

Comparative Effectiveness of Prophylactic Strategies for Perinatal Transmission of Hepatitis B Virus: A Network Meta-analysis of Randomized Controlled Trials

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Background. Perinatal transmission is the main route of hepatitis B virus (HBV) transmission. While several measures have been attempted as means of preventing perinatal HBV transmission, the optimal strategy remains inconclusive.

Methods. We conducted a comprehensive search, through December 2016, for randomized controlled trials (RCTs) that compared the following measures among pregnant women with HBV infection: placebo/none, active immunoprophylaxis (hepatitis B vaccine series starting at birth [HBVAc]), passive-active immunoprophylaxis (hepatitis B immunoglobulin and vaccine [HBIG+HBVAc]), prenatal HBIG administration (HBIG/HBIG+HBVAc), and prenatal antiviral therapy (AVT/HBIG+HBVAc). Direct, indirect, and network meta-analyses were performed for all treatment comparisons.

Results. Fifteen RCTs involving 2706 infants of HBV carrier mothers were eligible for analysis. Network meta-analysis demonstrated similar results as direct and indirect comparisons. HBVAc alone significantly reduced the risk of hepatitis B infection in infants of HBV carrier mothers (relative risk [RR], 0.32; 95% confidence interval [CI], 0.21–0.50). The combination of immunoglobulin with vaccine is superior to vaccine alone (RR, 0.37; 95% CI, 0.20–0.67). Prenatal HBIG administration and antiviral therapy offer further advantages over current passive-active immunoprophylaxis for infants of highly viremic (HBV DNA level higher than 2×10^5 IU/mL) mothers (RR, 0.47; 95% CI, 0.29–0.75; and RR, 0.31; 95% CI, 0.10–0.99, respectively). There was no significant publication bias.

Conclusions. Based on the universal infantile vaccination program, HBIG for infants born to HBV carrier mothers further reduces transmission. For highly viremic mothers whose children are still at risk for transmission under current immunoprophylaxis, prenatal HBIG administration or antiviral therapy in late pregnancy may be considered if more long-term evidence supports its efficacy and safety.

Keywords. hepatitis B virus; network meta-analysis; perinatal transmission; prophylaxis.

Chronic hepatitis B virus (HBV) infection is a major cause of liver cirrhosis and cancer globally, attributing a heavy disease burden. More than 90% of perinatal infected newborns become chronic carriers, while infected children and adolescents/adults have lower risks of chronicity (20%–40% and 0%–10%, respectively) [1]. Perinatal transmission contributes significantly to the high HBV prevalence in endemic countries.

Since the introduction of hepatitis B vaccine (HBVAc), active immunoprophylaxis has proven efficient for preventing perinatal HBV transmission. The World Health Organization (WHO) recommends that all countries include HBVAc starting with a

birth dose into routine national infant immunization programs [2]. However, for infants of HBV carrier (hepatitis B surface antigen/HBsAg-positive) mothers, even after being vaccinated with both hepatitis B immunoglobulin and vaccine (HBIG+HBVAc, termed passive-active immunoprophylaxis), 10%–20% of them may still become chronic HBV carriers, mostly due to intrauterine infection [3].

Several studies reporting effects for maternal HBIG administration or antiviral therapy (AVT) during late pregnancy have not yet provided conclusive evidence. Most of these studies might have potentially biased results due to lack of randomization. There is paucity of head-to-head randomized controlled trials (RCTs) comparing different prophylactic interventions, which can inform clinicians regarding the comparative effectiveness of these interventions. Moreover, direct pairwise meta-analyses can only answer questions about pairs of treatments with partial information. In contrast, network meta-analyses combine the simultaneous analyses of direct and indirect evidence for mixed-effect estimate calculation, hence helping to evaluate the comparative effectiveness of multiple interventions [4].

In this study, we performed direct, indirect, and network meta-analyses to assess the relative efficacy of all prophylactic

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interventions (HBV_{ac}, HBIG+HBV_{ac}, HBIG/HBIG+HBV_{ac}, and AVT/HBIG+HBV_{ac}) for the management of HBV carrier mothers and their infants.

