Hepatitis B vaccine alone or with hepatitis B immunoglobulin in neonates of HBsAg+/HBeAg− mothers: a systematic review and meta-analysis

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Objectives: The cost-effectiveness of augmenting immunization against hepatitis B infection with hepatitis B immunoglobulin (HBIG) remains controversial, particularly for the subpopulation of babies of HBsAg+/HBeAg− mothers that are considered as low-infective. We aimed to evaluate the effectiveness of vaccine alone compared with vaccine plus HBIG for the immunization of babies of HBsAg+/HBeAg− mothers.

Methods: We searched PubMed, Scopus and Cochrane Central Register of Controlled Trials databases to identify studies comparing the effectiveness of combined immunization (vaccine plus HBIG) with vaccine alone in neonates of HBsAg+/HBeAg− mothers. A systematic review and meta-analysis of eligible studies was performed.

Results: A total of nine eligible studies were identified (four randomized controlled trials). No difference was found regarding the primary outcome of our meta-analysis, namely occurrence of hepatitis B infection, between neonates who received vaccine only, compared with those who received both vaccine and HBIG (four studies, 3426 patients, OR = 0.82, 95% CI = 0.41–1.64). This finding was consistent with regards to seroprotection rate (four studies, 1323 patients, OR = 1.24, 95% CI = 0.97–1.58). Safety data were not reported in the included studies.

Conclusions: The available limited published evidence suggests that vaccine alone seems to be equally effective to the combination of HBIG and hepatitis B vaccine for neonates of HBsAg+/HBeAg− mothers in preventing infection. Further studies are needed in order to clarify the potential benefit of combined immunization to this specific subgroup of patients.

Keywords: hepatitis B virus, HBV, immunization

Introduction

Hepatitis B (HB) is a chronic viral infection, associated with considerable morbidity and mortality, and social and economical implications. Recent reports suggest that 2 billion people have been infected with HB virus (HBV) worldwide. Additionally, more than 240 million people have been reported to present with long-term liver infections.1

Mother-to-child transmission, occurring during the perinatal period, is the most important cause of chronic infection, accounting for 35%–50% of carriers.2 Evidence suggests that the mother’s serological status (HBsAg/HBeAg) may have a role in perinatal transmission.1 Specifically, data deriving from relevant studies suggest that the risk of infection in infants born to HBsAg+/HBeAg− mothers is considerably higher compared with those born to HBsAg+/HBeAg− mothers.4–6 On the other hand, cases of fulminant hepatitis have also been reported for infants born to HBeAg− mothers.7–9

The combined use of vaccine and HB immunoglobulin (HBIG) within 24 h of birth is reported to reduce the risk of chronic HB infection to 10%–15% and <1% for infants born to HBeAg+ and HBeAg− mothers, respectively.7 Yet, due to the considerable cost of screening for HBeAg positivity and administration of HBIG, some countries with inadequate resources use only hepatitis vaccine for immunization of infants born to HBsAg+ mothers, while most do not screen for the maternal HBeAg status.7,10
The literature provides controversial evidence regarding the effectiveness of administration of HBIG in infants born to HBeAg+/HBeAg− mothers.3,11,12 The aim of our study was to evaluate the effectiveness of vaccine alone compared with combined immunization (HBIG and vaccine) of infants born to HBsAg+/HBeAg− mothers by performing a meta-analysis of relevant studies.

Methods

Data sources
The articles included in this meta-analysis were retrieved from searches performed in PubMed and Scopus databases. Both of these databases were last assessed in June 2014. An additional search in the Cochrane Central Register of Controlled Trials was performed. Bibliographies were also hand-searched. The registry of clinical trials, namely ‘ClinicalTrials.gov‘, was also searched.

Study selection criteria
A study was regarded as eligible for inclusion in this meta-analysis if it provided comparative data regarding the effectiveness of HB immunization strategies, including vaccine only, compared with the combination of vaccine plus HBIG in babies of HBsAg+/HBeAg− mothers. Studies providing relevant data concerning anti-HBeAg+ mothers were regarded as eligible for inclusion. Articles published in languages other than English, German, Italian or Spanish were regarded as not eligible for inclusion. Specifically, our search revealed two potentially relevant studies that were published in Chinese but were not included because of the language barrier.13,14 Case reports and abstracts presented in scientific conferences were also excluded.

