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Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status (Review)

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Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

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ABSTRACT

Background
The benefits and harms of hepatitis B vaccination in persons not previously exposed to hepatitis B infection or with unknown exposure status have not been established.

Objectives
To assess the benefits and harms of hepatitis B vaccination in people not previously exposed to hepatitis B infection or with unknown exposure status.

Search strategy
Trials were identified from The Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, Science Citation Index Expanded (last search, March 2007). Additionally, we contacted experts and vaccine manufacturers, and read through reference lists for eligible trials.

Selection criteria
Randomised clinical trials comparing hepatitis B vaccine versus placebo, no intervention, or another vaccine in persons not previously exposed to hepatitis B (HBsAg negative) or with unknown exposure status.

Data collection and analysis
The primary outcome was hepatitis B infection (detecting HBsAg, HBeAg, HBV DNA, or anti-HBc). Secondary outcomes were lack of sero-protection, antibody titre, clinical complications, adverse events, lack of compliance, and cost-effectiveness. Dichotomous outcomes were reported as relative risk (RR) with 95% confidence interval (CI), using intention-to-treat analysis assuming an unfavourable event for missing data. Sensitivity analyses based on methodological quality (risk of bias), available data analysis, intention-to-treat analysis assuming a favourable event for missing data, best-case scenario, and worst-case scenario were conducted.

Main results
Twelve trials were eligible. All had high risk of bias and reporting was inconsistent. Hepatitis B vaccine did not show a clear effect on the risk of developing HBsAg (RR 0.96, 95% CI 0.89 to 1.03, 4 trials, 1230 participants) and anti-HBc (RR 0.81, 95% CI 0.61 to 1.07; 4 trials, 1230 participants, random-effects) when data were analysed using intention-to-treat analysis assuming an unfavourable event for missing data. Analysis based on data of available participants showed reduced risk of developing HBsAg (RR 0.12, 95% CI 0.03 to 0.44, 4 trials, 576 participants) and anti-HBc (RR 0.36, 95% CI 0.17 to 0.76, 4 trials, 576 participants, random-effects). Intention-to-treat analysis assuming favourable outcome for missing data showed similar reduction in risk. Hepatitis B vaccination had an unclear effect on the risk of lacking protective antibody levels (RR 0.57, 95% CI 0.26 to 1.27, 3 trials, 1210 participants, random-effects). Development of adverse events was sparsely reported.

Authors’ conclusions

In people not previously exposed to hepatitis B, vaccination has unclear effect on the risk of developing infection, as compared to no vaccination. The risk of lacking protective antibody levels as well as serious and non-serious adverse events appear comparable among recipients and non-recipients of hepatitis B vaccine.

**Plain Language Summary**

In children or grown-ups who have not been previously exposed to hepatitis B infection or whose exposure status is not known, hepatitis B vaccination as compared with no hepatitis B vaccination has an unclear effect on the risk of developing hepatitis B infection

Several million people world-wide are infected with hepatitis B virus. The infection may cause serious short-term and long-term effects including portal hypertension, liver failure, liver cancer, and death. Hepatitis B vaccination is reported to be beneficial in some specific groups of people such as babies born to women infected with hepatitis B, health-care workers, and people with long-standing kidney failure. Whether hepatitis B vaccine is beneficial in people who have not been exposed to hepatitis B infection or those whose exposure status is not known is assessed in the present review.

Twelve randomised clinical trials fulfilled the inclusion criteria of this review. Primary analysis of the data based on criteria described beforehand (intention-to-treat model assigning unfavourable outcome for missing data) showed that hepatitis B vaccination has an unclear effect on the risk of developing hepatitis B infection. Analysis of data of available participants in the various trials showed that as compared to not vaccinating, hepatitis B vaccination reduces the risk of developing hepatitis B infection; by 88% for hepatitis B surface antigen marker and 62% for anti-core antibody marker. One should note, that these findings are based on only four randomised clinical trials of poor methodological quality involving 1230 participants. When compared with other vaccines or placebo, hepatitis B vaccination results in comparable risk of developing adverse events. This includes serious adverse events such as admission to hospital and convulsions, as well as less serious events such as fever, local redness, and pain. This shows that the risk of developing these adverse events is not more than with other vaccinations. There was not enough data to draw definite conclusions on the effect of hepatitis B vaccination on compliance and cost-effectiveness.

**Background**

Hepatitis B virus (HBV) infection is a global problem. Current estimates suggest that over two billion people all over the world have been infected, of whom approximately 350 million have chronic infection (Beasley 1984; Maddrey 2000; Walsh 2001; Rizzetto 2002). About one million deaths each year are attributable to hepatocellular carcinoma and cirrhosis, related to chronic hepatitis B virus infection (WHO 2004).

Clinically, hepatitis B can result in a spectrum of clinical problems ranging from asymptomatic infection to symptomatic infection (McMahon 1985; Walsh 2001). The long-term danger is that some infected persons develop persistent infection, of whom a fraction develop chronic liver disease and associated complications such as cirrhosis, portal hypertension, hepatocellular carcinoma, and hepatocellular failure (Liaw 1998; Rehermann 2003). The risk of developing persistent infection and its complications is inversely proportional to the age at infection; the younger the person at the time of initial infection, the greater is the risk of persistence, and vice versa (McMahon 1985; Moyer 1994; Hyams 1995; Gall 2001; Aggarwal 2004). Therefore, children infected at the time of birth have the highest risk of persistent hepatitis B infection. Persons with persistent infection, even if asymptomatic themselves, can still transmit the infection to others. The major routes of transmission are through sexual contact, sharing contaminated objects such as needles, razors, etc, and transfusion of infected blood or blood...
products. Another important route is from an infected pregnant woman to her child before or during delivery, ie, perinatal or vertical transmission (Gitlin 1997; Walsh 2001).

Vaccination against hepatitis B is expected to protect people from infection. If we assume that hepatitis B vaccine is safe and efficacious, every individual residing in geographical regions with high incidence of infection should receive hepatitis B vaccination early in life. This is often not feasible due to logistic and economic considerations. Therefore, to obtain maximum cost-benefit two strategies are possible (CDC 1999; Aggarwal 2004). The 'high risk strategy' focuses on people believed to be at highest risk of infection, eg, health-care professionals, recipients of blood products, intravenous drug abusers, babies born to infected mothers, etc. This strategy depends on identification of all high-risk people and vaccination compliance. The high risk strategy is less cost intensive, but likely to work only in areas of low population prevalence of hepatitis B infection.

This contrasts the strategy of universal immunisation, wherein all individuals are vaccinated, irrespective of individual risk. Universal immunisation can be used in populations with high prevalence of hepatitis B infection and where it is difficult to identify individuals at highest risk (Chen 1996). This is economically and logistically more demanding and its success also depends on vaccination compliance. Individuals at high risk frequently refuse vaccination or fail to complete the vaccination series (Wong 1994; Nystrom 2000).

Previous systematic reviews have shown the benefit of hepatitis B immunisation in newborns of mothers with hepatitis B infection (Lee 2006a; Lee 2006b) and other high risk groups such as healthcare workers (Chen 2005) and patients with chronic renal failure (Schroth 2004). However, no meta-analyses or systematic reviews have addressed the issue of immunisation in persons who are not at high risk of hepatitis B exposure or individuals in the general population whose hepatitis B exposure status is not known. As the majority of the world's population fits into either of these categories, this review was undertaken to assess whether hepatitis B vaccination protects against hepatitis B virus infection in such persons.

**OBJECTIVES**

To assess the benefits and harms of hepatitis B vaccination in persons not previously exposed to hepatitis B or with unknown exposure status.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We included randomised clinical trials, irrespective of blinding, publication status, or language.

**Types of participants**

We included trials that recruited participants of any age who were either hepatitis B surface antigen (HBsAg) negative or whose status was not known. Absence of HBsAg suggests absence of hepatitis B infection, although this may not always be the case. We excluded trials on newborns who were born to mothers known to be infected with hepatitis B, and also trials on participants suspected to be at high risk of hepatitis B infection (health-care workers, intravenous drug abusers, homosexual persons, patients undergoing haemodialysis, those with haemato-oncological malignancy, frequent recipients of blood or blood products, participants with immune compromised status, and those who were receiving immunoglobulins for any reason). These groups were excluded because they constitute "high-risk groups" and there already exist Cochrane reviews on some of these groups of people (Schroth 2004; Chen 2005; Lee 2006a).

**Types of interventions**

We analysed hepatitis B vaccine versus placebo, or no intervention, or another vaccine. We considered hepatitis B immunisation with either type of vaccine (plasma derived or recombinant), administered by any route (intramuscularly, subcutaneously, or intradermally), using any schedule, with or without simultaneous administration of other vaccines, administered singly or as a combination vaccine. Trials that only compared different doses, schedules or types of hepatitis B vaccine, without a comparator group who received placebo or another vaccine or no vaccination were excluded.

**Types of outcome measures**

The following outcome measures were considered.

**Primary outcome**

1. Hepatitis B occurrence determined by detection of HBsAg, HBe antigen (HBeAg), HBV DNA, or antibody to HBc antigen in serum (anti-HBc).

**Secondary outcomes**

2. Lack of sero-protection, ie, number of vaccine recipients with anti-HBs antibody titre less than 10 IU/L, which is generally considered protective (sufficient to prevent hepatitis B virus infection) (Mahoney 1999; Walsh 2001).
3. Geometric mean titre (GMT) of anti-HBs antibodies.
4. Number of people developing clinical complication related to chronic hepatitis B infection including ascites, variceal bleeding, encephalopathy, hepatocellular carcinoma, and liver-related death.
5. Number of people who developed serious adverse events. Serious adverse event was defined as per the International Conference on Harmonisation - Good Clinical Practice guidelines (ICH-GCP 1996) as any event that would lead to death; was life-threatening; required inpatient hospitalization; resulted in a persistent or significant disability; or any important medical event, which might have jeopardised the patient or required intervention to prevent it.

6. Number of people who developed local or systemic adverse events.

7. Lack of compliance to vaccination series, ie, number of enrolled participants who failed to complete the full vaccination series.


If a trial reported outcomes at multiple time intervals following vaccination series, the data at longest follow-up were included in the analysis.

**Search methods for identification of studies**

We searched the following databases: The Cochrane Hepato-Biliary Group Controlled Trials Register (searched on 17 January 2007) (Gluud 2007a), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2/2007); MEDLINE (1966 to 31 March 2007); EMBASE (1980 to 31 March 2007); LILACS (1982 to 31 March 2007), and Science Citation Index Expanded (1945 to 31 March 2007) (Royle 2003). The search terms used, time span of search, and date of search are shown in Appendix 1.

We also contacted experts in the field, manufacturers of hepatitis B vaccine, and searched the reference lists of eligible trials for additional trials.

**Data collection and analysis**

We followed the instructions given in the Cochrane Handbook for Systematic Reviews of Intervention (Higgins 2006) and The Cochrane Hepato-Biliary Group Module (Gluud 2007a).

**Searching for trials**

RED conducted searches of all electronic databases; this was coordinated with The Cochrane Hepato-Biliary Review Group. RED conducted additional searches in LILACS and Science Citation Index Expanded. JLM contacted the corresponding authors and first authors of the included trials by e-mail requesting for unpublished data. This was done on 20 July 2007 through the Cochrane Hepato-Biliary Group. Vaccine manufacturing companies were jointly identified by JLM and The Cochrane Hepato-Biliary Group through an Internet search on www.google.com using the search terms ‘hepatitis B vaccine’ and ‘hepatitis B vaccine manufacture#’ on 18 July 2007. Ten companies with correspondence addresses were identified in this manner in addition to the seven identified by The Cochrane Hepato-Biliary Group. Postal and/or fax communication was sent to these manufacturers on 25 July 2007. RED searched reference lists of eligible trials for additional trials.

**Selection of trials**

The initial results of the search were independently screened by JLM and PJM, and potentially relevant trials were identified on the basis of title, abstract, and key words/MeSH headings. Those that appeared eligible for inclusion were obtained in full. JLM read through these and assessed the eligibility for inclusion in the review. RED validated the list of included and excluded trials.

