Cochrane Library

Cochrane Database of Systematic Reviews

Hepatitis B immunisation for adults with end-stage kidney disease (Protocol)

Borges do Nascimento IJ, Pac A, Zanghelini F, Civile VT, Correa NE, Abdulazeem HM

Borges do Nascimento IJ, Pac A, Zanghelini F, Civile VT, Correa NE, Abdulazeem HM.
Hepatitis B immunisation for adults with end-stage kidney disease (Protocol).
Cochrane Database of Systematic Reviews 2023, Issue 5. Art. No.: CD014764.
DOI: 10.1002/14651858.CD014764.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Hepatitis B immunisation for adults with end-stage kidney disease

Israel Junior Borges do Nascimento[1,2], Agnieszka Pac[3a], Fernando Zanghelini[4a], Vinicius T Civile[5a], Nadine E Correa[6a], Hebatullah M Abdulazeem[7a]

[1]School of Medicine and University Hospital, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil. [2]Data and Digital Health (DDH) at Division of Country Health Policies and Systems (CPS), World Health Organization - Regional Office for Europe, Copenhagen , Denmark. [3]Chair of Epidemiology and Preventive Medicine, Department of Epidemiology, Jagiellonian University Medical College, Krakow, Poland. [4]Newcastle University, Newcastle upon Tyne, UK. [5]Evidence-Based Health Post-Graduation Program, Universidade Federal de São Paulo; Cochrane Brazil; Department of Physiotherapy, Universidade Paulista, Sao Paulo, Brazil. [6]Health Sciences Department, Federal University of Santa Catarina, Araranguá, Brazil. [7]Institute for Medical Information Processing, Biometry, and Epidemiology, Pettenkofer School of Public Health LMU Munich, Munich, Germany

[a]These authors contributed equally to this work.

Contact: Israel Junior Borges do Nascimento, borgesi@who.int.

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New, published in Issue 5, 2023.

Citation: Borges do Nascimento IJ, Pac A, Zanghelini F, Civile VT, Correa NE, Abdulazeem HM. Hepatitis B immunisation for adults with end-stage kidney disease (Protocol). *Cochrane Database of Systematic Reviews* 2023, Issue 5. Art. No.: CD014764. DOI: 10.1002/14651858.CD014764.

ABSTRACT

Objectives

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

Primary objectives
We aim to evaluate the beneficial and harmful effects of:

- hepatitis B immunisation in people with end-stage kidney disease.

Secondary objectives
We aim to evaluate the beneficial and harmful effects of:

- reinforced vaccination series (three doses plus one additional booster) versus traditional triple inoculations; and
- intradermal versus intramuscular hepatitis B vaccination, in people with end-stage kidney disease.

BACKGROUND

Description of the condition

Hepatitis B infection has been considered a life-threatening liver infection and impactful disease responsible for significantly increasing morbidity and mortality worldwide (Harpaz 2000; Shah 2017; World Health Organization 2019). Although the association between end-stage kidney disease and hepatitis B infection is still inconclusive in the literature, the hepatitis B virus can lead to several end-stage kidney diseases (Kimmel 2020). Besides causing liver inflammation, it causes end-stage liver dysfunction and gives extra-hepatic complications in multiple organs, such as the kidneys (Baig 2008; Fabrizi 2017; Shah 2017), either through horizontal or perinatal transmission. The association of both diseases becomes even more expressive when people at higher risk of infection are considered (mainly people with end-stage kidney diseases) due to numerous and highly complex pathogenic processes, such as membranous nephropathy, membranoproliferative glomerulonephritis, and polyarteritis nodosa (Hong 2018). Interestingly, as a disease control standard practice, all stages of end-stage kidney disease require regular blood samplings, a factor that contributes to the increased number of invasive therapies and procedures (Cordeiro 2018; Fabrizi 2015a; Fabrizi 2015b) and, ultimately, to the increased risk of hepatitis B infection in people (Schroth 2004). Their compromised immune system and the potential requirement for haemodialysis also increase the chances of patients being contaminated with the hepatitis B virus (Guan 1990; Hsu 1988).

Epidemiologically, end-stage kidney disease affects approximately 9.1% of the general population worldwide and has been associated with a significant economic and health-related impact in low-, middle-, and high-income countries (Coresh 2003; GBD Chronic Kidney Disease Collaboration 2020; Golestaneh 2017). Its diagnosis fundamentally relies upon a comprehensive physical examination and laboratory examination (assessing the glomerular filtration rate (GFR), albuminuria, and evaluation of urine sediments) (Vaidya 2019). The diagnosis of end-stage kidney disease is usually incidental, shown through routine medical screening of serum chemistry profiles and urine studies. However, some histological and imaging studies might show shreds of evidence suggesting kidney damage. Clinically, the presence and severity of clinical signals and symptoms are directly related to the disease stage, which can frequently be reported as gross haematuria, "foamy urine", nocturia, flank pain, or even as oliguria. More severe or advanced cases can also be registered as weight loss, poor appetite, swollen ankles, feet, or hands, dyspnoea, and tiredness. Considering data from the Centers for Diseases Control and Prevention, just amongst individuals assisted by the USA Medicare system, treating end-stage kidney disease cost $87.2 billion in 2019, with $37.3 billion designated to end-stage kidney disease patients (CDCP 2020a; GBD Chronic Kidney Disease Collaboration 2020). End-stage kidney diseases vary in severity and worsen over time, eventually leading to kidney failure. For this end-stage renal disease, dialysis or kidney transplant are required for survival (CDCP 2020a).

Regarding preventive measures against hepatitis B infection, vaccination still stands as an efficient and safe alternative against hepatitis B infection (Poorolajal 2016). However, because of the impaired immunological response amongst end-stage kidney disease patients, its effectiveness is reduced beyond a specific limit, and a decrease in vaccine-driven seroconversion performance is hypothesised. To note, if the driving causes are not identified, or major underlying diseases associated with kidney deterioration are not treated intensively, patients commonly evolve to end-stage kidney disease, which requires kidney replacement therapies (dialysis or kidney transplantation) and, consequently, increases the economic and medico-epidemiological burden (Nistor 2015; Perazella 2006; Webster 2017). Therefore, identifying and implementing a safe, efficient, and adequate vaccination schedule or programme is essential to avoid elevated morbidity and decreased quality of life amongst end-stage kidney disease patients (Chen 2016; Valderrábano 2001).

Description of the intervention

Vaccination is the safest way to protect people with end-stage kidney disease against hepatitis B infection, and most countries administer the first dose at birth if no contraindication is identified (Chen 2005). Immunisation, usually distributed in public healthcare organisations, is given intramuscularly into the anterolateral thigh muscle for infants and the deltoid muscle for children and adults. The route of administration can be altered to the subcutaneous site if patients have severe bleeding disorders. Despite the number of pathogens being targeted, monovalent and polyvalent hepatitis B vaccines contain a purified hepatitis B virus surface antigen (HBsAg), obtained through a genetics engineer, buffered with aluminium hydroxide as an adjuvant and thimerosal as antigen preservative (Greenberg 2002; Lee 2019). Dose regimens vary widely and depend on countries' policies around the world. For instance, the North American vaccination schedule proposes either immunisation at one or six months after initial administration or after six and 14 weeks of age, and six months of age. Similarly, the Brazilian government has routinely endorsed only the administration of three shots given at one and six months after the initial immunisation (Ministério da Saúde 2007). Regardless of dose regimen, it is worthwhile mentioning that the minimum administration interval between the first and second dose is four weeks and eight weeks between the second and the third dose, provided that the interval from the first dose is at least four months and the child is already six months old (Ministério da Saúde 2007). Interestingly, studies have shown that the vaccine administration with larger intervals in between the doses has proportional and equivalent results, not suggesting the need to resume the vaccination schedule as primarily prioritised among international recommendations (Schweitzer 2017). Recent studies have also suggested that additional shots of the hepatitis B vaccine (booster vaccine) should be considered only for those immunocompromised patients (including those with HIV, haematopoietic stem-cell transplant recipients, and people receiving chemotherapy) (Chen 2005).

