Booster dose vaccination for preventing hepatitis B (Protocol)

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[Intervention Protocol]

Booster dose vaccination for preventing hepatitis B

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the benefits and harms of booster dose hepatitis B vaccination for preventing hepatitis B infection.

BACKGROUND

Description of the condition

The protection provided by hepatitis B vaccine has been well documented (Chen 2005; McMahon 2005; Mast 2006). Antibody to hepatitis B surface antigen (anti-HBs) concentrations equal to or greater than 10 mIU/ml is generally considered protective against hepatitis B virus (HBV) infection (WHO 2002; Mast 2006). However, the protective antibodies induced by hepatitis B vaccine wane gradually over time and may reach very low or even undetectable levels (Wainwright 1997; Dentinger 2005). It is not precisely known if anti-HBs concentrations below 10 mIU/ml may offer protection. Furthermore, we do not know the exact benefits and harms of booster dose vaccination in such persons.

Description of the intervention

Some long-term follow-up studies indicated that a three-dose vaccination schedule provides immunity against HBV infection for as long as 15 years (Liao 1999; McMahon 2005). In addition, immunologic studies revealed that hepatitis B vaccine induces immunologic memory, so that memory B cells can proliferate, differentiate, and retain the capacity to generate a rapid and vigorous anamnestic immune response upon reexposure to hepatitis B surface antigen (HBsAg), even if the anti-HBs titre falls below protective level (Watson 2001; Samandari 2007; van der Sande 2007). Hence disappearance of antibody does not necessarily imply loss of protection. Nonetheless, HBV breakthrough infection, which is detected by presence of antibody to hepatitis B core antigen (anti-HBc) in the blood, and chronic hepatitis B virus carriage, which is detected by presence of HBsAg in the blood, are reported in some vaccinees, especially in endemic regions (Hadler 1986; Liao 1999; McMahon 2005). Moreover, adults are less likely than infants to demonstrate an anamnestic response of their immunereaction to hepatitis B virus or hepatitis B vaccine as they grow older (Samandari 2007), and the risk of HBV infection increases by sexual and occupational exposures during adulthood (Whittle 2002). In the context of these relatively limited results, the duration of immunity provided by a complete course of vaccine is unknown, because vaccine protection is not parallel to the anti-HBs titre. Indeed, it is not clear whether a decline in serum anti-HBs level implies the possible need for booster dose of the vaccine.

How the intervention might work

There is a practical approach to determine the duration of protection provided by hepatitis B vaccine. In this approach, we assume that the response to booster dose mimics the response to hepatitis B wild virus. Therefore, through measuring the immune response to booster doses of vaccine in definite periods post primary vaccination, we can assess presence of anamnestic immune response indirectly and hence long-term immunity induced by hepatitis B vaccine against infection.

Why it is important to do this review

Since unnecessary hepatitis B revaccination is wasteful, none of the international guidelines recommend booster doses to be applied universally (WHO 2003; John 2005; Puro 2005; Mast 2006). Furthermore, duration of protection provided by hepatitis B vaccine is important for public health authorities who have to plan the immunisation programs and formulate future booster policies. Hence protective immunity of vaccine still requires further investigations (European Consensus Group 2000; FitzSimons 2005; John 2005). We found a few review articles (European Consensus Group 2000; Banatvala 2003; Chen 2005; FitzSimons 2005; Lee 2006; Mast 2006) but not a meta-analysis or a systematic review addressing the anamnestic immune response to booster dose of hepatitis B vaccine. In this systematic review, we will consider an approach to determine long-term protection provided by hepatitis B vaccine and the need for hepatitis B vaccine booster dose.

OBJECTIVES

To assess the benefits and harms of booster dose hepatitis B vaccination for preventing hepatitis B infection.