**Data extraction**

JLM and RED extracted the following data from the selected trials: characteristics of the trial design, participant characteristics, interventions (dosage, type, schedule), primary and secondary outcome measures, assessment of methodological quality (risk of bias), and sub-groups into which the trial could be included. We also marked the additional information sought from the authors.

**Assessment of bias risk**

The methodological quality (and hence risk of bias due to the methodology) of the trials was assessed following the Cochrane methodology (Higgins 2006) and as per the recommendations of The Cochrane Hepato-Biliary Group (Gluud 2007a). This was done by assessment of each trial as given below.

**Generation of the allocation sequence**

- Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice were also considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- Inadequate, if a system involving dates, names, or attendance numbers were used for the allocation of patients.

**Allocation concealment**

- Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.
Blinding

- Adequate, if the trial was described as double blind and both the investigator assessing outcomes as well as participants were blinded to the nature of intervention. Blinding was also considered adequate if trials reported single blinding of the investigator assessing outcomes.
- Unclear, if the trial was described as double blind, but the method of blinding was not described.
- Not performed, if the trial was not double blind.

Trials were assumed to have low risk of bias if at least two of the three quality components were adequate. Otherwise, trials were classified as having high risk of bias.

Data analysis

Data from trials were combined for meta-analysis using Review Manager 4.2. (RevMan 2003). We used relative risk (RR) for dichotomous data and weighted mean difference (WMD) for continuous data both with 95% confidence intervals (CI). Data were analyzed by the fixed-effect model. If there was significant heterogeneity interpreted as defined below, the data were also analysed using the random-effects model and both analyses are presented. We performed intention-to-treat analysis for dichotomous data assuming an unfavourable outcome for participants whose data were not reported.

Heterogeneity

We qualified inconsistency among the pooled estimates using the $I^2 = \frac{[Q - df]/Q}{Q} \times 100\%$ test, where Q is the chi-squared statistic and df is its degrees of freedom. This illustrates the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error. We assumed significant heterogeneity when $I^2$ is more than 50% and analysed such outcomes using both a fixed-effect model and random-effects model (Higgins 2003; Higgins 2006).

Subgroup analyses

We performed the following sub-group analyses on the primary outcome (markers of hepatitis B occurrence).

- Age of participants at initiation of vaccination, ie, newborns (within first 28 days of birth), children (28 days to 10 years), adolescents (11 to 18 years), and adults (more than 18 years).
- Presence or absence of first dose of vaccine at birth.
- Prevalence of HBsAg among the population from which the trial participants originated. This was categorized as low (less than 2%), moderate (2% to 7%), and high (more than 7%) prevalence of hepatitis B (Van Damme 1997; Mahoney 1999).
- Follow-up periods less than 1 year, from 1 to 5 years, and more than 5 years.
- Schedule of vaccination, ie, three doses with conventional 0,1,6 months schedule, three doses with any accelerated schedule, and four doses by any schedule.
- Administration of hepatitis B vaccine alone versus administration as part of a combination or along with other vaccines in the same syringe.

We used the test for interaction to estimate the difference between two subgroups (Altman 2003).

Sensitivity analyses

We performed sensitivity analyses whenever appropriate in order to explore causes of heterogeneity and the robustness of the results of the primary outcome. We separated studies according to:

1. Risk of bias: including only trials with low risk of bias.
2. Attrition bias: including only trials with low drop-out rate (less than 10%).
3. Follow-up:
   (a) available data analysis, ie, including only data of those participants who were followed up and ignoring those whose data were not reported. For this analysis, the total number at follow-up was used as the denominator;
   (b) intention-to-treat analysis assuming favourable outcome for those whose data were not reported, ie, none of the drop-outs in the experimental (hepatitis B vaccine) and control group had the primary outcomes;
   (c) best-case scenario favouring hepatitis B vaccine, ie, none of the dropouts in the experimental (hepatitis B vaccine) group had the primary outcome, but all dropouts from the control group had the primary outcome;
   (d) worst-case scenario favouring control, ie, all the dropouts from the experimental (hepatitis B vaccine) group had the primary outcome, but none from the control group had the primary outcome.

Bias

Funnel plots were constructed for each primary outcome to test for possible bias.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Search results

Search of the electronic databases identified 2964 citations. Of these 328 were considered relevant for this review. Of these, 66 publications were considered potential trials for inclusion. Full text of these was obtained and 14 publications met the inclusion criteria for this review describing 12 trials (see Included studies...
references) and 52 publications were excluded (see Characteristics of excluded studies table). One of the included trials (Xueliang 2000) had three publications. Forty-eight experts were contacted by e-mail on 20 July 2007 and one response was received; however, the trial details supplied had already been included in the review. Seventeen vaccine manufacturers were contacted by post or fax in the last week of July 2007; one was returned owing to incomplete address. However, no responses were received from the manufacturers. Search of the reference lists of eligible trials identified 10 potential studies; of these 9 had already been included in the review and full text of the tenth showed that it was not eligible for inclusion.

Included trials

The twelve included trials had different participant characteristics. One included adults; mostly medical students (Ambrosch 1992), three included neonates less than 28 days old (Wang 1985; Perrin 1986; Aristegui 1995), four recruited infants (Tsega 1990; Giammanco 1991; Bassily 1995; Greenberg 1996), and four included older children (Coursaget 1984; Sun 1991; Liao 1999; Xueliang 2000). None of the trials included adolescents.

Four trials were conducted in populations regarded to have low sero-prevalence of HBsAg (Giammanco 1991; Ambrosch 1992; Aristegui 1995; Greenberg 1996), one in a population with intermediate prevalence (Bassily 1995), and seven in populations with high prevalence (Coursaget 1984; Wang 1985; Perrin 1986; Tsega 1990; Sun 1991; Liao 1999; Xueliang 2000).

Design of trials

Nine of the twelve trials were based in a hospital setting and three were community based (Sun 1991; Liao 1999; Xueliang 2000); all these three were conducted in China. Only one of the twelve trials was conducted as a multi-centre trial (Greenberg 1996).

Experimental interventions

Four trials used a plasma derived hepatitis B vaccine (Wang 1985; Tsega 1990; Liao 1999; Xueliang 2000); six used a recombinant hepatitis B vaccine (Coursaget 1984; Giammanco 1991; Ambrosch 1992; Aristegui 1995; Bassily 1995; Greenberg 1996), and two trials did not specify the type of hepatitis B vaccine used (Perrin 1986; Sun 1991).

The twelve trials incorporated 12 different vaccination schedules; four trials used the conventional 0,1,6 months schedule (Sun 1991; Ambrosch 1992; Liao 1999; Xueliang 2000), four trials incorporated a four-dose schedule (Coursaget 1984; Wang 1985; Tsega 1990; Giammanco 1991). Two trials also had arms that compared different hepatitis B vaccine schedules with a control group (Giammanco 1991; Aristegui 1995). The dosage of hepatitis B vaccine in the trials varied from 2 µg to 40 µg of hepatitis B surface antigen. Two trials (Sun 1991; Xueliang 2000) did not mention the dosage of HBsAg. Five trials did not specify the route of administration (Perrin 1986; Tsega 1990; Sun 1991; Liao 1999; Xueliang 2000), five used intramuscular route (Giammanco 1991; Ambrosch 1992; Aristegui 1995; Bassily 1995; Greenberg 1996), one used subcutaneous route (Coursaget 1984), and one trial offered vaccine by either of the two routes (Wang 1985). Four trials reported the site of administration as deltoid muscle or anterolateral thigh (Giammanco 1991; Ambrosch 1992; Aristegui 1995; Greenberg 1996).

Control interventions

Four trials administered placebo products to participants in the control group; these included vaccine diluent (Liao 1999), placenta immunoglobulin (Wang 1985), or an unspecified product (Sun 1991; Xueliang 2000). Eight trials used another vaccine in the control group; these included hepatitis A vaccine (Ambrosch 1992) and other routine childhood vaccines (Coursaget 1984; Perrin 1986; Tsega 1990; Giammanco 1991; Aristegui 1995; Bassily 1995; Greenberg 1996). None of the trials used ‘no intervention’ in the control group.

Follow-up

The follow-up period ranged from 1 month to 15 years. Five trials had follow-up periods less than one year (Wang 1985; Tsega 1990; Giammanco 1991; Ambrosch 1992; Aristegui 1995), of which two had follow-up less than three months (Tsega 1990; Ambrosch 1992). Four trials had follow-up for one to five years (Coursaget 1984; Perrin 1986; Bassily 1995; Greenberg 1996), and three trials followed participants for five or more years (Sun 1991; Liao 1999; Xueliang 2000).

Risk of bias in included studies

Bias risk

None of the twelve trials met the criteria for high methodological quality and hence low risk of bias. Almost all of the trials had unclear allocation generation, allocation concealment, and blinding methodology (see Characteristics of included studies table).

Description of drop-outs and withdrawals

All trials had significant drop-outs; the reasons for this were not described and intention-to-treat analysis was not used in any of the trials.

Effects of interventions

Primary outcomes

Hepatitis B occurrence
**Presence of HBsAg**

Nine of the twelve trials included HBsAg as an outcome. However, five trials did not clearly report the exact number of events and/or participants in each intervention group. Of these, two (Bassily 1995; Giammanco 1991) did not report findings in either arm of the trial, in two trials the outcome was assessed in a fraction of subjects, but the relationship of the fraction to the original number enrolled was not clear (Coursaget 1984; Sun 1991). One trial did not specify the denominator (Perrin 1986). Thus, only four trials reported data which could be included in the meta-analysis. Hepatitis B vaccination had an unclear effect on the risk of HBsAg presence (RR 0.96, 95% CI 0.89 to 1.03, 4 trials with 1230 participants, $I^2 = 0\%$). Analysis of data of available participants showed RR 0.12, 95% CI 0.03 to 0.44, 4 trials with 576 participants, $I^2 = 0\%$.

**HBeAg and HBV DNA**

None of the included trials reported these markers of infectivity as an outcome.

**Anti-HBc antibodies**

Eight trials included serum anti-HBc antibodies (anti-HBc) as an outcome, but only four trials reported data that could be included in the meta-analysis (Wang 1985; Tseg 1990; Liao 1999; Xueliang 2000). These trials also reported presence of HBsAg. Two trials (Giammanco 1991; Bassily 1995) did not report the outcome in either arm, one did not specify the denominator in either arm (Coursaget 1984), and one presented this outcome as antibody level rather than presence or absence (Perrin 1986). Three of the trials whose data could be included in the meta-analysis were in children (Tseg 1990; Liao 1999; Xuelfiang 2000) and one in newborn babies (Wang 1985). Hepatitis B vaccination showed an unclear effect on the risk of presence of anti-HBc antibodies (RR 0.81, 95% CI 0.61 to 1.07, 4 trials with 1230 participants; $I^2 = 84.4\%$, random-effects and RR 0.86, 95% CI 0.80 to 0.92, fixed-effect). When data of available participants were analysed, it showed RR 0.36, 95% CI 0.17 to 0.76, 4 trials with 576 participants, $I^2 = 55.9\%$, random-effects and RR 0.38, 95% CI 0.28 to 0.52, fixed-effect.

**Subgroup analyses**

Analysis by age of participants showed unclear effect on the risk of HBsAg presence in children (RR 0.96, 95% CI 0.89 to 1.03, 3 trials with 1210 participants, $I^2 = 0\%$). One trial with newborn babies did not report any event in either arm. Test of interaction revealed no significant difference ($P > 0.05$).

Subgroup analysis by presence or absence of birth dose of hepatitis B vaccine could not be done as one trial (Wang 1985) did not observe any events in either arm and two trials (Perrin 1986; Aristegui 1995) did not report the primary outcome. Subgroup analysis comparing different HBsAg prevalence was not possible as all four trials were conducted in populations with high prevalence (more than 8%).

Analysis by duration of follow-up showed unclear effect on the risk of developing HBsAg in trials with less than one year follow-up (RR 0.76, 95% CI 0.41 to 1.40, 2 trials with 320 participants) as well as in trials with more than five years follow-up (RR 0.97, 95% CI 0.90 to 1.04; 2 trials with 910 participants, $I^2 = 0\%$). Test of interaction revealed no significant difference ($P > 0.05$).

