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Research

Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis

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Abstract

Objective To evaluate the effects of hepatitis B vaccine and immunoglobulin in newborn infants of mothers positive for hepatitis B surface antigen.
Design Systematic review and meta-analysis of randomised clinical trials.
Data sources Electronic databases and hand searches.
Review methods Randomised clinical trials were assessed for methodological quality. Meta-analysis was undertaken on three outcomes: the relative risks of hepatitis B occurrence, antibody levels to hepatitis B surface antigen, and adverse events.
Results 29 randomised clinical trials were identified, five of which were considered high quality. Only three trials reported inclusion of mothers negative for hepatitis B e antigen. Compared with placebo or no intervention, vaccination reduced the occurrence of hepatitis B (relative risk 0.28, 95% confidence interval 0.20 to 0.40; four trials). No significant difference in hepatitis B occurrence was found between recombinant vaccine and plasma derived vaccine (1.00, 0.71 to 1.42; four trials) and between high dose versus low dose vaccine (plasma derived vaccine 0.97, 0.55 to 1.68, three trials; recombinant vaccine 0.78, 0.31 to 1.94, one trial). Compared with placebo or no intervention, hepatitis B immunoglobulin or the combination of plasma derived vaccine and hepatitis B immunoglobulin reduced hepatitis B occurrence (immunoglobulin 0.50, 0.41 to 0.60, one trial; vaccine and immunoglobulin 0.08, 0.03 to 0.17, three trials). Compared with vaccine alone, vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (0.54, 0.41 to 0.73; 10 trials). Hepatitis B vaccine and hepatitis B immunoglobulin seem safe, but few trials reported adverse events.
Conclusion Hepatitis B vaccine, hepatitis B immunoglobulin, and vaccine plus immunoglobulin prevent hepatitis B occurrence in newborn infants of mothers positive for hepatitis B surface antigen.

Introduction

Hepatitis B is a global communicable disease, associated with an estimated 350 million chronically infected patients.[1] Mother to child transmission occurs often, either in utero or through exposure to blood or blood contaminated fluids at or around birth. Such perinatal transmission is believed to account for 35% to 50% of hepatitis B carriers.[2] The risk of perinatal transmission is associated with the hepatitis B e antigen status of the mother. If a mother is positive for both hepatitis B surface antigen and e antigen, 70% to 90% of her children become chronically infected.[3 4] If a mother is positive for the surface antigen but negative for the e antigen, the risk of transmission is significantly lower.[5–9]

Two types of vaccines for hepatitis B have been licensed. One is derived from plasma (plasma derived vaccine) and the other is derived from yeast or mammalian cells (recombinant vaccine).[10] Repeated injections over months are required to mount an effective antibody response with vaccination. Hepatitis B immunoglobulin has high levels of antibody to hepatitis B surface antigen. The immunoglobulin is immediately effective and seems protective for several months, after which it wanes.[11 12] In the present systematic review, we assessed the beneficial and harmful effects of hepatitis B vaccines and hepatitis B immunoglobulin in newborn infants of mothers positive for hepatitis B surface antigen.

Methods

We applied the Cochrane Collaboration methodology[13] described in our predefined and peer reviewed protocol for this review.[14]We included all trials that randomised newborn infants of mothers positive for hepatitis B surface antigen to hepatitis B vaccination and hepatitis B immunoglobulin within the first month of life. We identified randomised trials from the registers of the Cochrane Neonatal Group, the Cochrane Hepato-Biliary Group, the Cochrane central register of controlled trials, Medline, PubMed, and Embase. The last search was carried out in February 2004. We scanned references lists and contacted manufacturers of hepatitis B vaccine to ask for unpublished randomised trials. We wrote to the authors of trials when data were not provided in the report. Our primary outcome measure was the occurrence of hepatitis B, defined as a blood specimen positive for hepatitis B surface antigen, hepatitis B e antigen, or antibody to hepatitis B core antigen.[15] The secondary outcome measures were antibody levels to hepatitis B surface antigen <10 IU/l (considered insufficient to prevent hepatitis B virus infection[16 17]) and adverse events.

We assessed the methodological quality of trials on the basis of their published reports, and information from the authors. We post hoc classified trials as high quality if they had at least two of the following components: adequate generation of allocation sequence, adequate allocation concealment, or adequate blinding. We did this because only one trial had high quality for all the components. We carried out meta-analyses using a fixed effect model and a random effects model in RevMan analyses 4.2. If the results of both analyses concurred, we reported the results of the fixed effect model only.

We presented binary outcomes as relative risks with 95% confidence intervals. Data were analysed by the intention to treat principle, including all randomised participants. Heterogeneity was explored by χ^2 test, with significance set at a P value <0.10. The extent of heterogeneity was measured by I^2.[18] We carried out metaregression analysis using Stata if more than 10 trials were included on hepatitis B occurrence. Metaregression examined the intervention effect in relation to methodological quality of trials, dosage of hepatitis B immunoglobulin and vaccine, and time of injection.[13] We carried out subgroup analyses according to methodological quality, hepatitis B e antigen status of the mother, and time of injection. We used the test for interaction to estimate the difference between two subgroups.[19] For hepatitis B occurrence we included infants with incomplete or missing data in sensitivity analyses by imputing them into the following scenarios (the last four being intention to treat analyses): case analysis available, poor outcome assumed, good outcome assumed, extreme case favours experimental intervention, and extreme case favours control group.[20] We used funnel plot and Stata to detect publication bias and other biases according to the methods of Begg and Egger.[21 22]