With regard to the levels of protective antibodies against hepatitis B infection (anti-HBs), both monovalent and combined vaccines were found to provide similar seroprotection or vaccine response rates in healthy populations (Greenberg 2002; Lee 2018; Lee 2019). Commonly used commercial brands are Engerix-B, Recombivax hepatitis B virus, OHBVaxPro, Elovac B, Genevac B, and Shanvac B. Current recommendations for adults on haemodialysis are either 40 µg of Recombivax HB administered intramuscularly at 0, 1, and 6 months or 40 µg of Engerix-B administered intramuscularly at 0, 1, 2, and 6 months (Lewis-Ximenez 2001; Reddy 2019; Schillie 2018). These are greater doses than the regular doses of 10 µg

of Recombivax HB or 20 µg of Engerix-B administered at 0, 1, and 6 months to adult individuals that are immunocompetent (Kim 2018). Notably, the titers of anti-HBs should be evaluated one to two months after the final dose, especially in people with end-stage kidney disease (Mast 2005). If the anti-HBs titer is < 10 mIU/mL, repeating the entire dosing series is suggested with the determination of the antibody response in 1 to 4 months (Kim 2018; Lewis-Ximenez 2001). For people on haemodialysis, the need for booster doses should be assessed by an annual assessment of the anti-HBs levels. It is recommended that a booster dose be administered when anti-HBs levels decline to < 10mIU/mL (Reddy 2019).

Recently, several studies reported that the proportion of haemodialysis patients who develop a protective antibody response after vaccination with the HBsAg vaccine (even at higher dosages) is lower than in adults with normal immune status (CDCP 2001; Finelli 2005). Numerous approaches have been adopted to improve the immunogenicity of recombinant hepatitis B virus vaccine in people with end-stage kidney disease including reinforced schedule (Fabrizi 1996), concomitant use of immunomodulatory agents (Fabrizi 2010; Fabrizi 2020; Sali 2008), use of third-generation vaccines, vaccination by intradermal route (Fabrizi 1997), use of newer adjuvant agents (Fabrizi 2020; Leroux-Roels 2015), vaccination at pre-dialysis stage (Da Roza 2003), and development of vaccines containing the pre-S1 and pre-S2 portions of the HBsAg (Shouval 2015).

How the intervention might work

In general, all available hepatitis B virus vaccines contain specific components of the virus envelope protein, including HBsAg, pre-S1, and pre-S2 proteins (Shouval 2015). The administered HBV vaccine enters antigen-presenting cells, mainly dendritic cells, where it is processed and subsequently presented to T-helper cells, inducing their proliferation and activation together with the production of memory T cells (Das 2019). The presented antigen is also recognised by lymphocytes B (Das 2019). Binding to the antigen and stimulation from cytokines released by T-helper cells results in maturation of lymphocytes B to plasma cells, which then undergo clonal proliferation to produce specific antibodies against HBsAg (anti-HBs) and form memory cells as well (Das 2019). The generation of immune memory and the production of anti-HBs antibodies are crucial for long-term protection by providing an anamnestic response after exposure to the hepatitis B virus (Das 2019). Although anti-HBs titre decreases during time after vaccination, the acquired immunologic memory of B cells enables the rapid production of specific antibodies upon a future encounter with the same antigen (West 1996).

People with end-stage kidney disease have been shown to have lower rates of immunisation after standard vaccination compared to healthy controls (Kausz 2004). Apart from factors directly linked to impaired immunity and end-stage kidney disease itself, a variety of other factors have been implicated to affect vaccination efficacy, including age, sex, smoking, nutritional status, concomitant end-stage disease, and route of vaccine administration (Fabrizi 2004; Kausz 2004). Widely available recombinant second-generation vaccines achieve an insufficient seroconversion rate of 60% to 70% in adult dialysis patients (Fabrizi 2004; Grzegorzewska 2014).

Third-generation recombinant hepatitis B vaccines contain pre-S1 and pre-S2 epitopes. They are expected to be more immunogenic and are aimed at boosting the immune response in non-responders and immunocompromised people, including people with end-stage kidney failure (Halperin 2013; Janssen 2013). Furthermore, various adjuvant systems have been investigated as substances that may enhance immunogenicity and modulate the immune response induced by vaccines. Some of these adjuvants include derivatives from bacterial lipopolysaccharide (monophosphoryl lipid, MPL), substances based on vitamin E and squalene, immunostimulatory DNA sequences, etc. (Leroux-Roels 2015). Some of these adjuvants have shown promising results, but there are also certain safety concerns, which all require further research (Leroux-Roels 2015).

Why it is important to do this review

Some Cochrane and non-Cochrane systematic reviews have been published lately in order to understand multiple preventive alternatives against hepatitis B infection in people with end-stage kidney disease (Schroth 2004; Yousaf 2015). For instance, in 2004, a Cochrane review focusing on randomised clinical trials comparing several combinations of immunisation found that plasma vaccine was significantly more effective than placebo in achieving hepatitis B antibodies (RR 23.0, 95% CI 14.39 to 36.76, 3 trials) and no statistically significant difference between plasma vaccine or placebo regarding hepatitis B virus infections (RR 0.50, 95% CI 0.20 to 1.24) was observed (Schroth 2004). However, the review included a limited number of trials and did not find sufficient evidence of any preferred or more effective vaccination protocol for hepatitis B in end-stage kidney disease patients. In addition, an earlier review from 2015 assessed additional vaccination protocols of immunisation, but lacked critical methodological components, hindering the decision-making process and exact definition of a standardised vaccination programme for end-stage liver disease individuals (Yousaf 2015).

Based on the recognition of recent literature improvement assessing hepatitis B vaccines for people with end-stage kidney disease and the increased interest of pharmaceutical companies and academics, the development of a high-quality and timely review is essential to provide a global evidence summary for healthcare providers and patients. Therefore, this review aims to assess the beneficial and harmful effects of hepatitis B immunisation in people with end-stage kidney disease and the beneficial and harmful effects of a reinforced vaccination series (three doses plus one additional booster) versus traditional triple inoculations as well as to compare the beneficial and harmful effects of intradermal versus intramuscular hepatitis B vaccination in people with end-stage kidney disease.

OBJECTIVES

Primary objectives

We aim to evaluate the beneficial and harmful effects of:

- hepatitis B immunisation in people with end-stage kidney disease.

Secondary objectives

We aim to evaluate the beneficial and harmful effects of:

- reinforced vaccination series (three doses plus one additional booster) versus traditional triple inoculations; and

- intradermal versus intramuscular hepatitis B vaccination, in people with end-stage kidney disease.

METHODS

Criteria for considering studies for this review

Types of studies

We plan to include adequately randomised clinical trials (RCTs) evaluating the administration of the hepatitis B vaccine to people with end-stage kidney disease. We will also include cluster-randomised trials (trials in which groups of participants are randomised) if the trial authors have accounted for the clustering effect, or these trials contain sufficient data to account for it in the statistical analysis. We will include the first phase of cross-over trials, but we will exclude the second phase because of a potential 'bystander effect' (residual effect) (Elbourne 2002; Higgins 2022c).

We will include trials irrespective of language of publication or the format in which they were reported. If we identify trials with unpublished data, these will also be considered for inclusion in the review. We will include trials irrespective of the reported outcomes.

We will exclude quasi-randomised studies as the method of their allocation is not truly random (e.g. medical record numbers, date of birth) as well as other observational studies.

Types of participants

We will include trials with participants diagnosed with end-stage kidney disease or undergoing dialysis interventions (either peritoneal or haemodialysis) because of chronic kidney disease. Furthermore, we will include seronegative trial participants for HBsAg and for anti-HBsAg antibodies, or those previously immunised against the hepatitis B virus without success (< 10 mIU/mL, < 10 IU/L, or equivalent) (CDCP 2006; CDCP 2020b).

We will exclude trials involving mixed populations unless they reported their results separately or the results were shared by the authors (after two ResearchGate (www.researchgate.net/) and two email attempts). Based on the 'Improving Global Outcomes' study, we will define a person with end-stage kidney disease if they had kidney damage for more than three months, with or without decreased glomerular filtration rate, manifested by either: (1) pathological alterations; (2) biomarkers of kidney damage; or (3) glomerular filtration rate lower than 60 mL/min/1.73 m^2 for ≥ three months, with or without kidney injury (Levey 2005). If no detailed information is reported in the trial publications, then we will rely on the definitions of the trial authors or the mention of "chronic kidney disease" characterising the type of participants being evaluated.

Types of interventions

- Trials comparing any hepatitis B vaccination (plasma or recombinant, therefore, experimental intervention) with placebo or no vaccination (control intervention).
- Trials comparing reinforced programme of immunisation of three inoculations plus additional administration (i.e. three doses plus one additional booster) (experimental intervention)) versus regular vaccination (triple doses, therefore, control intervention).
- Trials assessing the differences between intradermal (experimental intervention) versus intramuscular (control intervention) hepatitis B vaccination.