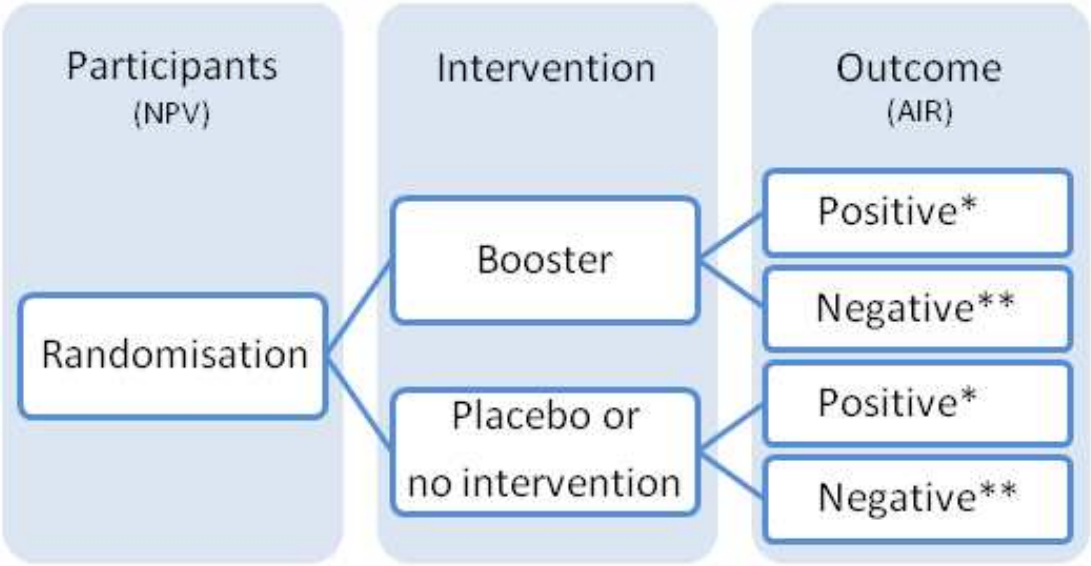
METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials addressing response to hepatitis B vaccine booster dose in non-protected vaccinees, ie, vaccines with anti-HBs level under 10 mIU/mL (Figure 1).

**Figure 1. NPV: non-protected vaccinees (with anti-HBs less than 10 mIU/ml).
AIR: anamnestic immune response.
* Positive: number with anti-HBs at or above 10 mIU/mL
** Negative: number with anti-HBs below 10 mIU/mL**



We will include trials, irrespective of randomisation, blinding, publication status, or language.

We will restrict our review to long-term studies with more than five years follow-up after the primary vaccination, because several follow-up studies indicated that none of the vaccinated participants became HBsAg positive in the first five years post-primary vaccination (Wainwright 1989; Lai 1993; Mintai 1993; Zhang 1993; Goh 1995; Joshi 1995; Yuen 1999; Chadha 2000; Durlach 2003; But 2008; Gilca 2008). In addition, World Health Organization (WHO) has stated that the duration of vaccine-induced immunity is uncertain, but it is definitely long term (more than 15 years) (WHO 2002). Accordingly, we will exclude short-term (less than five years) trials from the initial vaccination (Appendix 1).

Types of participants

We will include those apparently healthy participants with intact immune status, without previous HBV infection (ie, HBsAg positive and/or anti-HBc positive) and who have already received vaccination against hepatitis B in a three-dose or four-dose schedule. We will exclude studies whose participants: a) were not screened for serologic markers of HBV infection (HBsAg and anti-HBc) before admission into the trial; b) have no clear vaccination history; c) were immunised in a less than three-dose vaccination schedule; d) received hepatitis B vaccine plus immunoglobulin; and e) have predisposing factors for immunodeficiency such as HIV positive or haemodialysis (Appendix 1).

Types of interventions

The intervention of interest is administering a booster dose of hepatitis B vaccine versus placebo or no intervention to already immunised participants to assess long-term (5 years or more) presence of anamnestic immune response to booster dose versus placebo (Figure 1). The term 'booster' refers to an additional dose of hepatitis B vaccine given some time post-primary vaccination to induce immune memory and improve protection against HBV infection. We will assess booster effect, irrespective of type, dosage, route, or site of injection (Appendix 1).

Types of outcome measures

Primary outcomes

The dichotomous outcome of interest is the proportion with anamnestic immune response (AIR) in non-protected participants (P_{AIR}) and signs of hepatitis B virus infection. The continuous outcome of interest is intensity of AIR in non-protected participants (I_{AIR}).

Non-protected participants are those vaccinees whose anti-HBs concentrations decreased to less than 10 mIU/ml (WHO 2002; Mast 2006). The intensity of immune response is the amount of fold rise in geometric mean titre (GMT) post-booster compared to pre-booster administration. Anamnestic immune response to booster doses is defined in two ways (Watson 2001; Williams 2003; Yuen 2004; van der Sande 2007):

- Proportion with a four-fold or greater rise in the post-booster anti-HBs titre within 2 to 4 weeks of the booster dose administration in participants having detectable antibody.
- Proportion with development of post-booster anti-HBs level equal to or greater than 10 mIU/ml within 2 to 4 weeks of the booster dose administration in participants with no detectable antibody.

Signs of hepatitis B virus infection will be assessed by:
- Any sign of hepatitis B virus infection, either acute or chronic hepatitis B infection or antibody to hepatitis B core antigen (anti-HBc).
- Cirrhosis or hepatocellular carcinoma caused or associated with chronic hepatitis B infection and all-cause mortality.