Results

Overall, 226 references were identified, 187 of which were excluded. The remaining 39 references,[7 23–60] referring to 29 randomised clinical trials, were included. Three of the trials did not provide relevant data on our outcome measures (fig 1).[29 58 60]

The immunisation schedules varied substantially. A number of trials had several intervention groups. Table 1 lists the relevant comparisons of the included trials. Eighteen trials included mothers positive for hepatitis B e antigen, three included mothers positive and negative for hepatitis B e antigen, and eight did not report on the mother's hepatitis B e antigen status. Ten trials reported exclusion of low birthweight infants (the limits for exclusion varied from 1600 g to 3000 g). The remaining 19 trials did not report any exclusion criteria for birth weight. The average duration of follow-up was 19 months (range 6 to 60 months).

Methodological quality of included trials

Generation of the allocation sequence was adequately described in six trials.[23 26 30 31 43 44] Treatment allocation was adequately concealed in six trials.[29–32 40 44] Adequate methods of double blinding were reported in three trials.[30 32 40] Five trials were classified by us as of high quality (table 2).[30–32 40 44] The numbers and reasons for drop outs and withdrawals were adequately described in six trials.[7 24 29 30 44 52]

Hepatitis B vaccine versus placebo or no intervention

Compared with placebo or no intervention, hepatitis B vaccination significantly decreased the risk of hepatitis B occurrence (relative risk 0.28, 95% confidence interval 0.20 to 0.40; four trials) (fig 2). Heterogeneity was considerable ($P=0.07$, $I^2=54.2\%$). The results of sensitivity analyses for drop outs were consistent, indicating the robustness of the finding. Analyses of plasma derived vaccine and recombinant vaccine individually showed that both vaccines significantly decreased the risk of hepatitis B occurrence.

Subgroup analyses between high quality and low quality trials, the mother's hepatitis B e antigen status, or time of vaccination were not significantly different (tests for interaction, $P=0.25$, $P=0.07$, and $P=0.11$, respectively).

Retrospective subgroup analyses according to vaccine schedules (0, 1, and 6 months *v* 0, 1, 2, and 6 or 12 months) showed no significant difference (test for interaction, $P=0.75$). No data on adverse events were reported.

Recombinant vaccine versus plasma derived vaccine

Recombinant vaccine and plasma derived vaccine showed no significant difference in hepatitis B occurrence (1.00, 0.70 to 1.42; four trials) (fig 3). Heterogeneity was moderate ($I^2=29.4\%$). Sensitivity analyses for drop outs confirmed the finding of no significant difference between the two vaccines. Subgroup analyses for methodological quality or mother's hepatitis B e antigen status showed no significant difference (tests for interaction, both $P=0.21$).

Significantly fewer infants receiving recombinant vaccine compared with plasma derived vaccine had antibody levels to hepatitis B surface antigen <10 IU/l (0.51, 0.36 to 0.72; three trials).

High dose versus low dose vaccine

High dose vaccine and low dose vaccine showed no significant difference in hepatitis B occurrence (plasma derived vaccine 0.97, 0.55 to 1.68, three trials; recombinant vaccine 0.78, 0.31 to 1.94, one trial). Owing to too few trials, it was inappropriate to carry out sensitivity and subgroup analyses. No significant difference was found between high dose vaccine versus low dose vaccine on antibody levels to hepatitis B surface antigen <10 IU/l (1.02, 0.82 to 1.27; two trials).

Schedules and types of recombinant vaccine and plasma derived vaccine

No significant differences were found in hepatitis B occurrences among different vaccination schedules, different recombinant vaccines, and different plasma derived vaccines (data not shown).

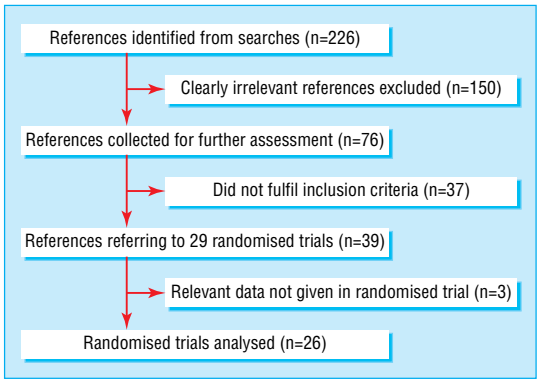

Fig 1 Flow diagram of trial selection

Table 1 Interventions in experimental and control groups of included randomised clinical trials assessing effects of hepatitis B vaccines and immunoglobulin for newborn infants of hepatitis B surface antigen positive mothers

