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[Intervention Protocol]

Hepatitis A immunisation in persons not previously exposed to hepatitis A

Jenna Patterson[1], Greg J Irving[2], Yu Qi Li[3], Yue Jiang[3], Helen Mearns[4], Daniel Pope[5], Rudzani Muloiwa[6], Gregory D Hussey[1], Benjamin M Kagina[1]

[1]Vaccines for Africa Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town Health Sciences, Cape Town, South Africa. [2]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. [3]Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China. [4]Vaccines for Africa Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town Health Sciences, Cape Town, South Africa. [5]Health Inequalities and the Social Determinants of Health, University of Liverpool, Liverpool, UK. [6]Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa

Contact address: Jenna Patterson, Vaccines for Africa Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town Health Sciences, Werhner Beit Building, N09.9A, Observatory, Cape Town, Cape Town, 7708, South Africa. pattersonjenna@icloud.com, pttjen005@myuct.ac.za.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the beneficial and harmful effects of pre-exposure hepatitis A vaccines (inactivated and live-attenuated) administered to adults and children versus no intervention, placebo, or any other vaccine.

BACKGROUND

Hepatitis A infection is caused by the hepatitis A virus (HAV). Hepatitis A is transmitted through contact with infectious persons as well as through foodborne and waterborne transmission routes (WHO 2016). Poor hygiene and sanitation pose the greatest risk related to HAV infection in low- and middle-income regions (de Jong 2007). In high-income regions, at-risk groups include those participating in anal sex, injection drug users, day-care employees or families of children in day care, and consumers of high-risk foods (e.g. raw shellfish) (Heathcote 2012). The epidemiology of hepatitis A is largely driven by socioeconomic indicators including economic development, sanitation, and access to clean water (WHO 2012; Ott 2013).

Infection with HAV early in life usually leads to asymptomatic disease and development of long-lasting immunity through IgG seroconversion (de Jong 2007). Levels of HAV endemicity are based on the proportion of those who are IgG positive in a population (Nelson 2006). The World Health Organization (WHO) describes the levels of endemicity on the basis of seroprevalence as: high (≥ 90% by age 10 years); intermediate (≥ 50% by age 15 years, with < 90% by age 10 years); low (≥ 50% by age 30 years, with < 50% by age 15); and very low (< 50% by age 30 years) (WHO 2012). As a result of early life HAV infections in high endemicity settings, there are few susceptible adolescents and adults in these populations. Intermediate HAV endemicity is often observed in regions with developing urban populations where IgG seroprevalence is often mixed. Low HAV endemicity is observed in high-income settings where circulation of HAV and IgG seropositivity in the population are both low. In these setting, a majority of the population is susceptible to HAV; however, the risk of infection remains low as the virus rarely circulates.

Description of the condition

Once infection occurs, HAV is replicated in the liver and excreted in the bile and stools of infected persons (WHO 2012). The peak of virus excretion occurs two weeks before the onset of hepatitis A symptoms and the incubation period is approximately 28 days (de Jong 2007). Following infection with HAV, five clinical patterns are possible: asymptomatic infection; symptomatic infection; relapsing hepatitis A; cholestasis hepatitis A; and fulminant hepatitis A (Lemon 2017). Hepatitis A symptoms are strongly correlated with age and clinical severity increases as infected individuals get older (Rajan 2000; de Jong 2007; Ellis 2007). Chronic infection with HAV does not occur as infection with HAV resolves spontaneously and leads to development of immunity through IgG anti-HAV antibodies 8 to 12 weeks after initial infection (de Jong 2007; Heathcote 2012).

Symptoms of HAV infection most commonly include a loss of appetite, fatigue, upper-right-quadrant abdominal pain, nausea, vomiting, jaundice, dark urine, and fever (de Jong 2007; Lemon 2017). The fatality rate associated with hepatitis A in children and adults under 50 years old ranges from 0.3% to 0.6%, while fatality rates in adults aged 50 years or older range from 1.8% to 5.4% (Lemon 2017). Complications of hepatitis A include cholestasis, relapsing hepatitis A, and fulminant hepatic failure. Cholestatic hepatitis A develops when bile flow is decreased due to impaired secretion by hepatocytes or blocked bile ducts. Relapsing hepatitis A involves relapse of symptoms and abnormal liver function one to four months after initial symptoms have resolved (Glickson 1992; de Jong 2007). This is uncommon and occurs in approximately 3% to 20% of infected individuals (Glickson 1992). Fulminant hepatic failure is rare but serious, occurring in approximately 0.01% of infected individuals, in which extensive liver damage occurs within the first six to eight weeks of HAV infection (de Jong 2007; Heathcote 2012). Mortality rates associated with fulminant hepatic failure range from 70% to 95% (Koff 1998; de Jong 2007; Heathcote 2012).

