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Title

Accuracy of hepatitis B e antigen (HBeAg) to identify pregnant women at risk of transmitting hepatitis B virus to their neonates: a systematic review and meta-analysis

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Abstract

Background

Prevention of mother-to-child transmission (MTCT) of hepatitis B virus (HBV) involves neonatal immunoprophylaxis, using birth dose of hepatitis B vaccine and immune globulin, and provision of peripartum antiviral prophylaxis in highly viremic women. However, access to assays to quantify HBV DNA levels remains severely limited in resource-poor settings. This systematic review, commissioned by the WHO, evaluated the HBV DNA threshold for MTCT and the sensitivity and specificity of maternal hepatitis B e antigen (HBeAg) for identifying pregnant women with HBV DNA levels above this threshold and for predicting MTCT.

Methods

Four English-language (PubMed/EMBASE/Scopus/CENTRAL) and two Chinese-language databases (CNKI/Wanfang) were searched for studies of HBV-infected pregnant women without concurrent antiviral therapy, published by Apr 3, 2019. This study was registered at PROSPERO (CRD42019138227).

Findings

Of 9007 articles identified, 67 articles (66 studies) met inclusion criteria. The risk of MTCT despite infant immunoprophylaxis was negligible (0.04%, 95% CI: 0.00-0.11) below a maternal HBV DNA level of 200,000 IU/mL, and increased above this threshold. The pooled sensitivity and specificity of HBeAg testing were 88.2% (83.9-91.5) and 92.6% (90.0-94.5), respectively, to identify HBV DNA levels \geq 200,000 IU/mL in pregnant women, and 99.5% (91.7-100) and 62.2% (55.2-68.7), respectively, to predict the MTCT despite infant immunoprophylaxis.

Interpretation

A maternal HBV DNA level $\geq 200,000$ IU/mL appears to be the optimal threshold for MTCT. HBeAg is accurate for identifying women with HBV DNA levels above this threshold and has high sensitivity for predicting cases of immunoprophylaxis failure. In areas where HBV DNA assays are unavailable, HBeAg can be used as an alternative to assess eligibility for antiviral prophylaxis.

Funding

WHO

RESEARCH IN CONTEXT

Evidence before this study

Preventing mother-to-child transmission (MTCT) of hepatitis B virus (HBV) is key to the global elimination of HBV infection as a public health threat by 2030. There is accumulating evidence for the efficacy of peripartum antiviral prophylaxis in pregnant women with high viral load, in addition to infant immunoprophylaxis using hepatitis B vaccine birth dose (HepB-BD) and immune globulin (HBIG) (see companion systematic review). However, there is no consensus on the optimal HBV DNA threshold at which pregnant women should receive antivirals for preventing MTCT. Moreover, access to assays to quantify HBV DNA levels is highly limited in some low- and middle-income countries; in such settings, hepatitis B e antigen (HBeAg) might be an attractive alternative to select women for antiviral prophylaxis. We therefore searched PubMed for systematic reviews of studies assessing the performance of HBV markers (HBV DNA, HBeAg) to identify pregnant women at risk of MTCT, published up to 3rd Apr, 2019, using the following terms: “systematic review” AND “hepatitis B” AND “mother-to-child transmission”. We identified one systematic review (Chen HL et al., 2018) that showed a linear association between maternal viral load and the risk of MTCT. However, this systematic review had limitations; it included only HBeAg-positive mothers, and pooled estimates from studies that were highly heterogeneous in terms of HBV preventive measures utilized and MTCT definitions. We did not identify any study evaluating the accuracy of HBeAg testing for detecting high viral load or predicting immunoprophylaxis failure.