Analysis by vaccination schedule showed unclear effect with three doses of hepatitis B vaccine administered by the conventional 0,1,6 months schedule (RR 0.97, 95% CI 0.90 to 1.04, 2 trials with 910 participants, $I^2 = 0\%$), and the four dose schedule (RR 0.76, 95% CI 0.41 to 1.40, 2 trials with 320 participants). Test of interaction revealed no significant difference between these subgroups ($P > 0.05$).

Subgroup analysis comparing administration of hepatitis B vaccine alone compared to part of a combination could not be done as the included trials did not report this aspect.

**Sensitivity analysis**

Methodological quality (risk of bias)

Sensitivity analysis based on methodological quality could not be performed as all trials were of low methodological quality, ie, had high risk of bias.

**Attrition**

Only one trial had less than 10% drop-outs (Wang 1985), but there were no events in either arm, hence could not be analysed.

**Follow-up**

Analysis of data of available participants showed that hepatitis B vaccination reduced risk of developing HBsAg (RR 0.12, 95% CI 0.03 to 0.44, 4 trials with 576 participants, $I^2 = 0\%$).

Intention-to-treat analysis assuming that all participants whose data were not reported had a favourable outcome, ie, none developed HBsAg, showed identical reduction in risk (RR 0.12, 95% CI 0.03 to 0.44, 4 trials with 1230 participants, $I^2 = 0\%$). Best-case scenario analysis showed reduced risk (RR 0.01, 95% CI 0.00 to 0.03, 4 trials with 1230 participants, $I^2 = 18.3\%$).

Worst case-scenario showed RR 9.45, 95% CI 2.14 to 41.67, 4 trials with 1230 participants, $I^2 = 90.7\%$, random-effects model and RR 15.59, 95% CI 10.29 to 23.64, fixed-effect model.

**Table 1 summarises the relative risk using different analyses models as described.**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Trials</th>
<th>Participants</th>
<th>RR (95% CI)</th>
<th>$I^2$</th>
</tr>
</thead>
</table>

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Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status (Review)  
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<table>
<thead>
<tr>
<th>Outcome</th>
<th>ITT Assumption</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg (ITT assuming unfavourable outcome for all drop-outs)</td>
<td>4</td>
<td>1230</td>
<td>0.96 (0.89-1.03)</td>
<td>0%</td>
</tr>
<tr>
<td>HBsAg (ITT analysis assuming favourable outcome for all drop-outs)</td>
<td>4</td>
<td>1230</td>
<td>0.12 (0.03-0.44)</td>
<td>0%</td>
</tr>
<tr>
<td>HBsAg (analysis of available participants)</td>
<td>4</td>
<td>576</td>
<td>0.12 (0.03-0.44)</td>
<td>0%</td>
</tr>
<tr>
<td>HBsAg (best-case scenario)</td>
<td>4</td>
<td>1230</td>
<td>0.01 (0.00-0.03)</td>
<td>18.3%</td>
</tr>
<tr>
<td>HBsAg: worst-case scenario (random-effects model)</td>
<td>4</td>
<td>1230</td>
<td>9.45 (2.14-41.67)</td>
<td>90.7%</td>
</tr>
<tr>
<td>HBsAg: worst-case scenario (fixed-effect model)</td>
<td>4</td>
<td>1230</td>
<td>15.59 (10.29-23.64)</td>
<td>90.7%</td>
</tr>
<tr>
<td>Anti-HBc antibodies (ITT analysis assuming unfavourable outcome for all drop-outs) Random-effects model</td>
<td>4</td>
<td>1230</td>
<td>0.81 (0.61-1.07)</td>
<td>84.4%</td>
</tr>
<tr>
<td>Anti-HBc antibodies (ITT analysis assuming favourable outcome for all drop-outs) Fixed-effect model</td>
<td>4</td>
<td>1230</td>
<td>0.86 (0.80-0.92)</td>
<td>84.4%</td>
</tr>
<tr>
<td>Anti-HBc antibodies (analysis based on available participants) Fixed-effect model</td>
<td>4</td>
<td>576</td>
<td>0.38 (0.28-0.52)</td>
<td>55.9%</td>
</tr>
<tr>
<td>Anti-HBc antibodies (analysis based on available participants) Random-effects model</td>
<td>4</td>
<td>576</td>
<td>0.36 (0.17-0.76)</td>
<td>55.9%</td>
</tr>
<tr>
<td>Anti-HBc antibodies: best-case scenario (random-effects model)</td>
<td>4</td>
<td>1230</td>
<td>0.08 (0.01-1.03)</td>
<td>96.7%</td>
</tr>
<tr>
<td>Anti-HBc antibodies: best-case scenario (fixed-effect model)</td>
<td>4</td>
<td>1230</td>
<td>0.08 (0.06-0.12)</td>
<td>96.7%</td>
</tr>
<tr>
<td>Anti-HBc antibodies: worst-case scenario (random-effects model)</td>
<td>4</td>
<td>1230</td>
<td>3.45 (0.38-31.57)</td>
<td>99%</td>
</tr>
<tr>
<td>Anti-HBc antibodies: worst-case scenario (fixed-effects model)</td>
<td>4</td>
<td>1230</td>
<td>3.66 (3.03-4.42)</td>
<td>99%</td>
</tr>
</tbody>
</table>
Sensitivity analysis on anti-HBc antibodies showed reduction in risk based on analysis of data of available participants (RR 0.36, 95% CI 0.17 to 0.76, 4 trials with 576 participants, $I^2 = 55.9\%$, random-effects model and RR 0.38, 95% CI 0.28 to 0.52, fixed-effect model).

Intention-to-treat analysis assuming that all participants whose data were not reported had a favourable outcome, ie, none developed anti-HBc at follow-up showed similar result (RR 0.35, 95% CI 0.25 to 0.50, 4 trials with 1230 participants, $I^2 = 42\%$). Best-case scenario analysis showed RR 0.08, 95% CI 0.01 to 1.03, 4 trials with 1230 participants, $I^2 = 96.7\%$, random-effects model and RR 0.08, 95% CI 0.06 to 0.12, fixed-effect model.

Worst-case scenario analysis showed RR 3.45, 95% CI 0.38 to 31.57, 4 trials with 1230 participants, $I^2 = 99.0\%$, random-effects model and RR 3.66, 95% CI 3.03 to 4.42, fixed-effect model.

**Bias**
The funnel plots appeared symmetric and did not suggest significant bias. Figure 1 shows the funnel plot for HBsAg at follow-up for all trials reporting the outcome, and Figure 2 shows the funnel plot for anti-HBc in serum.
Review: Hepatitis B immunization in persons not previously exposed to hepatitis B or with unknown exposure status
Comparison: 02 HB vaccine versus control: presence of antibodies to HBC antigen in serum
Outcome: 01 Presence of anti HBC antibodies in serum
Secondary outcomes

Lack of sero-protection

Nine trials included lack of sero-protection as an outcome. Of these, six did not measure antibody level in the control group (Giammanco 1991; Sun 1991; Ambrosch 1992; Aristegui 1995; Bassily 1995; Greenberg 1996). Three trials reported sero-protection; meta-analysis showed an unclear effect of vaccination (RR 0.57, 95% CI 0.26 to 1.27, 3 trials with 1210 participants, $I^2 = 99.1\%$, random-effects model); however, the fixed-effect model showed RR 0.73, 95% CI 0.69 to 0.78.

Geometric mean titre (GMT) of anti-HBs antibodies

Six trials measured the GMT of anti-HBs antibodies, but only one reported data in both arms of the trial (Xueliang 2000) and showed a mean GMT of 9.71 among vaccinees and 1.23 among controls. However, standard deviation was neither reported nor could be calculated. The other five trials did not report the GMT in participants of the control group (Tseg a 1990; Giammanco 1991; Ambrosch 1992; Aristegui 1995; Bassily 1995).

Clinical complications attributable to hepatitis B infection

None of the trials reported an outcome that could be included as a clinical complication of hepatitis B infection.

Serious adverse events

One trial (Greenberg 1996) reported three serious adverse events; mortality (all-cause), seizures, and hospitalisation. Hepatitis B vaccination did not significantly affect all-cause mortality (RR 1.16, 95% CI 0.47 to 2.84, 10317 participants). Data for seizures and hospitalisation were not reported in the control group. Another trial (Sun 1991) mentioned serious adverse events among hepatitis B vaccine recipients, but did not report the number in either group.

Systemic, local, and other adverse events

The reported systemic adverse events were fever (Aristegui 1995; Greenberg 1996), headache (Ambrosch 1992), diarrhoea (Aristegui 1995), etc. The trials recorded adverse events by providing diary cards to care-givers of children or participants themselves (adults). Six trials recorded local adverse events such as redness at injection site (Aristegui 1995), local pain (Giammanco 1991), soreness, swelling (Aristegui 1995), etc. One trial reported clinical hepatitis as an outcome of interest (Xueliang 2000) and another (Ambrosch 1992) reported levels of hepatic enzymes as an outcome.

For the meta-analysis, adverse events were analysed in three groups: systemic, local, and other. The denominator for these was calculated based on the number of potential events (calculated as number of participants multiplied by the number of doses). The risk of developing fever with hepatitis B vaccine was not significantly affected (RR 1.42, 95% CI 0.60 to 3.38, 2 trials with 14169 potential events, $I^2 = 92.3\%$, random-effects model). The fixed-effect model showed RR 1.03, 95% CI 0.90 to 1.18. The two trials compared hepatitis B vaccine co-administered with other childhood vaccines versus routine childhood vaccines alone (Bassily 1995; Greenberg 1996).

Local reactions included pain, redness, and soreness, singly or in combination. The risk of developing local reactions was significantly increased among hepatitis B vaccine recipients (RR 2.93, 95% CI 1.72 to 4.99, 2 trials with 1904 potential events, $I^2 = 36.9\%$). The two trials compared hepatitis B vaccine either alone or co-administered with other childhood vaccine versus routine childhood vaccine (Bassily 1995; Giammanco 1991).

One trial reported headache (Ambrosch 1992), and the risk of developing this event was unclear (RR 2.33, 95% CI 0.64 to 8.56, 1 trial with 110 participants). The comparator group received hepatitis A vaccine.

Lack of compliance

Six trials reported lack of compliance among enrolled participants. However, three did not report data for controls (Giammanco 1991; Greenberg 1996; Liao 1999) and one (Xueliang 2000) mentioned lack of compliance in 4 of 265 participants without specifying the group(s) to which the four participants belonged. The two trials with data that could be combined in meta-analysis had controls that received routine childhood vaccinations. Although the risk of failure to comply was remarkably different in the two trials, the pooled effect showed no significant difference in the risk of failing to comply with hepatitis B vaccination series as compared to controls (RR 0.91, 95% CI 0.03 to 24.39, 2 trials with 1976 participants, $I^2 = 98.0\%$, random-effects model). The fixed-effect model showed RR 0.26, 95% CI 0.21 to 0.32.

Cost-effectiveness

There were no randomised clinical trials comparing cost effectiveness.

Discussion

Justification for this systematic review

Hepatitis B vaccination has become increasingly popular, especially because it is recommended both for universal vaccination and protection of high-risk groups by the World Health Organization and many professional bodies. Therefore, the very idea of performing a systematic review to assess the benefits and harms of this vaccine may appear strange to some people. Some critics could suggest that this review was undertaken for the purpose of proving a foregone conclusion in favour of the vaccine, making it an unnecessary exercise. Skeptics of the concept and process of evidence-based medicine may also argue that irrespective of the conclusions of the review, one cannot but continue with
hepatitis B vaccination; hence such a review is nothing more than a frivolous scientific exercise. The authors of this review may even be (mis)labeled as evidence-based medicine fanatics demanding proof for ‘the obvious’.

We must emphasize that despite being aware of such opinions, we have undertaken this review for three important reasons. The first aim was to test whether the popular belief in the beneficial effects of hepatitis B vaccine can be proven (or otherwise) in a scientifically rigorous manner. Second and more important, we have tried to assess whether there is evidence to answer a central question that is missed in most trials on hepatitis B vaccine, namely, whether hepatitis B vaccine prevents the occurrence of hepatitis B, in other words the protective efficacy of the vaccine. Numerous trials have implied this conclusion through the use of surrogate outcome measures, especially sero-protection (development of a ‘protective’ titre of antibodies) within a limited time frame (usually four weeks after the last vaccine dose), but this review shows that only a limited number of trials have evaluated protective efficacy measuring relevant outcomes. We believe that this is an important issue to resolve before recommending whether or not hepatitis B vaccine should be used in people not previously exposed to the infection. Thirdly, we have tried to assess the benefits and harms of hepatitis B vaccine with reference to several other outcome measures such as adverse events, cost effectiveness, and compliance pattern among recipients. These issues also are important when hepatitis B vaccination is being considered in a country or region.