Management for acute hepatitis A is generally supportive (Heathcote 2012). Abstinence from alcohol is often advised during HAV infection (Heathcote 2012). Nausea and vomiting are treated with antiemetics; and acetaminophen may be administered to adults but is restricted at a maximum of 4 g per day (Gilroy 2019). Dehydration may be managed with hospital admission and administration of intravenous fluids.

Description of the intervention

Pre-exposure prophylaxis for hepatitis A includes vaccination. There are currently two types of hepatitis A vaccine available: inactivated vaccines; and live-attenuated vaccines (WHO 2012). Inactivated hepatitis A vaccines are licensed for use globally in adults and children aged 12 months or older. There are currently five different inactivated hepatitis A vaccines on the market (Avaxim(R), Epaxal(R), Havrix(R), Healive(R) and Vaqta(R)), each requiring two doses to be administered within 6 to 12 months of each other (WHO 2012). Havrix(R) and Healive(R) are both WHO pre-qualified vaccines for the prevention of hepatitis A (WHO 2012). Within two to four weeks of the first dose of inactivated hepatitis A, up to 100% of children and young adults achieve seroconversion (WHO 2012). Some studies further indicate that inactivated hepatitis A vaccines are protective after a single dose (Iwarson 2004; WHO 2012; Ott 2013). Inactivated hepatitis A vaccines can be prepared as a single antigen vaccine or combined with hepatitis B recombinant antigens or typhoid (Proell 2002). Inactivated hepatitis A vaccines have a widely accepted safety profile with no reports of serious adverse events (Bryan 2001; Ott 2012; Rao 2016). The most frequently reported adverse events associated with inactivated hepatitis A are injection-site pain, headache, and general malaise (Wasley 2006).

Live-attenuated hepatitis A vaccines are manufactured in China and licensed for use in several other countries (WHO 2012). Live-attenuated vaccines are administered in a single-dose schedule. Previous systematic reviews have concluded that significant protection is offered by both live-attenuated and inactivated hepatitis A vaccines and both inactivated and live-attenuated hepatitis A vaccines are capable of providing protection for up to 15 years (Van Herck 2004). Quality vaccine safety data are, however, lacking to adequately compare the safety profiles of the two types of hepatitis A vaccines (Demicheli 2003; WHO 2012). The cost effectiveness of hepatitis A vaccination in low endemicity settings is well documented, with high coverage being most cost effective in areas with high hepatitis A incidence (Anonychuck 2008; WHO 2012).

Other methods of primary hepatitis A prevention include adequate sanitation, frequent hand washing, and access to safe food and water (de Jong 2007). Post-exposure prophylaxis (PEP) against HAV infections includes administration of human immune globulin (IG) (Liu 2009). Post-exposure prophylaxis is 80% to 90% effective when administered no more than 14 days after HAV exposure (Liu 2009; Lemon 2017). It may prevent hepatitis A symptoms and liver disease but in most cases does not prevent HAV infection (Lemon 2017).

How the intervention might work

Vaccination with hepatitis A vaccines results in the induction of anti-HAV antibodies (IgG), inducing both cellular and humoral immune memory (Van Damme 1994). The vaccine-induced anti-HAV antibodies bind to and neutralise HAV upon infection (Flehmig 1997). Detectable anti-HAV antibody titre levels of 10 mIU/mL or more are used as a correlate of protective immunity (Purcell 1992; Flehmig 1997; Wasley 2006). Inactivated HAV vaccines have been documented to generate antibody responses that persist for up to 20 years and have been modelled to persist for an additional 20 years (WHO 2012; Van Damme 2017). Immune memory responses to live-attenuated HAV vaccines are not as well documented. Limited studies have been performed which indicate that inactivated hepatitis A vaccines are safe and immunogenic for patients living with HIV, although patients with lower CD4 T-cell counts are more likely to be non-responders than those with higher counts (Mena 2015).

