Comparative efficacy and safety of pharmacologic interventions to prevent mother-to-child transmission of hepatitis B virus: a systematic review and network meta-analysis

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OBJECTIVE: This study investigated the efficacy and safety of pharmacologic interventions to prevent vertical transmission of the hepatitis B virus.

DATA SOURCES: Medline, Cochrane, and Scopus databases were searched up to October 28, 2020.

STUDY ELIGIBILITY CRITERIA: All randomized controlled trials reporting vertical hepatitis B virus transmission with pharmacologic intervention were included.

METHODS: Risk of bias was assessed using the Cochrane Risk-of-Bias tool, version 2. Treatment efficacy was estimated using stratified network meta-analysis on the basis of maternal hepatitis B envelope antigen status.

RESULTS: Nineteen studies were included for mothers positive for hepatitis B surface and envelope antigens. Pooling indicated that a combination of hepatitis B vaccination and hepatitis B immunoglobulin in infants significantly reduced transmission risk compared with vaccination alone, with a risk ratio of 0.52 (95% confidence interval: 0.30–0.91). Only the addition of maternal tenofovir disoproxil fumarate, but not telbivudine, lamivudine, or maternal hepatitis B immunoglobulin further reduced transmission risk compared with a combination of hepatitis B vaccination and hepatitis B immunoglobulin in infants, with a pooled risk ratio of 0.10 (0.03–0.35). Twelve studies conducted in mothers with hepatitis B surface antigen positivity and mixed, unknown, or negative hepatitis B envelope antigen status provided limited evidence to suggest that maternal hepatitis B immunoglobulin combined with hepatitis B vaccination and immunoglobulin in infants was the likely best treatment, but this failed to reach statistical significance compared with a combination of hepatitis B vaccination and immunoglobulin in infants. Similarly, infant hepatitis B immunoglobulin, added to vaccination, likely provides additional benefit but failed to reach statistical significance.

CONCLUSION: A combination of hepatitis B vaccination and immunoglobulin in infants is the cornerstone for prevention of vertical transmission for mothers positive for both hepatitis B surface and envelope antigens. The addition of maternal tenofovir to this infant combination regimen was considered the likely most effective treatment. For infants of mothers with hepatitis B surface antigen positivity and mixed, unknown, or negative hepatitis B envelope antigen status, no additional agents provided further benefit beyond hepatitis B vaccination alone.

Key words: hepatitis B immune globulin, hepatitis B virus, lamivudine, telbivudine, tenofovir, vertical transmission
Why was this study conducted?
There has been a lack of granularity in pooling evidence by maternal hepatitis B envelope antigen (HBeAg) status to determine the most effective strategy for preventing vertical transmission of hepatitis B virus (HBV) infection. Although perinatal tenofovir disoproxil fumarate (TDF) is preferable to other antiviral therapies (AVTs), evidence on its effectiveness compared with other AVTs is unclear.

Key findings
Considering the addition of maternal AVT to infant immunizations with hepatitis B immune globulin and HBV vaccination, only the addition of TDF significantly reduced the risk of vertical transmission of HBV, and represents the most effective intervention for hepatitis B surface antigen–positive (HBsAg(+)) and HBeAg–positive (HBeAg(+)) mothers. For infants of HBsAg(+) /HBeAg(+/−) mothers, no additional agents provided added significant benefit compared with vaccination.

What does this add to what is known?
This study provides empirical evidence to support current clinical guidelines for the use of TDF to prevent vertical transmission of HBV among HBsAg(+) /HBeAg(+) mothers.

Introduction
Chronic hepatitis B virus (HBV) infection is a major public health concern. Mother-to-child transmission (hereafter referred to as vertical transmission) represents a major path of HBV transmission. Approximately 90% of infants infected through vertical transmission later develop chronic hepatitis B. Pregnant women with high HBV DNA levels (ie, ≥5.3 log10 IU/mL or ≥200,000 IU/mL) have a higher chance of vertical transmission. Recently, it was also reported that hepatitis B envelope antigen (HBeAg) can act as a surrogate to identify women with HBV DNA levels above this threshold.