Added value of this study

To our knowledge, our systematic review is the first to identify an HBV DNA threshold below which MTCT is rare, and to assess the performance of an HBeAg test to diagnose high

HBV DNA levels in pregnant women and to predict the risk of MTCT. We found that the risk of passive-active immunoprophylaxis failure despite timely administration of HepB-BD and HBIG started increasing at viral loads of $\geq 200,000$ IU/mL in untreated pregnant women. The sensitivity and specificity of a maternal HBeAg testing during pregnancy were 88.2% (95% CI: 83.9-91.5) and 92.6% (90.0-94.5) to diagnose this viral load threshold, and 99.5% (91.7-100) and 62.2 % (55.3-68.7) to predict passive-active immunoprophylaxis failure.

Implications of all the available evidence

Our meta-analyses indicate that HBV-infected women with viral loads of $\geq 200,000$ IU/mL will have infants at an increased risk of passive-active immunoprophylaxis failure, and could benefit from maternal peripartum antiviral therapy to reduce the residual risk. In areas with limited access to assays for HBV DNA quantification in pregnancy, HBeAg serology appears to have sufficient diagnostic accuracy to be considered as an alternative to identify high-risk pregnant women with HBV DNA $\geq 200,000$ IU/mL (high strength of evidence), and to predict infant immunoprophylaxis failure despite HepB-BD and HBIG (high strength of evidence). Findings from our review informed WHO recommendations on the use of peripartum anti-HBV prophylaxis and could help member states to develop evidence-based national policies to accelerate elimination of HBV MTCT.

Introduction

Hepatitis B virus (HBV) infection is a major global health issue. Worldwide, 257 million people have chronic HBV infection (CHB), of whom >95% live in low- and middle-income countries (LMICs).^{1,2} An estimated 900,000 CHB-related deaths occur annually due to cirrhosis or hepatocellular carcinoma (HCC).² In 2016, the World Health Organization (WHO) adopted a global strategy to eliminate HBV infection as a public health threat by 2030, aiming to reduce incidence by 90% and mortality by 65%.³

In order to achieve this goal, preventing mother-to-child transmission (MTCT) is crucial.^{4,5} The risks of developing CHB and subsequent liver diseases are higher when infection occurs perinatally through MTCT rather than later in life through horizontal transmission.^{6,7} Since 2009, the WHO recommends that all infants receive their first dose of hepatitis B vaccine immediately after birth, preferably within 24 hours, to prevent MTCT.⁸ However, the birth dose of hepatitis B vaccine (HepB-BD), even with timely administration and combined hepatitis B immune globulin (HBIG), does not prevent all MTCT, particularly in mothers with high viremia.⁹ The risk of immunoprophylaxis failure is correlated with higher maternal HBV DNA levels, and can be decreased by reducing the viral load through antiviral prophylaxis during the third trimester, as reported in our companion systematic review (*Funk AL et al.*).^{10,11} Consequently, prenatal screening for hepatitis B surface antigen (HBsAg), followed by HBV DNA quantification to assess eligibility for antiviral prophylaxis, is now recommended by the WHO in addition to at least three doses of hepatitis B vaccine, including HepB-BD.¹²

Access to assays to quantify HBV DNA levels, however, is seriously limited in most LMICs, representing a significant impediment to widespread implementation of this new

recommendation in such settings.¹³ Real-time polymerase chain reaction (PCR), a standard nucleic acid test (NAT) to quantify serum HBV DNA levels, is expensive (US\$ 20-130/assay) and requires sophisticated laboratories with highly trained staff.¹⁴ Alternatively, the use of hepatitis B e antigen (HBeAg), a classical serological marker for high HBV replication, may largely overcome these limitations. Rapid diagnostic tests (RDTs) and laboratory-based immunoassays to detect HBeAg are often more available and affordable (US\$ 0.5-20/assay) than PCR testing in LMICs.

This systematic review, commissioned by the WHO to inform guidelines on maternal peripartum antiviral prophylaxis, was designed to achieve the following three objectives: Q1) identify the viral load threshold in HBV-infected pregnant women from which the risk of immunoprophylaxis failure increases, indicating that additional peripartum antiviral prophylaxis should be considered; Q2) examine the accuracy of an HBeAg test during pregnancy to diagnose the viral load threshold defined by Q1; and Q3) assess the performance of an HBeAg test during pregnancy to predict infant immunoprophylaxis failure.