Why it is important to do this review

A systematic review with meta-analysis of randomised clinical trials published in 2003 aimed to assess the efficacy and safety of inactivated hepatitis A vaccines (Demicheli 2003). The review determined inactivated hepatitis A vaccines to be effective in the prevention of hepatitis A infections, but it did not assess the efficacy or safety of live-attenuated vaccines. In 2012, a Cochrane Review with meta-analysis of randomised clinical trials aimed to compare the efficacy and safety of inactivated and live-attenuated hepatitis A vaccines (Irving 2011; Irving 2012). The review concluded that both vaccine types provide significant protective effects against hepatitis A, but it was unable to adequately compare the safety profiles of the two vaccine types as it included a limited number of comparative studies with data on adverse events following immunisation.

Our aim is to update the Irving 2012 Cochrane Review that assessed the efficacy and safety profiles of inactivated and live-attenuated hepatitis A. We will try to generate comparable safety profiles of the two types of hepatitis A vaccines by including a number of vaccine trials not included in the original 2012 review. It is important to generate comparable safety profiles of the two types of hepatitis A vaccines: the vaccine safety profile is a primary concern in the administration of vaccines in both clinical practice and in development of evidence-based vaccine recommendations.

We will also assess the duration of protection offered by single and multiple doses of inactivated and live-attenuated hepatitis A vaccines to inform the current debate on the optimal number of inactivated hepatitis A doses needed to prevent the disease (Van Damme 2003; WHO 2012; Ott 2013; Lim 2014).

OBJECTIVES

To assess the beneficial and harmful effects of pre-exposure hepatitis A vaccines (inactivated and live-attenuated) administered to adults and children versus no intervention, placebo, or any other vaccine.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of blinding, publication date, and language.

Types of participants

We will include adults and children aged 12 months or older of either sex and any country of residence and not previously exposed to hepatitis A. We define pre-exposure status as lack of anti-HAV IgG antibodies (Lemon 2017).

Types of interventions

- Any type of inactivated or live-attenuated hepatitis A vaccine (experimental intervention) versus placebo or no intervention (control intervention).
- Any type of inactivated or live-attenuated hepatitis A vaccine (experimental intervention) versus any vaccine other than HAV vaccine (control intervention).
- One type of inactivated or live-attenuated hepatitis A vaccine (experimental intervention) versus another type of inactivated or live-attenuated hepatitis A vaccine (control intervention).

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Proportion of participants with confirmed hepatitis A infection (that is, alanine transaminase (ALT) levels 2 to 3 times higher than normal limit ≦ 43 mIU/L) (Kim 2008) and/or laboratory confirmed hepatitis A infection (Immunoglobulin M-HAV (IgM-HAV)).
- Proportion of participants with one or more serious adverse events following immunisation with hepatitis A vaccines. A serious adverse event is defined as any untoward medical occurrence that at any dose: results in death; is life-threatening; requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect (ICH-GCP 1997).

Secondary outcomes

- Hepatitis A-specific mortality.
- Health-related quality of life.
- Proportion of participants with adverse events considered to be non-serious following immunisation with hepatitis A vaccines.
- Proportion of participants with anti-HAV antibody titre levels ≧ 10 mIU/mL at the last study day available following vaccination (Wiedermann 1992; WHO 2012).

We will collect data for all time periods reported in the included studies and, if possible, we will define them into groups. We will consider the longest follow-up as our primary analysis of the outcome data. We will analyse data for all outcomes following the administration of one, two, and three doses of hepatitis A vaccines.

We will allow co-interventions if administered equally to the experimental and control groups of the trial.

Search methods for identification of studies

Electronic searches

We will search The Cochrane Hepato-Biliary Group Controlled Trials Register (maintained and searched internally by the CHBG Information Specialist via the Cochrane Register of Studies – Web), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue), MEDLINE Ovid (1946 to date of search), Embase Ovid (1974 to date of search), LILACS (1982 to date of search; Bireme), Science Citation Index Expanded (1900 to the date of search; Web of Science), and Conference Proceedings Citation Index – Science (1990 to the date of search; Web of Science) (Royle 2003). Appendix 1 gives the preliminary search strategies with the expected time spans.