Explanation of the methodology used in this systematic review

This review is primarily focused on assessing the benefits and harms of hepatitis B vaccination in people who are either hepatitis B surface antigen negative, or have unknown exposure status; because these groups comprise the vast majority of the world’s population. We have deliberately excluded trials in ‘high-risk’ groups since their response to the vaccine could be different from the so-called ‘low-risk’ patient group. Therefore this review is likely to be helpful for countries planning to initiate hepatitis B vaccination for ‘low risk people’. Many vaccination trials recruit and randomise a reasonably large number of participants, but fail to follow all of them. Some trials report results in only a small fraction of those randomised, failing to account for the missing participants. Since vaccination cannot be assumed to have only beneficial effects, ignoring the participants whose data is not reported can affect the results of the systematic review. There are a number of ways of dealing with this problem, the least appropriate being to ignore it and use only the data of available participants during data analysis. Other analysis models are intention-to-treat analysis assuming unfavourable or favourable outcomes for all participants whose data are missing, in both arms of trials. Another possible analysis could be the best-case scenario and worst-case scenario models. Yet other analysis could be done, by assuming that a proportion of dropouts (in each arm of the trials) had favourable outcomes, while the rest had unfavourable outcomes. However it is not clear how the correct proportion can be calculated, hence this was not a realistic option. We also felt that intention-to-treat analysis merely carrying forward last-reported data is inaccurate because the primary outcomes considered in this review can change with time. It is difficult to judge which of these analysis models is likely to give the most correct result that represents the ‘true’ effect. Therefore, we decided a priori to use an intention-to-treat analysis assuming unfavourable outcomes for all missing data and undertake two sensitivity analyses, ie, analysis of data of available participants at follow-up and intention-to-treat analysis assuming that all participants in either arm whose data were not reported had a favourable outcome.

At the time of initiating this review, we did not realize that most of the trials eligible for inclusion had a large number of participants whose data was neither reported nor its absence explained. Since most trials reported outcomes in only a small fraction of randomised participants, the Contact Editors of this review opined that our original analysis using the intention-to-treat model (assuming unfavourable outcome for all participants whose data were not reported) and the two sensitivity analyses (available data analysis and intention-to-treat analysis assuming favourable outcomes for all missing data) would not be appropriate because the pooled effect could vary depending on the number of participants whose data are missing, in either arm of the trials. They therefore suggested that the data of available participants be presented as the primary analysis and the analysis described in the published protocol of this review be reported as a sensitivity analysis. However, this suggestion has not been accepted by us for two reasons. First, the published protocol specified the analysis performed by us a priori and second, we believe that it is inappropriate to change the reporting format after the results are evident. However, on the suggestion of the Contact Editors, two additional sensitivity analyses have been conducted and reported, ie, the best-case scenario and worst-case scenario. Although these have not been mentioned in the protocol, the Handbook describes both these analyses as methods to deal with data that is not reported. The four sensitivity analyses are presented only for the primary outcome, ie, occurrence of hepatitis B infection.

Since it is not clear which of the analysis models is closest to the ‘truth’, we recommend that all systematic reviews on vaccine efficacy report results using all these analysis models.

Conclusions that can be drawn from this review

This systematic review demonstrates that hepatitis B vaccination has an unclear effect on the risk of developing hepatitis B virus markers of infection (HBSAg and anti-HBc antibodies) in participants without previous knowledge about exposure to hepatitis B infection. However, alternate methods of analysis using the data of available participants shows a clear and dramatic reduction in the risk of developing hepatitis B infection. A similar result is observed
Strengths and limitations of this review

Some of the strengths of this systematic review are that we assessed the effect of hepatitis B vaccine on multiple outcome measures, the most important being protective efficacy. We did this by considering whether vaccination can prevent infection, rather than merely evaluating antibody levels or sero-conversion following vaccination. For this, we planned to analyse all serological markers of hepatitis B infection. Protective efficacy is the real proof of the beneficial effect of any vaccine; all other potential surrogate measurements are only indirect proof (Gluud 2007b). Another strength of this review is that we evaluated the effect of vaccination at the longest follow-up reported. This is important because hepatitis B can result in persistent infection with risk of chronic liver disease and its complications. Therefore, the real test of the vaccine is whether or not it can prevent infection in the long term and not only the short term (in contrast to some other vaccines where the infection predominantly affects children). We also determined the safety profile in terms of serious and non-serious adverse events. Besides these, we made efforts to determine cost effectiveness of vaccinating versus not vaccinating.

We performed a comprehensive search that included contacting experts and vaccine manufacturers, and unlike most Cochrane reviews, we have reported the process and outcome of these additional searches. At least two authors worked independently at all stages of the review. We also performed a rigorous intention-to-treat analysis assuming unfavourable outcome for participants whose data were not reported in the various trials. This was done in order to avoid the bias that could be created by ignoring the number of drop-outs from the trials. The importance of this has been described above. Besides this, we also performed four sensitivity analyses besides
analysis of subgroups of importance. Our methodology has been explicit and transparent. Nevertheless we acknowledge that this review has some important limitations, particularly that all included trials had low methodological quality, ie, had high risk of bias. Furthermore, the risk of bias is further increased by the fact that many of the included trials did not report on outcomes that seemed highly relevant to report on. This could lead to outcome reporting bias (Chan 2004a; Chan 2004b; Chan 2005; Furukawa 2007), which may also lead to significant overestimation of intervention effects.

We did not include publications that reported non-randomised trial design, some of which may be relevant, despite the high risk of bias.

Paucity of high quality data

This review highlights the paucity of methodologically sound trials (trials with low risk of bias) to address the central issue of whether or not hepatitis B vaccination protects against hepatitis B. As is the case with many vaccine trials, most hepatitis B vaccine trials also report limited outcomes such as antibody levels one month after vaccination along with recording a few adverse events. It has already been emphasised that post-vaccination antibodies are only a surrogate outcome that is believed or expected to correlate with protective efficacy.

Our review highlights several gaps in existing knowledge about hepatitis B vaccine. Some of these include information about serious adverse events, the concentration of antibodies generated by vaccination, duration of protective effect, the risk of developing infection if exposed during the vaccination series and the nature of long-term protection afforded by vaccination. A major missing piece is the cost-effectiveness as compared to not vaccinating a cohort of individuals.

Design of future trials

This review gives information that can help to design future trials in order to enhance knowledge about hepatitis B vaccine and its benefits or harms. Ideally, future trials should be conducted on low risk people by including those with unknown exposure status who form the vast majority of the population as well as those already known to be hepatitis B surface antigen negative, without resorting to a screening programme. This would make the participants in the trial similar to the population where a vaccination programme is proposed (should beneficial effect be demonstrated). Furthermore, the participants should be recruited consecutively without resorting to very strict exclusion criteria as is often the case with randomised trials. Such a trial (assuming the usual alpha of 0.05 and power of 0.80) in a population with low prevalence (2%) would require 861 participants in each arm, to demonstrate a reduction in HBsAg by 75%, ie, to 0.5%. Demonstration of a similar reduction in a population of intermediate prevalence (4%) would require 424 participants in each arm; 279 participants would be required in a population with 6% prevalence. For a high prevalence population of 8%, 206 subjects in each arm will be sufficient to demonstrate 75% reduction in risk. Trials should address protective efficacy by measuring clinical and serological outcomes that suggest hepatitis B infection indisputably (HBsAg, anti-HBc, HBV DNA), rather than limiting to surrogate measures of efficacy (sero-protection, GMT of antibodies, etc). These measurements should be performed serially, for the longest duration possible making effort to restrict drop-outs and carefully accounting for any that do occur. However, it is difficult to spell out for how long such trials must be conducted, since it depends on resources available. Intention-to-treat analysis and calculation of numbers needed-to-treat and numbers needed-to-harm will help to get a clearer picture of the effects of hepatitis B vaccination. It need not be emphasised that future trials ought to be conducted and reported according to the recommendations of the CONSORT Statement (www.consort-statement.org). However, it should be recognised that the practicalities of actually undertaking and completing such a trial, especially in the low-risk population, are substantial.

Issues that need to be resolved

Certain issues were outside the scope of this review. These include comparison of various doses of hepatitis B vaccine, ideal number of doses, best vaccination schedule, comparison of different routes of vaccination, comparison between vaccinating separately versus combining with other vaccines, relevance of a birth dose in infancy, duration of protection, impact on event-free survival, etc. These could become the topic of future trials and reviews.

Updating this review

We believe (and hope) that this review will generate considerable interest and correspondence from various quarters, particularly industry. We also recognise that it might bring to light some relevant trials that have not been disclosed so far. Recognising that additional data will be very useful to get a clearer understanding, we propose to submit the first update of this review, one year following its initial publication, instead of the more common practice of waiting for two to three years.

AUTHORS’ CONCLUSIONS

Implications for practice

Current evidence suggests that hepatitis B vaccination has an unclear effect on the risk of developing hepatitis B infection in persons not previously exposed to hepatitis B or with unknown exposure status.

Implications for research

There are several gaps in the knowledge about hepatitis B vaccination including serious adverse events, systemic adverse events, best
dose, best vaccination schedule, and long-term protective effect. The low methodological quality of available data argues strongly in favour of designing new randomised trials that can cover the lacunae in existing data.

ACKNOWLEDGEMENTS

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Peer Reviewers: G Bjelakovic, Serbia; G Aloj, Italy.

Contact Editors: RL Koretz, USA, and C Gluud, Denmark.

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Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status (Review)

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WHO 2004

Wong 1994

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ambrosch 1992

Methods
Randomised clinical trial
Generation of allocation sequence: unclear. Text mentions ‘participants were allocated at random’ to one of the three intervention groups.
Allocation concealment: unclear.
Blinding: not performed.
Follow-up: 1 month after last dose, corresponding to 7 months after first dose vaccine.
Withdrawals and drop-outs: not described.
Participants
Healthy adults, including volunteers and medical personnel found to be HBsAg negative on screening.
Mean age of participants: 18.4 years (Group I 22.3 years; group II 22.7 years group III 22.9 years).
Gender ratio (male to female): Group I 29/26; Group II 30/25; Group III 31/24.
Country: Austria
Inclusion criteria:
Those negative for HBsAg and anti HBc and anti HBs with normal SGOT (AST) and SGPT (ALT) as defined in the trial.
Exclusion criteria: none specified.

Interventions
Three groups were compared: group I received HAV vaccine, group II: received HBV vaccine, and group III: received HAV and HBV vaccine in different arms.
Type of HBV vaccine: recombinant vaccine.
Type of product in control group: HAV vaccine (formalin inactivated preparation containing 720 ELISA units per ml).
Schedule: 0,1,6 months.
Dosage: 20 mcg.
Route: intramuscular.
Site: deltoid muscle.

Outcomes
Lack of sero-protection (Ab < 10 mIU/ ml).
GMT of anti-HBs antibodies.
Adverse events: reported as mean total local symptom score (TLSS) comprising fever, nausea and malaise, without break-up of individual symptoms.
Headache
Mean SGOT (IU/ml).
Mean SGPT (IU/ml).

Notes
Centre: single centre.
Setting: hospital based.
The authors described this as a randomised prospective study designed to compare single and simultaneous administration of two vaccines, ie, hepatitis A and hepatitis B. The interventions in each group are described under Interventions.
The trial does not report two outcomes (lack of sero-protection and geometric mean titre of antibodies) for participants in the control group.

Risk of bias
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<td>Allocation concealment??</td>
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<td>B - Unclear</td>
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Aristegui 1995

Methods
Randomised clinical trial
Generation of allocation sequence: unclear.
Allocation concealment: unclear.
Blinding: unclear.
Follow-up: 40 to 60 days after last dose.
Withdrawals and drop-outs: described. 590 of 655 and 329 of 731 babies were available for the follow-up assessment.
Intention to treat: no.