Secondary outcomes

1. Proportion with local adverse events developed at booster injection site, including pain, redness, swellings, or any other local adverse events (WHO 2001).
2. Proportion with systemic adverse events developed after booster injection, including fever, headache, malaise, irritability, rash, nausea, myalgia, arthralgia, or any other systemic adverse events (WHO 2001).

Search methods for identification of studies

Electronic searches

We will search *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2009), the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE*, *EMBASE*, and *Science Citation Index Expanded* (Royle 2003). The preliminary search strategies with the time span of the searches are described in (Appendix 2).

Searching other resources

We will scan the reference lists of all included studies and pertinent reviews for additional references. We will contact the trials' authors of included studies as well as vaccine manufacturers for additional unpublished trials. The following conference databases will be searched for unpublished data:

- Annual Meeting of the Infectious Diseases Society of America (IDSA) available from http://www.idsociety.org.
- European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) available from http://www.escmid.org
- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) available from http://www.icaac.org

Data collection and analysis

Selection of studies

Two authors will independently make the decisions on which trials meet the inclusion criteria considered for this review. The authors will not be blinded to the names of the trials' authors, journals, and results. Any disagreements will be resolved through discussion among the authors until consensus is reached, or by adjudication with a third author. Excluded trials will be listed with the reasons for exclusion.

Data extraction and management

The extracted data regarding the 'Data Collection and Abstraction Form' will be entered in the electronic data sheet (Appendix 3). In cases of missing data or need for clarification, trial authors will be contacted.

Assessment of risk of bias in included studies

We will assess the risk of bias of the included studies using the 'risk of bias' tool recommended for assessing risk of bias in randomised trials (Higgins 2008) (Appendix 4).
Two authors will independently assess the risk of bias of the included studies by evaluating the methodological components described below (Appendix 4). Any disagreements will be resolved through discussion among the authors until consensus is reached, or by adjudication with a third author. If information is not available in the published trial, we will contact the trials' authors in order to assess the trials correctly.
The trials with adequate sequence generation, adequate allocation concealment, adequate blinding, adequate handling of incomplete outcome data, free of selective reporting, free of baseline imbalance, and without other bias risks will be considered low-bias risk trials.
The trials with one or more unclear or inadequate quality component will be considered trials with high risk of bias. Any disagreements will be resolved through discussion among the authors, until consensus is reached, or by adjudication with a third author.

Measures of treatment effect

The effect measure of choice for dichotomous outcome is risk ratio (RR) and the effect measure of choice for continuous outcome is

mean difference (MD). All estimates will be reported with 95% confidence interval (CI).

Dealing with missing data

To handle withdrawals and drop-outs in the analysis we will use '*available-participant approach*' and include data on only those whose results are known, using as a denominator the total number of people who have data recorded for anamnestic immune response (Higgins 2008).
We will conduct sensitivity analyses to assess the impact of dropouts and withdrawals for whom no outcome data are obtained based on the following two scenarios (Gamble 2005):

- *'Best-case scenario'*: assuming all missing participants experienced the event and responded to the booster dose, using the total number of participants as the denominator.
- *'Worst-case scenario'*: assuming all missing participants did not experience the event and did not respond to the booster dose, using the total number of participants as the denominator.

Assessment of heterogeneity

We will explore statistical heterogeneity using the chi-squared test at the 10% significance level (P less than 0.10). We will quantify inconsistency across studies results using I^2 statistic (Higgins 2003). We will also estimate the between-study variance by using tau-squared (τ^2 or tau^2) statistic (Higgins 2008).

Assessment of reporting biases

We will use the funnel plot to assess publication bias and other bias risks.

Data synthesis

We will use both Review Manager 5 (RevMan 2008) and Stata statistical program (version 9) (Stata 9) for data analysis. Data will be analysed and the results will be reported using a random-effects model (DerSimonian 1986) and the fixed-effect model (DeMets 1987) with 95% CI. We will report both analyses in case they disagree regarding the significance of the intervention effect.