Methods

Search strategy and selection criteria

We followed a protocol pre-registered in PROSPERO (CRD42019138227), and reported according to the PRISMA guidelines.¹⁵ We systematically searched four English-language (PubMed/EMBASE/Scopus/CENTRAL) and two Chinese-language databases (CNKI/Wanfang). We manually searched references of included studies and sought suggestions from experts to supplement the databases searches. We considered original articles and conference proceedings of any study design published in any language between 1st January 2000 and 3rd April 2019.

We used the following search terms and their variations: HBV, viral load, and pregnancy (see Appendix 1 for the full strategy). We defined specific eligibility criteria for each of the three questions. Q1 included studies evaluating mother-child pairs, in which child outcomes (MTCT events) could be stratified by different levels of maternal HBV DNA during pregnancy. In order to precisely define the viral load threshold associated with MTCT, we restricted inclusion to studies that reported viral load categories within a narrow range (≤ 1.0 log IU/mL), e.g. 4.0-4.9, 5.0-5.9, 6.0-6.9 log IU/mL. In addition, for each viral load level, there needed to be ≥ 10 infants assessed for MTCT. Q2 included studies of pregnant women whose HBeAg status could be stratified by HBV DNA level dichotomized into high and low at the threshold identified in Q1, in order to calculate sensitivity and specificity. Q3 included studies of mother-child pairs in which the MTCT status of children could be stratified by maternal HBeAg status during pregnancy, in order to calculate sensitivity and specificity. For all the key questions (Q1-3), pregnant women needed to be chronically infected with HBV, and HBV markers had to be measured in the absence of concomitant anti-HBV therapy. MTCT was defined as HBsAg or HBV DNA positivity in infants assessed between 6-12 months of age. However, if this was unavailable, an assessment of MTCT at 12-24 months of age was accepted as long as ≥ 3 doses of infant hepatitis B vaccine were given, because the risk of horizontal transmission is negligible in these children.¹⁶ For studies of mother-infant pairs (Q1 and Q3), outcomes were defined in the absence of peripartum antiviral prophylaxis and further stratified by the administration of HepB-BD and/or HBIG. We excluded studies that selected pregnant women based on HBeAg sero-status or HBV DNA levels, in order to avoid spectrum bias.

Two authors (PB and KY for English-language, YL and TZ for Chinese-language databases) independently screened titles and abstracts of all publications identified through the literature search, reviewed potentially eligible full-text papers using the predefined criteria, extracted data from included studies using a pre-piloted form, and assessed methodological quality. Discrepancies were resolved by a third reviewer (YS), and duplicate studies were excluded. Whenever critical information was missing, or there was uncertainty about potential duplication, we contacted corresponding authors. The following data were extracted: study design, maternal/infant HBV markers (type and timing of sampling, assay type), administration of HepB-BD and/or HBIG, number of participants at enrolment, participant characteristics, and outcomes (i.e. the risk of MTCT at different maternal HBV DNA levels [Q1], and the sensitivity and specificity of the HBeAg test during pregnancy to diagnose the viral load threshold [Q2] and to predict MTCT [Q3]) (Appendix 2). Viral load given as “copies/mL” was converted to “IU/mL” by dividing by five.¹³ We assessed the methodological quality of the studies using a list of “signalling” questions for risk of bias adapted from the Altman Framework for Q1, and the QUADAS-2 tool for Q2-3 (Appendices 3-4).^{17,18} We assessed publication bias for Q2-3 using Deeks’ test.¹⁹

Data analysis

We used STATA 14.2 (Stata Corp LP, College Station, TX) for statistical analysis. For Q1, we first presented a scatter plot of the relationship between maternal HBV DNA levels (horizontal axis) and MTCT risk (vertical axis) reported at each viral load category in each study. In the plot, the size of the dot was proportional to the sample size. We then pooled MTCT risks at each maternal viral load category using the DerSimonian-Laird random-effects model after stabilising the variance of the proportions by Freeman-Tukey double arcsine transformation.²⁰