To date, several pharmacologic strategies for the prevention of vertical transmission of HBV are available, including postnatal immunization with HBV vaccine and/or hepatitis B immune globulin (HBIG) in infants, and the combination of postnatal immunization in infants and perinatal treatment in mothers with either antiviral therapy (AVT) or HBIG. All guidelines recommend that HBV vaccination should be given to all infants born to hepatitis B surface antigen–positive (HBsAg(+)) mothers, preferably within 12 hours or 24 hours of birth. Most guidelines also recommend that HBIG should be given with HBV vaccination to all infants born to HBsAg(+) mothers or those with unknown HBsAg status but for whom evidence suggests active HBV infection, whereas the World Health Organization (WHO) guidelines recommend that HBIG should be given if available, especially for those with HBeAg(+) or high levels of HBV DNA. For mothers with a high level of HBV DNA, perinatal provision of AVT in combination with HBIG and HBV vaccination is currently recommended, starting either at weeks 24 to 28, week 28, or weeks 28 to 32 of pregnancy. In settings with limited access to HBV DNA testing, HBeAg is a recommended alternative to assess perinatal AVT eligibility, given its wider availability and affordability. Nevertheless, the most effective AVT remains unclear. The conclusion from a recent WHO-commissioned meta-analysis found no significant difference in terms of prevention of vertical transmission of HBV across different AVTs. Of the different AVTs available, most guidelines recommend tenofovir disoproxil fumarate (TDF), mainly because of its superior viral resistance profile. In addition, telbivudine (LDT) has also been recommended by the Asian Pacific Association for the Study of the Liver (APASL).

Currently, 3 network meta-analyses (NMAs) have compared the efficacy of different AVTs, but these were subject to some significant limitations: TDF was not included in 1 study; 2 of the NMAs identified LDT and TDF as the likely best treatments, but there was no significant difference across the investigated AVTs. The most comprehensive NMA compared the efficacy of all possible regimens (ie, HBV vaccine, HBV vaccine combined with HBIG, and maternal AVT or maternal HBIG together with HBV vaccine and HBIG in infants), but all AVTs were combined into a single group; furthermore, stratified analyses by maternal HBeAg status, an important risk factor for vertical transmission of HBV, were not performed.

In summary, there is a paucity of randomized controlled trial (RCT) data for different regimens for the prevention of vertical transmission of HBV, and there has been a lack of granularity in pooling evidence for the most effective AVT. Given the availability of recently published studies and a lack of previous stratification by maternal HBeAg status, this NMA was undertaken to compare the efficacy and safety of all available pharmacologic interventions to prevent vertical transmission of HBV, stratified by maternal HBeAg status.

Materials and Methods
A review protocol was developed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for NMA and registered at the International Prospective Register of Systematic Reviews.

Eligibility criteria, information sources, and search strategy
We included RCTs that: (1) were conducted in HBsAg(+) pregnant women; (2) compared any of the following treatments or their combinations regardless of trade name, dosage, and
course: Placebo/None, HBV vaccine, HBIG, and AVTs (eg, lamivudine [LAM], LDT, TDF); and (3) reported the primary outcomes with or without other outcomes. The primary outcome was vertical transmission of HBV, defined as HBsAg(+) or detectable levels of HBV DNA in infants aged 6 to 12 months. Secondary outcomes included: (1) efficacy in infants, which consisted of HBsAg positivity or HBV DNA in newborns at birth, and seroprotection (defined as anti-HBs ≥10 IU/L) in infants aged 6 to 12 months; (2) efficacy in mothers, which consisted of undetectable HBV DNA in mothers at delivery, and loss or seroconversion of HBsAg or HBeAg in mothers; and (3) safety in mothers and infants, which consisted of the absence of any adverse event (AE) in mothers and infants. Studies were excluded if they included pregnancies coinfected with other viral hepatitides and/or HIV, or if their full text was unavailable.

