–14	111.5	14.9	86.64
						15–44	15.5	4.2	72.90

			Biologicals, Rixensart, Belgium]; CR 326 25 U, VAQTA Merck Sharp & Dohme [Whitehouse Station, NJ]; GMB 80 U, AVAXIM [Sanofi-Pasteur, Lyon, France]; and RG-SB 12 UI, Virohep-A Junior [NOVARTIS, Buenos Aires, Argentina])			=>45	5.3	2.2	58.49
Brito et al., 2020	Brazil	2014	Inactivated (brand not specified)	2014 – 2018	3.5 years		2014	2015-2018	
						All ages	8.22	1.64 (Range: 0.73-3.82)	80.05
Fangcheng, 2012*	China	2008	Live attenuated (brand not specified)	1990-2009	20 years		1990-2007	2008–2009	
						All ages	20.41 (Range: 5.59-51.95)	4.07 (Range: 3.57-4.57)	80.06
Wang et al. 2016	China	2008	Live attenuated (L-HepA)	2005 – 2014	10 years		2005-2008	2014	
						All ages	2.2	0.9	59.09
						<=19	1.68	0.22	86.90
	China	2008					2004-2007	2008-2016	

Xiaojin et al., 2018#			Live attenuated (L-HepA)	2004 – 2016	13 years	All ages	6.29 (Range: 5.51-7.53)	2.49 (1.65-4.46)	60.41
Chironna ., 2012	Italy	2014	Until 2003, a combined hepatitis A plus	1998 – 2009	12 years		1998	2009	
						All ages	14.8	0.8	94.59
Mikhailov et al., 2020	Russia	2012	Inactivated (HAVRIX® 720 EU)	2001 – 2019	19 years		2001–2012	2013–2019	
						All ages	97.4	0.87 (Range: 0-3.2)	99.11
						<18 years	379.32 (Range: 71-869.5)	1.99 (Range: 0-7.5)	99.48
Two doses									
Thompson et.al, 2017	Australia	2005	Inactivated (brand not specified)	2000 – 2014	15 years		2000	2014	
						All ages	4.25	0.97	77.18
Wang et al. 2019**	China	2008	Inactivated (I-HepA)	1990-2017	28 years		2004–2011	2012–2017	
						All ages	1.19	0.28	76.40
						0–10	1.03	0.035	96.60
						10–20	0.68	0.16	76.47
						>20	1.87	0.65	65.24
Xiaojin et al., 2018*#	China	2008	Inactivated (I-HepA)	2004 – 2016	13 years		2004-2007	2008-2016	
						All ages	2.99 (Range: 2.57-3.89)	1.03 (Range: 0.58-2.11)	65.55
Levine et al. 2015	Israel	1999	Inactivated (brand not specified)	1993 – 2012	20 years		1993–1998	1999–2012	
						All ages	50.4 (Range: 32.4–68.0)	<1.0 (Range: 0.3–18.1)	98.02
Estripeaut et al., 2015	Panama	2007	Inactivated (Havrix®junior)	2000-2010	11 years		2000	2010	
						All ages	112.29	3.59	96.81
						<1	35.1	0	100.00
						1–4	130	3.2	97.54
						5–9	225.4	2.6	98.85

						10–14	214.8	3.6	98.32
						15–19	146.9	6.2	95.78
						20–24	84	6	92.86
						25–49	43.9	3	93.17
						≥50	18.2	4.1	77.47
Erhart et al., 2021	United States	1996	Inactivated (brand not specified)	1988-2007	20 years		1994–1995	2006–2007	
						All ages	41 (95% CI: 41; 42)	2.6 (95% CI: 2.5; 2.7)	93.66
						<1	40 (95% CI: 35; 46)	1.5 (95% CI: 0.6; 2.4)	96.25
						1–4	81 (95% CI: 77; 85)	0.6 (95% CI: 0.4; 0.9)	99.26
						5–9	146 (95% CI: 141; 150)	1.7 (95% CI: 1.2; 2.1)	98.84
						10–14	76 (95% CI: 72; 79)	4.7 (95% CI: 4.0; 5.4)	93.82
						15–19	54 (95% CI: 51; 57)	4.4 (95% CI: 3.7; 5.1)	91.85
						20–39	38 (95% CI: 37; 39)	3.5 (95% CI: 3.2; 3.8)	90.79
						40–64	12 (95% CI: 11; 13)	2.1 (95% CI: 1.9; 2.3)	82.50
						≥65	4.1 (95% CI: 3.5; 4.7)	1 (95% CI: 0.8; 1.3)	75.61

*China's Expanded Program of Immunization provides universal coverage for a single-dose schedule; however, individuals are able to pay for a two-dose schedule out of pocket. Therefore, it is assumed most of the population receive a single dose.
** 2008-2011 one dose, 2011 onwards two doses
# Xiaojin et al., 2018 is included in both groups as the study reports both single and two-dose impact

Table 8. Summary of vaccine impact on disease (non-incidence)