Data extraction, definitions and outcomes
Data extracted consisted of specific study/population characteristics (Table 1) and the respective evaluated outcomes (Table S1, available as Supplementary data at JAC Online). Occurrence of infection (the primary outcome of our meta-analysis) was defined as HBsAg positivity of the evaluated babies at any follow-up visit >1 month following immunization. Vaccine efficacy was evaluated as a cumulative outcome that comprised the different definitions provided by the individual evaluated studies. Seroprotection rate was defined as the proportion of the evaluated neonates with anti-HBsAg ≥10 IU/L at the time of the follow-up assessment. Transition to carrier state was also evaluated as an additional effectiveness outcome.

Data analysis
A meta-analysis was performed regarding the evaluated outcomes; randomized controlled trials (RCTs) and non-randomized studies were grouped and presented separately. We also performed a sensitivity analysis including studies that provided separate data for the subgroup of the included neonates born to HBsAg+/HBeAg− mothers. The Jadad score was used for methodological quality assessment of the included RCTs (a score >2 points denoted adequate methodological quality),15,16 whereas the Newcastle – Ottawa Scale was used for non-randomized comparative studies.

Statistical analysis
A random effects model was used for the estimation of the pooled ORs and the respective 95% CIs for the analysed outcomes.17 The I² test was used to test for statistical heterogeneity among the analysed studies.18 Funnel plots testing for publication bias were also performed. All statistical analyses were performed with the Review Manager (RevMan) version 5.0 Software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008).

Results

Nine studies were regarded as eligible for inclusion in our review/meta-analysis.12,19–26 The detailed process of the literature search is depicted in Figure 1.

Characteristics of the included studies
Four of the nine included studies were RCTs.19,22,23,26 Three were published after 2011.19–21 One study evaluated children aged 6 months to 10 years,21 whereas all other included studies evaluated neonates/infants. In one of the two most recent included studies, HBIG was administered to all evaluated infants, who also received three doses of HB vaccine.20 Yet in this study, HBIG was administered within 24 h of birth by protocol to all newborns born to HBeAg+ mothers, whereas for infants born to HBeAg− mothers, the administration of HBIG was optional and self-paid.20

Characteristics of the included patients
Seven studies provided data exclusively for neonates born to HBsAg+/HBeAg− mothers,12,20–25 whereas the remaining two provided cumulative data for neonates born to HBsAg+/HBeAg− mothers, regardless of their HBeAg status.19,26 In these two specific studies HBeAg− mothers constituted the majority (>72%) of the included HBsAg+ mothers.

Outcomes

Occurrence of infection
Four studies provided relevant data12,21,25,26 (one RCT26). No difference was found regarding the occurrence of infection between babies immunized with vaccine alone, compared with those immunized with vaccine and HBIG (four studies, 3426 patients, OR = 0.82, 95% CI = 0.41–1.64; Figure 2). Additionally, in one of the two recent studies that were not included in statistical analysis, no cases of HBV infection were identified in any of the two compared groups,20 whereas in the other study, occult infection was found to be more common in the (vaccine+HBIG) group for all included neonates.19

Seroprotection rate
Four studies provided relevant data12,23,25,26 (two RCTs23,26). No difference was found regarding the seroprotection rate between
## Table 1. Main characteristics of the included studies involving newborns from HBsAg+ mothers

