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SYSTEMATIC REVIEW

# Incidence of mother-to-child transmission of hepatitis B in relation to maternal peripartum antiviral prophylaxis: A systematic review and meta-analysis

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## Abstract

**Introduction:** Mother-to-child transmission (MTCT) of the hepatitis B virus (HBV) is a serious public health challenge. Estimating HBV MTCT incidence by region under different prophylaxis regimens is critical to understanding the regional disease burden and prioritizing interventions. This study aimed to calculate HBV MTCT incidence under different prophylaxis regimens globally and regionally and identify the HBV DNA threshold for maternal peripartum antiviral prophylaxis.

**Material and methods:** This review was registered in advance in PROSPERO (CRD 42019120567). We searched PubMed, Embase, China National Knowledge Infrastructure, ClinicalTrials.gov, and Cochrane Library databases for studies on MTCT in pregnant women with chronic HBV infection from their inception until June 13, 2022. MTCT was defined as hepatitis B surface antigen (HBsAg) or HBV DNA seropositivity in infants aged 6–12 months. We calculated the pooled HBV MTCT incidence using the DerSimonian-Laird random-effects model.

**Results:** Among 300 studies, 3402 of 63 293 infants had HBV due to MTCT. Without prophylaxis regimens, the pooled HBV MTCT incidence was 31.3%, ranging from 0.0% (95% confidence interval [CI] 0.0%–6.0%; European Region) to 46.1% (95% CI 29.7%–63.0%; Western Pacific Region). Following the introduction of the hepatitis B vaccine, the HBV MTCT incidence decreased from 82.9% to 15.9% in HBeAg-positive women and from 10.3% to 2.3% in HBeAg-negative women. Maternal peripartum antiviral treatment alongside infant immunoprophylaxis further decreased MTCT incidence to 0.3% (95% CI 0.1%–0.5%). Despite infant immunoprophylaxis, the incidences of MTCT at maternal HBV DNA levels of <2.30, 2.00–3.29, 3.00–4.29, 4.00–5.29, 5.00–6.29, 6.00–7.29 and ≥7.00 $\log_{10}$ IU/ml were 0.0% (95% CI 0.0%–0.0%), 0.0%

**Abbreviations:** HBeAg, hepatitis B E antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; MTCT, mother-to-child transmission.

Naijuan Yao and Shan Fu contributed equally to this study.

(95% CI 0.0%–0.0%), 0.0% (95% CI 0.0%–0.5%), 0.6% (95% CI 0.0%–2.6%), 1.0% (95% CI 0.0%–3.1%), 4.3% (95% CI 1.8%–7.5%), and 9.6% (95% CI 7.0%–12.5%), respectively. **Conclusions:** HBV MTCT incidence varies across regions. The Western Pacific Region bears the heaviest burden. Peripartum antiviral prophylaxis plus infant immunoprophylaxis is promising for interrupting HBV MTCT. Regarding the HBV DNA threshold for peripartum antiviral prophylaxis, maternal HBV DNA of 4.00 $\log_{10}$ IU/ml or greater seems justified.

**KEYWORDS**
hepatitis B virus, hepatitis B virus DNA threshold, incidence, infant immunoprophylaxis, meta-analysis, mother-to-child transmission, peripartum antiviral treatment, systematic review

## 1 | INTRODUCTION

Hepatitis B virus (HBV) infection remains a serious public health issue, affecting an estimated 296 million persons worldwide in 2019 and causing 820000 deaths annually resulting from complications of chronic HBV infection.[1] With an assumed proportion of 25.3%, approximately 75 million women of reproductive age are chronically infected by HBV,[2] serving as a huge reservoir for mother-to-child transmission (MTCT) of HBV. HBV infections in infancy are chiefly attributed to MTCT, with a 95% risk of evolving into chronic HBV infection later in life and a 40% life-long risk of progressing to cirrhosis and hepatocellular carcinoma.[1,3] In the absence of interventions, the high proportions of HBV MTCT and chronicity create a vicious circle of HBV infections.

The regional estimation of HBV MTCT incidence is critical to understanding the regional disease burden and prioritizing interventions. Concerning HBV MTCT incidence in the absence of prophylaxis, a systematic review (in 2016) in sub-Saharan Africa reported a lower HBV MTCT incidence than in individual Asian studies.[4] However, whether this fits after systematic evaluation by region remains unclear. Regarding prophylaxis for HBV MTCT, the efficacy of at least three doses of the hepatitis B vaccine and birth doses of hepatitis B immunoglobulin (HBIG), targeted to enhance infant resistance, has been proven.[5] However, infant immunoprophylaxis is insufficient for pregnant women with a high viral load.[6] By reducing maternal HBV DNA to a safe level, peripartum antiviral prophylaxis further reduces HBV MTCT risk with a good safety profile.[7–9] Previous systematic reviews have compared the benefits of prophylaxis regimens using odds ratios; however, the extent of HBV MTCT risk reduction by each prophylaxis regimen remains uncertain.