Relevant studies were identified from the following databases: Medline, Scopus, and Cochrane CENTRAL without language restriction from inception to October 28, 2020. Reference lists of the included studies and previous systematic reviews were also screened. Search terms were based on patients (ie, pregnant women with HBV infection, infants/newborns), intervention (ie, HBV vaccine, HBIG, AVT), and study design (ie, RCTs) domains. Further details are shown in in Appendix S1.

Study selection
Study selection was performed independently by 2 reviewers (N.T.H. and M.T.). Any disagreement was resolved by discussion and consensus within the research team.

Data extraction
Data were extracted by 2 independent reviewers (N.T.H and P.L.T) using a predesigned data extraction form. The following data were extracted: study characteristics (ie, setting, sample size, inclusion/exclusion criteria), patient characteristics (ie, maternal HBsAg and HBeAg status, maternal HBV DNA level), intervention and comparator (ie, treatment regimen, initiation time, dose, duration of treatment), and outcomes of interest. Intervention and comparators included the following: (1) Placebo/None, (2) HBV vaccine in infants (i.Vaccine), (3) HBIG in infants (i.HBIG), (4) HBIG and HBV vaccine in infants (i.HBIG+i.Vaccine), (5) HBIG in mothers combined with HBIG and HBV vaccine in infants (m.HBIG/ i.HBIG+i.Vaccine), (6) LAM in mothers combined with HBIG and HBV vaccine in infants (m.LDT/i.HBIG+i.Vaccine), (7) LDT in mothers combined with HBIG and HBV vaccine in infants (m.LDT/i.HBIG+i.Vaccine), and (8) TDF in mothers combined with HBIG and HBV vaccine in infants (m.TDF/i.HBIG+i.Vaccine).

Any discrepancy was resolved by discussion and consensus within the research team.

Assessment of risk of bias
Risk of bias was assessed independently by 2 reviewers (N.T.H and M.T) using the Cochrane Risk-of-Bias tool, version 2 (RoB 2; Cochrane, London, United Kingdom). Any discrepancy was resolved by discussion and consensus within the research team.

Data synthesis
Direct meta-analysis was performed by pooling risk ratios (RR) for all pairwise comparisons consisting of at least 3 studies. The random-effects model by DerSimonian and Laird was applied if heterogeneity was present (ie, I² >25% or Cochran Q test <0.1); otherwise, an inverse variance method was used. The source of heterogeneity was explored using a meta-regression analysis, in which covariables were fitted into the model one-by-one. Small-study effect (as a possible indication of publication bias) was assessed by funnel plot and Egger’s test. If any plots showed asymmetry, a contour-enhanced funnel plot was applied to distinguish if asymmetry was caused by small-study effect or by heterogeneity. Trim-and-fill analysis was applied when there was evidence of small-study effect.

To compare all intervention effects using both direct and indirect data, a 2-stage NMA with consistency model was applied. The probability of the best treatment with the highest efficacy was estimated and ranked using the surface under the cumulative ranking curve (SUCRA). Cluster rankings for efficacy and safety were constructed by plotting SUCRA values for efficacy in lowering vertical transmission (x-axis) and in lowering AEs (y-axis). The treatments that fell in the upper right quadrant were taken as the best in both lowering vertical transmission and reducing AEs. The consistency assumption was assessed using the design-by-treatment interaction inconsistency model. If there was evidence of inconsistency, a loop-specific approach was applied to estimate the inconsistency factor (IF) for all closed loops. The loops with significant IIFs were considered further to explore the source of inconsistency by comparing covariables and risk of bias for each study. If there was any factor that was different from the rest, a sensitivity analysis was performed by excluding those studies. In addition, the transitivity assumption was explored by considering the distribution of potential confounders or effect modifiers (ie, maternal HBV DNA level and HBeAg status) of treatment comparisons. Comparison-adjusted funnel plots and Egger’s tests were performed to assess small-study effects across studies.