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design/quality</th>
<th>Country, period</th>
<th>Total number of evaluated newborns</th>
<th>Study population</th>
<th>Laboratory methods (HBV serological markers)</th>
<th>Number of newborns from HBeAg+/− HBeAg+ mothers</th>
<th>Study groups of newborns from HBeAg+ mothers—a</th>
<th>Evaluated outcomes—definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pande, 2013</td>
<td>placebo-controlled RCT/Jadad score: 4</td>
<td>New Delhi, 2004–09</td>
<td>259 neonates and infants</td>
<td>ELISA diagnostic kits (Hepalisa, J. Mitra &amp; Co., New Delhi, India)</td>
<td>210/49</td>
<td>99 111</td>
<td>Overt HBV infection: HBsAg positivity; Occult HBV infection: babies who were negative for HBsAg, but were positive for HBV DNA by PCR; Adequate immune response: babies who had anti-HBs titres of &gt;10 IU/mL</td>
<td></td>
</tr>
<tr>
<td>Wen, 2013</td>
<td>prospective comparative study/ Ottawa Scale: 7 stars</td>
<td>Taipei–Taiwan, 2007–11</td>
<td>359 infants</td>
<td>AxSYM Meia Abbott Laboratories (Abbott Park, IL, USA)</td>
<td>262/97</td>
<td>33 189</td>
<td>HBV infection (HBsAg positivity); HBV chronicity (HBsAg positivity after 6 months)</td>
<td></td>
</tr>
<tr>
<td>Chen, 2012</td>
<td>MC prospective comparative study/ Ottawa Scale: 7 stars</td>
<td>Taiwan, 2007–09</td>
<td>2356 children aged from 6 months to 10 years</td>
<td>EIA Abbott Laboratories (North Chicago, IL, USA)</td>
<td>1773/583</td>
<td>1050 723</td>
<td>Anti-HBc rate was calculated in ages 2–10 years; HBsAg+ children for &gt;6 months were defined as chronic HBV carriers; Chronicity rate was defined as persistent HBsAg seropositivity rates among all children with breakthrough infection; Vaccine efficacy: prevention of HBsAg carrier state</td>
<td></td>
</tr>
<tr>
<td>Yang, 2003</td>
<td>MC prospective comparative study/ Ottawa Scale: 6 stars</td>
<td>Taiwan, 1999–2000</td>
<td>235 infants</td>
<td>Abbott Laboratories (Abbott Park, IL, USA)</td>
<td>216/19</td>
<td>122 94</td>
<td>Serum samples collected from infants at 2 and 7 months were tested for HBsAg and anti-HBs; Infants were considered to have protective immunity after vaccination if anti-HBs+, at a level &gt;10 mIU/mL; Chronicity: HBsAg+ and persisted for &gt;6 months; HBsAg+ infections were classified as events (HBsAg+ at any time &gt;1 month of age) or as chronic (HBsAg+ for &gt;6 months); HBsAg carrier state was defined HBsAg+ for &gt;6 months; HBsAg− infections were classified as early (persistence of anti-HBc from birth to end of follow-up) or late (seroconversion from anti-HBc− to + after 18 months of age)</td>
<td></td>
</tr>
<tr>
<td>Xu, 1995</td>
<td>SC placebo-controlled RCT/Jadad score: 2</td>
<td>NR, NR</td>
<td>208 infants</td>
<td>RIA Abbott (Abbott Park, IL, USA)</td>
<td>101/107</td>
<td>30 31</td>
<td>HBsAg+ infections were classified as events (HBsAg+ at any time &gt;1 month of age) or as chronic (HBsAg+ for &gt;6 months)</td>
<td></td>
</tr>
<tr>
<td>First author, year</td>
<td>Study design/quality</td>
<td>Country, period</td>
<td>Total number of evaluated newborns</td>
<td>Study population</td>
<td>Laboratory methods (HBV serological markers)</td>
<td>Number of newborns from HBeAg+/HBeAg− mothers</td>
<td>Study groups of newborns from HBeAg− mothers&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Evaluated outcomes—definitions</td>
</tr>
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<tr>
<td>Sehgal, 1992&lt;sup&gt;23&lt;/sup&gt;</td>
<td>SC RCT/Jadad score: 1</td>
<td>India, 1987–89</td>
<td>45 infants</td>
<td>ELISA Biotest Diagnostics (West Germany), ELISA Hoechst Diagnostics (India) Ltd</td>
<td>18 anti-HBe+, 14 HBeAg+ and 13 only HBsAg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8 vaccine only; 10 vaccine+HBIG</td>
<td>All the three groups were called for follow-up (blood sampling) at 3 and 6 months after the birth</td>
<td>Seroprotection rate is proportion of subjects with anti-HBs ≥10 IU/L</td>
</tr>
<tr>
<td>Wheeley, 1991&lt;sup&gt;24&lt;/sup&gt;</td>
<td>SC prospective comparative study/Ottawa Scale: 5 stars</td>
<td>England, 1986–87</td>
<td>101 infants</td>
<td>NR</td>
<td>23 HBeAg−/anti-HBe−, 62 anti-HBe+ and 16 HBeAg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11 HBeAg−/anti-HBe− and 32 anti-HBe+ only HepB vaccine</td>
<td>Immunity Poor response HB carrier state</td>
<td></td>
</tr>
<tr>
<td>Esteban, 1986&lt;sup&gt;25&lt;/sup&gt;</td>
<td>SC prospective comparative study/Ottawa Scale: 4 stars</td>
<td>Spain, 1982–84</td>
<td>85 infants</td>
<td>ELISA Ausria-Core (Abbott Laboratories), RIA Abbott-HBe and Ausab (Abbott Laboratories), RIA Core IgM (Sorin Biomedica)</td>
<td>96/5</td>
<td>33&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun, 1986&lt;sup&gt;26&lt;/sup&gt;</td>
<td>SC RCT/Jadad score: 1</td>
<td>China, NR</td>
<td>1703 infants</td>
<td>RIA (Abbott Laboratories)</td>
<td>1134/46</td>
<td>5 μg: 20/29 (69%); 2.5 μg: 28/39 (72%); 5 μg+HBIG: 21/26 (81%); 2.5 μg+HBIG: 28/39 (72%)</td>
<td>Sera from vaccinated babies were obtained at 6.5 months (2 weeks after third dose of vaccine) and 12 months of age Anti-HBs could only be measured to a level of 20 mIU/mL</td>
<td></td>
</tr>
</tbody>
</table>