We will also endeavour to identify non-English randomised clinical trials references using the following databases: the China National Knowledge Infrastructure (CNKI); the Chinese Scientific Journals database (CSJD-VIP); the China Science Periodical Database (CSPD); Wanfang Data (www.wanfangdata.com.cn); the Russian Federation Clinical Trials Register (CenterWatch); the Latin American Ongoing Clinical Trial Register (LATINREC); the Indonesian Clinical Trials Registry; and the European Clinical Trials Register (EudraCT). We will also use our personal contacts, local access and/or refer to the Cochrane Hepato-Biliary Group (CHBG) Information Specialist to contact Cochrane collaborators from around the world with the intent of finding relevant non-English randomised clinical trials.

Searching other resources

We will conduct additional searches for eligible randomised trials by cross-checking the reference list of published randomised clinical trials and systematic reviews.

We will search on-line trial registries such as ClinicalTrials.gov, European Medicines Agency (EMA) (www.ema.europa.eu/ema), WHO International Clinical Trial Registry Platform (www.who.int/ictrp), and the Food and Drug Administration (FDA) (www.fda.gov), as well as pharmaceutical company sources, for ongoing or unpublished trials. We will also search for grey literature in the System for Information on Grey Literature in Europe "OpenGrey" (www.opengrey.eu).

Data collection and analysis

Selection of studies

Two authors, Jenna Patterson (JP) and Helen Mearns (HM), will independently screen all titles and abstracts for inclusion of potentially eligible randomised trials sourced from non-Chinese databases. Yu Qi Li (YQL) and Yue Jiang (YJ) will screen all titles and abstracts sourced from the Chinese databases we search. JP, HM, YQL, and YJ will collect full-text trial reports/publications of potentially eligible studies and independently screen them for inclusion. Trials reporting one or more of the primary outcomes will be eligible for inclusion in this review. The authors will consult Greg Irving (GI) when they cannot agree on eligibility. We will record the selection process with reasons for exclusion using a PRISMA flow diagram.

If, during the selection of trials, we identify observational studies such as quasi-randomised or controlled clinical studies with the same characteristics of participants and interventions as in our protocol and reporting adverse events relevant to the outcomes of this review, then we will extract the adverse event data in their experimental and control groups separately from the data from the randomised clinical trials. We will not specifically search for observational studies for inclusion in this review, which is a known limitation of the study in terms of adverse events. We are aware that the decision not to search systematically for all observational studies as well as extracting data on harm only from quasi-randomised and controlled clinical studies might bias our review towards assessment of benefits and might overlook certain harms such as late or rare harms. If we demonstrate benefits from using hepatitis A vaccines in persons not previously exposed to hepatitis A, then a systematic review of the harms of hepatitis A vaccines in persons not previously exposed to hepatitis A in observational studies ought to be launched (Storebø 2018).

Data extraction and management

Two authors (JP and HM) will independently extract data from the included non-Chinese trials. YQL and YJ will extract data from all Chinese trials included in the review. In the event of any disagreement between the authors, they will consult GI.

We will seek data on all participants, irrespective of compliance or follow-up, to allow intention-to-treat analyses. In cases where trials have cross-over designs, we will consider data from only the first period. We will identify trials by the name of the first author and the year of publication.

We will collect the following data; and where sufficient data exist, we will perform subgroup analyses according to the Subgroup analysis and investigation of heterogeneity section.

- Characteristics of the trial: date, trial registration number, sample size, HAV endemicity setting, generation of allocation sequence, allocation concealment method, blinding methods and other information following the definitions of the bias risk domains (see below).
- Characteristics of the participants: number of participants in each group, age, sex, nationality, ethnic group, presence of known HAV infection risk factors (including injection drug users, living in poor socioeconomic areas, and poor access to clean water and sanitation facilities), presence of immunodeficiency, baseline comparability from trial demographic information.
- Characteristics of the intervention: type of vaccine, type of control, number of doses administered, immunisation schedule, route of administration.
- Characteristics of outcomes measures as presented in the trial publications (these will be presented in the 'Characteristics of included studies' table) and following our review outcomes: primary and secondary outcomes, type of antibody test used, adverse events, length of follow-up, and loss to follow-up before the end of trial.