HBV DNA thresholds for peripartum antiviral therapy vary from 5.3 to 7.0 $\log_{10}$ IU/ml. However, current major guidelines have recommended that pregnant women with high viral load receive antiviral prophylaxis supplemented with infant immunoprophylaxis.[10–12] We identified a systematic review assessing the relation between maternal viral load and MTCT risk.[13] However, an important limitation of this study was including original studies with inappropriate diagnostic criteria for MTCT. Moreover, the estimate of HBV MTCT incidence by hepatitis B E antigen (HBeAg) status is warranted, as HBeAg helps to identify high-risk pregnant women in quantitative HBV DNA-limited settings.

**Key message**

The hepatitis B virus mother-to-child transmission incidence under different prophylaxis regimens differs by region. Peripartum antiviral therapy plus infant immunoprophylaxis is a promising strategy to block mother-to-child transmission. Maternal hepatitis B virus DNA of ≥4.00 $\log_{10}$ IU/ml is a reasonable threshold for peripartum antiviral therapy.

This systematic review and meta-analysis set out to achieve the following objectives: first, to assess the effectiveness of different preventive measures by pooling the MTCT incidence of HBV; second, to estimate the HBV MTCT risk under different prophylaxis regimens in HBeAg-positive and HBeAg-negative mothers; third, to calculate MTCT incidence across regions and to assess the response to different prophylaxis regimens by region; and fourth, to identify the threshold viral load for antiviral prophylaxis initiation by grouping maternal HBV DNA levels in a narrow range. The goal of this systematic review is to help physicians to optimize prophylaxis regimens and determine the priority of MTCT prevention for policy-makers.

## 2 | MATERIAL AND METHODS

This meta-analysis was registered in advance in PROSPERO (CRD 42019120567) and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Two investigators independently performed the literature search, study selection, information extraction, and quality assessment. Discrepancies were resolved by consulting with the third investigator.

## 2.1 | Data sources and search strategy

We searched PubMed, Embase, China National Knowledge Infrastructure, ClinicalTrials.gov, and the Cochrane Library from inception until June 13, 2022. The search strategy included Medical Subject Headings and free texts, using the following search terms and their variations: hepatitis B, mother, infant, and vertical transmission (Table S1). In addition, we manually searched for additional relevant studies.

## 2.2 | Main outcomes measures

This included HBV MTCT incidence.

## 2.3 | Eligibility criteria

We identified interventional, cohort, nested case–control, and cross-sectional studies, or original data regarding the MTCT incidence of pregnant women with chronic HBV infection (hepatitis B surface antigen [HBsAg] positive ≥6 months). MTCT was defined as the detection of HBsAg or HBV DNA in the infant at 6–12 months of age. We chose the one with more subgroup data and/or the larger sample size if there were duplicates. We excluded studies in which prophylaxis measures against MTCT were unclear, outcomes were insufficient to extract, the study sample size was less than 30, and patients were co-infected with HIV and other viruses to enhance the homogeneity of this study.

## 2.4 | Data extraction

We extracted the data using a standardized data extraction form. Table S2 summarizes the detailed data extracted. Regarding prophylaxis regimens, we had the following four groups based on the particular prophylaxis taken by the mother and infant: neither mother nor infant received any preventive measures (no prophylaxis group); mother took no interventions, and the infant received hepatitis B vaccine (hepatitis B vaccine group) or co-injected HBIG (combined immunoprophylaxis group); mother undertook peripartum antiviral therapy plus infant combined immunoprophylaxis (antiviral therapy plus combined immunoprophylaxis group). Regarding HBV MTCT events, we adopted the first result with multiple outcomes between 6 and 12 months. Concerning maternal information on HBV DNA levels, the data obtained during pregnancy were applicable for mothers without antiviral prophylaxis; however, the one before delivery was employed among women with antiviral therapy during pregnancy. Moreover, we contacted the corresponding authors for additional information if necessary.

## 2.5 | Study quality assessment

We employed The Newcastle–Ottawa Scale (Table S3) to assess the bias risk of observational studies, where three aspects were evaluated, ie selection of study groups (0–4 stars), comparability (0–2 stars), and outcome ascertainment (0–3 stars). We categorized studies as follows: a score of less than or equal to 4 indicated a high risk of bias, and moderate and low risks were indicated by scores of 5–6 and more than or equal to 7, respectively. Then, we used the Cochrane Risk of Bias Assessment tool for interventional studies. We made overall risk-of-bias judgments primarily based on two domains: random sequence generation (selection bias) and incomplete outcome data (attrition bias). Studies were at low risk of bias when both domains were low risk, at high risk of bias when either domain was high risk, and at moderate risk of bias in the remaining cases.