MC, multicentre; NR, not reported; SC, single-centre; NA, not applicable.
<sup>a</sup>The type of immunization is reported as that administered at birth.
<sup>b</sup>HBIG at birth was self-paid, whereas HBV vaccine was administered to all infants born to HBsAg+ mothers by protocol.
<sup>c</sup>In these two studies the evaluated neonates were classified according to the anti-HBe status of the respective mothers.
<sup>d</sup>This study included also a third group of 40 newborns who received only HBIG.
the compared groups (four studies, 1323 patients, OR = 1.24, 95% CI = 0.97–1.58, Figure 3).

**Sensitivity analysis**

No difference was found regarding the occurrence of infection between the compared groups (three studies (0 RCTs), 2041 patients, OR = 1.16, 95% CI = 0.26–5.17; Figure 4).12,21,25 Similarly, no difference was found regarding the seroprotection rate between the compared groups (three studies (one RCT19), 258 patients, OR = 2.2.1, 95% CI = 0.57–8.41, Figure 5).12,23,24 Funnel plots were generated in order to assess publication bias (Figure S1).

**Other evaluated outcomes**

Four studies provided data regarding the transition to carrier state12,22–24 (two RCTs22,23). In three of these four studies, none of the babies became an HBV carrier in either of the compared groups.12,23,24 The detailed data presented from the fourth study are presented in Table S1.22 Two of the included studies presented data with regard to vaccine efficacy23,26 (detailed data are presented in Table S1). None of the included studies reported safety data regarding the use of the compared immunization strategies. Additional outcomes were reported from one of the three most recent included studies.21 Specifically, fulminant hepatic failure was reported in 1/1050 (0.09%) of the neonates who were immunized with HB vaccine only, compared with none of the neonates 0/723 (0%) who were immunized with the combination of HB vaccine and HBIG.21 Moreover, the cost–benefit analysis for preventing fulminant hepatic failure, which was performed in this study, favoured the co-administration of HB vaccine and HBIG (Table S1).21

**Discussion**

The main finding of our study is that no difference was observed in occurrence of HB infection in neonates of HBsAg+/HBeAg– mothers who received either combined immunization (vaccine plus HBIG) or vaccine alone. This finding was consistent with regard to seroprotection rate. Limited data were available regarding the other evaluated outcomes, which precluded us from incorporating the above-mentioned outcomes in a meta-analysis.