Where any predefined outcome is not reported, we will contact the investigators or study sponsors to ask for the reason.

Assessment of risk of bias in included studies

We will follow the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias of each included clinical trial (Higgins 2019). We will assess the risk of bias of trials on the basis of the domains described in the following sections of the review and provide reasons for judgement in a

'Risk of bias' table for each bias domain (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018). We will create 'Risk of bias' plots in Review Manager 5 (Review Manager 2014).

Sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if an independent person not otherwise involved in the study performed them. If block randomisation was used, we will consider it adequate if a computer random number generator was used for selection of random permuted blocks for the randomisation list of the participants. We will judge if the block randomisation was adequate also by looking into the details of the block randomisation regarding ratio, size, and stratification of the block randomisation.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random or only quasi-randomised. 'Herd effect' or recruitment bias in the cluster-randomised clinical trials appears likely. We will only include such studies for assessment of harm.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. The investigators were unaware of the allocation sequence. A central and independent randomisation unit was used to control allocation or sealed envelopes allocating drug assignments were prepared by an independent pharmacist.
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We will only include such studies for assessment of harm.

Blinding of participants and personnel

- Low risk of bias: blinding of participants, healthcare workers and key study personnel was ensured until completion of the study. It is unlikely that the blinding could have been broken given the methods described.
- Unclear: insufficient information to permit judgement of 'low risk' or 'high risk' or the trial did not address blinding.
- High risk of bias: the trial was not blinded to participants, healthcare workers and key study personnel. It is likely that the blinding could have been broken given the methods described.

Blinding of outcome assessment

- Low risk of bias: blinding of outcome assessment was ensured until completion of the study analysis. It is unlikely that the blinding could have been broken given the methods described.
- Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk' or the trial did not address blinding of outcome assessment.
- High risk of bias: no blinding of outcome assessment took place or the outcome measurement was likely to be influenced by lack of blinding, or both.

Incomplete outcome data reporting

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data. Data for all individuals within clusters or all clusters in cluster-randomised clinical trials are reported.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to bias the results. Data for one or more individuals or clusters in cluster-randomised clinical trials are missing.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: if the original trial protocol was available, the outcomes reported should have been those called for in the protocol. If we obtained the trial protocol from a trial registry, the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time the trial was begun. If the trial protocol was registered after the beginning of the trial, we will not consider those outcomes to be reliable. The trial reported the following predefined outcomes with at least one of the outcomes related to the main reason of prevention of hepatitis A through immunisation, namely:
  * proportion of participants with all-cause mortality
  * proportion of participants with hepatitis-A-specific mortality
  * proportion of participants with clinically confirmed hepatitis A infection
  * proportion of participants with serious adverse events following immunisation with hepatitis A vaccines
  * proportion of participants with non-serious adverse events following immunisation with hepatitis A vaccines
  * proportion of participants responding to hepatitis A immunisation
- Unclear risk of bias: not all predefined or clinically relevant and reasonably expected outcomes were reported fully or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, despite the fact that data on these outcomes should have been available and even recorded.

Overall bias assessment

We will assess overall risk of bias in each trial as:

- low risk of bias, if we have assessed all domains in a trial at low risk of bias; or
- high risk of bias, if we have assessed one or more of the domains in a trial at unclear or high risk of bias.

Measures of treatment effect

We will use the statistical package Review Manger 5 provided by Cochrane for statistical analyses (Review Manager 2014). We plan to present dichotomous outcome data as risk ratios (RRs) with 95% confidence intervals (CIs). We plan to present continuous outcome data as mean difference (MD) if all studies reported their outcomes using the same scale, and as standardised mean difference (SMD) if

the studies used different scales to report their outcomes. We will use 95% confidence intervals (CIs). We will re-express calculated SMD using the rule of thumb where Cohen's d = 0.2 will be considered a 'small' effect size, 0.5 represents a 'medium' effect size, and 0.8 a 'large' effect size (Cohen 1988). For time-to-event data, we will calculate hazard ratio (HR) with 95% CI.