## 2.6 | Data analysis

We calculated MTCT incidences using the DerSimonian–Laird random-effects model and adopted the score confidence interval. To avoid deleting studies with zero events, we stabilized the available data using the Freeman–Tukey double arcsine transformation. We assessed the heterogeneity of included studies using the Cochran's Q statistic and the inconsistency ($I^2$) statistic ($p < 0.05$ or $I^2 > 50\%$). In testing for publication bias, 0.5 was applied to zero cells, and one was added to the study sample size. Regarding MTCT incidence stratified by maternal HBV DNA levels, HBV DNA values in copies per ml unit were converted to IU/ml by dividing them by 5.[14] All analyses were performed using the "metaprop" command with STATA version 13 (StataCorp).

# 3 | RESULTS

Our systematic search identified 11 722 records published between 1983 and 2022. After excluding duplicates and screening based on title and abstract, 1930 records were retrieved for full-text assessment, and 300 of them were finally included (Figure 1), covering 22 countries/regions. The main characteristics of the included studies are summarized in Tables S4 and S5. Subsequently, 258 studies were assessed for methodological quality (Table S6), of which 60/102 observational studies and 7/156 interventional studies had a low risk of bias; most were at moderate risk (37/102 for observation studies and 79/156 for interventional studies).

## 3.1 | MTCT incidence of HBV under different prophylaxis regimens

The included 300 studies comprised 425 data sets, where 3402 of 63 293 infants were diagnosed with chronic HBV infection owing to MTCT. The overall MTCT incidence of HBV was 31.3% (95% confidence interval [CI] 15.8%–49.3%) for the no prophylaxis group, 11.2% (95% CI 8.9%–13.6%) for the hepatitis B vaccine group, 8.1% (95% CI 7.2%–9.0%) for the combined immunoprophylaxis group, and 0.3% (95% CI 0.1%–0.5%) for the antiviral therapy plus combined

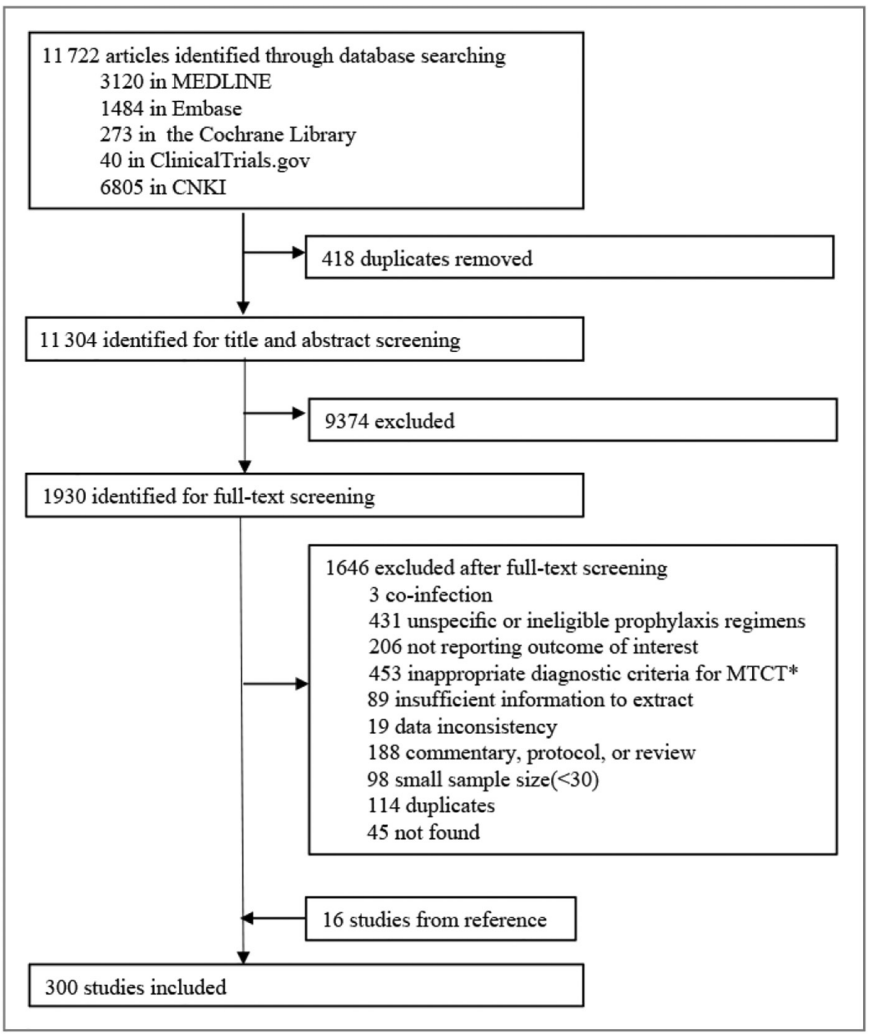


**FIGURE 1** Flow diagram of study selection. *Mother-to-child transmission (MTCT) was assessed by finger/heel prick blood or when the infant was <6 months or >12 months of age

immunoprophylaxis group (Figure 2; Figure S1). Significant heterogeneity existed in MTCT incidence analysis except for the antiviral therapy plus combined immunoprophylaxis group. Funnel plots revealed publication bias in the no prophylaxis group (Figure S2).