We will accept adjuvants or co-interventions if provided similarly to the intervention groups of the trial. Additionally, we will include any dose, route of administration, and duration of treatment.

Types of outcome measures

We will extract data on the following outcomes, using the methods specified below. Our main analysis will include outcome results at the longest follow-up unless defined differently for each separate outcome below.

Primary outcomes

- All-cause mortality.
- Proportion of participants with clinically confirmed acute hepatitis B defined as hepatitis B core antigen positivity (anti-HBc) or persistence of HBsAg positivity up to six months after vaccination. Acute hepatitis B virus infection will be defined as clinical diagnosis identified by the detection of HBsAg, symptoms, high serum amino transferases, anti-HBc IgM detected, and HBV DNA present.
- Proportion of participants with clinically confirmed end-stage hepatitis B infection, defined as persistent levels of HBsAg for more than six months or relevant detection of HBsAg, and liver biopsy compatible with a diagnosis of end-stage hepatitis B.
- Proportion of participants with one or more serious adverse events following immunisation with hepatitis B vaccination, regardless of the reporting period. We will follow the definition of serious adverse events of the International Council for Harmonisation (ICH) Guidelines; i.e. 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 or incapacity, or is a congenital abnormality or birth defect (ICH-GCP 2016).
- Health-related quality of life measured by Kidney Disease Quality of Life (KDQOL) or any other validated tool to assess the impact of the disease in daily activities, physical, and mental health (Rand Corporation 2020).

Secondary outcomes

- Proportion of participants without seroconversion (without confirmed anti-HBs responses higher than 10 mIU x mL^{-1}) (up to one month after the last dose).
- Proportion of participants with one or more adverse medical events considered to be non-serious following immunisation with hepatitis B vaccine.
- Proportion of participants with recorded worsening kidney function compared to baseline status (progressive and permanent worsening in glomerular filtration rate, requiring or not requiring kidney replacement therapy, reported as a dichotomous outcome by authors).
- Proportion of participants with individual serious adverse events.
- Proportion of participants with individual adverse events that were considered not serious.

- Proportion of participants with hyperkalaemia (defined as serum potassium > 5.0 mEq/L or mmol/L).
- Time to achieve peak titres (months).

We decided to assess the time to achieve peak titers along with the peak titer itself because it is believed that the maintenance of serum anti-HBs over time is frequently associated with the peak level of anti-HBs, right after initial vaccine administration (Jilg 1989). Therefore, by evaluating the correlation of peak titer and the time to achieve it, we plan to analyse the effect on the proportion of individuals with evolved both acute and end-stage hepatitis B, as well as the proportion of individuals without seroconversion.

For those trials reporting values at various time intervals, we will consider only the latest reporting time point following vaccination as a primary analysis of the outcome data.

Search methods for identification of studies

To minimise bias in our search results, we have followed the guidance in Chapter 4 of the Cochrane Handbook (Lefebvre 2022a) and in PRISMA-S (Rethlefsen 2021) to plan and describe the search process for the review.

Electronic searches

We will perform electronic searches in the Cochrane Hepato-Biliary Group Controlled Trials Register which will be searched internally by the Cochrane Hepato-Biliary Group Information Specialist via the Cochrane Register of Studies Web. We will also search the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS (Bireme), Science Citation Index Expanded, and Conference Proceedings Citation Index-Science. The latter two will be searched simultaneously through the Web of Science.

Appendix 1 gives the preliminary search strategies for the respective databases, with the expected date range of the searches. We will provide the actual date of the electronic searches at the review stage.

Searching other resources

We will also search the Food and Drug Administration (FDA; www.fda.gov); European Medicines Agency (EMA; www.ema.europa.eu/ema/); WHO International Clinical Trial Registry Platform (ictrptest.azurewebsites.net/Default.aspx); ClinicalTrial.gov (clinicaltrials.gov/); Australian Clinical Trials Registry (www.anzctr.org.au/); Latin American Ongoing Clinical Trial Register and *Registro Brasileiro de Ensaios Clínicos* (Brazilian Clinical Trials Registry; ensaiosclinicos.gov.br/); the first 1000 entries of Google Scholar, as well as pharmaceutical company sources, reference lists of potentially eligible studies, and relevant reviews for ongoing or unpublished trials.

We will contact authors of identified trials for additional published or unpublished trials.

We will also examine any relevant retraction statements and errata for information, as errata can reveal important limitations or even fatal flaws in the included studies (Lefebvre 2022b).

We will use the PubMed/MEDLINE “similar articles search” tool on all included trials. We will manually check citations and reference lists of the included trials, and any relevant systematic reviews identified.

We will provide the actual date of searching other sources at the review stage. We will also use, relevant to our review, items from the PRISMA-S checklist to ensure that we have reported and documented our searches as advised (PRISMA-S Checklist; Rethlefsen 2021).

Data collection and analysis

We will perform the review following the recommendations of Cochrane (Higgins 2022a), and we will perform the data analyses using Review Manager Web (RevMan Web 2020).

Selection of studies

We will combine retrieved records from different databases and carry out the entire screening process using the Covidence software (Covidence). Of note, Covidence can also identify duplicates as standard reference manager systems. Initially, two review authors (IJBN and HMA) will screen titles and abstracts and will identify potentially eligible studies according to our eligibility criteria. In case of any conflict between decisions, we will resolve them by group discussion. Secondly, for those primarily qualifying studies in the first review phase, we will acquire the full text and will assess once more the eligibility of these trials for inclusion. During this stage, we will also resolve any conflicts by group discussion. If needed, we will contact the authors of primary studies for further information (after two ResearchGate and/or two email attempts). Lastly, we will identify study duplicates (those reporting the same set of patients) and merge them under one study identification. We will register this primary selection phase in order to fulfil the PRISMA-S flow diagram (Page 2021a; Page 2021b) and 'Characteristics of excluded studies' section.

If, during the selection of trials, we identify observational studies such as quasi-randomised studies or controlled or uncontrolled 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, we will extract the adverse event data reported for the experimental or control groups, or both, separately from the data found in the randomised clinical trials, without doing a formal meta-analysis and risk of bias assessments. We have decided to do so because uncommon and late adverse events can be most often found in observational studies, or in post-marketing phase publications of the use of drugs, and in case reports.

We will check if a trial is retracted. If yes, then we will exclude it (Retraction Watch Database; Moylan 2016; Wager 2011).

Data extraction and management

Two independent authors (VTC and IJBN) will perform data extraction and management by using a template layout form in Covidence. They will extract summary and study identification data (trial registration, ethics committee approval, sponsorship resource, country, setting, and authors details), data on the characteristics of the participants (age, sex, health background, geographical location, and baseline conditions), interventions (description of vaccine, dose, timing, and route of intervention), outcome measures (as defined above), length of follow-up, and study design. We will extract the number of

participants with outcome results and the number of participants evaluated. In case of disagreements, we will re-examine the conflicts until a consensus is reached. When data are missing, we will contact the study authors (initially by electronic correspondence and occasionally by phone contact) for additional information.

Assessment of risk of bias in included studies

Two review authors (IJBN and VTC) will independently assess the risk of bias of each included trial using version 2 of the Cochrane 'Risk of bias' tool (RoB2) (Sterne 2019) according to the recommendations in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b) and methodological studies (Kjaergard 2001; Moher 1998; Savović 2012a; Savović 2012b; Savović 2018; Schulz 1995; Wood 2008). Any disagreements will be resolved by consensus.

We will assess the effect of assignment to the intervention. We will analyse participants in the intervention groups to which they were randomised, regardless of the intervention they actually received; and we will include all randomised participants in the outcome analyses, i.e. we will perform our analyses based on the intention-to-treat principle. We will assess the risk of bias of all primary and secondary outcomes. We will use the below five domains to assess the risk of bias in the individual randomised trials (Higgins 2022b; Higgins 2022c; Sterne 2019).

- Bias arising from the randomisation process;
- Bias due to deviations from intended interventions;
- Bias due to missing outcome data;
- Bias in measurement of the outcome;
- Bias in selection of the reported results.

For trials that allocated clusters of individuals, we will assess and report on the risk of bias associated with one additional domain (as a second domain), specific to the trial design to assess bias (Eldridge 2016):

- Bias arising from the timing of identification and recruitment of individual participants in relation to the timing of randomisation.

For cross-over trials, as mentioned earlier, we will use the data only from the first period of the cross-over, and therefore, we will use the standard version of RoB2 (Sterne 2019).