Study	Country	Year of vaccination start	Vaccine	Study period	Follow up duration	Anti-HAV IgG antibody levels at last year of follow-up	% Seroprotected at last year of follow-up	Outcome	Age	Before universal vaccination	After universal vaccination	% change
One dose												
Yonghao et al. 2020*	China	2008	Live attenuated (L-HepA)	2005-2018 (2017 - 2018 sub-cohort)	14 years (No follow up sub-cohort)	Not reported	64.5%	Count		2007	2018	
									All ages	7489	237	-30.60
									0–9	3593	9	-398.22
								Seroprevalence (sub-cohort)	All ages	Not reported	64.5	-
									0-1.5	Not reported	38.6	-
									1.5-4	Not reported	71.6	-
									4-6	Not reported	75	-
									4-9	Not reported	61	-
									9-15	Not reported	61.4	-
									15	Not reported	60.8	-

									30-70	Not reported	92.7	-
Yan et al., 2019*	China	2008	Live attenuated (L-HepA)	2006-2014	9 years	N/A	83.54 %	Seroprevalence		2006	2014	
									All ages	80.56% (95% CI 77.34–83.78%)	83.54% (95% CI 81.34–85.74%)	3.70
									1.5–7	30.76% (95% CI 26.24–35.28%)	77.46% (95% CI 74.04–80.87%)	151.82
									8–14	35.32% (95% CI 29.31–41.33%)	66.69% (95% CI 55.59–77.80%)	88.82
									20–29	85.72% (95% CI 80.29–91.14%)	69.24% (95% CI 62.02–76.45%)	-19.23
Gallone et al., 2017	Italy	1997	Not specified	May 2011 to June 2012	1 year	Not reported	64.1% (overall) 96.1% (two dose) 11.3% (one dose)	Seroprevalence (sub-cohort)		N/A	2011/2012	
									All ages	Not reported	64.1	-
									18-26	Not reported	64.5	-
									27-35	Not reported	32.9	-
									36-45	Not reported	58.9	-
									46-55	Not reported	87.3	-
	Italy	2014	Until 2003, a	2014–2018	5 years		42.2%	Susceptibility to HAV		2001–2012	2013–2019	

Chironna et al., 2012			combined hepatitis A plus	(subcohort 2008)	(sub-cohort no follow up)	Not reported		infection - negative for anti-HAV IgG antibodies (sub-cohort)	All age groups	Not reported	57.8% (CI: 54.55-61.12)	-
									0-5	Not reported	69.9% (no CI reported)	-
									6-10	Not reported	70.9% (CI: 62.10-79.65)	-
									16-20	Not reported	22.1% (CI: 14.47-29.78)	-
									21-25	Not reported	70.0% (CI: 61.02-78.98)	-
									26-30	Not reported	69.4% (no CI reported)	-
									31-35	Not reported	Not reported	-
									36-40	Not reported	46.5% (CI: 37.90-55.12)	-
Mikhailov et al., 2020	Russia	2012	Inactivated (HAVRIX®	2001–2019	19 years		77.3 %	Seropositive (sub-cohort)		2001-2003	2011-2013	
									All ages	Not reported	77.3 (74.7–79.8)	-

		720 EU)						<1	Not reported	55.7 (45.3–65.6) -
								1–4	Not reported	28.0 (20/1–37.5) * -
								5–9	Not reported	42.0 (32.8–51.8) * -
								10–14	Not reported	66.0 (56.3–74.6) * -
				5 years: GMC mIU/mL 57.73 (16.51 – 98.95)				15–19	Not reported	86.0 (77.7–91.6) -
								20–29	Not reported	98.0 (92.6–99.9) -
								30–39	Not reported	96.0 (89.8–98.8) -
								40–49	Not reported	98.0 (92.6–99.9) -
								50–59	Not reported	97.0 (91.2–99.4) -
								>60	Not reported	99.2 (95.1–100.0) -
Two dose										
	1999-2006	Inactivated	2003–2010	8 years	N/A	37.6%	Seroprevalence		2003–2006	2007–2010

Kruszon-Moran et al., 2013	United States		(brand not specified)					6–19	24.4 (95% CI: 16.6-33.9)	37.6 (95% CI: 32.6-42.7)	54.10
Galor et al, 2020	Israel	1993	Inactivated (brand not specified)	2011-2017	N/A	Not reported	34.50 %	Seroprotection (sub-cohort)		2011-2017	
								18–19(born before UV)	-	68.00%	-
								18–19 (born after UV)	-	34.50%	-
Papaevangelou et al, 2016	Greece	2008	Not reported	1992-2013	22 years	N/A	N/A	HA hospital admission per 1000 admission	1999-2007	2008-2013	
								All age-groups	50.5 (95%CI 29.2–67.1)	20.8 (95%CI 19.2–30.1)	-58.81
Chung et al. 2014	South Korea	1997 (paeds) 2012 (adult)	Not reported	2001-2013	13 years	Not reported	53.58 %	Seroprevalence (sub-cohort)	2001-2003	2011-2013	
								All ages	54.68%	53.58%	-2.00
								<1	68.40%	38.90%	-43.13
								1-4	30.20%	64.90%	114.90
								5-9	16%	69%	331.25
								10-14	17.90%	56.90%	217.88
								15-19	11.10%	22.70%	104.50
								20-24	17.60%	18.40%	4.55
								25-29	58.30%	16.30%	-72.04
								30-34	70.80%	26%	-63.28
								35-39	87.80%	54.80%	-37.59
								40-44	94.50%	81.20%	-14.07

								45-49	94.60%	95.80%	1.27
								50-54	88.90%	98.10%	10.35
Yin et al. 2020	United States	2006	Inactivated (not specified)	2007-2016	10 years	Not reported	21% HAV susceptibility	HAV susceptibility	2007	2016	
								2–11	57.7%	13.7%	44.00 %
								12–19	66.8%	28.2%	38.60 %
								20–29	85.9%	65.2%	20.70 %
*China's Expanded Program of Immunization provides universal coverage for a single-dose schedule; however, individuals are able to pay for a two-dose schedule out of pocket. Therefore, it is assumed most of the population receive a single dose.											