Unit of analysis issues

The unit of analysis will be the individual trial participant in the experimental or control group of the included trial to which the participant was randomly assigned.

Cluster-randomised clinical trials

For cluster-randomised clinical trials that have used correct statistical methods regarding clustering, we will use the generic inverse variance approach to analyse effect estimates and their standard errors. If incorrect statistical methods regarding clustering were used, we will implement methods for correcting trial results according to the *Cochrane Handbook for Systematic Reviews of Interventions* Section 16.3.6 (Higgins 2019).

Trials with more than two intervention groups (multi-group trials)

In case of multi-group trials, we will analyse multiple intervention groups in a way that would avoid arbitrary omission of relevant groups and double-counting of participants. We will only extract data from the trial groups that correspond to the interventions being considered for this review. In case of two experimental intervention groups of interest to our review and only one common control group, we will divide the control group into two to avoid double-counting while adding data to the review meta-analysis.

We do not expect trials with a cross-over design.

Dealing with missing data

We will perform our analyses based on the intention-to-treat principle whenever possible, including all randomly assigned participants, irrespective of completeness of data. We will contact investigators or study sponsors if data are missing. In the event of no reply within six months, we will impute a replacement value for the missing data in sensitivity analyses according to the following two extreme case scenarios for our primary outcomes (Hollis 1999).

- Extreme case analysis favouring the experimental intervention ('best-worst' case scenario): none of the dropouts/participants lost from the experimental arm but all of the dropouts/participants lost from the control arm experienced the outcome, including all randomised participants in the denominator.
- Extreme case analysis favouring the control ('worst-best' case scenario): all dropouts/participants lost from the experimental arm but none from the control arm experienced the outcome, including all randomised participants in the denominator.

We will report the impact of any missing data on our findings.

Assessment of heterogeneity

We will first document the variability in the participants, interventions, and outcomes in the included trials to assess clinical heterogeneity. Then we will document the variability in study design and risk of bias of the included trials to assess methodological heterogeneity.

We will use forest plots to graphically assess statistical heterogeneity in the intervention effects (Review Manager 2014; Higgins 2019). We will calculate Chi^2 values and I^2 statistics to statistically measure the presence of heterogeneity. The Chi^2 threshold for presence of heterogeneity is P less than 0.1 and the I^2 statistic threshold is I^2 greater than 40%. The values of the I^2 statistic for heterogeneity are defined in the *Cochrane Handbook for Systematic Reviews of Interventions* as follows: not important (0% to 40%); moderate (41% to 60%); substantial (61% to 80%); and considerable (81% to 100%).

Assessment of reporting biases

We will use funnel plots if there are 10 or more trials included per comparison. Symmetry or asymmetry of each funnel plot enables visual assessment of whether treatment estimates are associated with trial size. We will use the Egger test to test for the funnel plot symmetry (Egger 1997).

Data synthesis

We will conduct this systematic review according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2019).

We will perform statistical analyses according to the statistical guidelines referenced in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

For the statistical analyses we will use Review Manager 5 (Review Manager 2014). We will analyse the data using the random-effects model meta-analyses (DerSimonian 1986). For dichotomous outcomes, we will calculate risk ratios (RRs) and for continuous outcomes such as health-related quality of life, we will calculate mean difference (MD) or standardised mean difference (SMD). For all association measures, we will use 95% CIs.

We will incorporate data from cluster-randomised trials using the Mantel-Haenszel and generic inverse variance method (Higgins 2019).

We will present the data on adverse events from the included quasi-randomised and controlled clinical studies in a tabular or narrative format (Loke 2007).

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses to further explore heterogeneity.

- Vaccines type: inactivated compared to live-attenuated
  - It is important to the objectives of the review to separate vaccine types in the review analysis.
- Number of vaccine doses: single dose compared to multiple doses
  - It is important to the objectives of the review to separate vaccine doses in the review analysis. Length of follow-up: 1 to 12 months compared to 13 to 24 months compared to 25 to 36 months compared to 37 to 48 months, compared to 49 months or more. It is important to understand the duration of immunity to separate follow-up times in the review analysis.