Participants
Newborns.
Country: Spain
Inclusion criteria: healthy newborns.
Exclusion criteria: none specified.
Mean weight (range): Group A: 3260g (2060 to 4630) and Group B: 3300g (2000 to 6600).

Interventions
Babies receiving simultaneous vaccination with HB vaccine and DPT vaccine plus OPV were compared with babies receiving only DPT plus OPV.
Group A: HB plus DPT vaccines.
Group B: DPT vaccine alone.
Type of vaccine/placebo: recombinant HB vaccine/DPT vaccine.
Schedule: 0, 2, 6 months for HB vaccine and 2, 4, 6 months for DPT vaccine for babies in both groups.
Dosage: 10 mcg in 0.5 ml.
Route: intramuscular in antero-lateral thigh.

Outcomes
Lack of sero-protection (anti HBs Ab <10 mIU/ml).
Adverse events.
Lack of compliance.

Notes
Prospective randomised clinical trial comparing babies receiving simultaneous vaccination with HB vaccine and DPT vaccine plus OPV against those receiving only DPT plus OPV.
590 of 655 and 329 of 731 babies were available for the follow-up assessment.
Single centre.
Setting: hospital based.
Both groups received diphtheria/pertussis/tetanus and oral polio vaccines.

Risk of bias

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Bassily 1995

Methods
Randomised clinical trial
Generation of allocation sequence: adequate (random number table).
Allocation concealment: unclear.
Blinding: not performed.
Follow-up: 1 year.
Withdrawals and drop-outs: described.
Intention to treat: no.

Participants
Infants including a group at birth itself.
Country: Egypt
Inclusion criteria: Babies born to mothers screened for hepatitis B markers and found to be negative.
Exclusion criteria: renal, haematologic, liver, chest and cardiac disease; babies on corticosteroids/ immunosuppressive drugs; birth weight less than 2000 g.
Interventions

Group A: HB vaccine plus routine childhood vaccines (HB given with 0,2,6 months schedule).
Group B: HB plus routine childhood vaccines (HB vaccine given with 2,4,9 months schedule), and
Group C: routine childhood vaccine only (BCG, polio, DPT, and measles vaccines).

Type of vaccine/ placebo: recombinant vaccine/ another vaccine as above.

Schedule:
Group A = 0,2,6 months;
Group B = 2,4,9 months.
Dosage: 2.5 mcg.
Route: intramuscular.

Outcomes

HBsAg.
HBe antigen
HBC antibodies in serum
Lack of sero-protection (Ab < 10 mIU/ ml)
GMT of anti-HBs antibodies.
Adverse events.

Notes
Adverse events were expressed in percentage (Absolute numbers were not mentioned).
This trial randomised 198 (0,2,6 months schedule) and 196 (2,4,9 months schedule) participants to receive the hepatitis B vaccine, but reported data in 90 and 107 respectively.

Risk of bias

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<tbody>
<tr>
<td>Allocation concealment??</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Coursaget 1984

Methods

Randomised clinical trial
Generation of allocation sequence: adequate (random number table).
Allocation concealment: unclear.
Blinding: not performed.
Follow-up: maximum follow-up to 3 years after first dose.
Withdrawals and drop-outs: described, but reasons not mentioned.
Intention to treat: no.

Participants

Children aged 3 to 24 months.
Country: Senegal
Inclusion criteria: none specified.
Exclusion criteria: none specified.

Interventions

Group A: HB vaccine.
Group B: DT-polio vaccine.

Type of vaccine/placebo: recombinant/another vaccine.
Schedule: 3 injections one month apart followed by booster after 1 year.
Dosage: 5 mcg
Route: subcutaneous.

Outcomes

HBsAg.
anti-HBC antibodies in serum.

Notes
Four part study comprising:
Coursaget 1984  (Continued)

I: HB vaccine versus control (DT and polio vaccines)
II: HB vaccine versus control versus both vaccines in different arms
III: 2 HB doses followed by booster (not randomised clinical trial)

The total number randomised is not mentioned.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment??</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Giammanco 1991

Methods

Prospective trial with four arms; three of which included hepatitis B vaccine.
Generation of allocation sequence: unclear.
Allocation concealment: unclear.
Blinding: yes.
Follow-up: 1 month after final dose.
Withdrawals and drop-outs: yes.
Intention to treat: no.

Participants

Infants sero-negative for antibodies to HBsAg.
Country: Italy
Inclusion criteria: not described.
Exclusion criteria: not described.

Interventions

Groups A,B,C: HB vaccine.
Group D: DT vaccine plus OPV.
Type of HB vaccine/placebo: recombinant vaccine/ another vaccine.
Group A: (0,3,4,10 mo schedule).
Group B: (0,1,3,10 mo schedule).
Group C: (3,4,10 mo schedule).
Dosage: 10 mcg in 0.5 ml.
Route: intramuscular.
Site: deltoid.

Outcomes

HBsAg.
HBc antibodies in serum.
Lack of sero-protection (Ab < 10 mIU/ ml
GMT of anti HBs antibodies.
Adverse events.

Notes

Authors do not specify how the arms in the trial were formed. They report that 111 infants received hepatitis B vaccine according to one of three different schedules, in addition to routine childhood vaccines (DT and oral polio vaccine) and ‘control group’ of 21 infants received only DT and oral polio vaccine. Data were extracted for the adverse events.
Single centre.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
</table>
Greenberg 1996

Methods
Randomised clinical trial
Generation of allocation sequence: adequate.
Allocation concealment: unclear.
Blinding: unclear.
Follow-up:
Withdrawals and drop-outs: no
Intention to treat: no.

Participants
6 to 15 week old infants.
Country: United States of America
Inclusion criteria: not described.
Exclusion criteria: neurologic disease; seizures; altered immune function including maternal HIV infection; those who had received immunoglobulin or blood products in the preceding 3 months; acute fever.

Interventions
Group A: HB plus DT vaccine.
Group B: Hib plus DT vaccine.
Type of HB vaccine and control product: recombinant HB vaccine/PRP-T Hib vaccine.
Schedule: 2, 4, 6 months.
Dosage: 10 mcg.
Route: Intramuscular.
Site of administration: anterolateral thigh.

Outcomes
Lack of sero-protection (Ab < 10 mIU/ml).
Serious adverse events.
Mortality (all cause).
Seizures
Hospitalizations
Adverse events.
Lack of compliance.

Notes
Multi-centre
Setting: 13 clinics in Southern California
The trial randomised 5056 participants to receive hepatitis B vaccine, but reported lack of sero-protection in only 135 of them. This data was not presented for participants in the control arm.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment??</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
Liao 1999

Methods
Randomised clinical trial
Generation of allocation sequence: unclear.
Allocation concealment: unclear.
Blinding: not performed.
Follow-up: 15 years.
Withdrawals and drop-outs: no.
Intention to treat: no.

Participants
3 to 36 month-old children recruited from vaccination clinics.
Country: China
Inclusion criteria: not described.
Exclusion criteria: not described.

Interventions
Group A: HB vaccine
Group B: vaccine diluent.
Type of HB vaccine and control product: plasma derived/placebo.
Schedule: 0,1,6 months.
Dosage: 17.5 mcg.

Outcomes
HBsAg (at 15 years).
Lack of sero-protection (Ab < 10 mIU/ ml).
Lack of compliance.

Notes
Multi centre: seven vaccination clinics in one county of a province in China.
This trial randomised 308 participants to the intervention arm and 341 to the control arm, but reported data at fifteen years for only 52 and 54 respectively.
The authors also reported the cumulative number of participants who became HBsAg positive during the fifteen year follow-up, despite the high attrition rate.
Sero-protection in this trial was defined as greater than 10 'Sample to Negative control ratio' based on a radio-immunoassay method to detect anti-HBs antibodies.

Risk of bias

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Perrin 1986

Methods
Randomised clinical trial
Generation of allocation sequence: unclear.
Allocation concealment: unclear.
Blinding: not performed.
Follow-up: 12 months after the third dose. Although 480 babies were recruited, the number in each intervention arm has not been described.
Withdrawals and drop-outs: no.
Intention to treat: no.

Participants
Newborn babies.
Country: Burundi
Inclusion criteria: not specified.
Exclusion criteria: not specified.

Interventions
Group A: HB vaccine.
Group B: other vaccines in routine immunization programme (not mentioned).
Type of HB vaccine and control product: Not specified/another vaccine.
Schedule: 0,2,12 months.
Dosage: 5 mcg.
Route: not specified.

Outcomes
HBsAg at 24 months after first dose.
HBC antibodies in serum.

Notes
Single centre.
Setting: hospital.
This trial does not mention the number of participants randomised.

Risk of bias
<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment??</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Sun 1991

Methods
Randomised clinical trial
Generation of allocation sequence: unclear.
Allocation concealment: unclear.
Blinding: not performed.
Follow-up: 5 years. 261 out of 265 completed vaccination; but break up in each arm is not mentioned
Withdrawals and drop-outs: no.
Intention to treat: no.

Participants
Children between 5 to 9 years recruited from primary schools.
Country: China
Inclusion criteria: not described.
Exclusion criteria: not described.

Interventions
Group A: HB vaccine
Group B: Not mentioned.
Type of HB vaccine and control product: HB vaccine/placebo but nature not specified.
Schedule: 0,1,6 months.
Dosage: not mentioned.
Route: not specified.

Outcomes
HBsAg (at 11 years)
HBC antibodies in serum
GMT of anti HBs antibodies
Clinical hepatitis
Lack of compliance

Notes
Setting: community.
Sun 1991  
(Continued)

Single centre.
This trial randomised almost 38000 participants in each arm, but reported HBsAg in 682 and 312 participants in the intervention and control arms respectively.

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment??</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Tseg 1990

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generation of allocation sequence: inadequate.</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment: unclear.</td>
<td></td>
</tr>
<tr>
<td>Blinding: no.</td>
<td></td>
</tr>
<tr>
<td>Follow-up: 1 month after third dose.</td>
<td></td>
</tr>
<tr>
<td>Withdrawals and drop-outs: yes.</td>
<td></td>
</tr>
<tr>
<td>Intention to treat: no.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Infants between 6 weeks and 6 months of age.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: Ethiopia</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria: described as healthy infants.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: not specified.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group A: HBV vaccine plus routine EPI vaccines.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B: EPI vaccines.</td>
<td></td>
</tr>
<tr>
<td>Type of HB vaccine and control product: plasma derived vaccine/another vaccine.</td>
<td></td>
</tr>
<tr>
<td>Schedule: 0,1,2,6 months.</td>
<td></td>
</tr>
<tr>
<td>Dosage: 2 mcg.</td>
<td></td>
</tr>
<tr>
<td>Route: not mentioned.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HBsAg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBC antibodies in serum.</td>
<td></td>
</tr>
<tr>
<td>Lack of sero-protection (Ab &lt; 10 mIU/ ml).</td>
<td></td>
</tr>
<tr>
<td>GMT of anti HBs antibodies.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>Prospective hospital based.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single centre.</td>
<td></td>
</tr>
<tr>
<td>This trial randomised 150 participants each to the intervention and control arms, but reported outcomes in 134 and 132 respectively.</td>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment??</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
**Wang 1985**

**Methods**
- Randomised clinical trial
- Generation of allocation sequence: unclear.
- Allocation concealment: unclear.
- Blinding: not performed.
- Follow-up: 6 months after the last (fourth) dose.
- Withdrawals and drop-outs: no.
- Intention to treat: no.

**Participants**
- Newborn babies
- Country: China
- Inclusion criteria: not mentioned except that babies were born to mothers who were HBsAg negative (for the arms being included in the systematic review).
- Exclusion criteria: not described.

**Interventions**
- Group A: HB vaccine.
- Group B: placebo.
- Type of HB vaccine and control product: plasma derived/placenta immunoglobulin.
- Schedule: 0,1,3,6 months.
- Dosage: 30 mcg.
- Route: intramuscular or subcutaneous.

**Outcomes**
- HBsAg
- HBc antibodies in serum

**Notes**
- Prospective trial comparing four arms of which two were babies born to HBsAg negative mothers who received HB vaccine or placebo.
- Single centre.
- This trial reports that at least 10 babies were present in each group, although it does not specify the exact number. The data in the trial are reported for 10 babies in each group.