4.4.5 Safety and adverse events (Secondary outcome)

We only identified four publications having vaccine safety as a primary or secondary aim. This was not unexpected given HAV vaccines have been approved by regulatory authorities and available in commercial markets for more than 2 decades. Therefore, consistent evidence on the safety profile of HAV vaccines has been accumulated through both epidemiological surveillance, national vaccine adverse event reporting systems, and research over a long period of time (more than 20 years).

Two studies were longitudinal, one study was a phase IV single-arm trial and one study was an analysis of secondary data derived from nationwide surveys. Studies reported on adverse events following immunization with both one- and two doses. Study age groups ranged from infanthood through adolescence. Sample size in most studies was generally low, and in studies following up participants (Beran et al., 2016; Mitra et al., 2015), loss to follow up at the end of observation period varied between 30 and 78%, with follow-up times between 5 and 15% years.

Incidence of adverse events following immunization was low across all studies. Inflammatory local site reactions was the most frequent. Only one study (Xiaojin et al., 2020) reported occurrence of serious adverse events, although with a very low incidence, primary anaphylaxis.

One included systematic review (Irving, Holden, Yang, & Pope, 2012) systematically examined published literature on vaccine safety and adverse events in the period until 2011.

We will not present the result here, but refer to the original study. Meta-analysis did not identify any adverse events of note, although data from live vaccines was limited. The authors concluded that:

"*There is a lack of trials with low risk of bias to conclude whether or not live attenuated HAV vaccine has a significant risk of any adverse events in comparison to placebo, adequate control, or no intervention. A number of studies investigating adverse events in live attenuated HAV vaccine used non-comparative study designs with non-standardised definitions of what constituted an adverse event. This paucity of high quality data for the live attenuated HAV vaccine is of particular concern given the theoretical possibility of virulent atavism where the attenuated virus reverts back to its 'wild type'.*

For the inactivated HAV vaccine, no significant difference was noted for either local or serious adverse events when compared to placebo, ap- propriate control, or no vaccine. Although only one trial looked at this outcome, the trial itself had low risk of bias and was appropriately powered".

Table 9. Summary of findings for adverse events following administration of hepatitis A vaccine.

Study	Country and population	Intervention	Outcome	Follow up period	Illustrative comparative risks	Summary
Mitra M, 2015.	India Children 1- 12 years	Single dose live attenuated vaccine (Biovac-A)	hepatitis A-related mortality	5 years	Not applicable	No Adverse events registered during entire follow-up period
Beran 2016	Belgium Adolescents	Two vs three dose combined hepatitis A and B vaccine (Twinrix)	All-cause mortality	15 years	Not applicable	Pain at the injection site (2-dose group: 5/8; 3-dose group: 4/11) and fatigue (2-dose group:3/8; 3-dose group: 3/11) were the most reported local and general symptoms, respectively, during a period of 4-day follow-up after a challenging dose of monovalent hepatitis B vaccine. However no subjects received a challenge dose of hepatitis A vaccine as all remained seropositive.
Shi 2019	China Infants and toddlers (< 2 years of age), children (2 to 11 years of age), and adolescents(≥ 12 years of age)	Two dose inactivated vaccine (Avaxim pediatric)	Clinically apparent hepatitis	Up to 30 days following second dose	Not reported	The incidence of solicited injection site reactions (being tenderness and pain the most frequent events) was lower in infants and toddlers (17.9%) compared to children and adolescents (33.3%) Incidence of solicited systemic reactions (being fever the most frequent event) was similar for each group. The incidence of unsolicited AEs (rash, diarrhoea, signs of upper respiratory infection) in infants and toddlers was 6.3% and none in children and adolescents. For solicited and unsolicited AEs the incidence was slightly higher after the first vaccination. There were no serious adverse events.

Xiaojin 2020	China Children <14 years old	Inactivated hepatitis A vaccine (I-HepA) and live attenuated hepatitis A vaccine (L-HepA)	Non-serious systemic adverse events	Not applicable (cross-sectional design)	Not reported	Serious AEFI: annual incidence of serious AEFI was <0.5/100 000 * dose for both vaccines. The most common serious AEFIs were anaphylactic shock and febrile convulsion. Non serious AEFI: 10.11/100 000 doses for I-HepA and 8.52/100 000 doses for L-HepA. There were no meaningful differences in the types of common, mild AEFI between the two vaccines

AEFI: adverse events following immunization

4.4.6 Modeling studies and economic impact analysis of HAV vaccine and programming (secondary outcome)

The search identified 13 studies (Agrawal et al., 2020; Ayouni et al., 2020; Carlos, Gómez, Anaya, & Romano-Mazzotti, 2016; Curran, de Ridder, & Van Effelterre, 2016; Dhankhar et al., 2015; Dimitrova et al., 2014; Espul et al., 2020; Hankin-Wei et al., 2016; Hayajneh et al., 2018; Lopez et al., 2015; Sartori et al., 2012; Suwantika, Beutels, & Postma, 2014; Suwantika, Yegenoglu, Riewpaiboon, Tu, & Postma, 2013; Van Effelterre, De Antonio-Suarez, Cassidy, Romano-Mazzotti, & Marano, 2012; Y. P. Yu et al., 2020) which used mathematical extrapolation or modeling of data to investigate the effectiveness and impact of HAV vaccination. Some studies had multiple publications.