Trial	Experimental group	Control group
Assateerawatt 1993[23]	A*: Hepatitis B immunoglobulin 100 IU at birth and recombinant vaccine 20 μg at birth and at 1, 2, and 12 months	B: Recombinant vaccine 20 μg at birth and at 1, 2, and 12 months
Beasley 1983[7 24]	A: Hepatitis B immunoglobulin 1.0 ml (180 IU) at birth and saline at 3 and 6 months. C: Hepatitis B immunoglobulin 0.5 ml (90 IU) diluted in 0.5 ml of immune serum globulin at birth and at 3 and 6 months	B: Saline at birth and 3 and 6 months
Beasley 1983[25]	A: Hepatitis B immunoglobulin 0.5 ml (145 IU) at birth and plasma derived vaccine 20 μg at 4 to 7 days. Followed by boosters 1 and 6 months later	B: Hepatitis B immunoglobulin 0.5 ml (145 IU) and plasma derived vaccine 20 μg at 1 month. Followed by boosters 1 and 6 months later
Farmer 1987[26]	A: Plasma derived vaccine 0.25 ml (5 μg)+hepatitis B immunoglobulin 0.25 ml (25 IU/kg) at birth then plasma derived vaccine+hepatitis B immunoglobulin 0.25 ml (25 IU/kg) at 6 weeks and plasma derived vaccine at 6 months	B: Plasma derived vaccine 0.25 ml (5 μg) at birth and at 6 weeks and 6 months
Garcia 1992[27]	A: 10 μg recombinant vaccine-1 at birth and at 1 and 2 months	B: 10 μg recombinant vaccine-2 at birth and at 1 and 2 months
Grosheide 1993[29]	A: Hepatitis B immunoglobulin 0.5 ml/kg body weight at birth and plasma derived vaccine 10 μg at 2 days and at 1, 2, and 11 months	B: Hepatitis B immunoglobulin 0.5 ml/kg body weight and plasma derived vaccine 10 μg at 3, 4, 5, and 11 months (with diphtheria, pertussis, tetanus, poliomyelitis concomitantly). Hepatitis B immunoglobulin 0.5 ml/kg body weight at 3 months
Halliday 1992[30]	A: Recombinant vaccine 20 μg at birth and at 1 and 6 months. C: Hepatitis B immunoglobulin 260 IU at birth and recombinant vaccine 20 μg at birth and at 1 and 6 months	B: Plasma derived vaccine 20 μg at birth and at 1 and 6 months. D: Hepatitis B immunoglobulin 260 IU at birth and recombinant vaccine 10 μg at birth and at 1 and 6 months
Hieu 2002[31]	A: Hepatitis B immunoglobulin 100 μg and 10 μg recombinant vaccine-1 at birth and Hepavax at 30 and 180 days	B: Hepatitis B immunoglobulin 100 μg and 10 μg recombinant vaccine-2 at birth and Engerix-B at 30 and 180 days
Ip 1989[32 33 54]	A: Plasma derived vaccine 3 μg at birth and at 1, 2, and 6 months. Also, hepatitis B immunoglobulin 200 IU at birth and hepatitis B immunoglobulin 100 IU at monthly intervals during 6 months after birth. C: Plasma derived vaccine 3 μg at birth and at 1, 2, and 6 months	B: Plasma derived vaccine 3 μg at birth and at 1, 2, and 6 months+hepatitis B immunoglobulin 200 IU at birth. D: Placebo
Kang 1995[34]	A: 20 μg recombinant vaccine-1 at birth and at 1 and 6 months	B: 20 μg recombinant vaccine-2 at birth and at 1 and 6 months
Khukhlovich 1996[35]	A: Recombinant vaccine 1 ml at birth and at 1, 2, and 14 months	B: No vaccines
Kuru 1995[36]	A: Plasma derived vaccine 0.5 ml (2.5 μg) and hepatitis B immunoglobulin 200 IU at birth and plasma derived vaccine at 1, 2, and 12 months. C: Recombinant vaccine 0.5 ml (10 μg), hepatitis B immunoglobulin 200 IU at birth and recombinant vaccine at 1, 2, and 12 months	B: Plasma derived vaccine 1 ml (5 μg) and hepatitis B immunoglobulin 200 IU at birth and plasma derived vaccine at 1, 2, and 12 months
Lee 1995[37-39]	A: Hepatitis B immunoglobulin 145 IU and plasma derived vaccine 5 μg at birth and 10 μg recombinant vaccine-1 at 1, 2, and 12 months. C: Hepatitis B immunoglobulin 145 IU and plasma derived vaccine 5 μg at birth and 5 μg recombinant vaccine-2 at 1, 2, and 12 months. E: Hepatitis B immunoglobulin 145 IU at birth and plasma derived vaccine 5 μg at birth and 1 month and 5 μg recombinant vaccine-2 at 2 and 12 months	B: Hepatitis B immunoglobulin 145 IU and plasma derived vaccine 5 μg at birth and plasma derived vaccine 5 μg at 1, 2, and 12 months. D: Hepatitis B immunoglobulin 145 IU and plasma derived vaccine 5 μg at birth and plasma derived vaccine 5 μg at 1, 2, and 12 months. F: Hepatitis B immunoglobulin 145 IU at birth and plasma derived vaccine 5 μg at birth and at 1 month and 10 μg recombinant vaccine-1 at 2 and 12 months
Liu 1987[40]	A: Plasma derived vaccine 20 μg at birth and at 1, 2, and 6 months. C: Plasma derived vaccine 20 μg at birth and at 1, 2, and 6 months and hepatitis B immunoglobulin at birth	B: Placebo (normal saline) at birth and at 1, 2, and 6 months