- Proportion of participants with long-term persistence of anti-HAV antibody titre levels ≧ 10 mIU/mL following administration of a single or multiple dose(s) of hepatitis A vaccine
  * It is important to the objectives of the review to separate the long-term persistence of anti-HAV antibody titre levels by the number of vaccine doses administered.

Sensitivity analysis

In addition to the sensitivity analysis aiming to explore how imputed values impact the robustness of outcome estimates (see Dealing with missing data), we will perform the following sensitivity analyses to explore the impact of trial size and risk of bias.

- We will remove cluster-randomised trials from outcome analyses to explore their impact of bias on the robustness of outcome estimates.
- We will remove trials with vested interests to explore their impact of bias on the robustness of outcome estimates.
- We will remove small trials (those providing less than 10% weight to the analysis) from outcome analyses to explore their impact of the robustness of outcome estimates.
- We will remove trials judged to have an overall 'high' risk of bias from outcome analyses to explore their impact of bias on the robustness of outcome estimates.

We will also compare our GRADE imprecision assessments for outcomes listed below to those assessed with Trial Sequential Analysis (Jakobsen 2014).

- All-cause mortality.
- Proportion of participants with clinically confirmed hepatitis A infection (alanine transaminase (ALT) levels 2 to 3 times higher than normal limit ≦ 43 mIU/L), and/or laboratory confirmed hepatitis A infection (Immunoglobulin M-HAV (IgM-HAV)).
- Proportion of participants with one or more serious adverse events following immunisation with hepatitis A vaccines.
- Proportion of participants with adverse events considered to be non-serious, following immunisation with hepatitis A vaccines.
- Proportion of participants with anti-HAV antibody titre levels ≧ 10 mIU/mL at the last study day available following vaccination.

Trial Sequential Analysis

Trial Sequential Analysis is a statistical method which controls the risk of random error caused by sparse data and formal or informal repetitive testing of accumulating data (Thorlund 2011; TSA 2011; Wetterslev 2017). When a few small trials are combined in a meta-analysis, the risk of introducing random errors increases due to sparse data and due to multiplicity when conducting cumulative meta-analyses. We will employ Trial Sequential Analysis to control the risk of random errors for the primary outcomes including all-cause mortality and occurrence of hepatitis A and serious adverse events (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010; Thorlund 2011; TSA 2011; Wetterslev 2017). We will estimate the required information size based on the proportion of participants with an outcome in the control group, a relative risk reduction of 20%, an alpha of 2.5% because of three primary dichotomous outcome assessments and 2.0% because of four secondary outcomes, a beta of 10%, and the observed diversity in the trials in the meta-analysis (Jakobsen 2014; Wetterslev 2017). We will add the trials according to the year of publication, and if more than one trial has been published in a year, we will add trials alphabetically according to the last name of the first author. On the basis of the required information size we will construct trial sequential monitoring boundaries (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009, Wetterslev 2009; Thorlund 2010; Wetterslev 2017), which will help us formulate implications for research regarding cumulative meta-analysis that do not reach the required information size (e.g. whether further trials are still necessary or are superfluous to detect or reject a certain intervention effect). We will conduct Trial Sequential Analysis using software from the Copenhagen Trial Unit (Thorlund 2011; TSA 2011).

'Summary of findings' tables

We will create 'Summary of findings' tables for the following clinically relevant outcomes.

- All-cause mortality.
- Proportion of participants with clinically confirmed hepatitis A infection (alanine transaminase (ALT) levels 2 to 3 times higher than normal limit ≦ 43 mIU/L) (Kim 2008) and/or laboratory confirmed hepatitis A infection (Immunoglobulin M-HAV (IgM-HAV)).
- Proportion of participants with one or more serious adverse events following immunisation with hepatitis A vaccines
- Health-related quality of life.
- Proportion of participants with adverse events considered to be non-serious following immunisation with hepatitis A vaccines.
- Proportion of participants with anti-HAV antibody titre levels ≧ 10 mIU/mL at the last study day available following vaccination.

We will report the longest follow-up with range of follow-up.

The GRADE approach appraises the 'certainty' (or 'quality') of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The certainty of a body of evidence includes consideration of within-study risk of bias (methodological quality), indirectness of the evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of effect estimates (e.g. wide CIs), and a high probability of publication bias (Balshem 2011; Mustafa 2013). We will define the levels of evidence as 'high', 'moderate', 'low', or 'very low'. These grades are defined as follows.