These studies focused on three primary areas, with a number of studies covering more than 1 domain: (1) those modeling the longevity of immune response to vaccine based on individual studies (often an extension of the primary study data) – 4 studies (2) population based models examining the epidemiological impact of single or two, universal or targeted HAV vaccine programs compared to no HAV vaccination – 7 studies (3) economic impact models to assess the cost effectiveness, cost benefit or budgetary impact of such programs – 8 studies.

4.4.6.1 Studies modeling the duration of immune response to HAV vaccination

There were 4 models which estimated the longevity of antibody persistence. Two were based on data from separate Argentina cohorts followed for 10 (Espul et al., 2020) and 15 years(Lopez et al., 2015), a the third was based on a Chinese RCT comparing 2 different inactivated vaccines over 5 years (Y. P. Yu et al., 2020) and a four based on data from clinical trials in Belgium and the Czech Republic.(Agrawal et al., 2020) All studies used fitted extrapolation models to estimate the duration of antibody response based on seroprotection and GMC data from the original study. While assumptions varied, all 4 models estimated very high seroprotection levels to at least 30 years. Espul 2020 (Espul et al., 2020) modeled both single and two dose antibody longevity and found no difference at 30 years, as well as the the impact of natural boosting in levels of seroprotection at 30 years and found only 5% difference. Agrewal 2020 (Agrawal et al., 2020), a 2 dose study, modeled to 50 years showing that 85% of subjects would remain seropositive through years 40 and 50. Yu 2020(Y. P. Yu et al., 2020) modelled out to 60 years showing the cohort would remain above the 20 seroprotection mark of 20IU/mL, however this was a 2 dose study.

Key limitations of these duration of immune response modeling (extrapolation) studies reviewed here were the narrow range of empiric data used to build the extrapolation models and that only one extrapolation model examined the longevity of single dose and the effect of natural boosting.

Table 10. Mathematical models for the duration of immune protection from HAV vaccination (1 or 2 dose) (Agrawal et al., 2020; Espul et al., 2020; Lopez et al., 2015; Y. P. Yu et al., 2020)

Author, year	Aim of modeling	Model structure	Setting/country	Population examined (impact)	No of doses	Vaccine efficacy	Vaccine coverage	Scenarios	Duration of protection (waning)	Weaknesses	Time horizon (years)	Key outcomes
Agrawal 2020	Duration of immune protection	linear-mixed model fitted to long-term immunogenicity trials	Belgium/Czech Republic GSK database data, studies of >10 years follow up	Mixed children and adults	2 dose	No specified (appears 100% @ 15 years	Individual level modeling	N/A	Seroprotection for 50 years	Only 2 dose. No population impact. Data from GSK database. Includes adults	Up to 50 years	Models predicted that over 90% and over 85% of subjects would remain seropositive at year 40 and year 50, respectively, following 2-dose HAV 1440 EU vaccination [8]. Similarly, over 97% of subjects were predicted to remain seropositive at year 40 following 3-dose HAB 720 EU vaccination 2-dose HAV 1440 studies, namely[85% remain protected after 50 years.

Espul 2020	Individual level Longevity of immune response to primary HAV vaccine	Bayesian Markov Chain Monte-Carlo methods	Argentina	Extrapolation from data from existing cohort study	1 or 2 doses	Model fitted to GMC/seroprotection data up to year 10 of follow up	NA	NA	Linear vs piecemeal decay, natural boosting vs no natural boosting	Limited data source (1 study, small sample), only extrapolated to 30 years.	30 years	**No clear difference at 20 & 30 years for 1 vs 2 dose regimens** Similarly, predicted seroprotection was similar for the 1-dose and 2-dose regimens at 20 years (98-99% vs 96-97%) and 30 years (84-89% vs 80-85%) Predicted antibody GMCs declined in a linear manner to 30 years for the 1- and 2-dose regimens, with and without natural boosting. At both 20 years and 30 years, predicted antibody concentrations are higher when a natural booster was included in the model, and higher for the 2-dose model than the 1-dose model. However natural boosting had a limited impact on predicted seroprotection at 20 years or 30 years for the 1-dose regimen (99 versus 98% [20 years] and 89 versus 84% [30 years] with and without a booster) or the 2-dose regimen (97 versus 96% [20 years] and 85 versus 80% [30 years] with and without a booster).