As a primary analysis to pool sensitivity and specificity [Q2-3], we used the DerSimonian-Laird bivariate random-effects model to take into account correlation between sensitivity and specificity, and presented in a paired forest plot. As a secondary analysis, we performed univariate random-effects meta-analysis to include studies that only reported sensitivity or specificity. As reliable methods to assess statistical heterogeneity in pooled estimates of diagnostic accuracy studies are lacking, we visually assessed heterogeneity through the coupled forest plots and summary scatter plots.²¹ We defined *a priori* study-level potential sources of heterogeneity as below: WHO region, type of HBeAg assay, type of NAT, and maternal characteristics (median age, co-infection with HIV/HCV/HDV, HBV genotypes). Subgroup analysis was performed whenever there were ≥ 10 studies in total.

For Q2-3, we rated the quality of evidence based on risk of bias, indirectness, imprecision, inconsistency, and reporting bias from high (further research is very unlikely to change the estimate) to very low (all estimates are very uncertain) using the GRADE scoring system (Appendix 5).²²

Role of the funding source

This project was funded by the WHO. The funder formulated the review questions, but had no role in study design, data collection, analysis, interpretation, or report writing. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 9007 records, of which 1347 potentially eligible articles were assessed fully. Of these, 67 articles (66 studies) ultimately met inclusion criteria (Figure 1). Study characteristics

are presented in Table 1. There were 13, 41, and 31 studies included for Q1, Q2, and Q3, respectively. Most studies were conducted in the WHO Western Pacific region (n=47, 71.2%), followed by Africa (n=9, 13.6%), Europe (n=5, 7.6%), the Americas (n=3, 4.5%), the Eastern Mediterranean (n=2, 3.0%), and South-East Asia (n=1, 1.5%). The majority of studies (78.8%, 52/66) were conducted in countries with a high HBV prevalence ($\geq 5\%$),^{13,23} and also the majority in LMICs (83.3%, 55/66). Fifty-three studies (80.3%) reported the type of HBsAg assay used to diagnose chronic HBV infection in pregnant women; all used laboratory immunoassay to confirm HBsAg positivity, and none solely used RDT. To detect HBeAg, enzyme-immunoassay (EIA) was the most frequently used (n=30, 48.4%), then chemiluminescent-immunoassay (CLIA) (n=21, 33.9%), CLIA or EIA (n=5, 8.1%), fluorescent-immunoassay (FIA) (n=3, 4.8%), and rapid diagnostic tests (RDTs) (n=3, 4.8%). Except for one study using branched DNA,²⁴ all of the studies used PCR to quantify HBV DNA. Thirty-one studies reported maternal HIV status, including three studies of HIV co-infected mothers only and 22 studies of HIV-uninfected mothers only. There were 27, 14, and 10 studies reporting maternal HCV, HDV, and HBV genotypes, respectively; however, none provided sufficient information to conduct subgroup analyses on these factors.

The risk of bias assessment, applicability to the review questions, and publication bias are summarised in Appendices 6-8. Most studies did not mention whether or not the examiners of the exposure/index test were blinded to the results of the outcome/reference test, and vice versa. The studies were assessed as having high applicability to the review questions. There was no evidence of publication bias.

Viral load threshold for immunoprophylaxis failure [Q1]

Q1 included 4198 mother-child pairs from 13 studies. All infants received both HepB-BD and HBIG. The risk of immunoprophylaxis failure was negligible when maternal viral load was <5.30 log IU/mL ($<200,000$ IU/mL) (0.04%, 1/2633, 95% CI: 0.00-0.11). However, the risk increased substantially at viral loads ≥ 5.30 log IU/mL, with a dose-response relationship: 3.8% (95% CI: 0.3-10.1), 6.2% (2.2-11.6), and 8.3% (4.2-13.5), at viral loads of 5.30-6.29, 6.30-7.29, and ≥ 7.30 log IU/mL respectively (Figure 2). In 181 mothers with viral loads of 5.30-6.29 log IU/mL, there were nine cases of the passive-active immunoprophylaxis failure with the following maternal viral loads (log IU/mL): 5.7 (n=1); 5.8 (n=2); 5.9 (n=2); 6.1 (n=2); and 6.2 (n=2).