### 3.2 | MTCT incidence of HBV under different prophylaxis regimens by maternal HBeAg status

Among 300 studies, 173 reported maternal HBeAg status. MTCT incidence decreased consistently over prophylaxis regimens regardless of HBeAg status (Figure 2; Figure S3). Upon comparing HBeAg-positive and HBeAg-negative mothers, MTCT estimates were 82.9% (95% CI 74.9%–89.7%) vs. 10.3% (95% CI 0.5%–28.2%) for the no prophylaxis group, 15.9% (95% CI 12.1%–20.0%) vs. 2.3% (95% CI 0.1%–6.2%) for the hepatitis B vaccine group, and 9.6% (95% CI 8.4%–10.9%) vs. 0.5% (95% CI 0.1%–1.0%) for the combined immunoprophylaxis group ($p < 0.001$). When peripartum antiviral prophylaxis was introduced, the MTCT estimate did not significantly differ between HBeAg-positive and HBeAg-negative mothers (0.3% vs. 0.0%, $p = 0.938$).

### 3.3 | Regional MTCT incidence of HBV under different prophylaxis regimens

Regional MTCT incidences of HBV were then summarized (Figure 3; Table S7). Without prophylaxis regimens, the lowest MTCT incidence occurred in the European Region (0.0%; 95% CI 0.0%–6.0%), with an increased MTCT incidence of HBV in South-East Asia (15.3%; 95% CI 9.3%–22.3%) and the African region (13.7%; 95% CI 6.8%–25.7%), respectively, and the highest one in the Western Pacific Region (46.1%; 95% CI 29.7%–63.0%). When hepatitis B vaccine and combined immunoprophylaxis were implemented independently, MTCT incidence decreased remarkably to 4.3% (95% CI 1.1%–9.0%) and 1.0% (95% CI 0.1%–2.6%), respectively, in the South-East Asia Region, as well 12.7% (95% CI 10.3%–15.2%) and 8.8% (95% CI 7.8%–9.8%) in the Western Pacific Region. When antiviral prophylaxis was introduced to pregnant women, the pooled MTCT rate was close to 0% in most countries and regions, except for Turkey (1.7%; 95% CI 0.3%–8.9%). However, the MTCT incidence in the European Region has remained consistently around zero. Notably, we identified no studies available for analysis in the African Region on MTCT incidence in the presence of prophylaxis.

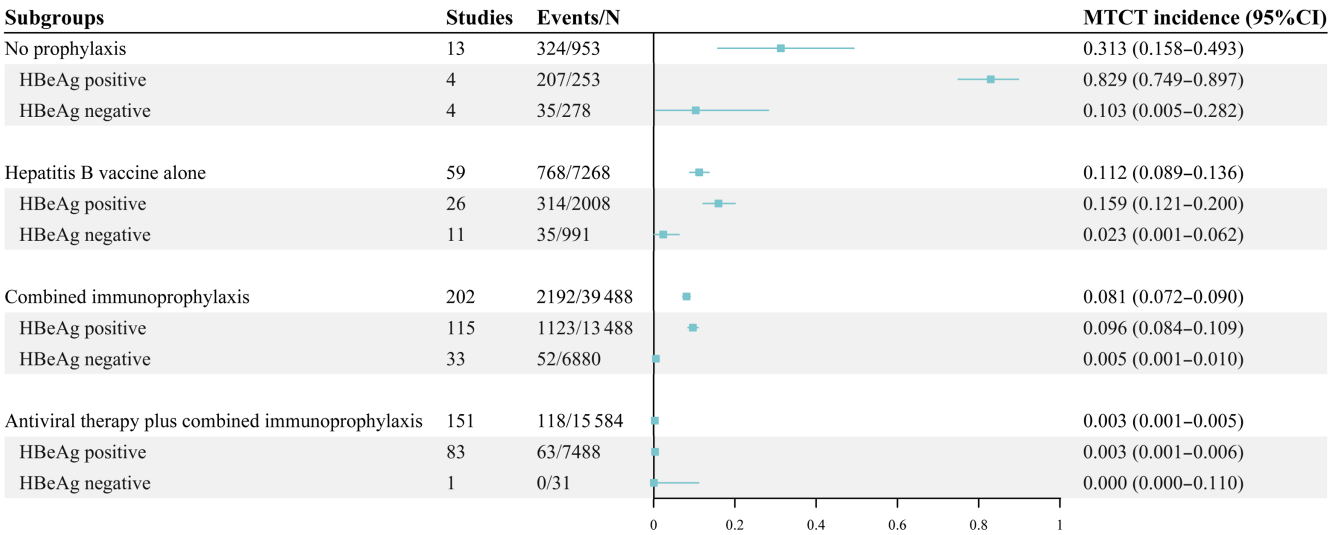


**FIGURE 2** Forest plot of mother-to-child transmission incidence of hepatitis B virus under different prophylaxis regimens