Lopez 2015	Individual level Longevity of immune response to primary HAV vaccine	Extrapolation models with linear or exponential decay or fitted curve of GMC	Argentina	Extrapolation from data from existing cohort study	2 doses	Model fitted to GMC/seroprotection data up to year 15 of follow up	NA	NA	6 models fitted to existing dataset to replicate and predict longevity. Also allowed for seropositivity prior to vaccination.	Limited data source (1 study, small sample), only extrapolated to 30 years.	30 years	Seroprotection rates for children seronegative prior to vaccination were 96%, 96% and 88% who are predicted to remain to have seroprotection at 20, 25 and 30 years post first vaccine dose. The predicted mean concentration of anti-HAV at years 20, 25 and 30 years are 208, 181 and 156 mIU/mL amongst children seronegative prior to vaccination
Yu 2020	Individual level Longevity of immune response to primary HAV vaccine	Two different nonlinear mixed-effects (power-law and modified power-law models)	China	Extrapolation from data from existing RCT study (2 different inactivated vaccines)	2 doses	Model fitted to GMC/seroprotection data up to year 5 of follow up	NA	NA	2 models fitted to existing dataset to replicate and predict longevity.	Limited data source (1 study, small sample), only extrapolated to 30 years	30 years	Model 1 predicted that at 30 years, more than 90% of participants would have seroconversion (anti-HAV $\geq$ 20 mIU/mL). In model 2, which showed better fitting, the predicted seroconversion rate of Healive remained above 95% for at least up to 35 years GMC projections to 60 years predicted the cohort would remain above the seroprotection cut-off of 20IU/mL

4.4.6.2 Population impact models for universal HAV vaccine programming

Given wide contextual variation between the population based epidemiological impact models, it is difficult to draw overarching conclusions from the data. Nevertheless, key themes include that universal, primary immunization programs have early and substantial epidemiological impact; that both single and 2 dose schedules are effective and the difference is determined by assumptions on waning immune protection, that herd immunity is a substantial contributor to the overall impact of a universal HAV vaccine program; that universal HAV vaccine programs are more impactful where endemicity is higher; and finally pros and cons of committing the extra resources necessary to initiate a complete catch-up vaccine program in settings of low endemicity require would require country and context specific investigation prior to initiation.

The Mexican models(Carlos et al., 2016; Curran et al., 2016) demonstrated at the population level that universal 2 dose strategies have a greater epidemiological impact, but with only the single dose strategy being cost saving. Sensitivity analyses show the profound impact of assumptions on immune protection longevity.

In the USA, one study examined the impact of a universal childhood vaccination program (to coverage of 81%) resulting in a substantial reduction in infections and hospital presentations (i.e. morbidity and subsequent costs), but just 228 deaths. The study found the impact of accounting for herd immunity was substantial in accelerating the impact of such a vaccine program. Another study modeled the epidemiologic impact of population based catch up programs for HAV vaccination. The model did not demonstrate marked impact, as 752 doses of vaccine would have to be administered to reduce HAV incidence by 1 case.

An analysis in Tunisia (Ayouni et al., 2020) reported that while the 2-dose regimen was impactful epidemiologically, for budgetary reasons the single dose regimen (though which reduced impact) would be more attractive.

The Jordanian model (Hayajneh et al., 2018), which indeed used a similar math model as the USA primary vaccine study(Dhankhar et al., 2015) demonstrated almost immediate and substantial impact of the introduction of a universal vaccine program, reducing HAV incidence from 900 to < 1 case/100000 population over the first 5 years of the program, dramatically changing the epidemiology of HAV in the country.

In Indonesia, an examination of the impact of vaccinating a full calendar year birth cohort on HAV disease in their lifetime showed a 40% further reduction in cases from the 2 dose regimen (~453 000) compared to a single dose strategy (~322 000), but again few additional deaths avoided. (Suwantika et al., 2014)

A model of the impact of universal HAV childhood vaccine (vs current policy of targeted) in Brazil (Sartori et al., 2012) showed substantial reductions in morbidity and mortality (around 60%) as well as years of life lost to HAV. In addition, the impact was greater for the north than the south of Brazil (prevalence is higher in the north of the country).

Table 11. Studies using mathematical models for population impact of HAV vaccine programming (1 or 2 dose).
)(Ayouni et al., 2020; Carlos et al., 2016; Curran et al., 2016; Dhankhar et al., 2015; Hankin-Wei et al., 2016; Hayajneh et al., 2018; Sartori et al., 2012; Suwantika et al., 2014; Suwantika et al., 2013; Van Effelterre et al., 2012; Y. P. Yu et al., 2020)

Author, year	Aim of modeling	Model structure	Setting/country	Population examined (impact)	No of doses	Vaccine efficacy	Vaccine coverage	Scenarios	Duration of protection (waning)	Weaknesses	Time horizon (years)	Key outcomes
Ayouni 2020	Impact of population vaccine program	linear age structured SEIR[3] compartmental model	Thala, rural Tunisia, based on household survey data	Children and adults	1 or 2 doses	97% (not clear if different for 1 or 2 doses)	Universal (primary +/- catch up)	Scenario1 two doses of HAV vaccine: a systematic vaccination at 12 months and a catch-up vaccination at 6 years of age during a period of 6 years. Scenario 2 one dose at 12 months of age Scenario3 in the introduction of one dose at 6 years of age.	Lifelong	Appears to assume 100% coverage Data derived from one small centre in Tunisia	Lifetime (80 years)	The vaccine model showed that the 3-scenarios lead to a significant reduction of the fraction of susceptibles. The two doses scenario gives the best results. Single-dose vaccination at 6-years of age provides more rapid decrease of disease burden in school-aged children, as compared to single-dose vaccination at 12-months, but keeps with a non-negligible fraction of susceptibles among children < 6-years. Taking into consideration budget limitations, the introduction of more than one dose of vaccine, in newborns and other ages, may not be possible and only one dose would be used.