HBeAg test to diagnose maternal viral load threshold [Q2]

Based on the findings from Q1, we defined the maternal HBV DNA threshold as ≥ 5.30 log IU/mL ($\geq 200,000$ IU/mL). Consequently, Q2 included 41 studies of HBeAg for identifying women with HBV viral load above a threshold of 5.30-6.29 log IU/mL: 5.30 (n=26), 5.85 (n=1), and 6.00 log IU/mL (n=14). All included studies allowed for estimation of both sensitivity and specificity. Heterogeneity did not appear to be high, as all studies except for two^{25,26} reported sensitivities or specificities $>80\%$ (Figure 3, Appendix 9). The pooled sensitivity and specificity of HBeAg to diagnose the HBV DNA threshold were 88.2% (95% CI: 83.9-91.5) and 92.6% (90.0-94.5), respectively; the strength of this evidence was high (Appendix 10). Based on a pre-test probability for a high viral load (≥ 5.30 log IU/mL) of 26.7%, the post-test probability was 76.3% and 3.4% after a positive and negative HBeAg test, respectively (Appendix 11).

Appendix 12 presents subgroup analyses. There was some variability in sensitivity and specificity estimates when studies were stratified according to the WHO region in which they

were conducted: 90.0% (95% CI: 85.0-93.5) and 89.1% (85.6-91.8), respectively in the Western Pacific (n=27), 82.0% (65.1-91.7) and 96.0% (94.4-97.1) in Africa (n=7), and 78.9% (67.3-87.1) and 98.0% (96.8-98.8) in Europe (n=5) (p<0.0001). Performance also varied by maternal age: the sensitivity and specificity were 94.2% (95% CI: 88.8-97.1) and 91.9% (87.8-94.8) in studies with median maternal age of <28 years (n=14), and 85.3% (79.0-90.0) and 95.6% (93.6-97.0) in those \geq 28 years (n=14), respectively (p=0.02). There were no statistically significant differences in subgroups based on HBeAg assay, HBV DNA assay, or maternal HIV status. Only two studies used RDTs to detect HBeAg;^{27,28} in these, the pooled sensitivity to diagnose high viremia (70.1%, 95% CI: 58.2-79.9) tended to be lower than the laboratory-based immunoassays: 91.2% (84.2-95.2) using CLIA, and 84.6% (77.4-89.8) using EIA. Nevertheless, their pooled specificities were similarly high >90%.

HBeAg test to predict MTCT [Q3]

Thirty-one cohort studies included in Q3 provided a total of 34 distinct cohorts on accuracy of HBeAg for predicting MTCT. Use of immunoprophylaxis varied: HepB-BD and HBIG (25 studies); HepB-BD only (7 studies); HBIG only (1 study); and no neonatal prophylaxis (1 study). Bivariate meta-analysis included 24 studies; the pooled sensitivity and specificity were 99.5% (95% CI: 91.7-100) and 62.2% (55.2-68.7), respectively, in 18 studies in which children received both HepB-BD and HBIG, and 97.9% (41.8-100) and 78.4% (66.8-86.8) in five studies in which children received HepB-BD alone (Figure 4). Of 280 cases of the passive-active immunoprophylaxis failure despite timely administration of HepB-BD and HBIG (Figure 4), few (n=13) were born to HBeAg-negative mothers. Of those HBeAg-negative mothers who transmitted HBV to their infants, HBV DNA levels during pregnancy were available in nine; most (8/9, 92.6%, 95% CI: 58.5-100) had low viral loads <5.30 log IU/mL and only one (1/9, 7.4%, 95% CI: 00.0-41.5) had a high viral load \geq 5.3 log