### 3.4 | MTCT incidence of HBV stratified by maternal viral load before delivery

For this analysis, we only included studies presenting prenatal HBV DNA within a narrow viral load increment (eg 2.00–2.99, 3.00–3.99, or 4.00–4.99 $\log_{10}$ IU/ml or $\log_{10}$ copies/ml, etc.). Finally, 22 studies (20 from China, one from Australia, and one from Israel; 268 infections from 6526 individuals) were available for stratified analysis, with HBV DNA units of IU/ml in 14 studies and copies/ml in eight studies. All the infants received the hepatitis B vaccine (three or more doses) with HBIG. After dividing copies/ml by 5 to unify as IU/ml, we first combined all 22 studies. Aggregate analysis revealed that the pooled MTCT incidence strongly correlated with maternal HBV DNA levels (Figure 4). Particularly, the estimated incidence was 0.0% when maternal viral load was less than 4.29 $\log_{10}$ IU/ml. They slightly increased to 0.6% (95% CI 0.0%–2.6%) and 1.0% (95% CI 0.0%–3.1%) for infants where HBV DNA levels of their mothers were 4.00–5.29 and 5.00–6.29 $\log_{10}$ IU/ml, respectively. Approximately four times higher risk, 4.3% (95% CI 1.8%–7.5%), occurred at a maternal HBV DNA of 6.00–7.29 $\log_{10}$ IU/ml. In the worst case, the MTCT incidence increased to 9.6% (95% CI 7.0%–12.5%) when the HBV DNA levels were more than 7.00 $\log_{10}$ IU/ml for pregnant women. Subsequently, separated analysis according to original HBV DNA units (IU/ml or copies/ml) displayed a similar tendency and threshold for immunoprophylaxis failure (Figures S4 and S5).

## 4 | DISCUSSION

This systematic review, including 300 studies with 63 293 individuals, provided four major findings relevant to clinical practice or policy decisions. First, each prophylaxis regimen effectively reduced HBV MTCT incidence. Second, infants born to HBeAg-negative mothers remained at a small but not negligible risk of MTCT after vaccination. Third, the MTCT risk of HBV and the response to preventive measures varied by region. Fourth, despite infant immunoprophylaxis, HBV MTCT appeared at a maternal viral load of 4.00 $\log_{10}$ IU/ml, and the incidence markedly increased to a maternal viral load of 6.00 $\log_{10}$ IU/ml.

Vaccination caused the largest reduction in the MTCT incidence of HBV. Cochrane review, by analyzing four trials, reported that the HBV vaccine significantly reduced HBV MTCT risk (relative risk 0.28; 95% CI 0.20–0.40).[5] In this meta-analysis, we quantified the effect of the HBV vaccine by estimating HBV MTCT incidence. Regarding the reduction of HBV MTCT incidence from 82.9% to 15.9% for HBeAg-positive mothers and from 10.3% to 2.3% for HBeAg-negative mothers, we convincingly demonstrated that vaccination for infants is a huge success. The prevalence of HBsAg infections for children under 5 years of age (an indicator of new chronic HBV) has dropped from 4.7% in the pre-vaccine era to 1.3%.[2] However, given that the global coverage of the hepatitis B birth dose vaccine was 42% in 2021,[15] more effort is required to improve vaccine coverage.

The positive relation between maternal HBeAg status and MTCT incidence has long been recognized; therefore, an HBeAg test is recommended to identify high-risk pregnant women when HBV DNA quantification is inaccessible.[16] As expected, we observed a higher MTCT incidence in HBeAg-positive mothers. A previous study reported an almost zero risk of HBV MTCT in vaccinated infants from HBeAg-negative mothers.[17] However, when the study included more extensive sample sizes and adopted more reliable diagnostic criteria, HBV MTCT incidence in infants with vaccination from HBeAg-negative mothers was 2.3% (95% CI 0.1%–6.2%), which was small but not negligible.

Peripartum antiviral prophylaxis combined with infant immunoprophylaxis had the potential to block HBV MTCT completely, with a pooled HBV MTCT incidence of approximately zero. Several reports have proved that maternal peripartum antiviral prophylaxis effectively prevents HBV MTCT with a good safety profile.[7–9] Compared with calculating odds ratios between the treated group