For signalling questions within each domain for each outcome, we will provide one of the five possible answers in the RoB2 tool ('Yes', 'Probably yes', 'No', 'Probably no' and 'No information'). After this step, we will make a judgement for each domain according to the algorithm result as 'Low risk of bias', 'Some concerns' or 'High risk of bias' for each outcome. The overall risk of bias judgement for each outcome will be the least favourable assessment across the domains.

The three levels of judgement to an overall rating are as follows:

- low risk of bias: the trial is judged to be at low risk of bias for all domains for this result;
- some concerns: the trial is judged to raise some concerns in at least one domain for this result, but is not at high risk of bias for any of the remaining domains;
- high risk of bias: the trial is judged to be at high risk of bias in at least one domain for this result, or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

During our work on the review, we will use the RoB 2.0 Microsoft Excel tool to store the data (which can be received at request) until we find a place to make them publicly available.

The RoB 2 assessments will feed into each domain of the GRADE approach for assessing the certainty of a body of evidence for each outcome (Schünemann 2022) (See "Summary of Findings" section below).

We will summarise our findings in the Risk of bias tables and figures ('Risk of bias graph' and 'Risk of bias summary').

Measures of treatment effect

We will employ the software RevMan Web (RevMan Web 2020) for all statistical analyses. For dichotomous outcomes, we plan to calculate risk ratios (RR) with a 95% confidence interval (CI). For continuous outcomes, we will measure the mean difference (MD) with 95% CI if all retrieved records provide data on the same scale, and as standardised mean difference (SMD) if different scales were used during reporting. For SMD, we will use 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 1998).

For the assessment of 'time to achieve peak titers (months)' and 'peak titers (IU/L)', we plan to analyse the results for the last reported period (longest period of follow-up) using measures of MD with its respective 95% CI.

Unit of analysis issues

For trials using parallel-group designs, we will assess participants as randomised per intervention group. When more than one intervention group is identified, we will collect data for those intervention groups that meet the inclusion criteria of approachable interventions. To overcome a unit of analysis error for a trial that could contribute multiple, correlated comparisons, we will combine all relevant experimental intervention groups of the trial into a single group, and combine all relevant comparator intervention groups into a single comparator group (Higgins 2022a). If we identify a trial with a common control group and two trial experimental groups that fall within the same comparison, we will halve the control group. If we identify a trial with a common experimental group and two trial control groups that fall within the same comparison, we will halve the experimental group. We will include cross-over trials, but for the analysis of the results from these trials, we will include in the overall analysis only the first reported result (i.e. use only data from the first treatment period, before the cross-over) (Higgins 2022c). We will include data from trials where participants were individually and randomly assigned to an experimental and a control group. In those trials where results were based on a long follow-up, we will select only the longest follow-up from each trial.

For cluster-randomised clinical trials, the unit of analysis will be the cluster. In order to avoid a unit of analysis error, we will reanalyse the data by taking account of the intra-cluster correlation (ICC). If these data are not provided, then we will exclude the trial (Higgins 2022c).

Dealing with missing data

As already mentioned, we will contact three main authors from each primary included trial to obtain missing data. If data are unavailable, we intend to perform an analysis, if possible, on an intention-to-treat (ITT) principle that includes participants regardless of compliance or follow-up. If intention-to-treat is still not possible as some participants could have inevitably dropped out, then we will impute the data for the missing participants. If this is not possible either, then we will use the data that are available to us, and we will ignore the missing data in our primary analyses (Higgins 2008).

We plan to perform the below two sensitivity analyses of the influence of participants with incomplete or missing outcome data (risk of attrition bias) using two imputation methods, for our four dichotomous primary outcomes (Hollis 1999).

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

Assessment of heterogeneity

First, we will analyse possible clinical heterogeneity documenting the variability in the participants, interventions, and outcomes in the included trials.

Second, we plan to assess methodological heterogeneity by comparing the distribution of important trial factors (randomisation concealment, blinding of outcome assessment, loss to follow-up, treatment type).

Third, we will check for statistical heterogeneity through visual inspection of the forest plots and assess it using the Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity is genuine. We will consider a threshold of P value < 0.1 as an indicator of whether heterogeneity (genuine variation in effect sizes) is present.

In addition, we will perform the I^2 statistic (Higgins 2022a), a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than to sampling error.

We will interpret the I^2 statistic according to the following recommendations in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022):

- 0 to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 74%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If we identify substantial or considerable heterogeneity (I^2 greater than 50%), we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

We will examine the possibility of within-study selective outcome reporting for each study included in the review. We will search for trial protocols of included trials on electronic sources such as PubMed, ClinicalTrials.gov, and the WHO ICTRP in order to assess whether outcome reporting seems to be sufficiently complete and transparent. We will investigate publication bias by using funnel plots if we include 10 or more clinical trials in the systematic review (Deeks 2022).

Data synthesis

We will perform statistical analysis according to the statistical recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a). We plan to include all trials in our meta-analyses, regardless of their risk of bias. We will compile RRs, hazard ratios (HR), and mean difference (MD) if relevant, with 95% CIs of individual trials using a random-effects meta-analysis, as our main analysis, for data compilation. We will use an intention-to-treat analysis as far as possible. We will analyse data using RevMan Web (RevMan Web 2020).

If meta-analysis is not possible for any of the outcomes, we will use narrative and table formats to present the data. We will provide the reasons for our decision. The scenarios that may preclude meta-analysis, with possible solutions, are presented in Table 12.1.a in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2022).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

- Risk of bias: trials at low risk of bias compared to trials at some concern and trials at high risk of bias because the latter two may overstate benefits and understate harms (Higgins 2022b; Kjaergard 2001; Moher 1998; Moynihan 2019; Savović 2012a; Savović 2012b; Savović 2018; Schulz 1995; Wood 2008).
- Participants' age: trials including participants above 50 years compared to trials including participants under 50 years. Ageing reduces immune cell production and alters body response to the vaccine (Fisman 2002), being, therefore, a potential interference factor that results in a higher or lower rate of immunisation.
- Stage of chronic kidney disease (I to V): each severity stage of the kidney condition because studies suggest that vaccination in the early stages of chronic kidney disease has a more successful seroconversion rate compared to patients in the late stage of the disease (Einollahi 2011; Krueger 2020).
- Type of hepatitis B vaccine: different types of vaccination to find out whether a recombinant or plasma vaccine from different manufacturers could affect differently the immune system of a person.
- Geographical area of the primary study: the prevalence, vaccination coverage, epidemiological aspects, and clinical presentation of hepatitis B might differ from other global geographic locations (Nelson 2016; Zampino 2015).

To determine whether a statistically significant subgroup difference is detected, we will consider the P value from the test for

subgroup differences. We will use this test to assess the difference between the meta-analysed effect estimates for each subgroup. A P value of less than 0.1 will be considered indicative of a significant subgroup effect. We will perform subgroup analyses for the following outcomes: 1. All-cause mortality at maximal follow-up; 2. Proportion of participants with clinically confirmed acute hepatitis B defined as hepatitis B core antigen positivity (anti-HBc) or persistence of HBsAg positivity up to six months after vaccination; 3. Proportion of participants with clinically confirmed chronic hepatitis B infection, defined as persistent levels of HBsAg for more than six months or relevant detection of HBsAg and liver biopsy compatible with a diagnosis of chronic hepatitis B; 4. Proportion of participants with one or more serious adverse events following immunisation with hepatitis B vaccination, regardless of the reporting period; and 5. Health-related quality of life measured by Kidney Disease Quality of Life (KDQOL) or any other validated tool to assess the impact of the disease in daily activities, physical and mental health (Rand Corporation 2020).

Sensitivity analysis

We plan to conduct the following sensitivity analyses.

- Carrying out an assessment based on trials that were funded by the pharmaceutical industry.
- Excluding trials at high risk of bias to explore the effect of the methodological quality of trials on the overestimation of the treatment effect.
- Excluding trials in which hepatitis B vaccine was compared with no vaccination in order to explore differences with the placebo effect.
- Repeating the analysis with the fixed-effect model to explore the presence or absence of statistical heterogeneity of outcome results.
- Excluding trials with missing data for all our four primary outcomes (see Dealing with missing data).
- Conducting Trial Sequential Analysis to assess the imprecision of the primary outcomes only (see below).

Trial Sequential Analysis

We plan to perform Trial Sequential Analysis for each meta-analysis (with at least two trials included) related to primary outcomes to control the risk of random error caused by sparse data and repetitive testing (Thorlund 2017; TSA 2017; Wetterslev 2017). We will calculate the diversity-adjusted required information size (DARIS) to estimate the number of participants needed to detect or reject the intervention effects in the meta-analyses, accounting for the possible presence of diversity (TSA 2017; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017).