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment??</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

**Xueliang 2000**

**Methods**
- Randomised clinical trial
- Generation of allocation sequence: unclear.
- Allocation concealment: unclear.
- Blinding: not performed.
- Follow-up: 11 years after vaccination.
- Withdrawals and drop-outs: no.
- Intention to treat: no.

**Participants**
- Children between 5 to 9 years recruited from primary schools.
- Country: China
- Inclusion criteria: not described.
Xueliang 2000  *(Continued)*

Exclusion criteria: not described.

**Interventions**

Group A: HB vaccine.
Group B: placebo.
Type of HB vaccine and control product: plasma derived/placebo, but nature not specified.
Schedule: 0,1,6 months.
Dosage: not mentioned.
Route: not specified.

**Outcomes**

HBsAg (at 11 years)
HBc antibodies in serum.
Lack of sero-protection (Ab < 10 mIU/ ml).
Clinical hepatitis.

Notes

Authors report this as a randomised, double-blind, placebo-controlled trial. However, there is no description of the ’placebo’ used. The authors report that a “blind code” was used in the laboratory assay.
Single centre.
This trial randomised 126 and 135 participants to the intervention and control arms, but reported outcomes in 84 and 100 respectively.
Setting: community.

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
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</tr>
</tbody>
</table>

Ab = antibodies
anti-HBc = antibodies to hepatitis B core antigen
DPT = diphtheria, pertussis, tetanus vaccine
DT = diphtheria, tetanus vaccine
HAV = hepatitis A vaccine
HB = hepatitis B
HBsAg = hepatitis B surface antigen
Hib = Haemophilus influenzae type b
mcg = micrograms
mIU = milli international units
OPV = oral polio vaccine
RCT = randomised clinical trial.
### Characteristics of excluded studies  
*ordered by study ID*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aach 1982</td>
<td>This is not a randomised clinical trial comparing hepatitis B vaccine versus control.</td>
</tr>
<tr>
<td>Abbas 1999</td>
<td>Trial is not designed as a randomised clinical trial to compare HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Abdurrahman 1984</td>
<td>This is not a randomised clinical trial comparing hepatitis B vaccine versus control.</td>
</tr>
<tr>
<td>Akbar 1997</td>
<td>Trial was conducted in mice.</td>
</tr>
<tr>
<td>Akram 2005</td>
<td>Trial is not designed as a randomised clinical trial to compare HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Alikasifoglu 2001</td>
<td>Trial is a comparison of different brands, doses, and schedules, and not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Ambrosch 1994</td>
<td>Trial is a comparison of a combined HB and hepatitis A vaccine administered either singly, separately, or in combination and is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Artan 2004</td>
<td>Trial is a comparison of different vaccination schedules and is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Assateerawatt 1993</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus control/placebo but reports observations in high risk neonates and normal children and adults, with no control group for comparison.</td>
</tr>
<tr>
<td>Ayoola 1984</td>
<td>Trial includes comparison of different routes and doses in healthy people, adults who are HBsAg positive and non-responders.</td>
</tr>
<tr>
<td>Ayoola 1986</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus control/placebo, but compares two routes of administering HB vaccine.</td>
</tr>
<tr>
<td>Baldy 2004</td>
<td>Trial is a comparison of three preparations of HB vaccine and not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Chunsuttiwat 1997</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Coutinho 1983</td>
<td>Trial was conducted in adult homosexual men.</td>
</tr>
<tr>
<td>Duclos 2003</td>
<td>Trial is not a randomised trial comparing HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Fortuin 1993</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Gomez 2002</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Guihua 1997</td>
<td>There is later data reported for this trial.</td>
</tr>
<tr>
<td>Guihua 1998</td>
<td>Trial is a randomised clinical trial of booster dose versus placebo in a cohort of responders to vaccination and not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Hall 1993</td>
<td>This is not a randomised clinical trial comparing hepatitis B vaccine with a control group.</td>
</tr>
<tr>
<td>Jones-Lecointe 2001</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Koff 1994</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Liao 1998</td>
<td>This study is succeeded by Liao 1999 that reports results of the same trial at a later follow-up date.</td>
</tr>
<tr>
<td>Lok 2004</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus control/placebo, but a review of previously published data.</td>
</tr>
<tr>
<td>Margolis 1995</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Martins 2004</td>
<td>Trial is a comparison of different brands of HB vaccine and not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Maupas 1976</td>
<td>Trial does not have a group for comparison and hence is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Maupas 1981</td>
<td>This was not a randomised trial. In addition, the number of participants enrolled in each arm was not specified.</td>
</tr>
<tr>
<td>Montesano 2002</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Perrilo 1987</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Perroni 1989</td>
<td>Trial includes babies born to HBsAg positive mothers and other high risk groups that are not part of this review.</td>
</tr>
<tr>
<td>Petersen 1993</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Phanuphak 1989</td>
<td>Trial is a comparison of four brands of the same vaccine (hepatitis B) and has no control group that did not receive hepatitis B vaccine.</td>
</tr>
<tr>
<td>Pongpipat 1987</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Ricciardi 1990</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Rodrigo 1992</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Stevens 1985</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Szmuness 1980</td>
<td>Trial was conducted in adult homosexual men.</td>
</tr>
<tr>
<td>Szmuness 1981</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Thanavala 2005</td>
<td>The antigen used in the trial is not a vaccine as yet.</td>
</tr>
<tr>
<td>Thies 2002</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Tong 2005</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Turchi 1997</td>
<td>Trial is a comparison of different routes and not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Xu 1985a</td>
<td>Trial is a randomised clinical trial in babies born to HBsAg positive mothers.</td>
</tr>
<tr>
<td>Xu 1985b</td>
<td>Trial was conducted in babies born to HBsAg positive mothers.</td>
</tr>
<tr>
<td>Xu 1992</td>
<td>There is a later analysis of data of this trial.</td>
</tr>
<tr>
<td>Xu 1993</td>
<td>There is nothing mentioned about a control group.</td>
</tr>
<tr>
<td>Xu 1995</td>
<td>There is a later analysis of data of this trial.</td>
</tr>
<tr>
<td>Yuen 2004</td>
<td>There is no control group in the trial hence not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
<tr>
<td>Yvonnet 1987</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus control/placebo, but a comparison of different doses of HB vaccine without a control group for comparison.</td>
</tr>
<tr>
<td>Zhuang 1998</td>
<td>Trial is not a randomised clinical trial of HB vaccine versus placebo or a control.</td>
</tr>
</tbody>
</table>

HB = hepatitis B  
HBsAg = hepatitis B surface antigen.
### Data and Analyses

#### Table 1. Comparison 1. Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 HBsAg at follow-up (all studies reporting this outcome)</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.89, 1.03]</td>
</tr>
<tr>
<td>1.1 Presence of HBsAg at follow-up (all trials)</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.89, 1.03]</td>
</tr>
<tr>
<td>2 HBsAg at follow-up (sub-group analysis based on age of enrolled participants)</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.89, 1.03]</td>
</tr>
<tr>
<td>2.3 Children (28 days to 10 years)</td>
<td>3</td>
<td>1210</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.89, 1.03]</td>
</tr>
<tr>
<td>2.4 Newborn babies (less than 28 days)</td>
<td>1</td>
<td>20</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>3 HBsAg at follow-up (sub-group analysis based on prevalence in participating population)</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.89, 1.03]</td>
</tr>
<tr>
<td>3.3 High prevalence (&gt; 8%)</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.89, 1.03]</td>
</tr>
<tr>
<td>4 HBsAg at follow-up (sub-group analysis based on duration of follow-up)</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.89, 1.03]</td>
</tr>
<tr>
<td>4.1 Follow-up less than 1 year</td>
<td>2</td>
<td>320</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.76 [0.41, 1.40]</td>
</tr>
<tr>
<td>4.3 Follow-up more than 5 years</td>
<td>2</td>
<td>910</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.97 [0.90, 1.04]</td>
</tr>
<tr>
<td>5 HBsAg at follow-up (sub-group analysis based on vaccination schedule)</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.89, 1.03]</td>
</tr>
<tr>
<td>5.1 Three doses administered with 0,1,6 schedule</td>
<td>2</td>
<td>910</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.97 [0.90, 1.04]</td>
</tr>
<tr>
<td>5.3 Four doses administered by any schedule</td>
<td>2</td>
<td>320</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.76 [0.41, 1.40]</td>
</tr>
</tbody>
</table>

#### Table 1. Comparison 2. HB vaccine versus control: presence of antibodies to HBc antigen in serum

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Anti-HBc antibodies in serum</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.86 [0.80, 0.92]</td>
</tr>
<tr>
<td>2 Anti-HBc antibodies in serum (random-effects model)</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.81 [0.61, 1.07]</td>
</tr>
</tbody>
</table>
### Table 1. Comparison 3. HB vaccine versus control: adverse events

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of sero-protection</td>
<td>3</td>
<td>1210</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.57 [0.26, 1.27]</td>
</tr>
<tr>
<td>(fixed-effect model)</td>
<td></td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.73 [0.69, 0.78]</td>
</tr>
</tbody>
</table>

### Table 1. Comparison 4. HB vaccine versus control: serious adverse events

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events: all-cause mortality</td>
<td>1</td>
<td>10317</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.16 [0.47, 2.84]</td>
</tr>
</tbody>
</table>

### Table 1. Comparison 5. HB vaccine versus control: adverse events

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>2</td>
<td>14169</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.42 [0.60, 3.38]</td>
</tr>
<tr>
<td>(fixed-effect model)</td>
<td></td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.03 [0.90, 1.18]</td>
</tr>
<tr>
<td>Local reactions (pain, redness, soreness)</td>
<td>2</td>
<td>1904</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.93 [1.72, 4.99]</td>
</tr>
<tr>
<td>Other adverse events</td>
<td>1</td>
<td>110</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.33 [0.64, 8.56]</td>
</tr>
</tbody>
</table>

### Table 1. Comparison 6. HB vaccine versus control: lack of compliance

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of compliance</td>
<td>2</td>
<td>1976</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.91 [0.03, 24.39]</td>
</tr>
<tr>
<td>(fixed-effect model)</td>
<td></td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.26 [0.21, 0.32]</td>
</tr>
</tbody>
</table>
### Table 1. Comparison 7. Sensitivity analysis

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 HBsAg based on percentage of drop-outs in the trial (ITT analysis)</td>
<td>1</td>
<td>20</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>1.1 Less than 10% drop-outs</td>
<td>1</td>
<td>20</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>2 Anti HBc antibodies based on percentage of drop-outs (ITT analysis)</td>
<td>1</td>
<td>20</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>2.1 Less than 10% drop-outs</td>
<td>1</td>
<td>20</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>3 HBsAg: intention to treat analysis assuming favourable outcome for all drop-outs</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.12 [0.03, 0.44]</td>
</tr>
<tr>
<td>4 HBsAg: available participant analysis</td>
<td>4</td>
<td>576</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.12 [0.03, 0.44]</td>
</tr>
<tr>
<td>5 HBsAg: best-case scenario</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.01 [0.00, 0.03]</td>
</tr>
<tr>
<td>6 HBsAg: worst-case scenario</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>9.45 [2.14, 41.67]</td>
</tr>
<tr>
<td>7 HBsAg: worst-case scenario</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>15.59 [10.29, 23.64]</td>
</tr>
<tr>
<td>8 Anti HBc antibodies: intention-to-treat analysis assuming favourable outcome for all drop-outs</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.35 [0.25, 0.50]</td>
</tr>
<tr>
<td>9 Anti HBc antibodies in serum based on analysis of available participants (fixed-effect model)</td>
<td>4</td>
<td>576</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.38 [0.28, 0.52]</td>
</tr>
<tr>
<td>10 Anti-HBc antibodies in serum based on analysis of available participants (random-effects model)</td>
<td>4</td>
<td>576</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.36 [0.17, 0.76]</td>
</tr>
<tr>
<td>11 Anti-HBc antibodies in serum: best-case scenario</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.08 [0.06, 0.12]</td>
</tr>
<tr>
<td>12 Anti HBc antibodies in serum: best-case scenario</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.08 [0.01, 1.03]</td>
</tr>
<tr>
<td>13 Anti HBc antibodies in serum: worst-case scenario</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>3.45 [0.38, 31.57]</td>
</tr>
<tr>
<td>14 Anti HBc antibodies in serum: worst-case scenario</td>
<td>4</td>
<td>1230</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>3.66 [3.03, 4.42]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. nbsp; Comparison 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up, Outcome 1 HBsAg at follow-up (all studies reporting this outcome).