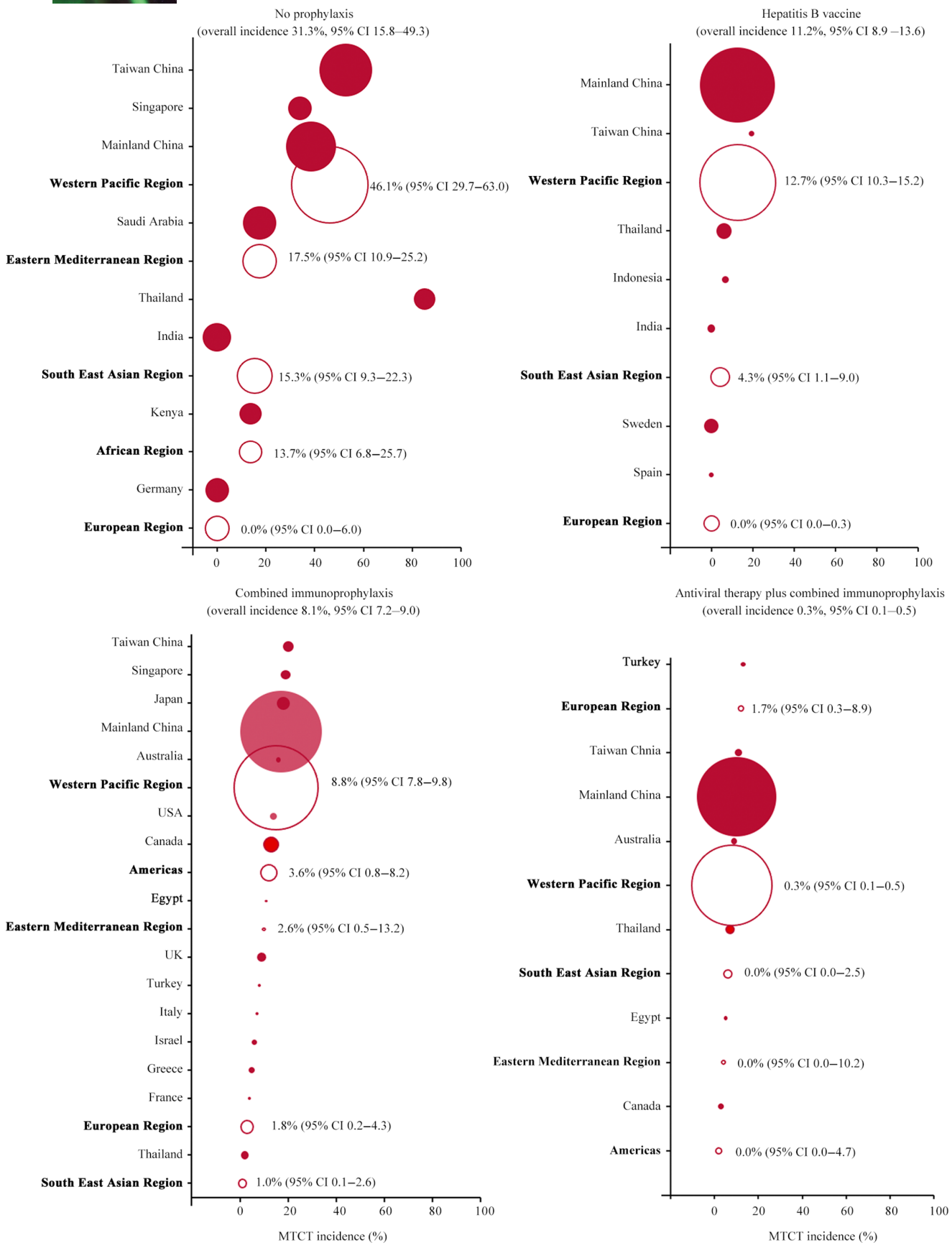


FIGURE 3 Mother-to-child transmission incidence of hepatitis B virus under different prophylaxis regimens by region. MTCT, mother-to-child transmission. Filled and unfilled circle sizes are proportional to the number of assessed infants. Ten studies were analyzed by study region, but the study population was not entirely derived from the study region