We will estimate the DARIS of the dichotomous outcomes based on the proportion of participants with an outcome in the control group, a relative risk reduction of 30%, an alpha of 1.67% because of five primary outcomes, a beta of 10%, and the observed diversity in the trials in the meta-analysis (Jakobsen 2014; Wetterslev 2017). We will estimate the DARIS of the continuous outcome based on a minimal relevant difference equal to half a standard deviation in the control group. We will construct the trial sequential monitoring boundaries to test statistical significance (for benefit or harm) and futility. We will estimate the Z-curve and if it crosses or not the trial sequential monitoring boundaries before reaching the DARIS (further trials are still necessary to detect or reject an intervention effect unless the trial monitoring boundaries for futility are crossed) or after reaching the DARIS (further trials are superfluous to detect or reject an intervention effect) (Thorlund 2017; Wetterslev 2008; Wetterslev 2017). In Trial Sequential Analysis where the cumulative Z-value does not cross the monitoring boundaries for benefit, harm, or futility, we will downgrade our assessment of imprecision in GRADE (see below) by two levels if the accrued number of participants is below 50% of the DARIS, and by one level if between 50% and 100% of DARIS. We will not downgrade for imprecision if the cumulative Z-value reaches or crosses benefit, harm, futility, or DARIS. We will perform Trial Sequential Analysis with Trial Sequential Analysis software, version 0.9.5.10 beta (TSA 2017).

Summary of findings and assessment of the certainty of the evidence

We will consider *The Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach for the preparation of the summary of findings tables, using the GRADEpro GDT software (GRADEpro GDT). We plan to create three summary of findings tables on the comparison of i) hepatitis B vaccination versus placebo or no vaccination; on the comparison of II) a reinforced programme of immunisation of three inoculations plus additional administration versus regular vaccination; and on the comparison of III) intradermal versus intramuscular hepatitis B vaccination, for six main outcomes. The outcomes to be summarised in the summary of findings table are: i) all-cause mortality, ii) proportion of participants with clinically confirmed hepatitis B, iii) proportion of participants with one or more serious adverse events after immunisation with hepatitis B vaccination, iv) health-related quality of life, v) proportion of participants without seroconversion, and vi) proportion of participants with one or more non-serious adverse medical events. We will provide outcome results at the maximum follow-up, with median or mean, and the range of follow-up for each of the outcomes (see Types of outcome measures).

GRADE uses five factors for assessing the certainty of evidence, i.e. risk of bias (i.e. overall RoB 2 judgement), heterogeneity, imprecision (we will calculate the optimal information size), indirectness, and publication bias. We will use the overall judgement of risk of bias for an outcome result. 'Low' risk of bias will indicate 'no limitation (the certainty will not be rated down)'; 'Some concerns' will indicate either 'no limitation' or 'serious limitation (the certainty will be rated down one level)'; and 'High' risk of bias will indicate either 'serious limitation' or 'very serious limitation (the certainty will be rated down two levels)'. We will justify all decisions to downgrade the quality of trials using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Based on defined criteria for risk of bias, inconsistency, indirectness of evidence, imprecision, and presence of publication bias, we will downgrade the evidence by one level for serious, or two levels for very serious limitations.

The levels of summary evidence are defined as 'high', 'moderate', 'low', or 'very low'.

- **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.

Two review authors (IJBN and VTC) will use the GRADE tool to assess the overall certainty of the evidence. Disagreement will be resolved by consensus. We will incorporate the GRADE judgements about the certainty of the evidence in our reporting of the results.

ACKNOWLEDGEMENTS

We thank Dimitrinka Nikolova, Managing Editor, and Christian Gluud, Co-ordinating Editor, for the advice and mentoring. We thank Maria Björklund and Sarah Louise Klingenberg for their assistance in the review as information specialists. We thank Matteo Bruschettini (Cochrane Sweden) for mentoring IJBN during the protocol submission and offering support and motivation for a long-term run.

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of the Cochrane Hepato-Biliary Group through its investment in the Copenhagen Trial Unit, Centre for Clinical Intervention Research, the Capital Region, Rigshospitalet, Copenhagen, Denmark.
Disclaimer: the views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.

Both the Cochrane Hepato-Biliary Group and the Cochrane Kidney and Transplant Group shared the editorial work on the protocol.

The following people from the Cochrane Hepato-Biliary Editorial Team conducted the editorial process for this protocol.
Sign-off Editor (final editorial decision): Christian Gluud, Co-ordinating Editor, Denmark
Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the protocol): Dimitrinka Nikolova, Denmark
Information Specialist (database searches): Sarah Louise Klingenberg, Denmark
Peer-reviewers (provided clinical and content review comments): Mirella Fraquelli, Italy; (peer review of review methods): Kerry Dwan, UK

The following people from the Cochrane Kidney and Transplant Editorial Team conducted the editorial process for this protocol.
Sign-off Editor (final editorial decision): Jonathan Craig, Co-ordinating Editor, Australia
Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the protocol): Tess Cooper, Australia
Assistant Managing Editor: Narelle Willis, Australia
Information Specialist (database searches): Gail Higgins, Australia
Peer-reviewers (provided clinical and content review comments): Giovanni Strippoli, Australia

Evidence Synthesis Development Editor (protocol screening): Leslie Choi, Evidence Production and Methods Department, Cochrane, UK
Copy Editor (copy editing and production): Anne Lethaby, UK

REFERENCES

Additional references

Baig 2008

Baig S, Alamgir M. The extrahepatic manifestations of hepatitis B virus. *Journal of the College of Physicians and Surgeons Pakistan* 2008;**18**(7):451-7. [PMID: 18760074]

CDCP 2001

Centers for Disease Control and Prevention. Recommendations for preventing transmission of infections among chronic hemodialysis patients. *MMWR - Recommendations and Reports : Morbidity and Mortality Weekly Report* 2001;**50**(RR-5):1-43. [PMID: 11349873]

CDCP 2006

Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States/recommendations of the Advisory Committee on Immunization Practices (ACIP) part II: immunization of adults. MMWR - Department of Health and Human Services Centers for Disease Control and Prevention 2006;**55**(RR-16):1-33.

CDCP 2020a

Centers for Disease Control and Prevention. Chronic kidney disease basics. www.cdc.gov/kidneydisease/basics.html (accessed 11 November 2022).

CDCP 2020b

Centers for Disease Control and Prevention. Hepatitis B questions and answers for health professionals. www.cdc.gov/hepatitis/hbv/hbvfaq.htm (accessed 11 November 2022).

Chen 2005

Chen W, Gluud C. Vaccines for preventing hepatitis B in healthcare workers. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No: CD000100. [DOI: 10.1002/14651858.CD000100.pub3]

Chen 2016

Chen SS, Al Mawed S, Unruh M. Health-related quality of life in end-stage renal disease patients: how often should we ask and what do we do with the answer? *Blood Purification* 2016;**41**(1-3):218-24. [DOI: 10.1159/000441462]

Cohen 1998

Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edition. New York: Routledge, 1988.

Cordeiro 2018

Cordeiro VM, Martins BC, Teles SA, Martins RM, Cruvinel KP, Matos MA, et al. Decline in hepatitis B and C prevalence among hemodialysis patients in Tocantins, Northern Brazil. *Revista do Instituto de Medicina Tropical de São Paulo* 2018;**60**(e36):1-6. [DOI: 10.1590/s1678-9946201860036]

Coresh 2003

Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: third National Health and Nutrition Examination Survey. *American Journal of Kidney Diseases* 2003;**41**(1):1-12. [DOI: 10.1053/ajkd.2003.50007]

Covidence [Computer program]

Covidence - Better systematic review management. Melbourne, Australia: Veritas Health Innovation, (accessed 11 November 2022). Available at www.covidence.org.