#### Review: Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

#### Comparison: 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up

#### Outcome: 1 HBsAg at follow-up (all studies reporting this outcome)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Presence of HBsAg at follow-up (all trials)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liao 1999</td>
<td>257/308</td>
<td>296/341</td>
<td>81.3 %</td>
<td>0.96 [ 0.90, 1.03 ]</td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>16/150</td>
<td>21/150</td>
<td>6.1 %</td>
<td>0.76 [ 0.41, 1.40 ]</td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>0.0 %</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>43/126</td>
<td>45/135</td>
<td>12.6 %</td>
<td>1.02 [ 0.73, 1.44 ]</td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td>594</td>
<td>636</td>
<td>100.0 %</td>
<td>0.96 [ 0.89, 1.03 ]</td>
</tr>
</tbody>
</table>

Total events: 316 (Hepatitis B vaccine), 362 (Control)

Heterogeneity: $\chi^2 = 0.71$, df = 2 ($P = 0.70$); $I^2 = 0.0$

Test for overall effect: $Z = 1.13$ ($P = 0.26$)

---

### Analysis 2.2. nbsp; Comparison 2 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up, Outcome 2 HBsAg at follow-up (all studies reporting this outcome)

#### Review: Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

#### Comparison: 2 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up

#### Outcome: 2 HBsAg at follow-up (all studies reporting this outcome)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Presence of HBsAg at follow-up (all trials)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liao 1999</td>
<td>257/308</td>
<td>296/341</td>
<td>0.96 [ 0.90, 1.03 ]</td>
<td></td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>16/150</td>
<td>21/150</td>
<td>0.76 [ 0.41, 1.40 ]</td>
<td></td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>43/126</td>
<td>45/135</td>
<td>1.02 [ 0.73, 1.44 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td>594</td>
<td>636</td>
<td>0.96 [ 0.89, 1.03 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 316 (Hepatitis B vaccine), 362 (Control)

Heterogeneity: $\chi^2 = 0.71$, df = 2 ($P = 0.70$); $I^2 = 0.0$

Test for overall effect: $Z = 1.13$ ($P = 0.26$)
Analysis 1.2. Comparison 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up, Outcome 2 HBsAg at follow-up (subgroup analysis based on age of enrolled participants).

Review: Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status
Comparison: 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up
Outcome: 2 HBsAg at follow-up (subgroup analysis based on age of enrolled participants)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>0 0</td>
<td>0 0</td>
<td>0.0 %</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 0 (Hepatitis B vaccine), 0 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Adolescents (11 to 18 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>0 0</td>
<td>0 0</td>
<td>0.0 %</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 0 (Hepatitis B vaccine), 0 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Children (28 days to 10 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liao 1999</td>
<td>257/308</td>
<td>296/341</td>
<td>81.3 %</td>
<td>0.96 [ 0.90, 1.03 ]</td>
<td></td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>16/150</td>
<td>21/150</td>
<td>6.1 %</td>
<td>0.76 [ 0.41, 1.40 ]</td>
<td></td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>43/126</td>
<td>45/135</td>
<td>12.6 %</td>
<td>1.02 [ 0.73, 1.44 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>584 626</td>
<td></td>
<td>100.0 %</td>
<td>0.96 [ 0.89, 1.03 ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 316 (Hepatitis B vaccine), 362 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Chi² = 0.71, df = 2 (P = 0.70); I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 1.13 (P = 0.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Newborn babies (less than 28 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>0.0 %</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>10 10</td>
<td></td>
<td>0.0 %</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 0 (Hepatitis B vaccine), 0 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>594 636</td>
<td></td>
<td>100.0 %</td>
<td>0.96 [ 0.89, 1.03 ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 316 (Hepatitis B vaccine), 362 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Chi² = 0.71, df = 2 (P = 0.70); I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 1.13 (P = 0.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours HB vaccine Favours control

Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status (Review) 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Review
Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

### Comparison
1. Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up

### Outcome
2. HBsAg at follow-up (sub-group analysis based on age of enrolled participants)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3 Children (28 days to 10 years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liao 1999</td>
<td>257/308</td>
<td>296/341</td>
<td>0.96 [ 0.90, 1.03 ]</td>
<td></td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>16/150</td>
<td>21/150</td>
<td>0.76 [ 0.41, 1.40 ]</td>
<td></td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>43/126</td>
<td>45/135</td>
<td>1.02 [ 0.73, 1.44 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>584</td>
<td>626</td>
<td>0.96 [ 0.89, 1.03 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 316 (Hepatitis B vaccine), 362 (Control)
Heterogeneity: Chi² = 0.71, df = 2 (P = 0.70); I² = 0.0%
Test for overall effect: Z = 1.13 (P = 0.26)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4 Newborn babies (less than 28 days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>10</td>
<td>10</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 0 (Hepatitis B vaccine), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: not applicable
### Analysis 1.3. Comparison: Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

**Comparison:** Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up

**Outcome:** HBsAg at follow-up (sub-group analysis based on prevalence in participating population).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>1 Low prevalence (&lt; 2%)</td>
<td>0/0</td>
<td>0/0</td>
<td>0.0 %</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

Total events: 0 (Hepatitis B vaccine), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: not applicable

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>2 Intermediate prevalence (2% to 8%)</td>
<td>0/0</td>
<td>0/0</td>
<td>0.0 %</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

Total events: 0 (Hepatitis B vaccine), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: not applicable

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>3 High prevalence (&gt; 8%)</td>
<td>257/308</td>
<td>296/341</td>
<td>81.3 %</td>
<td>0.96 [0.90, 1.03]</td>
<td></td>
</tr>
<tr>
<td>Liao 1999</td>
<td>257/308</td>
<td>296/341</td>
<td>81.3 %</td>
<td>0.96 [0.90, 1.03]</td>
<td></td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>16/150</td>
<td>21/150</td>
<td>6.1 %</td>
<td>0.76 [0.41, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>0.0 %</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>43/126</td>
<td>45/135</td>
<td>12.6 %</td>
<td>1.02 [0.73, 1.44]</td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

Total events: 316 (Hepatitis B vaccine), 362 (Control)

Heterogeneity: $\chi^2 = 0.71$, df = 2 ($P = 0.70$); $I^2 = 0.0$

Test for overall effect: $Z = 1.13$ ($P = 0.26$)

**Total (95% CI)**

Total events: 316 (Hepatitis B vaccine), 362 (Control)

Heterogeneity: $\chi^2 = 0.71$, df = 2 ($P = 0.70$); $I^2 = 0.0$

Test for overall effect: $Z = 1.13$ ($P = 0.26$)

---

Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status (Review)

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status  
**Comparison:** 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up  
**Outcome:** 3 HBsAg at follow-up (sub-group analysis based on prevalence in participating population)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>3 High prevalence (≥ 8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liao 1999</td>
<td>257/308</td>
<td>296/341</td>
<td>0.96 [0.90, 1.03]</td>
<td></td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>16/150</td>
<td>21/150</td>
<td>0.76 [0.41, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>43/126</td>
<td>45/135</td>
<td>1.02 [0.73, 1.44]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>594</td>
<td>636</td>
<td></td>
<td>0.96 [0.89, 1.03]</td>
</tr>
</tbody>
</table>

Total events: 316 (Hepatitis B vaccine), 362 (Control)  
Heterogeneity: Chi$^2 = 0.71$, df = 2 (P = 0.70); I$^2$ =0.0%  
Test for overall effect: Z = 1.13 (P = 0.26)

---

**Analysis 1.4. nbsp; Comparison 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up, Outcome 4 HBsAg at follow-up (sub-group analysis based on duration of follow-up).**

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status  
**Comparison:** 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up  
**Outcome:** 4 HBsAg at follow-up (sub-group analysis based on duration of follow-up)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Follow-up less than 1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>16/150</td>
<td>21/150</td>
<td>6.1 %</td>
<td>0.76 [0.41, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>0.0 %</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>160</td>
<td>160</td>
<td></td>
<td>6.1 %</td>
<td>0.76 [0.41, 1.40]</td>
</tr>
</tbody>
</table>

Total events: 16 (Hepatitis B vaccine), 21 (Control)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.87 (P = 0.38)  
2 Follow-up between 1 and 5 years  
Subtotal (95% CI)

|                  | 0                   | 0       | 0.0 %       | Not estimable |            |

Total events: 0 (Hepatitis B vaccine), 0 (Control)  
Heterogeneity: not applicable

---

(Continued ...)

*Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status (Review)*  
Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Study or subgroup

<table>
<thead>
<tr>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
</tbody>
</table>

#### Test for overall effect: not applicable

Follow-up more than 5 years

<table>
<thead>
<tr>
<th>Study</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
</tbody>
</table>

#### Subtotal (95% CI)

Total events: 300 (Hepatitis B vaccine), 341 (Control)

Test for overall effect: Z = 0.83 (P = 0.41)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
</tbody>
</table>

#### Total (95% CI)

Total events: 316 (Hepatitis B vaccine), 362 (Control)

Test for overall effect: Z = 1.13 (P = 0.26)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
</tbody>
</table>

---

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

**Comparison:** 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up

**Outcome:** 4 HBsAg at follow-up (sub-group analysis based on duration of follow-up)

#### 1 Follow-up less than 1 year

<table>
<thead>
<tr>
<th>Study</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
</tbody>
</table>

#### Subtotal (95% CI)

Total events: 16 (Hepatitis B vaccine), 21 (Control)

Test for overall effect: Z = 0.87 (P = 0.38)
### Analysis 1.5. Comparison 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up, Outcome 5 HBsAg at follow-up (subgroup analysis based on vaccination schedule).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Three doses administered with 0,1,6 schedule</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liao 1999</td>
<td>257/308</td>
<td>296/341</td>
<td>0.96 [ 0.90, 1.03 ]</td>
<td>81.3 %</td>
<td>0.96 [ 0.90, 1.03 ]</td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>43/126</td>
<td>45/135</td>
<td>1.02 [ 0.73, 1.44 ]</td>
<td>12.6 %</td>
<td>1.02 [ 0.73, 1.44 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>434</strong></td>
<td><strong>476</strong></td>
<td><strong>0.97 [ 0.90, 1.04 ]</strong></td>
<td><strong>93.9 %</strong></td>
<td><strong>0.97 [ 0.90, 1.04 ]</strong></td>
</tr>
<tr>
<td>Total events: 300 (Hepatitis B vaccine), 341 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: CHI^2 = 0.17, df = 1 (p = 0.68); P =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.83 (p = 0.41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 2 Three doses administered with an accelerated schedule |                     |         |                 |        |                 |
| **Subtotal (95% CI)** | **0**              | **0**   | **Not estimable** | **0.0 %** | **Not estimable** |
| Total events: 0 (Hepatitis B vaccine), 0 (Control) |                     |         |                 |        |                 |
| Heterogeneity: not applicable |                     |         |                 |        |                 |
| Test for overall effect: not applicable |                     |         |                 |        |                 |

| 3 Four doses administered by any schedule |                     |         |                 |        |                 |
| Tsega 1990 | 16/150 | 21/150 | 0.76 [ 0.41, 1.40 ] | 6.1 % | 0.76 [ 0.41, 1.40 ] |