Lo 1985[28 41]	A: Hepatitis B immunoglobulin 50 IU at birth and plasma derived vaccine 5 μg at 2, 6, and 10 weeks. C: Plasma derived vaccine 5 μg at 2, 6, and 10 weeks and hepatitis B immunoglobulin 50 IU at birth and at 1 month	B: Plasma derived vaccine 5 μg at 2, 6, and 10 weeks
Lolekha 2002[42]	A: Recombinant vaccine 5 μg at birth and at 1 and 6 months	B: Recombinant vaccine 5 μg at birth and at 1, 2, and 12 months
Oon 1986[43]	A: Plasma derived vaccine 10 μg at birth and at 1 and 2 months. C: Hepatitis B immunoglobulin 100 IU and plasma derived vaccine 10 μg at birth and plasma derived vaccine 10 μg at 1 and 2 months	B: Plasma derived vaccine 5 μg at birth and at 1 and 2 months. D: Hepatitis B immunoglobulin 100 IU and plasma derived vaccine 5 μg at birth and plasma derived vaccine 5 μg at 1 and 2 months
Piazza 1985[44]	A: Plasma derived vaccine 5 μg and hepatitis B immunoglobulin 50 IU at birth and plasma derived vaccine at 1 and 2 months	B: Plasma derived vaccine 5 μg and hepatitis B immunoglobulin 50 IU at birth and plasma derived vaccine at 2 months
Pongpipat 1986[45]	A: 200 IU hepatitis B immunoglobulin-1 at birth and 5 μg plasma derived vaccine-1 at birth and at 1 and 6 months	B: 100 IU hepatitis B immunoglobulin-2 at birth and 10 μg plasma derived vaccine-2 at birth and at 1 and 6 months
Pongpipat 1988[46]	A: Plasma derived vaccine 5 μg and hepatitis B immunoglobulin 100 IU at birth and plasma derived vaccine at 1, 2, and 12 months	B: Plasma derived vaccine 2 μg and hepatitis B immunoglobulin 100 IU at birth and plasma derived vaccine at 1, 2, and 12 months
Pongpipat 1989[47]	A: Recombinant vaccine 5 μg and hepatitis B immunoglobulin 100 IU at birth and recombinant vaccine at 1, 2, and 12 months	B: Plasma derived vaccine 10 μg and hepatitis B immunoglobulin 100 IU at birth and plasma derived vaccine at 1, 2, and 12 months
Poovorawan 1997[48 49]	A: Recombinant vaccine 10 μg and hepatitis B immunoglobulin 100 IU at birth and recombinant vaccine 10 μg at 1 and 6 months. A booster was given at 60 months	B: Recombinant vaccine 10 μg at birth and at 1 and 6 months. A booster was given at 60 months
Sehgal 1992[50 51]	A: Hepatitis B immunoglobulin 0.5 ml and plasma derived vaccine 10 μg at birth and plasma derived vaccine at 4 and 8 weeks	B: Plasma derived vaccine 10 μg at birth and at 4 and 8 weeks
Theppisai 1987[52]	A: Hepatitis B immunoglobulin 200 IU and plasma derived vaccine 10 μg at birth and plasma derived vaccine 10 μg at 1 and 6 months	B: Plasma derived vaccine 10 μg at birth and at 1 and 6 months
Theppisai 1990[53]	A: Hepatitis B immunoglobulin 200 IU at birth and plasma derived vaccine 5 μg at 2 days and 1, 2, and 12 months	B: Hepatitis B immunoglobulin 200 IU at birth and plasma derived vaccine 2 μg at 2 days and 1, 2, and 12 months
Xu 1995[55-57]	A: 16 μg plasma derived vaccine-1 at birth and at 1 and 6 months. C: Hepatitis B immunoglobulin 250 IU at birth and 20 μg plasma derived vaccine-2 at birth and at 1 and 6 months	B: 20 μg plasma derived vaccine-2 at birth and at 1 and 6 months. D: Vaccine diluent plus adjuvant at birth and at 1 and 6 months
Yeoh 1986[58]	A: Mothers positive for hepatitis B surface antigen and positive for hepatitis B e antigen (150 infants): Hepatitis B immunoglobulin 0.5 ml at birth and plasma derived vaccine 10 μg at birth and at 1 and 6 months. C: Mothers positive for hepatitis B surface antigen and negative for hepatitis B e antigen mothers (150 infants). Hepatitis B immunoglobulin 0.5 ml at birth and plasma derived vaccine 10 μg at birth and at 1 and 6 months	B: Mothers positive for hepatitis B surface antigen and positive for hepatitis B e antigen (150 infants): Hepatitis B immunoglobulin 0.5 ml at birth and recombinant vaccine 5 μg at birth and at 1 and 6 months. D: Mothers positive for hepatitis B surface antigen and negative for hepatitis B e antigen (150 infants). Hepatitis B immunoglobulin 0.5 ml at birth and recombinant vaccine 5 μg at birth and at 1 and 6 months
Zhu 1987[60]	A: 16 μg vaccine given at birth, 1 and 6 months	B: Buffer of vaccine given at birth, 1 and 6 months
Zhu 1994[59]	A: Recombinant vaccine 20 μg at birth and at 1 and 6 months	B: Plasma derived vaccine 20 μg at birth and at 1 and 6 months