To our knowledge, this is the first meta-analysis to date that has focused on the evaluation of the effectiveness and safety of the above-mentioned immunization strategies in neonates of HBsAg+/HBeAg– mothers. Indeed, in a previous relevant meta-analysis only 3 of 29 included studies involved HBsAg+/

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**Figure 1.** Flow diagram of the detailed process of selection of studies for inclusion in the review/meta-analysis.
In that meta-analysis, the combination of vaccine plus HBIG reduced the occurrence of HB in neonates, compared with HBV vaccine alone, regardless of the mother’s serological status. On the other hand, according to the findings of a recent relevant study that was not included in our statistical analysis, occult infection was more common in neonates who

### Table 1

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaccine only</th>
<th>Vaccine + HBIG</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>1.1.1 Non-randomized studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen 2012</td>
<td>3</td>
<td>1050</td>
<td>1</td>
</tr>
<tr>
<td>Esteban 1986</td>
<td>1</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Yang 2003</td>
<td>1</td>
<td>122</td>
<td>1</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>1202</td>
<td>839</td>
</tr>
<tr>
<td>Total events</td>
<td>5</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\chi^2 = 0.00; \chi^2 = 0.44, df = 2 (P = 0.80); I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.20 (P = 0.84)$</td>
<td></td>
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</tbody>
</table>

### Figure 2

Occurrence of HB infection in neonates born to HBsAg+/HBeAg– mothers, who received either vaccine or a combination of vaccine and HBIG. The vertical line denotes no difference between the compared groups. Pooled ORs and 95% CIs are depicted by diamond shapes and horizontal lines, respectively. Squares indicate individual point estimates. The size of the square denotes the weight that each individual study has in the meta-analysis. Non-randomized comparative studies and RCTs are presented separately as subgroups.

### Table 2

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaccine only</th>
<th>Vaccine + HBIG</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>1.1.2 RCTs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun 1986</td>
<td>13</td>
<td>790</td>
<td>13</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>129</td>
<td>103</td>
</tr>
<tr>
<td>Total events</td>
<td>18</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\chi^2 = 0.00; \chi^2 = 0.70, df = 3 (P = 0.87); I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.73 (P = 0.47)$</td>
<td></td>
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<td></td>
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</tbody>
</table>

### Figure 3

Seroprotection rate in neonates born to HBsAg+/HBeAg– mothers, who received either vaccine or the combination of vaccine and HBIG. The vertical line denotes no difference between the compared groups. Pooled ORs and 95% CIs are depicted by diamond shapes and horizontal lines, respectively. Squares indicate individual point estimates. The size of the square denotes the weight that each individual study has in the meta-analysis. Non-randomized comparative studies and RCTs are presented separately as subgroups.
received both vaccine and HBIG, possibly due to the immune pressure induced by HBIG.19

Most recently, a meta-analysis that aimed to evaluate the response to recombinant vaccine among infants irrespective of the maternal HBsAg status reported that seroprotection rates did not vary appreciably by HBIG administration.17 In our meta-analysis, the combination of vaccine plus HBIG was not significantly associated with lower seroprotection rates, compared with HBV vaccine alone. The small number of studies included in the above-mentioned analysis may possibly account for this particular finding. The long-term effects of this observation may remain unknown, but the literature provides evidence that the co-administration of HBIG may offer additional protection during early infancy from horizontal transmission, in the event of delayed administration of the second vaccine dose.12,28

It is noteworthy that data regarding the safety of the evaluated immunization strategies were not reported in any of the studies included in our meta-analysis. Indeed, published evidence suggests that safety data regarding immunization strategies, mainly vaccines, are scarcely reported in the literature.29,30

Another important outcome is the risk of chronic HB infection in neonates born to HBsAg+/HBeAg− mothers. In our study, the scarcity of data regarding the occurrence of chronic infection precluded the evaluation of this outcome in a meta-analysis. On the other hand, although the risk of chronic infection in children born to HBsAg+/HBeAg− mothers is low, there have been several reports of fulminant acute hepatitis, thus supporting the need for effective prevention of transmission.31–33 Yet the very low incidence of fulminant hepatitis (<1% of cases), in view of the high cost of HBIG, warrants further investigation.21 In particular, a