IU/mL.^{26,29} Univariate analyses based on all 31 studies, including those that reported only sensitivity or specificity, provided results similar to the bivariate analyses (Appendix 13). The strength of evidence for the performance of HBeAg to predict MTCT was high when both HepB-BD and HBIG were administered, but very low when HepB-BD alone was given because of the small number of studies, with imprecision (Appendix 14). Post-test probabilities are presented in Appendix 15.

We performed subgroup analyses on studies in which children received both HepB-BD and HBIG (Appendix 16). These studies were all conducted in the Western Pacific region, using EIA or CLIA for HBeAg, and none included HIV co-infected women. Performance varied by maternal age: sensitivity and specificity were 100.0% (95% CI: 1.8-100.0) and 53.9% (95% CI: 44.4-63.2) for younger women (median age <28 years), and 96.5% (64.2-99.8) and 71.1% (62.9-78.3) in older women (≥ 28 years) ($p=0.02$), respectively.

Discussion

Our systematic review found that the risk of infant passive-active immunoprophylaxis failure starts increasing at a viral load of 5.3 log IU/mL (200,000 IU/mL) in untreated pregnant women. The pooled sensitivity and specificity of an HBeAg test were 88.2% (95% CI: 83.9-91.5) and 92.6% (90.0-94.5), respectively, to diagnose women above this HBV DNA threshold; and 99.5% (91.7-100) and 62.2 % (55.2-68.7), respectively, for prediction of infant passive-active immunoprophylaxis failure.

Several professional societies recommended treating highly viremic pregnant women in order to prevent MTCT, though HBV DNA thresholds did vary between different guidelines. While the Asian Pacific and Chinese guidelines recommend 6.0-7.0 log IU/mL and 6.3 log IU/mL,

respectively,^{27,28} the American and European guidelines recommend a 5·3 log IU/mL cut-off,^{25,26} which was supported by our findings.

Although our study suggested the use of an HBeAg test as a reliable alternative to an HBV DNA assay in order to identify high-risk pregnant women, there were some differences in performance in analyses stratified according to several factors. In some cases, this may be explained by a difference in the HBeAg prevalence between the subgroups. Younger maternal age was associated with higher sensitivity and lower specificity to diagnose viral load $\geq 200,000$ IU/mL. This could be because HBeAg loss occurs spontaneously with age, resulting in a higher HBeAg prevalence in young HBsAg-positive mothers.³⁰ Similarly, higher sensitivity and lower specificity observed in Asian studies may be due to slower HBeAg loss and therefore higher HBeAg prevalence in HBV-infected Asian women of childbearing age (30-40%) compared to African women (10-20%).^{31,32} These geographical differences are partly due to differences in circulating HBV genotypes across the continents.³³ The lower clinical sensitivity of RDTs might be related to their limited analytical sensitivity to detect HBeAg.³⁴ Of note, despite these subgroup effects, results were consistent in showing high accuracy across subgroups.

We also found that an HBeAg test in pregnant women was highly sensitive in predicting infant passive-active immunoprophylaxis failure (99·5%), implying that almost all pregnant women who would transmit the infection otherwise could be correctly identified using this test. By contrast, the specificity was moderate (62·2%); about a third of women who would not transmit the infection might be unnecessarily given antiviral prophylaxis. However, such overtreatment may be less problematic than missing women at increased risk of MTCT, since peripartum antiviral prophylaxis is considered to have a good safety profile (see companion

review), and is relatively low-cost if using generics (US\$ 3-5/month).² Although the strength of evidence was very low given the limited number of included studies and imprecise estimates, we found similarly good performance of HBeAg to predict MTCT when HepB-BD alone was provided. This result is highly relevant in LMICs, where there is no access to HBV DNA quantification or HBIG. Field evaluation is ongoing in Laos and Thailand to understand the efficacy of an HBIG-free strategy (i.e. maternal peripartum antiviral therapy combined with infant HepB-BD) in HBeAg-positive women.³⁵