*A-F depicts the different intervention arms used to identify comparisons in trials with more than two interventions shown in figures 2-5.

Table 2 Reported methodological quality of included randomised clinical trials assessing effects of hepatitis B vaccines and immunoglobulin for newborn infants of mothers positive for hepatitis B surface antigen

Trial	Generation of allocation sequence	Allocation concealment	Blinding	Methodological quality
Assateerawatt 1993[23]	Adequate	Unclear	Not done	Low
Beasley 1983[7 24]	Unclear	Unclear	Unclear	Low
Beasley 1983[25]	Unclear	Unclear	Unclear	Low
Farmer 1987[26]	Adequate	Unclear	Not done	Low
Garcia 1992[27]	Unclear	Unclear	Unclear	Low
Grosheide 1993[29]	Unclear	Adequate	Not done	Low
Halliday 1992[30]	Adequate	Adequate	Adequate	High*
Hieu 2002[31]	Adequate	Adequate	Not done	High*
Ip 1989[32 33 54]	Unclear	Adequate	Adequate	High*
Kang 1995[34]	Unclear	Unclear	Not done	Low
Khukhlovich 1996[35]	Unclear	Unclear	Unclear	Low
Kuru 1995[36]	Unclear	Unclear	Not reported	Low
Lee 1995[37-39]	Unclear	Unclear	Not done	Low
Liu 1987[40]	Unclear	Adequate	Adequate	High*
Lo 1985[28 41]	Unclear	Unclear	Not done	Low
Lolekha 2002[42]	Unclear	Unclear	Not done	Low
Oon 1986[43]	Adequate	Unclear	Not done	Low
Piazza 1985[44]	Adequate	Adequate	Unclear	High*
Pongpipat 1986[45]	Unclear	Unclear	Not done	Low
Pongpipat 1988[46]	Unclear	Unclear	Not done	Low
Pongpipat 1989[47]	Unclear	Unclear	Not done	Low
Poovorawan 1997[48 49]	Unclear	Unclear	Not done	Low
Sehgal 1992[50 51]	Unclear	Unclear	Not done	Low
Theppisai 1987[52]	Unclear	Unclear	Not done	Low
Theppisai 1990[53]	Unclear	Unclear	Not done	Low
Xu 1995[55-57]	Unclear	Unclear	Unclear	Low
Yeoh 1986[58]	Unclear	Unclear	Not done	Low
Zhu 1987[60]	Unclear	Unclear	Unclear	Low
Zhu 1994[59]	Unclear	Unclear	Not done	Low

* Trials having low risk of bias.

Hepatitis B immunoglobulin versus placebo or no intervention

Overall, hepatitis B immunoglobulin significantly decreased the risk of hepatitis B occurrence in infants (0.52, 0.44 to 0.63; 11 trials) (fig 4). Compared with placebo or no intervention, hepatitis B immunoglobulin alone significantly reduced hepatitis B occurrence (0.50, 0.41 to 0.60; one trial). Compared with vaccination, vaccination plus hepatitis B immunoglobulin significantly reduced hepatitis B occurrence (0.54, 0.41 to 0.73; 10 trials). The sensitivity analyses for drop outs were consistent, indicating the robustness of the findings. In the metaregression analyses, none of the trial characteristics (methodological quality, dosage of hepatitis B immunoglobulin, or time of hepatitis B immunoglobulin injection) was significantly associated with the effect of hepatitis B immunoglobulin ($P=0.92$, $P=0.67$, and $P=0.79$, respectively). Subgroup analyses did not show a significant difference between high quality and low quality trials, the mother's hepatitis B e antigen status, or time of hepatitis B immunoglobulin injection (tests for interaction, $P=0.70$, 0.62, and 0.63, respectively).

Hepatitis B immunoglobulin did not significantly reduce the number of infants with antibody levels to hepatitis B surface antigen <10 IU/l (1.55, 0.89 to 2.73; four trials).

Few trials reported adverse events. If reported, the authors did not specify in which intervention group they occurred. A meta-analysis on adverse events could not, therefore, be carried out. In one trial,[24] one infant who received hepatitis B immunoglobulin died. The death seemed to be unrelated to the immunoglobulin.

Neither funnel plot on hepatitis B occurrence showed asymmetry (Egger test, $P=0.31$; Begg test, $P=0.23$).

Multiple versus single injection of hepatitis B immunoglobulin

Multiple hepatitis B immunoglobulin plus plasma derived vaccine versus single hepatitis B immunoglobulin injection plus plasma derived vaccine did not significantly reduce the risk of hepatitis B occurrence (0.87, 0.30 to 2.47; two trials, $I^2=0\%$).