METHODS

Search Strategy

We included the following 4 interventions: (1) infants were injected with a 3- or 4-dose vaccine series starting within 24 hours after delivery (HBV_{ac}); (2) infants were injected with both HBIG and HBV_{ac} (HBIG+HBV_{ac}); (3) pregnant women were injected with multiple doses of HBIG in the third trimester of pregnancy (typically on weeks 28, 32, and 36) while infants were injected with HBIG and HBV_{ac} (HBIG/HBIG+HBV_{ac}); (4) pregnant women with a high viral load (HBV DNA level higher than 2×10^5 IU/mL) were given antiviral therapy (lamivudine or telbivudine or tenofovir) during late pregnancy while infants were injected with HBIG and HBV_{ac} (AVT/HBIG+HBV_{ac}). Eligible studies were predefined as RCTs comparing any intervention with placebo/none or another intervention for HBV carrier mothers and their infants. PubMed, Ovid, Embase, and Cochrane Library were searched from the date of their inception to December 31, 2016, using combinations of the following terms: “HBV” (or “hepatitis B virus”) and “perinatal transmission” (or “mother-to-child transmission” or “MTCT” or “intra-uterine infection” or “ectopic” or “pregnant” or “pregnancy” or “mother” or “children” or “infant” or “newborn”) and “prophylaxis” (or “hepatitis B vaccine” or “HB vaccine” or “hepatitis B immunoglobulin” or “HBIG” or “lamivudine” or “telbivudine” or “tenofovir”).

Data Extraction and Quality Assessment

Two investigators (Z-XC and Y-LH) independently selected studies, reviewed the reports, and recorded information using

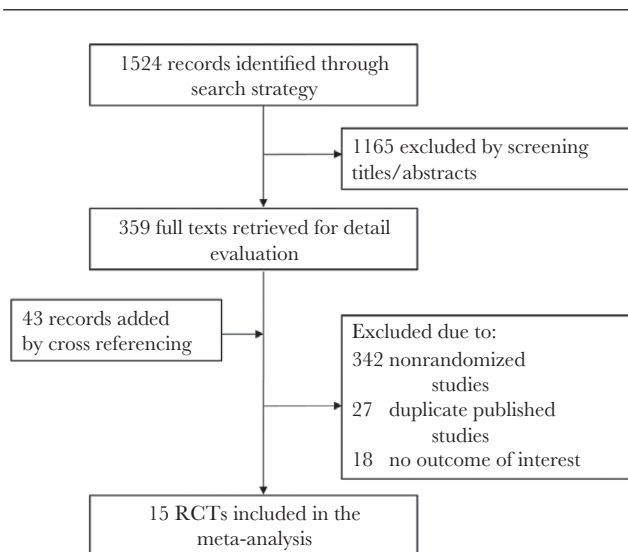


Figure 1. Flowchart of study selection. Abbreviation: RCT, randomized controlled trial.

a predefined data extraction sheet that included relevant items: the first author’s name, year of publication, region, study design, inclusion/exclusion criteria, sample size, duration of follow-up, and outcome data. Perinatal HBV transmission, the primary outcome, was defined as seropositivity rate for HBsAg or HBV DNA in the infants both at birth and at 6–12 months of follow-up.

Two investigators (G-FG and M-ZC) independently assessed the risk of bias and the quality of studies according to the Jadad score [5]. Discrepancies were resolved by consensus and consultation with other investigators (XZ and GQ).

Statistical Analysis

Data analysis was performed according to the per-protocol principle. All statistical analyses were conducted using Stata version 14.0 (StataCorp, TX). Direct meta-analysis with the random-effects model was applied to estimate pooled relative risks (RRs) and 95% confidence intervals (CIs). Indirect comparisons were performed using the adjusted indirect method described by Miladinovic et al. [6]. The network meta-analysis models, network diagram, predictive interval (PrI) plot, and ranking plots were constructed using commands of the network package in Stata [7]. In network meta-analysis, the RRs were presented with 95% CIs alongside their 95% PrIs to provide intervals within which the estimates of future studies are expected to be. The heterogeneity test was conducted with the chi-square test and I^2 . An I^2 index of 50% or more indicated a high degree of heterogeneity. Publication bias was assessed by examining Begg’s funnel plots and Egger’s regression tests.

We estimated number needed to treat (NNT) from the summary estimates for the primary outcome using the calculated absolute perinatal transmission risk with HBV_{ac} alone.