[3] Susceptible-Exposed-Infectious- Recovered model

Curran 2016 also published in Carlos 2015	Impact of population level HAV childhood vaccine program	Deterministic, compartmental and age-stratified dynamic transmission model of HAV in Mexico, calibrated to Mexican	Mexico	Adults and children	1 or 2 doses	97% first dose, 99% with second dose	80% first dose, 68% with second dose	Universal 1 or 2 dose vaccine program vs no program	Wane (2 doses) at 0.12% per year for the first 25 years and a rate of 0.62% per year Wane at (1 dose)1.62% per year for the first 10 years and 2.67% thereafter Sensitivity analysis examined different waning scenarios	Modeling study, but overall quality is good and extensive sensitivity analysis. Substantial vaccine waning was modelled, and duration of immune protection substantially impacts on population impact	25year and 100 year models	Compared with no vaccination and over 25y, the single-dose HAV vaccination strategy would be expected to reduce the number of anicteric HAV infections by 67% and the number of icteric HAV infections (reported or unreported) by 36%. The two-dose HAV vaccination strategy would be expected to reduce the number of anicteric HAV infections by 72% and the number of icteric HAV infections (reported or unreported) by 55%. The projected reduction in total HAV infections was 57% with single-dose HAV vaccination and 67% with 2-dose HAV vaccination In the 50y immune protection model, the best results in terms of reduced incidence, observed with a 1-dose strategy, are not as good as the worst scenario with a 2-dose strategy

Dhankhar 2015	Impact of population vaccine program	Dynamic deterministic disease transmission model (MSEI[4]R compartmental structure)	USA (national level)	Child and adults	1 or 2 doses	100% for 1 or 2 doses	Universal (81%) from age 1 (though ?1-2yos only)	Sensitivity analysis addressed impact of different assumptions, including 100% adherence strategy	Median duration of protection 21 – 32 years	Modeling study, but overall quality is good and extensive sensitivity analysis	100 years	On average, universal routine hepatitis A vaccination prevented 259,776 additional infections, 167,094 outpatient visits, 4781 hospitalizations, and 228 deaths annually. When herd protection was ignored in scenario analysis, universal vaccination only prevented 94,957 infections, 46,179 outpatient visits, 1286 hospitalizations, and 15 deaths annually.
Hankin-wei 2016	Impact of population based HAV vaccine catch up program	Markov disease progression model	USA	Children < 18 years	2 doses (catc h up)	Not clear	Not clear (~50%) of population would need catch up	Sensitivity analysis model proportion needing catch up range 37.5 – 62.5%	Not clear	2 dose catch up strategy in a country of low endemicity	Life time of cohort (~80years)	Catch-up vaccination at age 10 years would reduce total HAV infections relative to baseline by 741, with 556,989 additional vaccine doses administered. In total, for every 752 additional doses administered, one case of HAV infection would be averted.
Hayajneh 2018	Impact of population based HAV childhood vaccination	Dynamic deterministic disease transmission model (MSEI[5]R compartmental structure)	Jordan	Children and adults	2 doses	100% for 1 and 2 dose	95% for 1 dose ~90% for 2 doses	Deterministic and probabilistic sensitivity analysis were run for a variety of different scenarios	Median duration of protection of a completed one-dose (21 years) and two-dose (32 years)	Does not investigate a single dose scenario	50 years	The model predicts rapid and substantial decrease in overall incidence of hepatitis A (from 900 cases to less than one case per 100,000 within five years of launching) The 50 year time horizon there are 4.26 million infections avoided resulting in more than 1.4 million inpatient cases avoided

[4] Maternal-susceptible-exposed-infectious-recovered compartmental structure

[5] Maternal-susceptible-exposed-infectious-recovered compartmental structure

Sartori 2012	Impact of universal childhood vaccination vs targeted program	age and time-dependent susceptible – infected/infectious – recovered – vaccinated (SIRV) compartmental dynamic model of hepatitis A transmission	Brazil (national) and 5 regions of Brazil	**Children and adults**	2 doses	94%	90%	Universal vs targeted (existing strategy). Sensitivity analysis present	Not clear	Does not appear to allow for waning	24 years	The universal childhood immunization program would reduce icteric cases by 64%, deaths by 59% and reduce YLL (from HAV) by 62%. The reduction of the icteric cases would be slightly larger in the "North" (68%) than in the "South" (61%), as well as the reduction in deaths, "North" (65%) and "South" (57%).
Suwantika 2014	Impact of universal childhood vaccine program	I	Indonesia	A single year birth cohort	1 or 2 doses	93% (first dose) 95% (2 doses)	80%	Single vs 2 doses. Sensitivity analysis covered a range of assumption scenarios	Wane (2 doses) at 0.32% per year for the first 10 years and a rate of 0.62% per year Wane at (1 dose)1.62% per year for the first 10 years and 2.67% thereafter Sensitivity analysis examined different waning scenarios	Only examines a single year birth cohort	70 year (lifetime for Indonesia)	Vaccination of 4 200 000 infants (the 2012 calendar year birth cohort) would reduce HAV infection by 452 834 (2 doses) and 322 207 (single dose) cases The two-dose vaccine schedule would reduce hepatitis A cases (mild) by 247 694 (65.0%), (moderate) 148 670 (65.0%), (severe) 56 064 (68.7%), and deaths by 406 (59.8%) The single dose vaccine schedule would reduce hepatitis A cases by (mild) 174 157 (45.7%), (moderate) 104 579 (45.7%), (severe) 43 224 (53.0%), and deaths by 247 (36.3%)