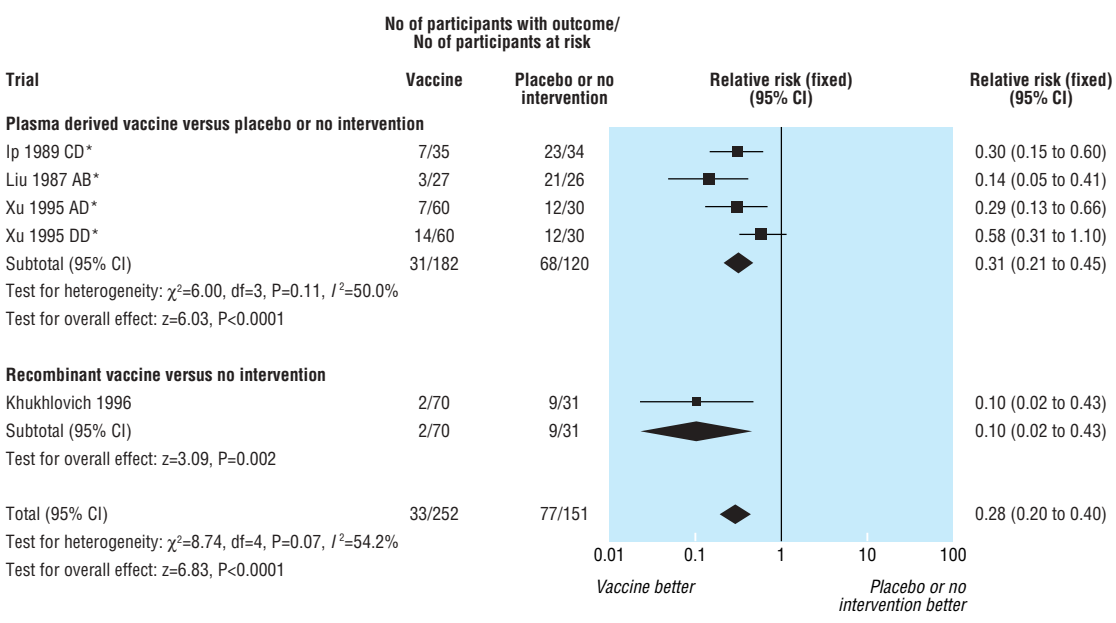

Fig 2 Effect of hepatitis B vaccine on occurrence of hepatitis B in newborn infants. *Experimental and control groups (see table 1 for definitions)

Vaccination plus hepatitis B immunoglobulin versus placebo or no intervention

Compared with placebo or no intervention, plasma derived vaccine plus hepatitis B immunoglobulin significantly reduced hepatitis B occurrence (0.08, 0.03 to 0.17; three trials) (fig 5). The sensitivity analyses confirmed the robustness of the finding. Subgroup analyses did not find a significant difference between high quality and low quality trials, the mother's hepatitis B e antigen status, or time of hepatitis B immunoglobulin injection (tests for interaction, P = 0.13, P = 0.28, and P = 0.22, respectively).

One trial reported the number of adverse events: three out of 71 infants given vaccination compared with five out of 34 in the control group.[32] The results showed no significant difference (0.29, 0.07 to 1.13; one trial).

Discussion

Our systematic reviews shows that hepatitis B vaccine, hepatitis B immunoglobulin, or the combination of vaccine plus immunoglobulin given to the newborn infants of mothers positive for hepatitis B surface antigen prevents the occurrence of hepatitis B. Furthermore, the combination of vaccine plus immunoglobulin was superior to vaccine alone. These benefits were not significantly associated with the methodological quality of the trials, the mother's hepatitis B e antigen status, time of injection, or number of infants dropping out of the study.

Our review has several potential limitations. Firstly, some analyses include few trials and a small number of newborn infants. Secondly, most trials were of low methodological quality. We did not, however, find a strong association between methodological quality and results. This supports the robustness of our results, but does not exclude the possibility of bias.[61–63] Thirdly, although we did not find asymmetries in funnel plots, we cannot exclude publication bias. Fourthly, only a few investigators responded to our request for further information and often that the details were lost. Fifthly, most trials reported only surrogate outcomes (hepatitis B surface antigen status or antibody levels to hepatitis B surface antigen) and not long term clinical outcomes. One trial with long term follow-up did find more patients with chronic hepatitis in the plasma derived vaccine plus hepatitis B immunoglobulin group compared with the plasma derived vaccine group.[32]

Our results show that hepatitis B vaccination prevents the occurrence of hepatitis B in the newborn infants of mothers positive for hepatitis B surface antigen. We found no significant difference between recombinant vaccine and plasma derived vaccine on hepatitis B infections (relative risk 1.00, 95% CI 0.70 to 1.42). However, more infants who received recombinant vaccine achieved antibody levels to hepatitis surface antigen >10 IU/l (1.96, 1.39 to 2.78). The advantage of recombinant vaccine might be due to the difference in chemical and physical characteristics of the antigen components of the vaccines.[64] Recombinant vaccine is used in high income countries owing to the fear of acquiring human immunodeficiency virus and other infections, including transmissible spongiform encephalopathies.[65] Our finding seems to support the introduction of recombinant vaccines in clinical practice.

The recommended schedules for immune prophylaxis against hepatitis B varies among countries.[66 67] In general we were unable to show significant differences among different doses, different schedules, and different forms of plasma derived vaccine and recombinant vaccine on hepatitis B occurrence. Furthermore, our subgroup analyses did not show a strong association between timing of injection (within 12, 24, or 48 hours) and magnitude of effects. The number of infants evaluated in these comparisons was small. Therefore larger trials are needed before equivalence or non-inferiority can be claimed.

Our meta-analyses found that hepatitis B immunoglobulin alone or when added to hepatitis B vaccine decreased the risk of hepatitis B infection (0.52, 0.44 to 0.63). A recent non-randomised study reported no benefit of adding hepatitis B immunoglobulin to vaccine in mothers negative for hepatitis B e antigen.[68] In our analysis, only one small trial out of 11 trials included infants of such mothers.[55] Our subgroup analysis did