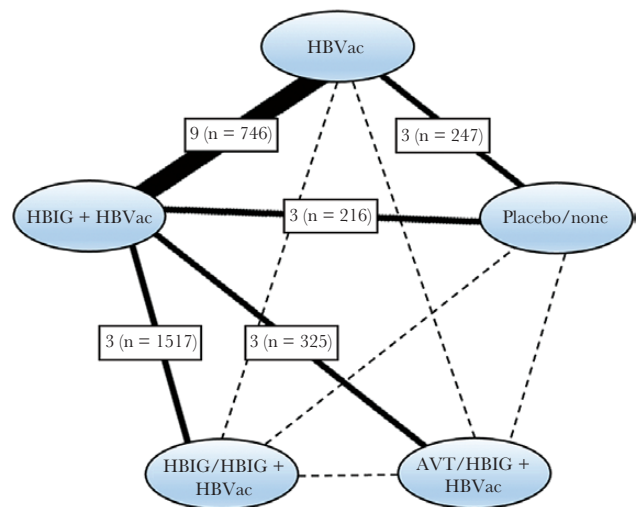


Figure 2. Network plot for different prophylactic interventions to prevent perinatal transmission among infants of hepatitis B virus carrier mothers. Abbreviations: AVT, antiviral therapy; HBIG, hepatitis B immunoglobulin; HBV_{ac}, hepatitis B vaccine.

RESULTS

Characteristics and Quality of Included Studies

We identified 1524 citations through our searches, from which 15 clinical trials involving 2706 infants of HBV carrier mothers were selected (Figure 1). Some studies had more than 2 “arms,” resulting in up to 21 relevant comparisons: HBVAc vs placebo/none: 3 trials [8–10]; HBIG+HBVAc vs placebo/none: 3 trials [8–10]; HBIG+HBVAc vs HBVAc: 9 trials [8–16]; HBIG/HBIG+HBVAc vs HBIG+HBVAc: 3 trials [17–19]; AVT+HBIG+HBVAc vs HBIG+HBVAc: 3 trials [20–22]. Five “RCTs” listed in the meta-analysis of Brown et al. [23] were not included in our study because their “randomization” was questioned [24].

Figure 2 demonstrates all available direct comparisons and the network. The mean sample size was 188 infants, ranging between 39 and 987. Fourteen (93.3%) trials recruited patients from Asia (mainland China: 7 trials; Thailand: 3 trials; India: 2 trials; Hong Kong: 1 trial; Taiwan: 1 trial), and 1 (6.7%) recruited patients from Oceania (New Zealand). Thirteen were published in English, and 2 were published in Chinese. Eight studies only recruited HBsAg- and HBeAg-positive mothers [8, 9, 11–13, 15, 18, 22]. Five studies had clear classifications of HBeAg-positive and HBeAg-negative mothers, with comparable numbers in experimental and control groups [14, 16, 17, 19, 20]. Two studies did not report the HBeAg status of enrolled HBV carrier mothers [21].

Eight studies reported the method to generate the sequence of randomization [8, 10, 15–17, 19, 20, 22]. Four studies adopted placebo and described the method of double blinding [8, 10, 16, 20]. Nine studies recorded withdrawals and dropouts. Study-level quality assessments with Jadad scores are summarized in Table 1.

Direct and Indirect Meta-Analyses

Three studies compared the efficacy of hepatitis B vaccine with placebo or no treatment among infants of HBV carrier mothers. At age 6 months or older, the infant HBsAg-positive rates were 20.2% (26/129) in the HBVAc group and 59.3% (70/118) in the placebo/none group (RR, 0.33; 95% CI, 0.23–0.48; I^2 , 22.7%). Nine studies comparing HBIG+HBVAc vs HBVAc demonstrated perinatal transmission rates of 3.6% (13/359) in the HBIG+HBVAc group and 11.6% (45/387) in the HBVAc group (RR, 0.34; 95% CI, 0.19–0.60; I^2 , 0%). For infants of highly viremic mothers, both HBIG/HBIG+HBVAc (3 RCTs) and AVT+HBIG+HBVAc (3 RCTs) led to further lower perinatal transmission rates compared with HBIG+HBVAc. At age of 6 months or more, the infant HBsAg-positive rates were 5.1% (39/768) in the HBIG/HBIG+HBVAc group and 11.2% (84/749) in the HBIG+HBVAc group (RR, 0.46; 95% CI, 0.32–0.65; I^2 , 59.9%). Likewise, the perinatal transmission rates were 1.8% (3/163) in the AVT/HBIG+HBVAc group and 9.9% (16/162) in the HBIG+HBVAc group (RR, 0.24; 95% CI, 0.09–0.69; I^2 , 18.3%).