4.4.6.3 Economic impact analyses (secondary outcome)

Given wide contextual variation between the population based epidemiological impact models, it is difficult to drawn overarching conclusions from the data. Nevertheless, key themes include that universal, primary immunization programs have early and substantial epidemiological impact; that both single and 2 dose schedules are effective and the difference is determined by assumptions on waning immune protection, that herd immunity is substantial contributor to the overall impact of a universal HAV vaccine program; that universal HAV vaccine programs are more impactful where endemicity is higher; and finally pros and cons of committing the extra resources necessary to initiate a complete catch-up vaccine program in settings of low endemicity require would require country and context specific investigation prior to initiation.

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Table 12. Studies of the economic impact of HAV vaccine programming

(Carlos et al., 2016; Curran et al., 2016; Dimitrova et al., 2014; Ghildayal, 2019; Hankin-Wei et al., 2016; Hayajneh et al., 2018; Sartori et al., 2012; Suwantika et al., 2014)

Authors (Year)	Intervention	Comparator	No. of Doses	Vaccine Efficacy, %	Vaccine Coverage, %	Price per Dose, $	ICER (Base Case)	Unit of ICER	Country/ GDP per capita	Conclusion of EE study
Curran 2016 also published in Carlos 2015	Single or 2 dose HAV program (initial)	No vaccination	1 vs 2	97% (1 lose 99% (2 lose) with vaning allowance 1 lose> 2 loses	80%	13.17MXN/dose; US$1/dose	If immune protection is > 10 years then 1 dose ICUR range – 1126 to –) 3835 MXN/QALY (ie cost saving) 2 dose (ICUR range: 8,034 to 14,829 MXN/QALY	Mexican pesos[6]/QALY	Mexico Threshold stated at 132465 MXN/QALY	1 dose cost saving, 2 doses cost effective vs no vaccination

[6] In 2012, 1000 Mexican Pesos = US$79; 132465MXN = US$10305

Dimitrova 2014	2 dose (initial)	No vaccination	2	Not available	Not available	56.64 BGN ($37) for 2 doses	The treatment costs of all registered patients with hepatitis A were higher than the costs that would have been paid for the vaccination of all one-year-old children (100%) in the same year. In these years, if vaccination had been carried out, the healthcare system would have saved from 1.5 to 2.2 million BGN (US$1 - $1.46m) from hospitalizations and additional pharmacotherapy costs.	Bulgarian leva (BGN)[7]	Bulgaria US$7,395/capita in 2012	Cost benefit analysis the result shows that vaccination is cost-effective investment which is paid out in the years with epidemiologic outbreaks (ie > 4600 cases/year)

[7] In 2012 US$1 = 1.50 BGN.

Dhankhar 2015	Single or two dose regional vs universal vaccination in > 1yo	No vaccination	0 vs 1 vs 2	100% for 1 or 2 doses	81% (sensitivity analysis examined other coverage levels)	$15 - $30/dose	Universal vaccination (compared to regional vaccine strategy) was cost saving in 10y, 50y, 100y projections. Regional vaccine strategy was cost saving when herd immunity effect was included.	USA (USD)	USA threshold $100 000/QALY	Compared with the regional vaccination policy, universal routine hepatitis A vaccination was cost saving. In scenario analysis, universal vaccination ICER increased $21,223/QALY when herd protection was ignored
Ghildayal 2019	2 doses (initial)	No vaccination	2	94%	77% (USA) 90% (Rio)	$60 (USA) $17 (Rio)	USA $55,778 per QALY Rio de Janeiro $8,194 per QALY	USA (USD); Rio de Janeiro, Brazil (USD)	USA threshold $100 000/QALY Rio de Janeiro GDP/capita $16,308.39	Analysis showed universal vaccination to be cost-effective as compared to no vaccination. In the USA it fell below the CE threshold, whereas in Rio it was around 0.5xGDP or highly CE.

Hankin-wei 2016	2 doses (catchup)	No vaccination	2	Not clear	Catch up defined as 1 – 17yo without a document history of 2 doses of HAV vaccines	$17 - $63	Most cost effective in 12 year olds, at $189,000 per QALY gained.	USA/USD	USA threshold $100 000/QALY	Given the low baseline of HAV disease incidence achieved by current vaccination recommendations, catch-up vaccination would become cost effective at a threshold of $50,000 per QALY only when incidence of HAV rises about 5.0 cases per 100,000 population.
Hayajneh 2018	2 doses	No vaccination	2	100% for 1 dose and 2 dose ~90% for 2 doses	95% for 1 dose ~90% for 2 doses	US1.91/dose	ICER is $75/QALY gained (with indirect costs) and $281/QALY gained with direct costs only Cost savings is achieved within 6 years considering indirect costs and within 8 years if indirect costs are excluded.	Jordan/USD	Jordan WTP threshold of $3600/QALY.	The vaccination program covering 1 year old children became cost-saving within 6 years of its introduction and was highly cost-effective during the first 5 years.