- 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.

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APPENDICES

Appendix 1. Search strategy

Database	Time Span	Search Strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage	(hepatitis A OR hep A OR HAV) AND ((vaccine* AND (attenuated OR inactivated)) OR vaccin* OR immuni* OR inoculat*)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor Vaccination explode all trees #2 MeSH descriptor Immunization explode all trees #3 ((vaccine* AND (attenuated OR inactivated)) OR vaccin* OR immuni* OR inoculat*) #4 (#1 OR #2 OR #3) #5 MeSH descriptor Hepatitis A explode all trees #6 hepatitis A OR hep A OR HAV #7 (#5 OR #6) #8 (#4 AND #7)
MEDLINE Ovid	1946 to the date of search	1. exp VACCINATION/ 2. exp IMMUNIZATION/ 3. ((vaccine* and (attenuated or inactivated)) or vaccin* or immuni* or inoculat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 4. 1 or 2 or 3 5. exp Hepatitis A/ 6. (hepatitis A or hep A or HAV).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 7. 5 or 6 8. 4 and 7 9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 10. 8 and 9
Embase Ovid	1974 to the date of search	1. exp vaccination/ 2. exp immunization/ 3. ((vaccine* and (attenuated or inactivated)) or vaccin* or immuni* or inoculat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 4. 1 or 2 or 3 5. exp hepatitis A/ 6. (hepatitis A or hep A or HAV).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 7. 5 or 6 8. 4 and 7 9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 10. 8 and 9

(Continued)

LILACS (Bireme)	1982 to the date of search	((vaccine$ AND (attenuated OR inactivated)) OR vaccin$ OR immuni$ OR inoculat$) [Words] and hepatitis A OR hep A OR HAV [Words]
Science Citation Index Expanded (Web of Science)	1900 to the date of search	# 5 #4 AND #3 # 4 TS=(random* OR blind* OR placebo* OR meta-analys*) # 3 #2 AND #1 # 2 TS=((vaccine* AND (attenuated OR inactivated)) OR vaccin* OR immuni* OR inoculat*) # 1 TS=(hepatitis A or hep A or HAV)
Conference Proceedings Citation Index - Science (Web of Science)	1990 to the date of search	# 5 #4 AND #3 # 4 TS=(random* OR blind* OR placebo* OR meta-analys*) # 3 #2 AND #1 # 2 TS=((vaccine* AND (attenuated OR inactivated)) OR vaccin* OR immuni* OR inoculat*) # 1 TS=(hepatitis A or hep A or HAV)

CONTRIBUTIONS OF AUTHORS

JP is the first author of the study as well as the corresponding author. JP helped conceive the study and is responsible for protocol development as well as conducting the review. JP will do the search of the studies, screening, data extraction, analysis and write-up of the review.
GI is the first author of the original review. GI is the second author of this study and will provide methodological oversight to standardise the update of the review as well as provide hepatitis A clinical expertise. GI will also provide contacts and support for translation of non-English articles as was done in the previous review.
YQL will be responsible for the search for studies in Chinese databases outlined in the protocol as well as screening and data extraction for all included Chinese trials.
YJ will be responsible for the search for studies in Chinese databases outlined in the protocol as well as screening and data extraction for all included Chinese trials.
HM will be responsible for the search for studies, screening and data extraction.
DP is an author of the original review. DP will provide methodological oversight to standardise the update of the review as well as clinical expertise.
RM will provide expertise on the clinical outcomes included in the study. He will provide consensus where disagreement on clinical outcome data extraction occurs. RM helped conceive the study and will supervise the review process.
BK will provide expertise on the immunological outcomes included in the study. He will provide consensus where disagreement on immunological outcome data extraction occurs. BK will provide input on data analysis and write-up of the review.
GDH will provide oversight of the review and give expertise of translating the review findings into policy in the South African setting. GDH conceived the study and will supervise the review process consensus.
All authors have been actively involved in the development of this protocol and all have approved the most up-to-date version.

DECLARATIONS OF INTEREST

JP: none known
GI: none known
HM: none known
YQL: none known
DP: none known
RM: none known
BK: none known
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