For the above direct comparisons, the results of indirect meta-analyses were largely similar, with overlapping confidence intervals. In addition, indirect meta-analyses demonstrated that HBIG/HBIG+HBVAc was superior to placebo/none and HBVAc in reducing perinatal transmission (RR, 0.05; 95% CI, 0.02–0.13; and RR, 0.15; 95% CI, 0.05–0.42, respectively). AVT/HBIG+HBVAc also further reduced transmission, as compared with placebo/none and HBVAc (RR, 0.03; 95% CI, 0.01–0.13; and RR, 0.10; 95% CI, 0.02–0.42, respectively). AVT/HBIG+HBVAc and HBIG/HBIG+HBVAc appear comparable with each other for decreasing perinatal transmission risk (RR, 0.63; 95% CI, 0.16–2.48).

Network Meta-analyses

Compared with HBVAc alone, HBIG+HBVAc (RR, 0.37; 95% CI, 0.20–0.67), HBIG/HBIG+HBVAc (RR, 0.17; 95% CI, 0.08–0.37), and AVT/HBIG+HBVAc (RR, 0.11; 95% CI, 0.03–0.42) further reduced perinatal HBV transmission (Figure 3). Using the absolute transmission risk of 11.6 (45/387) with HBVAc, the corresponding NNTs for HBIG+Vac, HBIG/HBIG+Vac, and AVT/HBIG+Vac to prevent 1 perinatal infection were 14, 11 and 10, respectively. All the above 3 interventions were superior to HBVAc in reducing perinatal HBV transmission.

For infants of highly viremic mothers, both HBIG/HBIG+HBVAc and AVT/HBIG+HBVAc were superior to HBIG+HBVAc in reducing perinatal infection (RR, 0.47; 95% CI, 0.29–0.75; and RR, 0.31; 95% CI, 0.10–0.99, respectively) (Figure 3).

The combination of prenatal antiviral therapy with passive-active immunoprophylaxis had the highest probability of being ranked best (for decreasing perinatal transmission), and the combination of prenatal HBIG administration with passive-active immunoprophylaxis had a high probability of being ranked second (Figure 4).

Safety Profiles

Both hepatitis vaccine and immunoglobulin appeared to be safe, while a few studies in this meta-analysis reported adverse effects without mentioning details. Data on maternal and fetal safety with antivirals remain limited.

Publication Bias

In general, there was no evidence of publication bias, both qualitatively based on funnel plot symmetry (Figure S1) and quantitatively based on Egger's regression tests ($P > .05$ for all comparisons). No significant differences were found between direct and indirect estimates where both were available. Besides, the 3 methods had overlapping CIs for all interventions (Table 2).

DISCUSSION

To the best of our knowledge, this is the first study that has combined both direct and indirect evidence in terms of comparative