Da Roza 2003

Da Roza G, Loewen A, Djurdjev O, Love J, Kempston C, Burnett S, et al. Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. *American Journal of Kidney Diseases* 2003;**42**(6):1184-92. [DOI: 10.1053/j.ajkd.2003.08.019]

Das 2019

Das S, Ramakrishnan K, Behera SK, Ganesapandian M, Xavier AS, Selvarajan S. Hepatitis B vaccine and immunoglobulin: key concepts. *Journal of Clinical and Translational Hepatology* 2019;**7**(2):165-71. [DOI: 10.14218/JCTH.2018.00037]

Deeks 2022

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Einollahi 2011

Einollahi B. Immune response to hepatitis B vaccine in patients with chronic kidney disease. *Hepatitis Monthly* 2011;**11**(10):781-2. [DOI: 10.5812/kowsar.1735143x.766]

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140-9. [DOI: 10.1093/ije/31.1.140]

Eldridge 2016

Eldridge S, Campbell M, Campbell M, Dahota A, Giraudeau B, Higgins J, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0). Additional considerations for cluster-randomized trials. www.riskofbias.info/welcome/rob-2-0-tool/archive-rob-2-0-cluster-randomized-trials-2016 (accessed 11 November 2022).

Fabrizi 1996

Fabrizi F, Di Filippo S, Marcelli D, Guarnori I, Raffaele L, Crepaldi M, et al. Recombinant hepatitis B vaccine use in chronic hemodialysis patients. Long-term evaluation and cost-effectiveness analysis. *Nephron* 1996;**72**(4):536-43. [DOI: 10.1159/000188935]

Fabrizi 1997

Fabrizi F, Andrulli S, Bacchini G, Corti M, Locatelli F. Intradermal versus intramuscular hepatitis B re-vaccination in non-responsive chronic dialysis patients: a prospective randomized study with cost-effectiveness evaluation. *Nephrology Dialysis Transplantation* 1997;**12**(6):1204-11. [DOI: 10.1093/ndt/12.6.1204]

Fabrizi 2010

Fabrizi F, Dixit V, Messa P, Martin P. Meta-analysis: levamisole improves the immune response to hepatitis B vaccine in dialysis patients. *Alimentary Pharmacology & Therapeutics* 2010;**32**(6):756-62. [DOI: 10.1111/j.1365-2036.2010.04410.x]

Fabrizi 2015a

Fabrizi F, Messa P. Transmission of hepatitis C virus in dialysis units: a systematic review of reports on outbreaks. *International Journal of Artificial Organs* 2015;**38**:471-80. [DOI: 10.5301/ijao.5000437]

Fabrizi 2017

Fabrizi F, Donato FM, Messa P. Hepatitis C and its metabolic complications in kidney disease. *Annals of Hepatolology* 2017;**16**(6):851-61. [DOI: 10.5604/01.3001.0010.5275]

Fabrizi 2020

Fabrizi F, Cerutti R, Garcia-Agudo R, Bellincioni C, Porata G, Frontini G, et al. Adjuvanted recombinant HBV vaccine (HBV-AS04) is effective over extended follow-up in dialysis population. An open-label nonrandomized trial. *Clinics and Research in Hepatology and Gastroenterology* 2020;**44**(6):905-12. [DOI: 10.1016/j.clinre.2020.01.010]

Fabrizi 2004

Fabrizi F, Martin P, Dixit V, Bunnapradist S, Dulai G. Meta-analysis: the effect of age on immunological response to hepatitis B vaccine in end-stage renal disease. *Alimentary Pharmacology & Therapeutics* 2004;**20**(10):1053-62. [DOI: 10.1111/j.1365-2036.2004.02264.x]

Fabrizi 2015b

Fabrizi F, Dixit V, Messa P, Martin P. Transmission of hepatitis B virus in dialysis units: a systematic review of reports on outbreaks. *International Journal of Artificial Organs* 2015;**38**:1-7. [DOI: 10.5301/ijao.5000376]

Finelli 2005

Finelli L, Miller JT, Tokars JI, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2002. *Seminars in Dialysis* 2005;**18**(1):52-61. [DOI: 10.1111/j.1525-139X.2005.18108.x]

Fisman 2002

Fisman DN, Agrawal D, Leder K. The effect of age on immunologic response to recombinant hepatitis B vaccine: a meta-analysis. *Clinical Infectious Diseases* 2002;**35**(11):1368–75. [DOI: 10.1086/344271]

GBD Chronic Kidney Disease Collaboration 2020

GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020;**395**(10225):709-33. [DOI: 10.1016/S0140-6736(20)30045-3]

Golestaneh 2017

Golestaneh L, Alvarez PJ, Reaven NL, Funk SE, McGaughey KJ, Romero A, et al. All-cause costs increase exponentially with increased chronic kidney disease stage. *American Journal of Managed Care* 2017;**23**(10 Suppl):S163-72. [PMID: 28978205]

GRADEpro GDT [Computer program]

GRADEpro GDT. Version (accessed 11 November 2022). Hamilton (ON): McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Greenberg 2002

Greenberg DP, Wong VK, Partridge S, Howe BJ, Ward JI. Safety and immunogenicity of a combination diphtheria-tetanus toxoids-acellular pertussis hepatitis B vaccine administered at two, four and six months of age compared with monovalent hepatitis B vaccine administered at birth, one month and six months of age. *Pediatric Infectious Disease Journal* 2002;**21**(8):769-77. [DOI: 10.1097/00006454-200208000-00014]

Grzegorzewska 2014

Grzegorzewska AE. Hepatitis B vaccination in chronic kidney disease patients: a call for novel vaccines. *Expert Review of Vaccines* 2014;**13**(11):1317-26. [DOI: 10.1586/14760584.2014.944508]

Guan 1990

Guan R, Tay HH, Choong HL, Yap I, Woo KT. Hepatitis B vaccination in chronic renal failure patients undergoing haemodialysis: the immunogenicity of an increased dose of a recombinant DNA hepatitis B vaccine. *Annals of the Academy of Medicine, Singapore* 1990;**19**(6):793-7. [PMID: 2151841]

Halperin 2013

Halperin SA, Ward BJ, Dionne M, Langley JM, McNeil SA, Smith B, et al. Immunogenicity of an investigational hepatitis B vaccine (hepatitis B surface antigen co-administered with an immunostimulatory phosphorothioate oligodeoxyribonucleotide) in nonresponders to licensed hepatitis B vaccine. *Human Vaccines & Immunotherapeutics* 2013;**9**(7):1438-44. [DOI: 10.4161/hv.24256]

Harpaz 2000

Harpaz R, McMahon BJ, Margolis HS, Shapiro CN, Havron D, Carpenter G, et al. Elimination of new chronic hepatitis B virus infections: results of the Alaska immunization program. *Journal of Infectious Diseases* 2000;**181**(2):413-8. [DOI: 10.1086/315259]

Higgins 2008

Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clinical Trials* 2008;**5**:225-39.

Higgins 2022a

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of

Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Higgins 2022b

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Higgins 2022c

Higgins JP, Eldridge S, Li T, editor(s). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Hollis 1999

Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ (Clinical Research Ed.)* 1999;**319**(7211):670-674. [DOI: 10.1136/bmj.319.7211.670] [PMID: 10480822]

Hong 2018

Hong YS, Ryu S, Chang Y, Cainzos-Achirica M, Kwon MJ, Zhao D, et al. Hepatitis B virus infection and development of chronic kidney disease: a cohort study. *BMC Nephrology* 2018;**19**(1):353. [DOI: 10.1186/s12882-018-1154-4]

Hsu 1988

Hsu HM, Chen DS, Chuang CH, Lu JC, Jwo DM, Lee CC, et al. Efficacy of a mass hepatitis B vaccination program in Taiwan. Studies on 3464 infants of hepatitis B surface antigen-carrier mothers. *JAMA* 1988;**260**(15):2231-5. [PMID: 2971827]

ICH-GCP 2016

International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH). ICH Harmonised Guideline. Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2). database.ich.org/sites/default/files/E6_R2_Addendum.pdf (accessed 11 November 2022).

Jakobsen 2014

Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Medical Research Methodology* 2014;**14**:120. [DOI: 10.1186/1471-2288-14-120]

Janssen 2013

Janssen RS, Mangoo-Karim R, Pergola PE, Girndt M, Namini H, Rahman S, et al. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HbsAg-1018) compared with a licensed hepatitis B vaccine in patients with chronic kidney disease. *Vaccine* 2013;**31**(46):5306-13. [DOI: 10.1016/j.vaccine.2013.05.067]

Jilg 1989

Jilg W, Schmidt M, Deinhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. *Journal of Infectious Diseases* 1989;**160**(5):766-9. [DOI: 10.1093/infdis/160.5.766]

Kausz 2004

Kausz A, Pahari D. The value of vaccination in chronic kidney disease. *Seminars in Dialysis* 2004;**17**(1):9-11. [DOI: 10.1111/j.1525-139x.2004.17104.x]

Kim 2018

Kim DK, Riley LE, Hunter P, Advisory Committee on Immunization Practices. Recommended immunization schedule for adults aged 19 years or older, United States, 2018. *Annals of Internal Medicine* 2018;**168**(3):210-20. [DOI: 10.7326/M17-3439]

Kimmel 2020

Kimmel PL, Rosenberg ME. Chronic Renal Disease. 2nd edition. Academic Press, 2020.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982-9. [DOI: 10.7326/0003-4819-135-11-200112040-00010]

Krueger 2020

Krueger KM, Ison MG, Ghossein C. Practical guide to vaccination in all stages of CKD, including patients treated by dialysis or kidney transplantation. *American Journal of Kidney Diseases* 2020;**75**(3):417-25. [DOI: 10.1053/j.ajkd.2019.06.014]

Lee 2018

Lee WC, Lee YT, Li LC, Ng HY, Kuo WH, Lin PT, et al. The number of comorbidities predicts renal outcomes in patients with stage 3–5 chronic kidney disease. *Journal of Clinical Medicine* 2018;**7**(12):493.