All analyses were stratified by maternal HBeAg status at baseline, that is, HBsAg(+) and HBeAg(+) mothers (denoted HbsAg+/HbeAg(+)) and mothers with HBsAg(-) but unknown, negative, or mixed status of HBeAg (denoted HbsAg[-]/HbeAg(±/-)). All analyses were performed with Stata, version 16.1 (Stata Corp, College Station, TX). The level of significance was set at .05 for all tests, except for the Cochran Q test, in which a cutoff value of 0.1 was used.

Results
Study selection
From a total of 3971 studies identified from all sources, 1288 duplicates were removed, leaving 2683 for title and abstract screening. Of those, 122 full texts were assessed for eligibility. Finally, 30 studies that provided data from 4459
infants were eligible for inclusion in this NMA (Figure 1).

**Study characteristics**
The characteristics of the eligible studies are summarized in Supplemental Table S1. Of the 30 studies included, only 3 studies were registered at clinicaltrials.gov and 2 had published protocols. Of the 28 studies that included the i.Vaccine, the vaccine was delivered at birth in 21 studies. For the remaining studies, the first dose of HBV vaccine was administered within 48 hours, 3 to 5 days, 2 weeks, or 1 month after birth, or not reported. Nineteen studies were conducted in HBsAg(+) mothers. Among these, all reported vertical transmission of HBV, 7 reported safety in infants, and 4 reported safety in mothers. Of the 12 studies with HBsAg(+) mothers, 7 studies were conducted in HBsAg(+) mothers,

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**FIGURE 1**
PRISMA flowchart of study selection

This figure illustrates the process and results of study selection.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

mothers with HBeAg mixed status, were conducted in mothers with unknown HBeAg status, and were conducted in HBeAg(−) mothers. One study reported HBeAg(+) and HBeAg(−) participants separately and hence contributed to both strata. There were 12 and 5 studies that reported vertical transmission of HBV and sero-protection in infants, respectively. Of note, analyses for other outcomes, such as HBsAg(+) infants at birth or seroconversion of HBsAg or HBeAg in mothers, could not be performed because of insufficient data.

Risk of bias of included studies
Among the 19 RCTs conducted in HBsAg(+) /HBeAg(+) mothers, 2, 20, 36 and 13 studies were at high risk of bias, low risk of bias, and of some concern, respectively. Of the 12 RCTs conducted in HBsAg(+) /HBeAg(+/−) mothers, 3 studies were at high risk of bias, whereas 9 studies were of some concern (Supplemental Figure S1).

Synthesis of results
Mothers with Hepatitis B surface antigen(+) /Hepatitis B envelop antigen(+)
Vertical transmission of hepatitis B virus. Direct meta-analysis. For mothers with HBsAg(+) /HBeAg(+), only 2 treatment comparisons provided a sufficient number of studies for pooling. According to data from 7 RCTs, i.HBIG + i.Vaccine significantly reduced risk of transmission compared with i.Vaccine, with a pooled RR (95% CI) of 0.44 (0.24–0.81). The transmission risk associated with the m.TDF / i.HBIG + i.Vaccine group was significantly lower than that of the i.HBIG + i.Vaccine group, with a pooled RR (95% CI) of 0.08 (0.02–0.44) (Supplemental Figure S2).