Table 1. Characteristics of Included RCTs

Study	Region	Period	Center	Mother HBeAg+/-	Prophylaxis Strategy			Baby Sample Size	No. of Transmissions	Jadad Score
					Mother	Child	Prophylaxis Strategy			
Wong VC (1984)	Hong Kong	1981–1983	1	All positive	C: none T1: none	C: Placebo T1: HBVAc	C: 34 T1: 35	C: 25 T1: 7	5 (2 + 2 + 1)	
Lo KJ (1985)	Taiwan	1981–1983	1	All positive	T2: none C: none T1: none T2: none	T2: HBIG+HBVAc C: none T1: HBVAc T2: HBIG+HBVAc	T2: 35 C: 29 T1: 38 T2: 36	T2: 2 C: 26 T1: 9 T2: 4	2 (1 + 0 + 1)	
Farmer K (1987)	New Zealand	1983–1985	1	All positive	C: none T: none	C: HBVAc T: HBIG+HBVAc	C: 18 T: 21	C: 4 T: 3	2 (1 + 0 + 1)	
Theppisai U (1987)	Thailand	1984–1985	1	All positive	T1: none T2: none	T1: HBVAc T2: HBIG+HBVAc	T1: 18 T2: 27	T1: 2 T2: 0	1 (1 + 0 + 0)	
Poovorawan Y (1992)	Thailand	NR	1	All positive	C: none T: none	C: HBVAc T: HBIG+HBVAc	C: 59 T: 60	C: 2 T: 0	2 (1 + 0 + 1)	
Sehgal A (1992)	India	1987–1989	1	T1: 7/14 T2: 7/17	T1: none T2: none	T1: HBVAc T2: HBIG+HBVAc	T1: 21 T2: 24	T1: 2 T2: 2	2 (1 + 0 + 1)	
Assateerawatt A (1993)	Thailand	1988–1989	1	All positive	T1: none T2: none	T1: HBVAc T2: HBIG+HBVAc	T1: 26 T2: 23	T1: 3 T2: 1	3 (2 + 0 + 1)	
Xu ZY (1995)	China	1982–1989	1	NR	C: none T1: none T2: none	C: placebo T1: HBVAc T2: HBIG+HBVAc	C: 55 T1: 56 T2: 27	C: 19 T1: 10 T2: 1	4 (2 + 2 + 0)	
Zhu QR (2003)	China	1995–1999	1	C: 189/304 T: 169/318	C: none T: HBIG 200–400U (78.9m)	C: HBIG+HBVAc T: HBIG+HBVAc	C: 496 T: 491	C: 48 T: 19	2 (2 + 0 + 0)	
Yuan J (2006)	China	1999–2004	1	All positive	C: none T: HBIG 200–400U (78.9m)	C: HBIG+HBVAc T: HBIG+HBVAc	C: 133 T: 118	C: 17 T: 13	2 (1 + 0 + 1)	
Wang FY (2008)	China	2001–2006	1	C: 60/60 T: 79/80	C: none T: HBIG 200–400U (78.9m)	C: HBIG+HBVAc T: HBIG+HBVAc	C: 120 T: 159	C: 19 T: 7	2 (2 + 0 + 0)	
Xu WM (2009)	China	NR	7	C: 61/0 T: 88/1	C: placebo T: LAM 100mg/d from 32w of gestation to 1m after delivery	C: HBIG+HBVAc T: HBIG+HBVAc	C: 44 T: 40	C: 6 T: 3	5 (2 + 2 + 1)	
Zhang LJ (2009)	China	2007–2008	1	NR	C: none T: LdT 600mg/d from 28–32w of gestation to 1m after delivery	T1: HBIG+HBVAc T2: HBIG+HBVAc	C: 30 T: 31	C: 4 T: 0	1 (1 + 0 + 0)	
Pande C (2013)	India	2004–2009	1	19% positive	C: none T: none	C: Placebo+HBVAc T: HBIG+HBVAc	C: 116 T: 106	C: 6 T: 0	5 (2 + 2 + 1)	
Pan CQ (2016)	China	2012–2013	6	All positive	C: none T: TDF 300mg/d from 30–32w of gestation to 1m after delivery	C: HBIG+HBVAc T: HBIG+HBVAc	C: 88 T: 92	C: 6 T: 0	3 (2 + 0 + 1)	

Abbreviations: C, control; HBIG, hepatitis B immunoglobulin; HBVAc, HBV vaccine; Jadad score, consists of randomization (2 points) + blindness (2 points) + withdrawal (1 point); LAM, lamivudine; LdT, telbivudine; NR, not reported; RCT, randomized controlled trial; T, treatment; TDF, tenofovir disoproxil fumarate.