Lee 2019

Lee LY, Chan SM, Ong C, Aw M, Wong F, Saw S, et al. Comparing monovalent and combination hepatitis B vaccine outcomes in children delivered by mothers with chronic hepatitis B. *Journal of Paediatrics and Child Health* 2019;**55**(3):327-32. [DOI: 10.1111/jpc.14194]

Lefebvre 2022a

Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Lefebvre 2022b

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Technical supplement to Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions

Version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Leroux-Roels 2015

Leroux-Roels G. Old and new adjuvants for hepatitis B vaccines. *Medical Microbiology and Immunology* 2015;**204**(1):69-78. [DOI: 10.1007/s00430-014-0375-9]

Levey 2005

Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International* 2005;**67**(6):2089-100. [DOI: 10.1111/j.1523-1755.2005.00365.x]

Lewis-Ximenez 2001

Lewis-Ximenez LL, Oliveira JM, Mercadante LA, De Castro L, Santa Catharina W, Stuver S, et al. Serological and vaccination profile of hemodialysis patients during an outbreak of hepatitis B virus infection. *Nephron* 2001;**87**(1):19-26. [DOI: 10.1159/000045880]

Mast 2005

Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, et al, Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recommendations and Reports* 2005;**54**(RR-16):1-31. [PMID: 16371945]

McKenzie 2022

McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Ministério da Saúde 2007

Brazil, Ministério da Saúde. Office of Health Attention. Immunizations [Secretaria de Atenção à Saúde. Imunizações]. https://bvsms.saude.gov.br/bvs/publicacoes/manual_procedimentos_vacinacao.pdf (accessed prior to 8 March 2023).

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**(9128):609-13. [DOI: 10.1016/S0140-6736(98)01085-X]

Moylan 2016

Moylan EC, Kowalczuk MK. Why articles are retracted: a retrospective cross-sectional study of retraction notices at BioMed Central. *BMJ Open* 2016;**6**:e012047. [DOI: 10.1136/bmjopen-2016-012047]

Moynihan 2019

Moynihan R, Bero L, Hill S, Johansson M, Lexchin J, Macdonald H, et al. Pathways to independence: towards producing and using trustworthy evidence. *BMJ (Clinical Research Ed.)* 2019;**367**:l6576. [DOI: 10.1136/bmj.l6576]

Nelson 2016

Nelson NP, Easterbrook PJ, McMahon BJ. Epidemiology of hepatitis B virus infection and impact of vaccination on disease. *Clinical Liver Disease* 2016;**20**(4):607-28. [DOI: 10.1016/j.cld.2016.06.006]

Nistor 2015

Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, et al. Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease. *Cochrane Database of Systematic Reviews* 2015, Issue 5. Art. No: CD006258. [DOI: 10.1002/14651858.CD006258.pub2]

Page 2021a

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)* 2021;**372**:n71.

Page 2021b

Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ (Clinical Research Ed.)* 2021;**372**:n160.

Perazella 2006

Perazella MA, Khan S. Increased mortality in chronic kidney disease: a call to action. *American Journal of the Medical Sciences* 2006;**331**(3):150-3. [DOI: 10.1097/00000441-200603000-00007]

Poorolajal 2016

Poorolajal J, Hooshmand E. Booster dose vaccination for preventing hepatitis B. *Cochrane Database of Systematic Reviews* 2016, Issue 6. Art. No: CD008256. [DOI: 10.1002/14651858.CD008256.pub3]

Rand Corporation 2020

Rand Health Care Corporation. Kidney Disease Quality of Life Instrument (KDQOL). www.rand.org/health-care/surveys_tools/kdqol.html (accessed on 11 November 2022).

Reddy 2019

Reddy S, Chitturi C, Yee J. Vaccination in chronic kidney disease. *Advances in Chronic Kidney Disease* 2019;**26**(1):72-8. [DOI: 10.1053/j.ackd.2018.10.002]

Rethlefsen 2021

Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al, PRISMA-S Group. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. *Systematic Reviews* 2021;**10**(1):39.

RevMan Web 2020 [Computer program]

Review Manager Web (RevMan Web). Version 1.22.0. The Cochrane Collaboration, 2020.

Sali 2008

Sali S, Alavian SM, Hajarizadeh B. Effect of levamisole supplementation on hepatitis B virus vaccination response in hemodialysis patients. *Nephrology (Carlton, Vic.)* 2008;**13**(5):376-9. [DOI: 10.1111/j.1440-1797.2008.00952.x]

Savović 2012a

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429-38. [DOI: 10.7326/0003-4819-157-6-201209180-00537]

Savović 2012b

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. *Health Technology Assessment* 2012;**16**(35):1-82. [DOI: 10.3310/hta16350]

Savović 2018

Savović J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JP, et al. Association between risk-of-bias assessments and results of randomized trials in Cochrane Reviews: the ROBES Meta-Epidemiologic Study. *American Journal of Epidemiology* 2018;**187**(5):1113-22. [DOI: 10.1093/aje/kwx344]

Schillie 2018

Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices. *MMWR Recommendations and Reports : Morbidity and Mortality Weekly Report* 2018;**67**(1):1-31. [DOI: 10.15585/mmwr.rr6701a1]

Schroth 2004

Schroth RJ, Hitchon CA, Uhanova J, Noreddin AM, Taback SP, Moffatt M, et al. Hepatitis B vaccination for patients with chronic renal failure. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No: CD003775. [DOI: 10.1002/14651858.CD003775.pub2]

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12. [DOI: 10.1001/jama.273.5.408]

Schweitzer 2017

Schweitzer A, Akmatov MK, Krause G. Hepatitis B vaccination timing: results from demographic health surveys in 47 countries. *Bull World Health Organ* 2017;**95**(3):199-209G. [PMID: 28250533]

Schünemann 2022

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Shah 2017

Shah AS, Amarapurkar DN. Spectrum of hepatitis B and renal involvement. *Liver International* 2017;**38**(1):23-32. [DOI: 10.1111/liv.13498]

Shouval 2015

Shouval D, Roggendorf H, Roggendorf M. Enhanced immune response to hepatitis B vaccination through immunization with a Pre-S1/Pre-S2/S vaccine. *Medical Microbiology and Immunology* 2015;**204**(1):57-68. [DOI: 10.1007/s00430-014-0374-x]

Sterne 2019

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed.)* 2019;**366**:l4898. [DOI: 10.1136/bmj.l4898]

Thorlund 2017

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User Manual for Trial Sequential Analysis (TSA); 2nd edition. Copenhagen Trial Unit, 2017. Available from ctu.dk/tsa/learn-more (accessed 11 November 2022).

TSA 2017 [Computer program]

TSA - Trial Sequential Analysis. Version 0.9.5.10 Beta. Copenhagen: Copenhagen Trial Unit, 2017. ctu.dk/tsa/downloads/.

Vaidya 2019

Vaidya SR, Aeddula NR. Chronic Renal Failure. Treasure Island (FL): StatPearls Publishing, 2019. [PMID: 30571025]

Valderrábano 2001

Valderrábano F, Jofre R, López-Gómez JM. Quality of life in end-stage renal disease patients. *American Journal of Kidney Diseases* 2001;**38**(3):443-64. [DOI: 10.1053/ajkd.2001.26824]

Wager 2011

Wager E, Williams P. Why and how do journals retract articles? An analysis of Medline retractions 1988-2008. *Journal of Medical Ethics* 2011;**37**:567-70.