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaccine only</th>
<th>Vaccine + HBIG</th>
<th>Odds ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2012</td>
<td>3</td>
<td>1050</td>
<td>2.07 (0.21, 19.93)</td>
</tr>
<tr>
<td>Esteban 1986</td>
<td>1</td>
<td>30</td>
<td>0.72 (0.04, 12.25)</td>
</tr>
<tr>
<td>Yang 2003</td>
<td>1</td>
<td>122</td>
<td>0.77 (0.05, 12.45)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1202</td>
<td>839</td>
<td>1.16 (0.26, 5.17)</td>
</tr>
</tbody>
</table>

Figure 4. Occurrence of HB infection in neonates born to HBsAg+/HBeAg− mothers, who received either vaccine or the combination of vaccine and HBIG, in studies providing exclusive data for neonates born to HBsAg+/HBeAg− mothers and not for the total study population. The vertical line denotes no difference between the compared groups. Pooled ORs and 95% CIs are depicted by diamond shapes and horizontal lines, respectively. Squares indicate individual point estimates. The size of the square denotes the weight that each individual study has in the meta-analysis.

Figure 5. Seroprotection rate in neonates born to HBsAg+/HBeAg− mothers, who received either vaccine or the combination of vaccine and HBIG, in studies providing exclusive data for neonates born to HBsAg+/HBeAg− mothers and not for the total study population. The vertical line denotes no difference between the compared groups. Pooled ORs and 95% CIs are depicted by diamond shapes and horizontal lines, respectively. Squares indicate individual point estimates. The size of the square denotes the weight that each individual study has in the meta-analysis. Non-randomized comparative studies and RCTs are presented separately as subgroups.
recently published cost-effectiveness study, which implemented a decision-analysis approach, suggested that administration of HBIG to neonates of HBsAg+ mothers seems to be a cost-effective addition to universal vaccination, especially in clinical settings with a healthcare infrastructure that may support this strategy.34

Recently, the role of maternal HBV viraemia has been further investigated.35 Published evidence suggests that increased maternal HBV viral load has been associated with breakthrough infections despite the administration of appropriate prophylaxis in babies of both HBeAg+ and HBeAg− mothers.23 Yet HBV-DNA PCR assays are also expensive and difficult to perform. In this regard, further cost-effectiveness studies evaluating the inclusion of HBeAg status as part of prenatal screening tests may also provide useful data.

Our meta-analysis has some limitations. Firstly, the number of individual studies that were finally incorporated into the statistical analysis was rather small. An explanation that may account for this observation is that most of the relevant studies focus on HBsAg+/HBeAg+ mothers, who are considered to be more infective to their offspring compared with HBsAg+/HBeAg− mothers.34 However, current evidence suggests that the importance of transmission from HBeAg− chronic HB carriers in highly endemic countries has been underestimated.35 Another fact that may account for the scarcity of data regarding HBsAg+/HBeAg− mothers is that most of the included studies involve populations from endemic countries where the majority of HBsAg+ mothers are also HBeAg+. Furthermore, restrictions imposed by language of publication should also be acknowledged as a limitation. Finally, only four of the nine included studies were RCTs. Despite ethical considerations, this may be explained by the fact that, in some clinical settings, the administration of HBIG is determined by parental will.21 Specifically, in some clinical settings the augmentation of hepatitis B immunization in babies born to HBsAg+/HBeAg− mothers with HBIG is self-paid and remains at the discretion of parents.21

In conclusion, the addition of HBIG to vaccination seems to be equally effective to vaccine alone for offspring of HBsAg+/HBeAg− mothers with regard to the prevention of infection. Further investigation, particularly cost-effectiveness studies, is warranted in order to clarify the potential benefit of additional HBIG administration to all newborns of HBsAg+ mothers regardless of their HBeAg status.

**Funding**
This study was carried out as part of our routine work.

**Transparency declarations**
None to declare.

**Supplementary data**
Table S1 and Figure S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

**References**
19 Pande C, Sarin SK, Patra S et al. Hepatitis B vaccination with or without hepatitis B immunoglobulin at birth to babies born of HBsAg-positive mothers prevents overt HBV transmission but may not prevent occult HBV infection in babies: a randomized controlled trial. J Viral Hepat 2013; 20: 801–10.