Subgroup analysis and investigation of heterogeneity

We plan to assess anamnestic immune response (AIR) to booster dose for the following subgroups:

- Various periods: every 5 years from initial vaccination.
- Various methodological quality: trials with low risk of bias compared to trials with high risk of bias.
- Various endemic regions: low endemicity (prevalence of HBV infection less than 2%) compared to intermediate endemicity (prevalence of HBV infection 2 to 7%) and high endemicity (prevalence of HBV infection more than 7%).
- Various age groups: every 10 years.
- Various participants: apparently healthy participants compared to health-care workers, or intravenous drug abusers, or sex partners.
- Various vaccination schedules of the primary vaccination: 3-dose compared to 4-dose.
- Various vaccine or booster types: recombinant vaccine (RV) compared to plasma derived vaccine (PDV).
- Various booster dosages: 5 mcg compared to 10 mcg.
- Various injection sites: deltoid or thigh compared to gluteus.
- Various injection routes: intramuscular (IM) compared to intradermal (ID).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Inclusion-exclusion criteria

Criteria	Included	Excluded
Types of studies		
Has the trial assessed anamnestic immune response to booster dose?	Yes	No
Have the participants been randomised to booster hepatitis B vaccination versus placebo or no vaccination?	Yes	No
Types of participants		
Were they apparently healthy participants, with intact immune status, without previous HBV infection?	Yes	No
Were they free of predisposing factors for immunodeficiency?	Yes	No
Were they screened for serologic markers of HBV infection before admission into the trial?	Yes	No
Have the participants already received a 3-dose or 4-dose schedule of hepatitis B vaccine?	Yes	No
Was their vaccination history clear and reliable?	Yes	No
Did they receive a monovalent hepatitis B vaccine not in fixed combination with other vaccines?	Yes	No
Did they receive hepatitis B vaccine without immunoglobulin?	Yes	No
Types of interventions		
Was the administered booster dose a monovalent vaccine of either recombinant vaccine (RV) or plasma derived vaccine (PDV)?	Yes	No

(*Continued*)

Primary outcomes		
Was the anamnestic immune response to booster dose of hepatitis B vaccine versus placebo investigated?	Yes	No

Appendix 2. Search strategies

Databases	**Time of searches**	**Search terms**
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will given at review stage.	vaccin* AND 'hepatitis B' AND boost*
The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Latest issue.	#1 MeSH descriptor 'Hepatitis B' explode all trees #2 MeSH descriptor 'Vaccines' explode all trees #3 MeSH descriptor 'Vaccination' explode all trees #4 MeSH descriptor 'Immunization' explode all trees #5 (#2 OR #3 OR #4) #6 (#1 AND #5)
MEDLINE (Ovid SP)	1950 to the date when the search is performed.	#1 MeSH descriptor 'Hepatitis B' explode all trees #2 MeSH descriptor 'Vaccines' explode all trees #3 MeSH descriptor 'Vaccination' explode all trees #4 MeSH descriptor 'Immunization' explode all trees #5 (#2 OR #3 OR #4) #6 (#1 AND #5) #7 #6 NOT animal #8 random* OR blind* OR placebo* OR meta-analys* #9 #7 AND #8
EMBASE (Ovid SP)	1980 to the date when the search is performed.	#1 MeSH descriptor 'Hepatitis B' explode all trees #2 MeSH descriptor 'Vaccines' explode all trees #3 MeSH descriptor 'Vaccination' explode

(*Continued*)

		all trees #4 MeSH descriptor 'Immunization' explode all trees #5 (#2 OR #3 OR #4) #6 (#1 AND #5) #7 #6 NOT animal #8 random* OR blind* OR placebo* OR meta-analys* #9 #7 AND #8
Science Citation Index Expanded (http://apps.isiknowledge.com)	1945 to the date when the search is performed.	#1 TS=vaccin* #2 TS='hepatitis B' #3 #1 AND #2 #4 TS=(boost* OR follow-up OR add* OR supplem*) #5 #3 AND #4 #6 TS=(random* OR blind* OR placebo* OR mask* OR meta-analys*) #7 #5 AND #6

Appendix 3. Data collection and abstraction form

Row	Data		Results	
			Booster	**Placebo**
1	1st author			
2	Date of publication			
3	Design of clinical trial	Randomised clinical trial		
		Quasi-randomised controlled study		
4	Follow-up time from last vaccination (year)			
5	Endemicity	High		
		Intermediate		
		Low		
6	Participants	General population		

(*Continued*)

			HCWs		
			Intravenous (IV) drug abusers		
			Sex partners		
			Others		
7	Mean age (year)				
8	Vaccine schedule		3-dose		
			4-dose		
9	Initial vaccine type		recombinant vaccine (RV)		
			plasma derived vaccine (PDV)?		
10	Proportion with response to initial vaccination (%)				
11	Booster type		RV		
			PDV		
12	Booster dosage (mcg)				
13	Injection site		Deltoid		
			Thigh		
			Gluteus		
14	Injection route		IM		
			ID		
			SD		
15	Sample size				
16	Dropouts				
17	Anamnestic immune response (AIR)				
18	Proportion of anamnestic immune response (P_{AIR})				
19	Before intervention	GMT (mIU/mL)			