Network meta-analysis. Data from 19 RCTs (n=2148) consisting of 10 comparisons from 8 interventions were pooled (Figure 2, A). Among the interventions in infants, i.HBIG + i.Vaccine represented the most effective strategy compared with i.Vaccine, i.HBIG, and Placebo/None, with pooled RRs (95% CI) of 0.52 (0.30–0.91), 0.26 (0.13–0.50), and 0.16 (0.08–0.31), respectively (Table 1). Considering the addition of HBIG or AVT in mothers, only m.TDF / i.HBIG + i.Vaccine was associated with a significantly lower risk of transmission when compared with i.HBIG + i.Vaccine, with a pooled RR (95% CI) of 0.10 (0.03–0.35). Furthermore, m.TDF / i.HBIG + i.Vaccine also significantly lowered transmission risk compared with m.LAM/i.HBIG + i.Vaccine and m.HBIG/i.HBIG + i.Vaccine, with pooled RRs (95% CI) of 0.15 (0.05–0.48) and 0.17 (0.04–0.63), respectively (Table 1 and Supplemental Figure S3).

A sensitivity analysis that only included studies with HBV birth dose for the i.Vaccine group demonstrated similar results to the primary analysis (Supplemental Table S2).
TABLE 1

<table>
<thead>
<tr>
<th>Placebo or None</th>
<th>0.63 (0.49–0.82)</th>
<th>0.31 (0.19–0.49)</th>
<th>0.10 (0.03–0.30)</th>
<th>0.02 (0.00–0.07)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.HBIG</td>
<td>0.49 (0.29–0.82)</td>
<td>0.26 (0.13–0.50)</td>
<td>0.07 (0.00–0.26)</td>
<td>0.01 (0.00–0.03)</td>
</tr>
<tr>
<td>i.Vaccine</td>
<td>0.52 (0.30–0.91)</td>
<td>0.32 (0.15–0.68)</td>
<td>0.11 (0.00–0.36)</td>
<td>0.05 (0.00–0.10)</td>
</tr>
<tr>
<td>3.23 (2.03–5.16)</td>
<td>2.04 (1.21–3.44)</td>
<td>1.93 (1.10–3.38)</td>
<td>0.95 (0.34–2.67)</td>
<td></td>
</tr>
<tr>
<td>m.HBIG/i.HBIG</td>
<td>0.62 (0.37–1.06)</td>
<td>0.69 (0.26–1.85)</td>
<td>0.11 (0.01–3.37)</td>
<td>0.05 (0.01–0.21)</td>
</tr>
<tr>
<td>9.97 (4.33–22.94)</td>
<td>6.27 (2.66–14.80)</td>
<td>1.11 (0.36–3.68)</td>
<td>0.05 (0.01–0.21)</td>
<td></td>
</tr>
<tr>
<td>m.LAM/i.HBIG</td>
<td>1.10 (0.36–3.37)</td>
<td>1.00 (0.34–3.32)</td>
<td>0.09 (0.00–0.30)</td>
<td>0.01 (0.00–0.03)</td>
</tr>
<tr>
<td>9.07 (2.78–29.59)</td>
<td>5.71 (1.12–26.60)</td>
<td>0.97 (0.26–3.68)</td>
<td>0.01 (0.00–0.03)</td>
<td></td>
</tr>
<tr>
<td>m.LDT/i.HBIG</td>
<td>0.97 (0.26–3.68)</td>
<td>1.00 (0.34–3.32)</td>
<td>0.09 (0.00–0.30)</td>
<td>0.01 (0.00–0.03)</td>
</tr>
<tr>
<td>5.69 (1.58–22.64)</td>
<td>2.81 (0.90–8.70)</td>
<td>0.97 (0.26–3.68)</td>
<td>0.01 (0.00–0.03)</td>
<td></td>
</tr>
</tbody>
</table>
Cluster rank for efficacy and safety
Cluster rank for efficacy in lowering both vertical transmission of HBV and AEs in infants indicated that m.LDT/i.HBIG+i.Vaccine followed by m.TDF/i.HBIG+i.Vaccine represented the optimum benefit for lowering both vertical transmission of HBV and infant AEs (Supplemental Figure S9).