This review has some limitations. First, this is a meta-analysis of aggregate data. Analysing individual participant data might have allowed additional refinement of the optimal HBV DNA threshold for MTCT (e.g., by constructing a receiver operating characteristic curve). Second, we could not examine whether the performance of HBeAg test varies by HBV genotype, or by HCV or HDV co-infection. We also could not assess the difference in the accuracy of HBV markers according to the precise timing of testing during pregnancy because this data was unavailable for most of the included studies. Nevertheless, we believe that its impact is minimal since HBV markers appear to remain stable during pregnancy in the absence of antiviral treatment.^{36,37} Finally, although the use of RDTs is less expensive, faster, easier to perform, and thus more feasible in some LMIC settings, no HBeAg RDT has been prequalified by the WHO, and we identified only three studies evaluating the performance of RDTs during pregnancy. This highlights a critical unmet need for a formal evaluation of HBeAg RDT.

Findings from this review informed the 2020 WHO recommendation for the use of peripartum anti-HBV prophylaxis in women with an HBV DNA $\geq 200,000$ IU/mL, in addition to administration of at least three doses of hepatitis B vaccine in infants, including HepB-BD.

The WHO also made a conditional recommendation for the use of HBeAg testing as an alternative to HBV DNA quantification to determine antiviral prophylaxis eligibility in settings where HBV DNA assays are unavailable. In order to achieve the elimination of HBV MTCT, further research is warranted to evaluate strategies such as use of an HBeAg test, as well as other promising assays such as hepatitis B core-related antigen (HBcrAg),³⁸ during antenatal care to guide peripartum antiviral prophylaxis. This may be particularly relevant within the framework of the triple elimination of MTCT of HIV, syphilis, and HBV which has been initiated in some of the WHO regions.³⁹

Contributors

PB, JVH, RC, MB, and YS formulated the research questions. PB and YS developed the study protocol, analysed the data, and wrote the manuscript. PB, YL, KY, and TZ performed the systematic review. ALF, FLF, AG, ET, JVH, RC, and MB supported and supervised the work. All authors reviewed the manuscript and approved the final version.

Declaration of interests

We declare no competing interests.

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TABLES

Table 1. Characteristics of the 66 studies (reported in 67 articles) included in the meta-analysis of Q1, Q2 or Q3