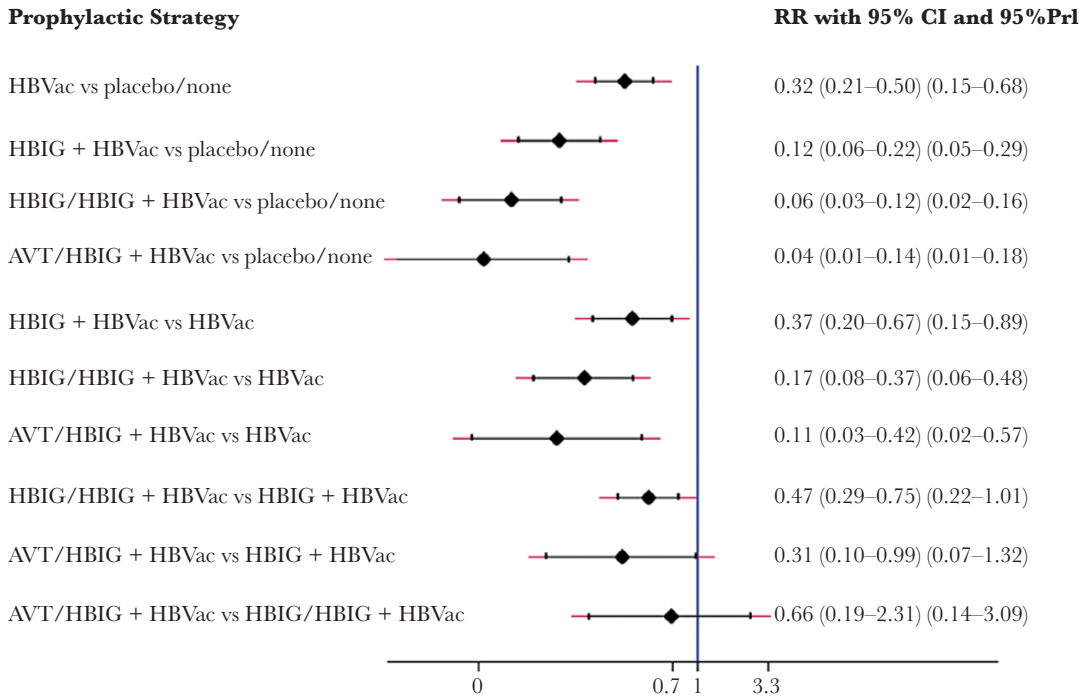


Figure 3. Predictive interval plot for the network of various prophylactic interventions for perinatal hepatitis B virus transmission. Abbreviations: AVT, antiviral therapy; HBIG, hepatitis B immunoglobulin; HBV_{ac}, hepatitis B vaccine.

effectiveness of available prophylaxis measures for the prevention of perinatal HBV transmission. Based on the analysis of the 15 currently available RCTs involving 2706 infants of HBV carrier

mothers, we made several key observations to estimate the relative efficacy of all prophylactic interventions to interrupt perinatal HBV transmission: (1) Hepatitis B vaccine alone significantly