Mothers with Hepatitis B surface antigen(+/−)/Hepatitis B envelop antigen(+/−)

Vertical transmission of hepatitis B virus. **Direct meta-analysis.** Among 12 studies in mothers with unknown, mixed, or negative status for HBeAg (HBsAg(+/−)), only 2 treatment comparisons provided sufficient studies for direct pooling. Compared with Placebo/None, i.Vaccine tended to reduce transmission risk, with a pooled RR of 0.22 (0.05−1.00). The i.HBIG+i.Vaccine lowered transmission risk, with a pooled RR (95% CI) of 0.53 (0.21−1.32) compared with i.Vaccine, but this was not statistically significant (Supplemental Figure S10).

Network meta-analysis. Data from 12 studies (n=2311) consisting of 7 comparisons from 5 interventions were pooled (Figure 2, B). Among interventions in infants, i.HBIG+i.Vaccine represented the most effective strategy compared with i.Vaccine, i.HBIG, and Placebo/None, with pooled RRs of 0.60 (0.21−1.73), 0.98 (0.13−7.52), and 0.16 (0.04−0.64), respectively (Table 2). Although, m.HBIG/i.HBIG+i.Vaccine tended to further reduce the risk of transmission compared with i.HBIG+i.Vaccine, with a pooled RR of 0.31 (0.09−1.10), this was not statistically significant (Table 2 and Supplemental Figure S11).

A sensitivity analysis that only included studies with HBV birth dose for the i.Vaccine group30,51,53−57 generated findings similar to those from the primary analysis (Supplemental Table S5).

**Treatment ranking of prevention of vertical transmission of hepatitis B virus.** Treatment ranking by SUCRA values suggested that m.HBIG/i.HBIG+i.Vaccine was the likely best treatment for lowering vertical transmission of HBV, followed by i.HBIG+i.Vaccine and i.HBIG, with SUCRA values of 94.2%, 59.4%, and 58.8%, respectively (Supplemental Figure S12).

Seroprotection in infants aged 6 to 12 months. **Direct meta-analysis.** Compared with i.Vaccine, i.HBIG+i.Vaccine did not increase the chance of achieving seroprotection at the age of 6 to 12 months, according to 5 studies with a pooled RR (95% CI) of 0.95 (0.85−1.06) (Supplemental Figure S13).

Network meta-analysis. Data from 5 studies (n=560) consisting of 3 comparisons from 3 interventions were pooled (Supplemental Figure S14). The i.Vaccine tended to be the most effective treatment compared with i.HBIG and i.HBIG+i.Vaccine in terms of achieving seroprotection, with pooled RRs (95% CI) of 2.48 (1.55−3.98) and 1.06 (0.95−1.18), respectively (Supplemental Table S6).

Small-study effect assessment
Evidence of a small-study effect was observed only in the comparison between i.Vaccine and Placebo/None for the prevention of vertical transmission of HBV among mothers with HBsAg(+/−)/HBeAg(+/−) (Supplemental Figure S15, A and B). However, results from trim-and-fill analyses indicated similar treatment effects, limiting any significant effect changes. All other direct meta-analyses showed no evidence of asymmetry of funnel plots and therefore no evidence of publication bias (Supplemental Figure S15, C; Supplemental Figures S16−S19). Results from comparison-adjusted funnel plots showed no evidence of publication bias for all 5 NMAs (Supplemental Figures S20 and S21).

Consistency assumption
All NMAs except for the NMA of maternal AEs were evaluated for consistency assumptions using design-by-treatment interaction approaches. Network forest plots indicated the assumption was not violated in any NMA (Supplemental Figures S22−S25).