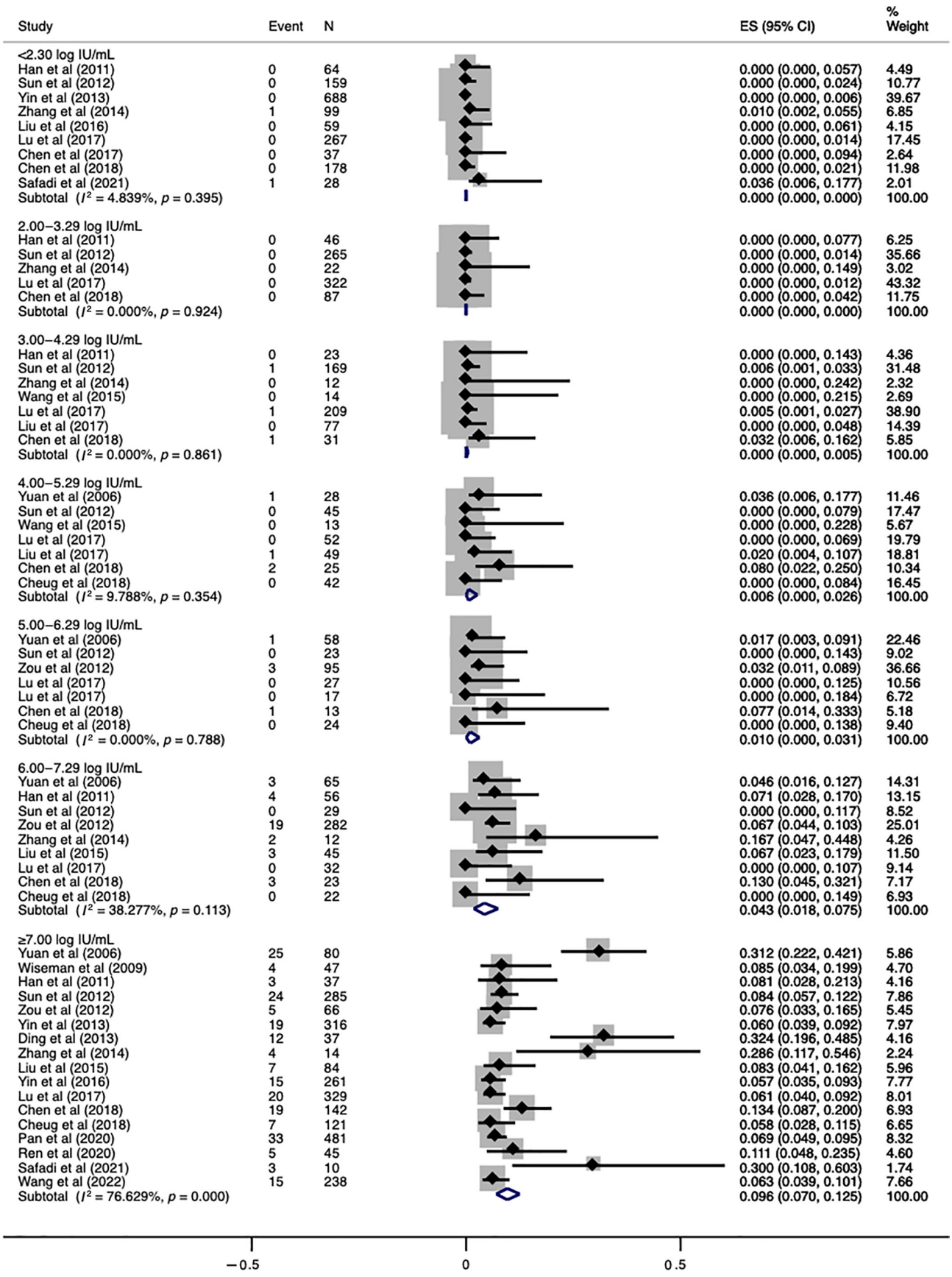


**FIGURE 4** Mother-to-child transmission incidence of hepatitis B virus according to maternal viral load before delivery. HBV DNA values in the unit of copies per ml were converted to IU/ml by dividing by 5. All infants received at least three doses of hepatitis B vaccine and birth doses of hepatitis B immunoglobulin

and the control groups in previous systematic reviews, our systematic review supported the high efficacy of antiviral prophylaxis by a pooling HBV MTCT incidence of 0.3%. Notably, HBV MTCT occurred in 57 original studies despite employing maternal antiviral prophylaxis and neonatal combined immunoprophylaxis. Possible causes mentioned in the original studies were the irregular administration of antivirals or amniocentesis. As an invasive procedure, amniocentesis may theoretically increase the risk of MTCT by transmitting maternal blood. This hypothesis has been proven by published literature and is more pronounced in pregnant women with high viral load.[18,19] Other obstetric factors with similar mechanisms, such as forceps delivery, did not affect HBV MTCT.[19] Detailed reporting on HBV MTCT cases is encouraged, and further investigations of risk factors for antiviral prophylaxis failure are required to eliminate HBV MTCT.

We observed that HBV MTCT incidence varied considerably across regions and countries. The European Region had virtually no HBV MTCT risk, whereas the Western Pacific Region was the most affected, consistent with the HBV epidemic.[2] However, the African Region presented a lower HBV MTCT incidence than the Western Pacific Region, despite a similarly high HBsAg prevalence in both regions.[20] This finding was also reported in a systematic review on HBV MTCT risk in sub-Saharan Africa, with a reported MTCT risk of 38.3% for HBeAg-positive women and 4.8% for HBeAg-negative women in the absence of prophylaxis regimens.[4] Horizontal transmission during childhood rather than MTCT may dominate most chronic HBV infections in the African Region.[21]

Responses to HBV MTCT preventive measures differed by region, and vaccines were effective in all regions where data were available. Peripartum antiviral treatment further blocked HBV MTCT in areas where MTCT was the predominant mode of HBV transmission. However, in HBV non-endemic areas, the changes in HBV MTCT incidence were less prominent across prophylaxis regimens because of the extremely low HBV MTCT risk in the absence of prophylaxis. Regional differences in HBV genotypes may account for the differences in MTCT risk and responsiveness to prophylaxis regimens.[22] The above findings suggest that the focus of MTCT prophylaxis differs across regions. Regarding the Western Pacific region and the African Region, accounting for 68% of the HBV infections,[2] peripartum antiviral therapy for high-risk mothers and vaccines for infants are important for the Western Pacific Region. Furthermore, countries in the Western Pacific Region have devoted considerable efforts to expanding hepatitis B vaccine coverage. China achieved 99% coverage of the three-dose hepatitis B vaccine in 2009.[15] Identifying pregnant women at high risk of MTCT and treating them will be the next critical step. Unfortunately, we could not analyze MTCT incidence with prophylaxis in the African Region. A possible explanation is that we strictly excluded studies with small sample sizes and patients with HIV co-infection.[4] However, we could speculate that expanding vaccine coverage is a priority for future efforts in the African Region as the three-dose and birth dose of HBV vaccine coverage were as low as 71% and 17% in 2021, respectively.[15]