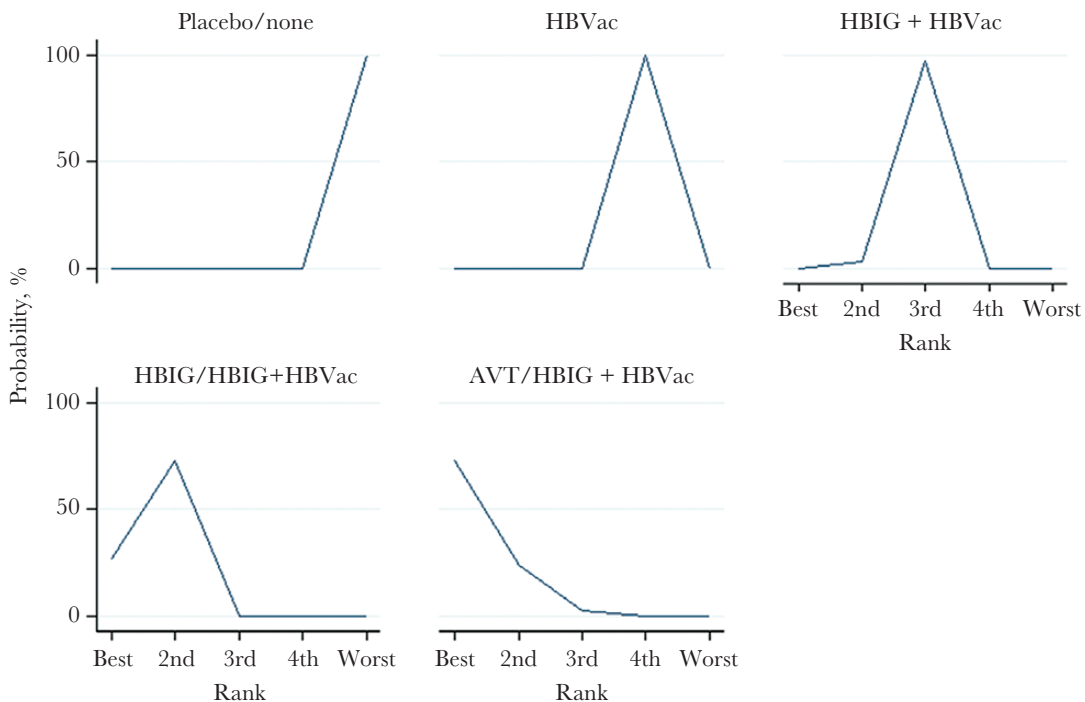


Figure 4. Rankograms for decreasing perinatal hepatitis B virus transmission risk and the surface under the cumulative ranking curve (SUCRA) for each prophylactic intervention. Abbreviations: AVT, antiviral therapy; HBIG, hepatitis B immunoglobulin; HBV_{ac}, hepatitis B vaccine.

Table 2. Pooled Summary Estimates of Evidence Derived From Direct or Indirect Meta-analysis Informing on Comparative Effectiveness of Prophylaxis Strategies for Reducing Perinatal Transmission of HBV

Prophylaxis Strategies	Direct Estimates			Indirect Estimates
	RR (95% CI)	Events, n/Total, N	I ² , %	RR (95% CI)
Compared with placebo/none				
HBVac	0.33 (0.23–0.48)	26/129 vs 70/118	22.7%	0.28 (0.11–0.70)
HBIG+HBVac	0.10 (0.05–0.22)	7/98 vs 70/118	0	0.13 (0.06–0.26)
HBIG/HBIG+HBVac	—			0.05 (0.02–0.13)
AVT/HBIG+HBVac	—			0.03 (0.01–0.13)
Compared with HBVac				
HBIG+HBVac	0.34 (0.19–0.60)	13/359 vs 45/387	0	0.32 (0.14–0.75)
HBIG/HBIG+HBVac	—			0.15 (0.05–0.42)
AVT/HBIG+HBVac	—			0.10 (0.02–0.42)
Compared with HBIG+HBVac				
HBIG/HBIG+HBVac	0.46 (0.32–0.65)	39/768 vs 84/749	59.9	—
AVT/HBIG+HBVac	0.24 (0.09–0.69)	3/163 vs 16/162	18.3	—
Compared with HBIG/HBIG+HBVac				
AVT/HBIG+HBVac	—			0.63 (0.16–2.48)

Abbreviations: AVT, antiviral therapy; CI, confidence interval; HBIG, hepatitis B immunoglobulin; HBVac, HBV vaccine; RR, relative risk.

decreased the risk of HBV infection among infants of HBV carrier mothers. (2) The combination of immunoglobulin with vaccine is superior to vaccine alone. (3) Maternal HBIG administration and antiviral therapy offer further advantages over passive-active immunoprophylaxis for highly viremic mothers.

Antibodies to HBsAg (Anti-HBs) are produced in response to exposure to HBV envelope protein HBsAg and confer protective immunity. Plasma-derived HBVac was first approved in 1981, while genetically engineered recombinant HBVac has been implemented since 1986 and is the current vaccine used worldwide [25]. Implementation of a universal HBVac program has proven successful in preventing infection and related complications. In our network meta-analysis, HBVac alone significantly reduced perinatal transmission risk by nearly 70%. However, in 2006, the reported proportion of newborn infants who received a birth dose of HBVac was only 27% globally, and it was 36% for the 87 countries with high endemicity of chronic HBV infection [26]. Efforts are still needed to improve global coverage of hepatitis B vaccination as well as the other strategies to prevent perinatal transmission for infants of HBV carrier mothers.

HBIG, prepared from the plasma of donors with high concentrations of anti-HBs, provides temporary protection (3–6 months) and is usually implemented as an adjunct to the hepatitis B vaccine for postexposure prophylaxis. While the response of neonates to the HBVac is satisfactory, it takes time to develop protective antibodies after vaccination. HBIG is offered to neonates of HBV carrier mothers in order to reduce the time window between exposure to infected mothers and production of anti-HBs induced by vaccine. Here, the combined preventive efficacy was 88%, compared with 68% for vaccine alone. It has been well accepted that HBIG should be given as soon as

possible after birth and that it does not need to be repeated if the infant is subsequently vaccinated.