Comments
Principal findings
We conducted a NMA that included 30 RCTs with data from 4459 infants stratified by maternal HBsAg/HBeAg status. Among HBsAg(+/−)/HBeAg(+/−) mothers, our review indicated that provision of HBIG to infants, in addition to HBV vaccination, significantly reduced the risk of vertical transmission of HBV by 48%. Considering the addition of maternal AVTs in infant interventions (i.HBIG+i.Vaccine), only the addition of TDF (m.TDF/i.HBIG+i.Vaccine) significantly reduced the risk of vertical transmission and represented the likely best treatment. No significant benefit of the provision of HBIG in HBsAg(+/−)/HBeAg(+/−) mothers and/or infants was identified compared with vaccination alone.

Safety profile data for all interventions were encouraging but limited. Among the interventions for HBsAg(+/−)/HBeAg(+/−) mothers, most intervention regimens showed lower point estimates for AEs than Placebo/None, indicating a strong safety profile, although confidence intervals were wide. The most common AE observed in infants of the Placebo/None group was transient and slight ALT elevation, a manifestation of HBV infection. Therefore, interventions that reduced the risk of vertical transmission of HBV also reduced the risk of AEs in infants. On the basis of the current evidence, all pharmaceutical interventions were considered safe for both mothers and infants.

Comparison with existing literature
For hepatitis B surface antigen(+/−)/hepatitis B envelope antigen(+/−) mothers
Contrary to previous studies11−13 that reported no significant difference among AVTs, we found that TDF significantly reduced the risk of vertical transmission...
of HBV compared with LAM, but not LDT. Our findings provide significant evidence to support existing guidelines on the addition of perinatal TDF to the combination therapy of HBIG and HBV vaccination in infants of mothers with high levels of HBV DNA.3–5 Because of the limited number of LDT studies, further investigations are warranted to support the efficacy of additional perinatal LDT, as recommended by APASL guidelines.6 In addition to previous recommendations in support of HBeAg as an alternative to HBV DNA testing for determining the eligibility of TDF prophylaxis in mitigating vertical transmission,4 our study provided evidence to support the efficacy of TDF in HBsAg(+) mothers of pregnant women.

In contrast to a previous meta-analysis8 and NMA,15 we found that m.HBIG/i.HBIG+i.Vaccine did not significantly lower the risk of vertical transmission of HBV in HBsAg(+) mothers compared with i.HBIG+i.Vaccine, although the point estimate was encouraging (RR 0.62; 95% CI 0.37, 1.06); this was likely caused by the limited number of RCTs that included HBsAg(+) mothers in our NMA. Of note, previous studies15,16 did not stratify by maternal HBeAg status, and included studies of low quality that were conducted in a single setting only (China).

For hepatitis B surface antigen(+) /hepatitis B envelope antigen(+/−) mothers

Given the unclear benefits associated with the provision of HBIG both in infants and mothers, and its scarcity in less developed regions, i.Vaccine is considered optimal for infants of HBsAg(+) mothers. This is consistent with current WHO guidelines, in which infant HBIG is recommended for all infants born to HBsAg(+) mothers, if available, especially for those with HBeAg(+)/HBeAg(−) status or with high levels of HBV DNA.8 However, of note, the point estimate for i.HBIG+i.Vaccine in HBsAg(+) mothers (0.52) was similar to that of HBsAg(+) mothers (0.60), although the latter failed to reach statistical significance, possibly because of a loss of power following stratification by HBeAg status. Indeed, some guidelines recommend HBIG for all infants of HBsAg(+) mothers, although some with unknown status but for whom evidence suggests active HBV infection.9 Our findings are consistent with current guidelines5–8 that do not recommend the provision of maternal HBIG. However, it is worth noting that for both strata of mothers, the point estimates for the addition of m.HBIG are encouraging (0.62 and 0.31) but do not reach statistical significance.

Strengths and limitations

We performed a NMA based on the consistency assumption; the relative treatment effects incorporate data from both direct (or head-to-head) and indirect comparisons. The latter comparisons of 2 interventions that have not been compared directly within a single trial are estimated by borrowing common or reference treatment arms in the network. Reassuringly, relative treatment effects estimated from direct meta-analysis and NMA were consistent. Furthermore, NMA also allowed an estimation of the ranking of treatment effects, an approach which has been reported to provide more precise estimates of effect.