(Continued...)
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td>0.0 %</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>160</strong></td>
<td><strong>160</strong></td>
<td><strong>6.1 %</strong></td>
<td><strong>0.76 [0.41, 1.40]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events: 16 (Hepatitis B vaccine), 21 (Control)</td>
<td><strong>Total (95% CI)</strong></td>
<td><strong>594</strong></td>
<td><strong>636</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.96 [0.89, 1.03]</strong></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td>Test for overall effect: Z = 0.87 (P = 0.38)</td>
<td>Heterogeneity: Chi² = 0.71, df = 2 (P = 0.70); I² =0.0%</td>
<td>Test for overall effect: Z = 1.13 (P = 0.26)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Review: Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status
Comparison: Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up
Outcome: HBsAg at follow-up (sub-group analysis based on vaccination schedule)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Three doses administered with 0,1,6 schedule</td>
<td>257/308</td>
<td>296/341</td>
<td>0.96 [0.90, 1.03]</td>
<td></td>
</tr>
<tr>
<td>Liao 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>43/126</td>
<td>45/135</td>
<td>1.02 [0.73, 1.44]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>434</strong></td>
<td><strong>476</strong></td>
<td><strong>0.97 [0.90, 1.04]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events: 300 (Hepatitis B vaccine), 341 (Control)</td>
<td>Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² =0.0%</td>
<td>Test for overall effect: Z = 0.83 (P = 0.41)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Analysis 2.1. Comparison 1 HB vaccine versus control: presence of HBsAg at follow-up

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status  
**Comparison:** 1 Hepatitis B vaccine versus control/placebo: presence of HBsAg at follow-up  
**Outcome:** 5 HBsAg at follow-up (sub-group analysis based on vaccination schedule)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>16/150</td>
<td>21/150</td>
<td>0.76 [ 0.41, 1.40 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**  
Total events: 16 (Hepatitis B vaccine), 21 (Control)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.87 (P = 0.38)

---

### Analysis 2.2. Comparison 2 HB vaccine versus control: presence of antibodies to HBc antigen in serum

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status  
**Comparison:** 2 HB vaccine versus control: presence of antibodies to HBc antigen in serum  
**Outcome:** 1 Anti-HBc antibodies in serum

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>Liao 1999</td>
<td>259/308</td>
<td>310/341</td>
<td>0.93 [ 0.87, 0.98 ]</td>
<td>69.5 %</td>
<td>69.5 %</td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>20/150</td>
<td>24/150</td>
<td>0.83 [ 0.48, 1.44 ]</td>
<td>5.7 %</td>
<td>5.7 %</td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td>0.0 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>69/126</td>
<td>109/135</td>
<td>0.68 [ 0.57, 0.81 ]</td>
<td>24.9 %</td>
<td>24.9 %</td>
</tr>
</tbody>
</table>

**Total (95% CI)**  
Total events: 348 (Hepatitis B vaccine), 443 (Control)  
Heterogeneity: Chi² = 12.82, df = 2 (P = 0.002); I² = 84%  
Test for overall effect: Z = 4.55 (P < 0.00001)
### Analysis 2.2. Comparison 2 HB vaccine versus control: presence of antibodies to HBc antigen in serum, Outcome 2 Anti-HBc antibodies in serum (random-effects model).

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

**Comparison:** 2 HB vaccine versus control: presence of antibodies to HBc antigen in serum

**Outcome:** 2 Anti-HBc antibodies in serum (random-effects model)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Liao 1999</td>
<td>259/308</td>
<td>310/341</td>
<td>44.8 %</td>
<td>0.93 [ 0.87, 0.98 ]</td>
<td></td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>20/150</td>
<td>24/150</td>
<td>16.7 %</td>
<td>0.83 [ 0.48, 1.44 ]</td>
<td></td>
</tr>
<tr>
<td>Wang 1985</td>
<td>0/10</td>
<td>0/10</td>
<td>0.0 %</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>69/126</td>
<td>109/135</td>
<td>38.5 %</td>
<td>0.68 [ 0.57, 0.81 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>594</strong></td>
<td><strong>636</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.81 [ 0.61, 1.07 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 348 (Hepatitis B vaccine), 443 (Control)

Heterogeneity: \( \tau^2 = 0.05 ; \chi^2 = 12.82, df = 2 (P = 0.002); I^2 = 84\% \)

Test for overall effect: \( Z = 1.50 (P = 0.13) \)

### Analysis 3.1. Comparison 3 HB vaccine versus control: adverse events, Outcome 1 Lack of sero-protection.

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

**Comparison:** 3 HB vaccine versus control: adverse events

**Outcome:** 1 Lack of sero-protection

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Liao 1999</td>
<td>282/308</td>
<td>323/341</td>
<td>33.9 %</td>
<td>0.97 [ 0.93, 1.01 ]</td>
<td></td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>38/150</td>
<td>150/150</td>
<td>32.6 %</td>
<td>0.25 [ 0.19, 0.33 ]</td>
<td></td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>82/126</td>
<td>120/135</td>
<td>33.5 %</td>
<td>0.73 [ 0.64, 0.84 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>584</strong></td>
<td><strong>626</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.57 [ 0.25, 1.27 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 402 (Hepatitis B vaccine), 593 (Control)

Heterogeneity: \( \tau^2 = 0.49 ; \chi^2 = 223.95, df = 2 (P<0.00001); I^2 = 99\% \)

Test for overall effect: \( Z = 1.37 (P = 0.17) \)
Analysis 3.2. Comparison 3 HB vaccine versus control: adverse events, Outcome 2 Lack of sero-protection (fixed-effect model).

Review: Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status
Comparison: 3 HB vaccine versus control: adverse events
Outcome: 2 Lack of sero-protection (fixed-effect model)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liao 1999</td>
<td>282/308</td>
<td>323/341</td>
<td></td>
<td>53.6 %</td>
<td>0.97 [ 0.93, 1.01 ]</td>
</tr>
<tr>
<td>Tsega 1990</td>
<td>38/150</td>
<td>150/150</td>
<td></td>
<td>26.2 %</td>
<td>0.25 [ 0.19, 0.33 ]</td>
</tr>
<tr>
<td>Xueliang 2000</td>
<td>82/126</td>
<td>120/135</td>
<td></td>
<td>20.2 %</td>
<td>0.73 [ 0.64, 0.84 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>584</strong></td>
<td><strong>626</strong></td>
<td></td>
<td>100.0 %</td>
<td><strong>0.73 [ 0.69, 0.78 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 402 (Hepatitis B vaccine), 593 (Control)
Heterogeneity: Chi$^2 = 223.95$, df = 2 ($P<0.00001$); $I^2 = 99$
Test for overall effect: $Z = 10.66$ ($P < 0.00001$)

Analysis 4.1. Comparison 4 HB vaccine versus control: serious adverse events, Outcome 1 Serious adverse events: all-cause mortality.

Review: Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status
Comparison: 4 HB vaccine versus control: serious adverse events
Outcome: 1 Serious adverse events: all-cause mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenberg 1996</td>
<td>10/5056</td>
<td>9/5261</td>
<td></td>
<td>100.0 %</td>
<td>1.16 [ 0.47, 2.84 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>5056</strong></td>
<td><strong>5261</strong></td>
<td></td>
<td>100.0 %</td>
<td><strong>1.16 [ 0.47, 2.84 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 10 (Hepatitis B vaccine), 9 (Control)
Heterogeneity: not applicable
Test for overall effect: $Z = 0.32$ ($P = 0.75$)
### Analysis 5.1. Comparison 5 HB vaccine versus control: adverse events, Outcome 1 Fever.

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

**Comparison:** 5 HB vaccine versus control: adverse events

**Outcome:** Fever

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bassily 1995</td>
<td>96/1184</td>
<td>21/588</td>
<td>-</td>
<td>46.8 %</td>
<td>2.27 [1.43, 3.60]</td>
</tr>
<tr>
<td>Greenberg 1996</td>
<td>358/6213</td>
<td>380/6184</td>
<td>-</td>
<td>53.2 %</td>
<td>0.94 [0.82, 1.08]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>7397</strong></td>
<td><strong>6772</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.42 [0.60, 3.38]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 454 (Hepatitis B vaccine), 401 (Control)

- Heterogeneity: $\tau^2 = 0.36$, $\chi^2 = 12.98$, df = 1 ($P = 0.00032$); $I^2 = 92$
- Test for overall effect: $Z = 0.79$ ($P = 0.43$)

### Analysis 5.2. Comparison 5 HB vaccine versus control: adverse events, Outcome 2 Fever

(fixed-effect model)

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

**Comparison:** 5 HB vaccine versus control: adverse events

**Outcome:** Fever (fixed-effect model)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bassily 1995</td>
<td>96/1184</td>
<td>21/588</td>
<td>-</td>
<td>6.9 %</td>
<td>2.27 [1.43, 3.60]</td>
</tr>
<tr>
<td>Greenberg 1996</td>
<td>358/6213</td>
<td>380/6184</td>
<td>-</td>
<td>93.1 %</td>
<td>0.94 [0.82, 1.08]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>7397</strong></td>
<td><strong>6772</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.03 [0.90, 1.18]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 454 (Hepatitis B vaccine), 401 (Control)

- Heterogeneity: $\chi^2 = 12.98$, df = 1 ($P = 0.00032$); $I^2 = 92$
- Test for overall effect: $Z = 0.42$ ($P = 0.67$)
### Analysis 5.3. Comparison 5 HB vaccine versus control: adverse events, Outcome 3 Local reactions (pain, redness, soreness).

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status  
**Comparison:** HB vaccine versus control: adverse events  
**Outcome:** 3 Local reactions (pain, redness, soreness)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bassily 1995</td>
<td>88/1184</td>
<td>14/588</td>
<td>3.12 [1.79, 5.44]</td>
<td>91.8%</td>
<td></td>
</tr>
<tr>
<td>Giammanco 1991</td>
<td>4/111</td>
<td>1/21</td>
<td>0.76 [0.09, 6.44]</td>
<td>8.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1295</strong></td>
<td><strong>609</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>2.93 [1.72, 4.99]</strong></td>
</tr>
</tbody>
</table>

Total events: 92 (Hepatitis B vaccine), 15 (Control)  
Heterogeneity: $\chi^2 = 1.58, df = 1 (P = 0.21)$; $I^2 = 37\%$  
Test for overall effect: $Z = 3.94 (P = 0.000080)$

### Analysis 5.4. Comparison 5 HB vaccine versus control: adverse events, Outcome 4 Other adverse events.

**Review:** Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status  
**Comparison:** HB vaccine versus control: adverse events  
**Outcome:** 4 Other adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambrosch 1992</td>
<td>7/55</td>
<td>3/55</td>
<td>2.33 [0.64, 8.56]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>55</strong></td>
<td><strong>55</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>2.33 [0.64, 8.56]</strong></td>
</tr>
</tbody>
</table>

Total events: 7 (Hepatitis B vaccine), 3 (Control)  
Heterogeneity: not applicable  
Test for overall effect: $Z = 1.28 (P = 0.20)$

Review: Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

Comparison: 6 HB vaccine versus control: lack of compliance

Outcome: 1 Lack of compliance

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Aristegui 1995</td>
<td>65/655</td>
<td>402/731</td>
<td>-</td>
<td>50.9 %</td>
<td>0.18 [0.14, 0.23]</td>
</tr>
<tr>
<td>Bassily 1995</td>
<td>49/394</td>
<td>5/196</td>
<td>-</td>
<td>49.1 %</td>
<td>4.88 [1.97, 12.04]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1049</strong></td>
<td><strong>927</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.91 [0.03, 24.39]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 114 (Hepatitis B vaccine), 407 (Control)
Heterogeneity: $\tau^2 = 5.51; \chi^2 = 49.42, df = 1 (P<0.0001); I^2 = 98%$
Test for overall effect: $Z = 0.06 (P = 0.96)$

Analysis 6.2. Comparison 6 HB vaccine versus control: lack of compliance, Outcome 2 Lack of compliance (fixed-effect model).

Review: Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status

Comparison: 6 HB vaccine versus control: lack of compliance (fixed-effect model)

Outcome: 2 Lack of compliance (fixed-effect model)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hepatitis B vaccine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Aristegui 1995</td>
<td>65/655</td>
<td>402/731</td>
<td>-</td>
<td>98.3 %</td>
<td>0.18 [0.14, 0.23]</td>
</tr>
<tr>
<td>Bassily 1995</td>
<td>49/394</td>
<td>5/196</td>
<td>-</td>
<td>1.7 %</td>
<td>4.88 [1.97, 12.04]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1049</strong></td>
<td><strong>927</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.26 [0.21, 0.32]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 114 (Hepatitis B vaccine), 407 (Control)
Heterogeneity: $\chi^2 = 49.42, df = 1 (P<0.0001); I^2 = 98%$
Test for overall effect: $Z = 12.69 (P < 0.00001)$