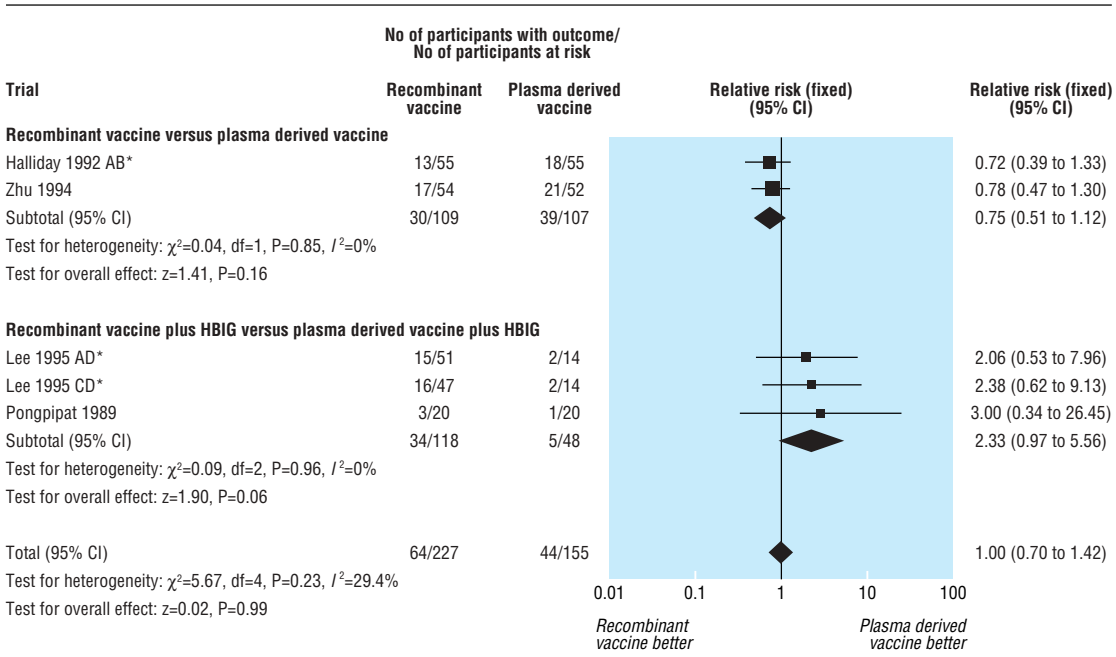

Fig 3 Effect of recombinant vaccine compared with plasma derived vaccine on occurrence of hepatitis B in newborn infants. HBIG=hepatitis B immunoglobulin. *Experimental and control groups (see table 1 for definitions)

not find any statistically significant difference between infants of mothers negative or positive for hepatitis B e antigen. More randomised trials seem warranted on the addition of hepatitis B immunoglobulin to vaccine for infants of mothers negative for hepatitis B e antigen. It should be noted that hepatitis B immunoglobulin, as with plasma derived vaccine, has the potential for transmission of bloodborne infections.[69]

Few trials reported sufficiently on adverse events. According to what was reported, hepatitis B vaccine and hepatitis B immunoglobulin seem safe. These results are in accordance with two Cochrane reviews on hepatitis B vaccination of healthcare workers and dialysis patients.[70 71] Furthermore, cohort studies found that hepatitis B vaccination is well tolerated and that severe adverse events are rare.[72–79] One cohort study did find, however,