Compared with the previous NMA,15 our review was almost double in size, included more studies (30 RCTs vs 15 RCTs) and a larger number of participants (4459 vs 2706). We also analyzed each AVT separately and stratified the population on the basis of maternal HBeAg status, which is considered an important risk factor for vertical transmission of HBV.4,16,17 Although our systematic review and NMA has several strengths, the results of this NMA should be interpreted with caution for the following reasons. Firstly, the number of RCTs that evaluated the efficacy of maternal HBIG and AVT, especially for the intervention with LDT, was limited. To date, only 1 RCT has compared LDT to placebo, and was based on a limited number of participants. Second, most studies included were considered as being of some concerns or having a high risk of bias. The main reasons for this were the lack of details on the allocation concealment and concerns about the selection of reported results. Thirdly, compared with previous NMAs,15,14 that focused on the efficacy of AVTs for the prevention of vertical transmission of HBV, our study included a smaller number of RCTs because of limited access to databases from China. Moreover, our NMA was unable to compare

| Placebo/None | 0.16 (0.03–0.86) | 0.26 (0.08–0.82) | 0.16 (0.04–0.64) | 0.05 (0.01–0.35) |
| 6.30 (1.16–34.20) | i.HBIG | 1.63 (0.24–10.98) | 0.98 (0.13–7.52) | 0.30 (0.03–3.48) |
| 3.86 (1.22–12.21) | i.Vaccine | 0.61 (0.09–4.12) | 0.60 (0.21–1.73) | 0.18 (0.04–0.93) |
| 6.42 (1.57–26.25) | i.HBIG+i.Vaccine | 1.02 (0.13–7.80) | 1.66 (0.58–4.78) | 0.31 (0.09–1.10) |
| 21.02 (2.88–153.34) | m.HBIG/i.HBIG+i.Vaccine | 3.34 (0.29–38.74) | 5.45 (1.07–27.68) | 3.27 (0.91–11.76) |

The value in each cell represents the risk ratio of the column-defining intervention using the row-defining intervention as the reference.

HBsAg(+) / HBIG, hepatitis B envelope antigen—positive; HBIG, hepatitis B immune globulin; HBV, hepatitis B virus; HBsAg(−), hepatitis B surface antigen—positive; i.Vaccine, HBV vaccine in infants; i.HBIG, HBIG in infants; i.HBIG+i.Vaccine, HBIG and HBV vaccine in infants; m.HBIG, HBIG in pregnant women.

efficacy of different interventions in preventing vertical transmission of HBV in mothers with HBsAg(+)/HBeAg(−) given there were only 2 RCTs35,39 conducted in this population. Lastly, there are limited data on AEs in both mothers and infants to fully summarize the safety profiles of included interventions.

Conclusions and implications

By incorporating information from both direct and indirect comparisons in this NMA, we have estimated relative treatment effects between pairs of pharmacologic treatments for prevention of vertical transmission of HBV in a network with higher precision than previously available, in addition to providing an efficacy ranking of the various available pharmacologic interventions. Our NMA provides important and comprehensive evidence on the efficacy and safety of interventions for the prevention of vertical transmission of HBV, and this is critical to achieve the WHO goal of HBV elimination by 2030. For HBsAg(+)/HBeAg(+) women, the perinatal provision of TDF in combination with HBIG and HBV vaccination of infants (m.TDF/i.HBIG+/i.Vaccine) likely represents the most effective intervention for the prevention of vertical transmission of HBV and should be encouraged. Although the addition of maternal or infant HBIG to vaccination of infants from HBsAg(+)/HBeAg(+-) mothers is likely to be effective, no significant benefit was confirmed thus far. The videos summarizing this review could be found in the Supplementary Data (Videos 1 and 2).

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