The effect of maternal HBIG administration, in terms of prevention of HBV transmission to infants, has been evaluated in quite a few studies in China. Our study found that maternal HBIG administration in the third trimester could further reduce the transmission risk by half, compared with infantile passive-active immunoprophylaxis. This result is in accordance with the previous published meta-analyses [27–29]. Nevertheless, most of the data in previous studies were derived from nonrandomized studies, which were subject to significant biases, especially selection bias. In contrast, we excluded those studies that claimed “RCTs” but where the “randomization” was questioned [24]. Thus, all included studies had low risk of bias. The possible mechanism for maternal HBIG administration might be that it binds HBsAg and reduces HBV levels in pregnant women, or transports HBsAg across the placenta and facilitates humoral immunity [27]. More evidence is still needed to confirm these assumptions.

Maternal viral load, rather than HBeAg status, has been extensively documented as the most important risk factor for perinatal HBV transmission [30]. Increasing evidence has shown promising efficacy and safety profiles with the use of nucleoside/nucleotide analogues (NAs) in highly infectious mothers. Current evidence shows that maternal antiviral therapy (lamivudine, telbivudine, or tenofovir) further reduces the transmission risk by nearly 70%, compared with the infantile passive-active immunoprophylaxis. In non-head-to-head studies, tenofovir and telbivudine showed higher rates of HBV DNA suppression, alanine aminotransferase (ALT) normalization, and HBeAg seroconversion than lamivudine [31]. For concerns regarding fetal exposure to these drugs used in pregnancy, no

significant safety issues for maternal or fetal outcomes were identified in our meta-analysis of included studies. Moreover, data from the Antiretroviral Pregnancy Registry (available from <http://www.apregistry.com/InterimReport.aspx>) have suggested a favorable safety profile for antiviral therapy in pregnancy. Additionally, cessation of therapy 1–3 months after delivery is recommended in mothers without hepatic flares and without preexisting cirrhosis [32].

There are also concerns that the modes of delivery and feeding might influence the risk of perinatal HBV transmission [33, 34]. Until now, no randomized trials have yet been conducted for comparison of the elective cesarean section vs vaginal delivery, or breastfeeding vs bottle-feeding. Given the evidence from observational studies, both vaginal delivery and breastfeeding are considered safe and low risk for HBV transmission, especially when passive-active immunoprophylaxis is appropriately administered [35].

Admittedly, our study has several limitations. First, given the small number of included studies, small number of studies per comparison, and small number of subjects (<30 subjects per arm) in 5 of the 15 RCTs, small study effects could not be avoided. In terms of probabilistic analysis by relative ranking probabilities, the 2 best options for reducing perinatal transmission were AVT/HBIG+HBVAc and HBIG/HBIG+HBVAc. There is a high degree of uncertainty about which measure works better. Second, we could not carry out subgroup analyses according to HBeAg status of the mothers, vaccination schedules, types and doses of HB vaccine, doses of HBIG, or types of antiviral agents. As most trials only enrolled mothers positive for both HBsAg and HBeAg, the applicability of our findings to HBeAg-negative mothers is limited. The trials that did not report HBeAg status of mothers have not been excluded from the meta-analysis because this might have led to exclusion of some good quality trials. Recombinant vaccine and plasma-derived vaccine have shown no significant difference in decreasing perinatal transmission [36]. Lamivudine, telbivudine, and tenofovir have been used in the nonpregnant population as potent agents against HBV while only tenofovir has a favorable resistance profile. In the setting of short-term use during late pregnancy, resistance is rare. With only 1 RCT for each agent, we feel it acceptable to combine these trials as an antiviral therapy group. Third, HBIG was used to prevent HBV transmission in infants of HBV carrier mothers even before the availability of the HBVAc. Yet we did not include it as an independent measure because it has been replaced by the current passive-active immunoprophylaxis. Last, more long-term safety data and continued epidemiological surveillance of children born to HBV carrier mothers are needed.

Multiple steps are involved in preventing perinatal HBV transmission. It is our firm belief that the transmission is preventable in most situations. Ensuring strategies for prevention should be made a priority.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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