Sartori 2012	2 doses	No vaccination	2	94%	90%	BRL$16.89 (US$7.23)	Not presented as ICER, but total costs to the entire health system and society.	N/A	Brazil/BRL	Vaccination against hepatitis A was a cost-saving strategy in the low and intermediate endemicity regions and in Brazil as a whole from both health system and society perspective.
Suwantika 2014	Single or 2 dose HAV program (initial)	No vaccination	1 vs 2	93% (1 lose 95% (2 lose)	80%	$3.21/dose	1 dose vs no intervention: US$ 4933 per QALY 2 dose vs 1 dose: US$ 14 568 per QALY gained.	$/QALYs	Indonesia US$ 3557	Cost effective. Single dose = <1/5xGDP/person 2 dose not CE if single dose is feasible

5 Discussion of addition considerations

There are specific areas of research, relevant to the long-term effectiveness and impact of HAV vaccines that were outside the above analysis, and are discussed here.

5.1.1.1 Natural boosting

Natural boosting occurs when immunized or exposed individuals are further exposed to HAV in the environment resulting in an immune boost, much like a booster dose of a vaccine. Several studies reported this effect in the context of single-dose regimens:

- (Bhave et al., 2015) Reported on 98 children 1-12yo given single dose live attenuated HAV vaccine (Biovac-A) at 10 years follow up. Cohort GMT was higher (101) at year 10 than at year 6 (66). At year 15 it was later reported as 80.(Bhave et al., 2021)
- (Bhave et al., 2021) Reported on 98 children 1-12yo given single dose live attenuated HAV vaccine (Biovac-A) at 15 years follow up. In 2010 (year 6), there were 25 children with anti-HAV titres <20mIU/mL. They were not given any additional dose / doses of live/inactivated HAV vaccine. The serial anti-HAV GMTs of these 25 children as compared to all 98 with single dose of live HAV vaccine is shown in Fig. 3. In 2014 (year 10) and 2019 (year 15), 23 of these 25 regained seroprotective levels.

The effect was noted in long-term studies of 2 doses. For example (Lopez et al., 2015) reported that In a minority of subjects, anti-HAV concentrations increased by the 14–15-year time point [from the 10year time point] as well as one shorter term study in an endemic region which saw an increase in GMC from years 2 -3 and attempted to control for this effect (3 years)(Luo et al., 2019). (Y. Wang et al., 2020) reported 97.5% and 99% seroprotection in both live attenuated and inactive arms at 5 years(C. Yu et al., 2016) but universal seroprotection in both arms at 11yeras follow up.

5.1.1.2 Vaccine boosting investigations to verify long-term anemnestic immunity

While second dose schedules of HAV vaccination provide an immune booster effect when given in a series, several studies demonstrated proof of long-term B and T cell immune memory through response to vaccine many years after initial single-dose immunization.

- Chen et al., 2018. single dose of the live attenuated HA vaccine showed good B cell and T cell immune memory and likely provides long-term protection.
    - 31/47 children 1-12yo received booster 17 years post live attenuated IMI single dose HAV vaccine, pre-booster
    - Pre-booster 29/47 (62%) had detectable antibody, with anti-HAV antibody GMC 64.8 mIU/mL (positive group) vs 6.4 (negative group)
    - Post booster detectable antibody in 94% (29/31) who agreed to receive – GMC markedly higher at 1832 vs 633mIU/mL respectively)
- Uruena et al., 2021.
    - In this study humoral and cellular immunogenicity were examined after an average of 12 years of single-dose HAV vaccination, among 81 healthy children who have received the vaccine in their infanthood.
    - Study participants were classified according to their serological status of anti-HAV antibodies after having received the vaccine, as having either protective (PAL) or unprotected antibody levels (UAL) against HAV. Humoral memory response was assessed by measuring anti-HAV Ab titers at admission in both groups, and 30 days after a booster dose in the UAL group.

- 48/52 (92%) individuals from UAL group who completed follow up reached protective levels after booster dose. In the PAL group, 2/27 (7%) individuals waned HAV Abs lacking seroprotection, while in 25/27 (93%) Abs remained >10 mUI/mL.
- In 47 participants (21 with PAL, 26 with UAL), flow citromerty of peripheral blood mononuclear cells stimulated with HAV antigen was carried out to examine both CD4+ and CD8+ cells response.
- HAV-specific memory CD4+ and CD8+ T cell responses were identified in 52.4% and 42.9% subjects with PAL, and in 53.8%and 26.9% individuals with UAL, demonstrating that cellular response remains over time regardless of antibodies waning.

6 List of included studies

Agrawal, A., Kolhapure, S., Andani, A., Ota, M. O. C., Badur, S., Karkada, N. & Mitra, M. ***2020***. **Long-Term Persistence of Antibody Response with Two Doses of Inactivated hepatitis A Vaccine in Children**. *Infectious Diseases and Therapy,* 9**,** 785-796.

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7 List of excluded studies

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