Webster 2017

Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet* 2017;**389**(100075):1238-52. [DOI: 10.1016/S0140-6736(16)32064-5]

West 1996

West DJ, Calandra GB. Vaccine induced immunologic memory for hepatitis B surface antigen: implications for policy on booster vaccination. *Vaccine* 1996;**14**(11):1019-27. [DOI: 10.1016/0264-410x(96)00062-x]

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in

cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75. [DOI: 10.1016/j.jclinepi.2007.03.013]

Wetterslev 2009

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in a random-effects meta-analysis. *BMC Medical Research Methodology* 2009;**9**:86. [DOI: 10.1186/1471-2288-9-86]

Wetterslev 2017

Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Medical Research Methodology* 2017;**17**(1):39. [DOI: 10.1186/s12874-017-0315-7]

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**(7644):601-5. [DOI: 10.1136/bmj.39465.451748.AD]

World Health Organization 2019

World Health Organization. Hepatitis B. www.who.int/news-room/fact-sheets/detail/hepatitis-b (accessed on 11 November 2022).

Yousaf 2015

Yousaf F, Gandham S, Galler M, Spinowitz B, Charytan C. Systematic review of the efficacy and safety of intradermal versus intramuscular hepatitis B vaccination in end-stage renal disease population unresponsive to primary vaccination series. *Renal Failure* 2015;**37**(7):1080-8. [PMID: 26258528]

Zampino 2015

Zampino R, Boemio A, Sagnelli C, Alessio L, Adinolfi LE, Sagnelli E, et al. Hepatitis B virus burden in developing countries. *World Journal of Gastroenterology* 2015;**21**(42):11941-53. [DOI: 10.3748/wjg.v21.i42.11941]

APPENDICES

Appendix 1. Appendix 1 - Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register (via the Cochrane Register of Studies Web)	Date of search will be given at review stage	(hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or dialysis or CAPD or CCPD or APD or end-stage renal or end-stage kidney or endstage renal or endstage kidney or ESRF or ESKF or ESRD or ESKD or chronic kidney or chronic renal or CKF or CKD or CRF or CRD or predialysis or pre-dialysis or ur?emi$) and (((hepatitis B or HBV or hep B) and (vaccin* or re-vaccin* or immuni* or inject* or booster)) or (engerix or heptavax or recombivax or pediatrix or twinrix or vaxelis or HB-VaxPro or Elovac or genevac or shanvac or fendrix or hepislav))
Cochrane Central Register of Controlled Trials in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Renal Replacement Therapy] this term only #2 MeSH descriptor: [Renal Dialysis] explode all trees #3 (hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or dialysis or CAPD or CCPD or APD) #4 MeSH descriptor: [Renal Insufficiency] this term only #5 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees #6 MeSH descriptor: [Kidney Diseases] this term only #7 MeSH descriptor: [Uremia] this term only #8 (end-stage renal or end-stage kidney or endstage renal or endstage kidney or ESRF or ESKF or ESRD or ESKD or chronic kidney or chronic renal or CKF or CKD or CRF or CRD or predialysis or pre-dialysis or ur?emi$) #9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 #10 MeSH descriptor: [Hepatitis B Vaccines] explode all trees

(Continued)

		#11 ((hepatitis B or HBV or hep B) and (vaccin* or re-vaccin* or immuni* or inject* or booster)) #12 (engerix or heptavax or recombivax or pediatrix or twinrix or vaxelis or HB-VaxPro or Elovac or genevac or shanvac or fendrix or hepislav) #13 #10 or #11 or #12 #14 #9 and #13
MEDLINE Ovid	1946 to date of search	1. Renal Replacement Therapy/ 2. exp Renal Dialysis/ 3. (hemodialysis or haemodialysis or hemofiltration or haemofiltration or haemodiafiltration or haemodiafiltration or dialysis or CAPD or CCPD or APD).tw. 4. Renal Insufficiency/ 5. exp Renal Insufficiency, Chronic/ 6. Kidney Diseases/ 7. Uremia/ 8. (end-stage renal or end-stage kidney or endstage renal or endstage kidney or ESRF or ESKF or ESRD or ESKD or chronic kidney or chronic renal or CKF or CKD or CRF or CRD or predialysis or pre-dialysis or ur?emi$).tw. 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. exp Hepatitis B Vaccines/ 11. ((hepatitis B or HBV or hep B) and (vaccin* or re-vaccin* or immuni* or inject* or booster)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 12. (engerix or heptavax or recombivax or pediatrix or twinrix or vaxelis or HB-VaxPro or Elovac or genevac or shanvac or fendrix or hepislav).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 13. 10 or 11 or 12 14. 9 and 13 15. (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or trial.ti. 16. (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, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 17. 14 and (15 or 16)
Embase Ovid	1974 to date of search	1. exp Renal Replacement Therapy/

(Continued)

		2. (hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or dialysis or CAPD or CCPD or APD).tw. 3. Kidney Disease/ 4. Chronic Kidney Disease/ 5. Kidney Failure/ 6. Chronic Kidney Failure/ 7. Uremia/ 8. (end-stage renal or end-stage kidney or endstage renal or endstage kidney or ESRF or ESKF or ESRD or ESKD or chronic kidney or chronic renal or CKF or CKD or CRF or CRD or predialysis or pre-dialysis or ur?emi$).tw. 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. exp hepatitis B vaccine/ 11. ((hepatitis B or HBV or hep B) and (vaccin* or re-vaccin* or immuni* or inject* or booster)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 12. (engerix or heptavax or recombivax or pediatrix or twinrix or vaxelis or HBVaxPro or Elovac or genevac or shanvac or fendrix or hepislav).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 13. 10 or 11 or 12 14. 9 and 13 15. Randomized controlled trial/ or Controlled clinical study/ or trial.ti. 16. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 17. 14 and (15 or 16)
LILACS (Bireme)	1982 to date of search	(hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or dialysis or CAPD or CCPD or APD or end-stage renal or end-stage kidney or endstage renal or endstage kidney or ESRF or ESKF or ESRD or ESKD or chronic kidney or chronic renal or CKF or CKD or CRF or CRD or predialysis or pre-dialysis or uremi) [Words] and ((hepatitis B or HBV or hep B) and (vaccin$ or re-vaccin$ or immuni$ or inject$ or booster)) or (engerix or heptavax or recombivax or pediatrix or twinrix or vaxelis or HBVaxPro or Elovac or genevac or shanvac or fendrix or hepislav) [Words]
Science Citation Index Expanded (Web of Science)	1900 to date of search	#6 #5 AND #4 #5 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #4 #1 AND (#2 or #3) #3 TS=(engerix or heptavax or recombivax or pediatrix or twinrix or vaxelis or HBVaxPro or Elovac or genevac or shanvac or fendrix or hepislav)

(Continued)

		#2 TS=((hepatitis B or HBV or hep B) and (vaccin* or re-vaccin* or immuni* or inject* or booster)) #1 TS=(hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or dialysis or CAPD or CCPD or APD or end-stage renal or end-stage kidney or endstage renal or endstage kidney or ESRF or ESKF or ESRD or ESKD or chronic kidney or chronic renal or CKF or CKD or CRF or CRD or predialysis or pre-dialysis or ur?emi*)
Conference Proceedings Citation Index – Science (Web of Science)	1990 to date of search	#6 #5 AND #4 #5 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #4 #1 AND (#2 or #3) #3 TS=(engerix or heptavax or recombivax or pediatrix or twinrix or vaxelis or HBVaxPro or Elovac or genevac or shanvac or fendrix or hepislav) #2 TS=((hepatitis B or HBV or hep B) and (vaccin* or re-vaccin* or immuni* or inject* or booster)) #1 TS=(hemodialysis or haemodialysis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or dialysis or CAPD or CCPD or APD or end-stage renal or end-stage kidney or endstage renal or endstage kidney or ESRF or ESKF or ESRD or ESKD or chronic kidney or chronic renal or CKF or CKD or CRF or CRD or predialysis or pre-dialysis or ur?emi*)

CONTRIBUTIONS OF AUTHORS

IJBN, AP, FZ, VTC, and HMA have contributed equally during the preparation of this protocol.

NEC joined the team at a later stage. NC contributed with comments to the protocol.

All authors approved the publication of the protocol.

DECLARATIONS OF INTEREST

IJBN has no known conflicts.
AP has no known conflicts.
FZ has no known conflicts.
VTC has no known conflicts.
NEC has no known conflicts.
HMA has no known conflicts.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Brazil

  IJBN receives a research scholarship by the Brazilian Research Agencies *Conselho* .

External sources

- Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital — Rigshospitalet, Copenhagen, Denmark, Denmark

  Provided help with the protocol preparation