(*Continued*)

			95% CI of GMT		
20	1 week after intervention		GMT (mIU/mLl)		
			95% CI of GMT		
21	2 weeks after booster dose		GMT (mIU/mL)		
			95% CI of GMT		
22	3 weeks after intervention		GMT (mIU/mL)		
			95% CI of GMT		
23	4 weeks after intervention		GMT (mIU/mL)		
			95% CI of GMT		
24	2 months after intervention		GMT (mIU/mL)		
			95% CI of GMT		
25	1 year after intervention		GMT (mIU/mL)		
			95% CI of GMT		
26	Adverse events of booster	Local	Pain		
			Tenderness		
			Redness		
			Swelling		
			Others		
		Systemic	Fever		
			Headache		
			Malaise		
			Irritability		
			Rash		
			Nausea		
			Myalgia		

(*Continued*)

			Arthralgia		
			Others		

Appendix 4. Assessment of risk of bias of the included studies

Item	Judgement		
Sequence generation?	**Yes**	**Unclear**	**No**

Adequate
- Sequence generation was achieved using computer random number generation or a random number table.
- Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent adjudicator.

Unclear
- The trial is described as randomised but the method of sequence generation was not specified.

Inadequate
- The sequence generation method is not, or may not be random.
- Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate participants are inadequate.

Allocation concealment?	**Yes**	**Unclear**	**No**

Adequate
- Participants and investigators enrolling participants could not foresee assignment because one of the following methods was used to conceal allocation.
    - Central allocation (including telephone or web-based randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

Unclear
- Insufficient information to permit judgement. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.

Inadequate
- Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:
    - Using an open random allocation schedule (eg, a list of random numbers); assignment envelopes were used without appropriate safeguards (eg, if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; any other explicitly unconcealed procedure.

Blinding?	**Yes**	**Unclear**	**No**

Yes, adequate
- The trial was described as double blind and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.

Unclear
- The trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trail.

(*Continued*)

No, not performed
- The trial was not double blind, so that the allocation was known during the trial.

Incomplete outcome data addressed?	**Yes**	**Unclear**	**No**

Adequate
- The numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.

Unclear
- The report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.

Inadequate
- The number or reasons for dropouts and withdrawals were not described.

Free of selective reporting?	**Yes**	**Unclear**	**No**

Yes, adequate
- Pre-defined, or clinically relevant and reasonably expected outcomes are reported.

Unclear
- Not all pre-defined, or clinically relevant and reasonably expected outcomes are reported fully, or it is unclear whether data on these outcomes were recorded or not.

Inadequate
- One or more clinically relevant and reasonably expected outcomes were not reported.

Free of baseline imbalance?	**Yes**	**Unclear**	**No**

Adequate
- There was no baseline imbalance in important characteristics.

Unclear
- The baseline characteristics were not reported.

Inadequate
- There was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Free of other bias?	**Yes**	**Unclear**	**No**

Adequate
- The trial appears to be free of other components that could put it at risk of bias.

Unclear
- The trial may or may not be free of other components that could put it at risk of bias.

Inadequate
- There are other factors in the trial that could put it at risk of bias, eg, no sample size calculation made, early stopping, industry involvement, or an extreme baseline imbalance.

HISTORY

Protocol first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

Jalal Poorolajal (JP): developed and wrote the protocol, and will be responsible for the reference searching, article retrieval, study inclusion and exclusion, data extraction, assessment of risk of bias in included studies, data analysis, interpretation of results, and writing of the review.

Akbar Fotouhi (AF): assisted with reviewing and editing the protocol, and will be responsible for the assessment of risk of bias in included studies, interpretation of results, and writing of the review.

Reza Majdzadeh (RM): assisted with reviewing and editing the protocol, and will be responsible for interpretation of results and writing of the review.

Mahmood Mahmoodi (MM): has assisted with reviewing and editing the protocol, and will be responsible for the data analysis, interpretation of results, and writing of the review.

Aliakbar Haghdoost (AH): will be responsible for the analysis, interpretation of results, and writing of the review.

Siavosh Nasseri-Moghaddam (SN): assisted with reviewing and editing the protocol, and will be responsible for the reference searching, interpretation of results, and writing of the review.

Leila Ghalichi (LG): will be responsible for article retrieval, study inclusion and exclusion, assessment of risk of bias in included studies, interpretation of results, and writing of the review.

DECLARATIONS OF INTEREST

We declare that we have no conflict of interest.

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