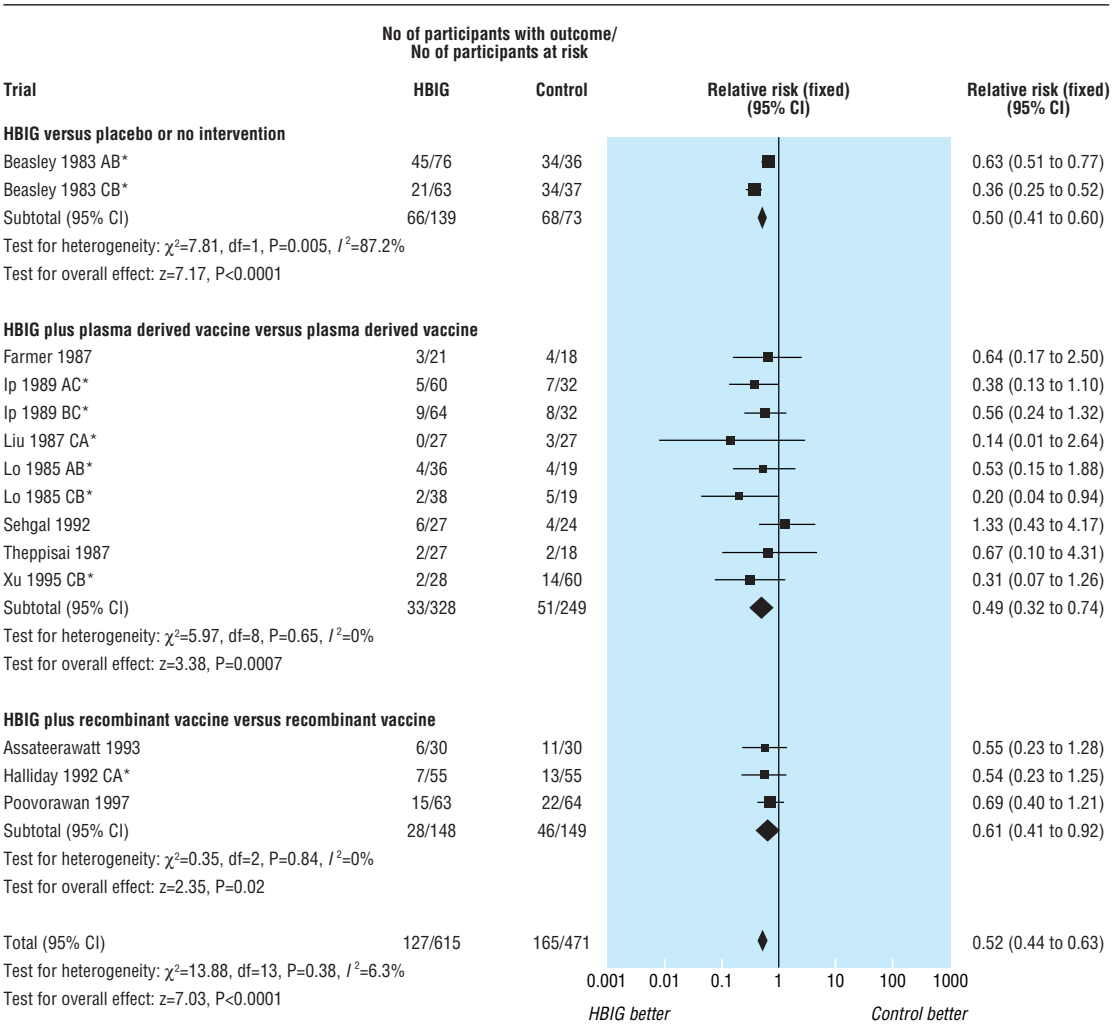

Fig 4 Effect of hepatitis B immunoglobulin (HBIG) on occurrence of hepatitis B in newborn infants. *Experimental and control groups (see table 1 for definitions)

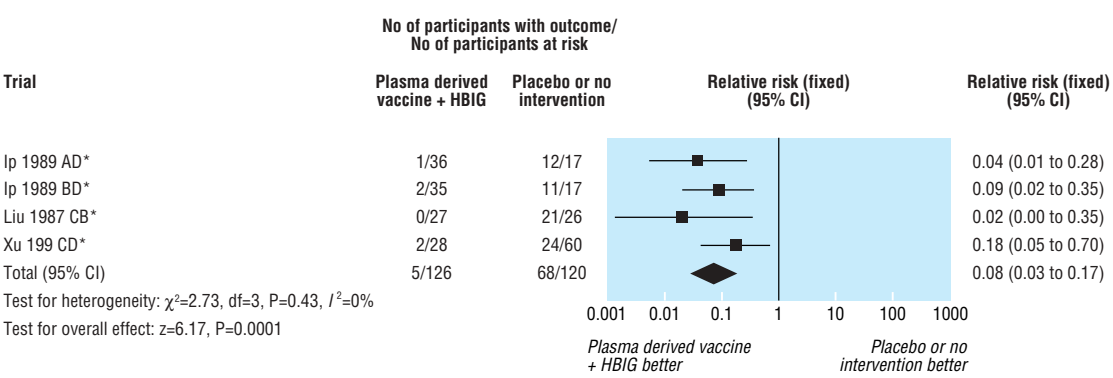

Fig 5 Effect of plasma derived vaccine and hepatitis B immunoglobulin (HBIG) on occurrence of hepatitis B in newborn infants. *Experimental and control groups (see table 1 for definitions)

What is already known on this topic

Mother to child transmission accounts for up to 50% of hepatitis B carriers

Repeated vaccination over months is required to mount an effective antibody response

Immunoglobulin is immediately effective and seems protective for several months, after which it wanes

What this study adds

Vaccine decreased the risk of hepatitis B infection among infants of mothers positive for hepatitis B surface antigen

Immunoglobulin alone or added to vaccine decreased the risk of hepatitis B infection among infants of mothers positive for hepatitis B surface antigen

Evidence on immunisation for infants of mothers positive for hepatitis B surface antigen but negative for hepatitis B e antigen is weak

that hepatitis B vaccine increased the risk of chronic arthritis and acute ear infections.[80] We are unable to determine if the reliability of this finding owing to the methodological weaknesses of cohort studies.[66] Randomised clinical trials may overlook adverse events because of the relatively low numbers of participants or poor reporting of adverse events.[81–83] Further trials ought to focus on adverse events after the International Conference on Harmonisation's guidelines for clinical trials.[79]

In general, the risk of perinatal transmission from mothers negative for hepatitis B e antigen is considered much lower than that from mothers who are positive for the antigen.[5–9] Further, the infants of hepatitis B e antigen negative mothers often clear an asymptomatic infection.[15] Our findings are mainly based on immune prophylaxis for infants of mothers positive for hepatitis B surface antigen and hepatitis B e antigen. Evidence from randomised clinical trials is insufficient to either support or refute immune prophylaxis for infants of mothers negative for hepatitis B e antigen. The applicability of our findings to mothers negative for hepatitis B e antigen, which are of high proportions in, for example, the United States and northern Europe, is therefore limited.[84] Cost effectiveness studies indicate that hepatitis B vaccination for infants of mothers positive for hepatitis B surface antigen are cost effective in countries with low,[85–88] intermediate, and high prevalence.[89–92] We identified no cost effectiveness studies assessing the effects of adding hepatitis B immunoglobulin to vaccine. As hepatitis B immunoglobulin may reduce the risk of hepatitis B infection, the need to carry out cost effectiveness studies based on randomised trials seems justified.

Two trials that discussed a new way to potentially prevent vertical transmission of hepatitis B did not fulfil our inclusion criteria.[14] The two trials randomised pregnant women positive for hepatitis B surface antigen to hepatitis B immunoglobulin versus no intervention before delivery.[93 94] In the group receiving immunoglobulin, fewer infants were positive for hepatitis B surface antigen at follow-up. The methodological quality of those trials was low. Furthermore, the mothers are at risk of developing immune complex disease due to hepatitis B immunoglobulin reacting with their own circulating hepatitis B surface antigens. More trials are therefore needed before this intervention should be adopted.

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