The HBV DNA threshold for maternal peripartum antiviral prophylaxis is a major issue for HBV MTCT prevention. In this study, HBV MTCT incidence was 1.0% at a maternal viral load of 5.00–6.29 $\log_{10}$ IU/ml and increased sharply at a maternal viral load of 6.00 $\log_{10}$ IU/ml, similar to previous reviews that identified 5.30 $\log_{10}$ IU/ml as a cut-off HBV DNA level.[13,16] However, differing from a zero risk,[16] an MTCT incidence of 0.6% (95% CI 0.0%–2.6%) was observed at maternal viral loads of 4.00–5.29 $\log_{10}$ IU/ml. This discrepancy could be attributed to excluding studies with peripartum antiviral prophylaxis in the previous review, resulting in a different MTCT incidence estimate in three studies.[23–25] Nevertheless, using the same diagnostic criteria for MTCT, both revealed a lower MTCT incidence than the 2.754% at a maternal viral load below 6.0 $\log_{10}$ copies/ml (5.3 $\log_{10}$ IU/ml) in another review, which included original studies with a wide definition for MTCT.[13] Our findings support the clinical practice guidelines' threshold HBV DNA levels for peripartum antiviral treatment (6.0–7.0 $\log_{10}$ IU/ml[10] or 5.3 $\log_{10}$ IU/ml[11,12]) and highlight the plausibility of antiviral treatment in individuals with HBV DNA of 4.00 $\log_{10}$ IU/ml or greater. In addition, our earlier observations revealed that the threshold HBV DNA levels for MTCT incidence differed between HBeAg-positive and HBeAg-negative mothers.[26] Unfortunately, we could not assess the MTCT incidence stratified by HBV DNA levels in combination with HBeAg status in this study because only a few data sets were presented in the original studies, which is an important issue for future studies.

This study had several limitations. First, there was significant heterogeneity in the analysis of HBV MTCT incidence under different prophylaxis regimens because of differences in the study region, detection method for HBV markers, and the proportion of pregnant women at high risk for MTCT. Therefore, we advocate for more detailed reporting of this information in the original studies in the future. Second, only the quality of four main types of studies was assessed, and no sensitivity analyses were conducted based on the risk of bias. Third, in the regional analysis, some studies included non-native races. However, the conclusions would likely not change, given that HBV MTCT incidence remained low in regions including races from endemic areas, such as the Americas. In addition, these findings should be interpreted cautiously given the few countries included in the regional analysis, ranging from one to six. Finally, in the analysis to identify the threshold for peripartum antiviral therapy, caution should be taken in generalizing the findings to all patients, as most of the studies included were from China. Nonetheless, this review provided an overview of HBV MTCT from the perspective of MTCT incidence.

## 5 | CONCLUSION

This study provide the following implications from the HBV MTCT incidence perspective: it reaffirms that the HBV vaccine is a fundamental and critical step for preventing HBV MTCT; it calls attention to HBeAg-negative pregnant women; it suggests that peripartum

antiviral treatment plus neonatal combined immunoprophylaxis is a promising way to block HBV MTCT; it demonstrates that HBV MTCT risk and the priority of different prophylaxis regimens vary by region; and lastly, it highlights that although HBV DNA of 5.30 $\log_{10}$ IU/ml or more appears to be the optimal HBV DNA threshold for peripartum antiviral prophylaxis, it is also reasonable to treat pregnant women with HBV DNA of 4.00 $\log_{10}$ IU/ml or greater. Future efforts to develop individualized preventive strategies considering the local socio-economic situation, the prevalence of HBsAg, patient willingness, and the availability of prophylaxis regimens are highly encouraged.

## AUTHOR CONTRIBUTIONS

TYC is the guarantor of the article. NJY and SF contributed to study design, study identification, data collection and extraction, quality assessment, data analysis and interpretation, and manuscript drafting and revision. YCW and ZT contributed to study design, study identification, data analysis and interpretation, and critical revision of the manuscript. YLF and JL contributed to data collection, quality assessment, and manuscript revision. XFL and YY contributed to study design, search term design, and critical review of the manuscript. FPJ, YLC, and FJL contributed to study design, data analysis and interpretation, and manuscript revision. YRZ and TYC contributed to study concept, study design, data analysis, interpretation of data, manuscript drafting and revision, quality control of algorithms, and study supervision.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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