General characteristics				Pregnant women				Infants			
Author, year	Country	Study design	Review question	HBV DNA assay	HBeAg assay	No. included in Q2	No. with HIV (%)	Preventive measures provided	Child outcome (MTCT)	Age at testing (months)	No. included in Q1/Q3
Bai H, 2010 ⁴⁰	China	Retrospective cohort	Q2	PCR (Da'an Gene)	FIA (Anytest, SYM-BIO)	120	NR	NA	NA	NA	NA
Carey I, 2018 ⁴¹	UK	Cross-sectional	Q2	PCR (Cobas TaqMan, Roche)	CLIA (Architect, Abbott)	514	NR	NA	NA	NA	NA
Chen T, 2018 ⁴²	China	Prospective cohort	Q2	PCR (Da'an Gene)	CLIA (Architect, Abbott)	499	NR	NA	NA	NA	NA
Chen Z, 2017 ²⁶	China	Prospective cohort	Q2, Q3	PCR (Kehua Bio-Engineering)	EIA (AxSYM, Abbott)	211	0/211 (0%)	HepB-BD & HBIG at birth	HBsAg (+) or HBV DNA (+)	7	NA (Q1) 168 (Q3)
Cheung K, 2018 ⁴³ (Q1 & Q3) & Cheung K, 2019 ⁴⁴ (Q2)	China	Cross-sectional (Q2) Prospective cohort (Q1 & Q3)	Q1, Q2, Q3	PCR (Cobas TaqMan, Roche)	CLIA (Elecsys, Roche)	325	NR	HepB-BD & HBIG at birth	HBsAg (+)	9-12	641 (Q1 & Q3)
Chotun N, 2017 ⁴⁵	South Africa	Prospective cohort	Q2, Q3	PCR (Cobas TaqMan, Roche)	CLIA (Architect, Abbott)	6	0/6 (0%)	HepB-BD only	HBsAg (+) or HBV DNA (+)	7	NA (Q1) 2 (Q3)
Cui-Ping L, 2015 ⁴⁶	China	Retrospective cohort	Q3	PCR (Da'an Gene)	EIA (Santa-Cruz)	256	0/256 (0%)	HepB-BD & HBIG at birth	HBsAg (+)	6	NA (Q1) 10 (Q3)
Ding Y, 2013 ⁴⁷	China	Prospective cohort	Q1, Q3	PCR (Cobas TaqMan, Roche)	CLIA (Architect, Abbott)	249	NR	HepB-BD & HBIG at birth and at 2 wk	HBsAg (+) & HBV DNA (+)	7	93 (Q1) 249 (Q3)
Dolman G, 2018 ⁴⁸	UK	Cross-sectional	Q2	PCR (Cobas TaqMan, Roche)	CLIA (Architect, Abbott)	423	NR	NA	NA	NA	NA
Ekra D, 2008 ⁴⁹	Côte d'Ivoire	Clinical trial	Q3	NA	EIA (Unknown)	NA	NR	HepB-BD only	HBsAg (+)	9	NA (Q1) 156 (Q3)
Evans A, 2015 ⁵⁰	China	Prospective cohort	Q3	NA	EIA (Kehua Bio-Engineering)	NA	NR	HepB-BD & HBIG at birth	HBsAg (+) & anti-HBs (-)	12	NA (Q1) 175 (Q3)
Foad H, 2019 ⁵¹	Egypt	Prospective cohort	Q3	PCR (MX 400, Stratagene)	EIA (ETI-EBK PLUS, Diasorin)	NA	0/41 (0%)	HepB-BD & HBIG at birth	HBV DNA (+)	6-18	NA (Q1) 32 (Q3)
Fujiko M, 2015 ⁵²	Indonesia	Cross-sectional	Q2	PCR (Cobas TaqMan, Roche)	EIA (Monolisa PLUS, Bio-Rad)	64	0/64 (0%)	NA	NA	NA	NA
Godbole G, 2013 ⁵³	UK	Cross-sectional	Q2	PCR (RealTime, Abbott)	CLIA (Architect, Abbott or Elecsys, Roche)	293	NR	NA	NA	NA	NA
Guingane A, 2017 ²⁷	Burkina Faso	Prospective cohort	Q2	PCR (Cobas TaqMan, Roche)	RDT (SD Bioline, Standard Diagnostics)	361	6/266 (2.3%)	NA	NA	NA	NA
Guo F, 2007 ⁵⁴	China	Cross-sectional	Q2	PCR (PG Biotech)	EIA (Intec)	319	NR	NA	NA	NA	NA

Hao X, 2015 ⁵⁵	China	Prospective cohort	Q2	PCR (Fosun Pharmaceutical Group)	EIA (Kehua Bio-Engineering)	154	NR	NA	NA	NA	NA
Huang L, 2014 ⁵⁶	China	Retrospective cohort	Q2	NR	EIA (Dayou, Dakewe)	324	NR	NA	NA	NA	NA
Johannessen A, 2017 ⁵⁷	Ethiopia	Prospective cohort	Q2	PCR (RealTime, Abbott)	EIA (Vidas, Biomérieux)	63	NR	NA	NA	NA	NA
Kubo A, 2014 ⁵⁸	USA	Retrospective cohort	Q2	PCR (Kehua Bio-Engineering)	EIA (unknown)	835	NR	NA	NA	NA	NA
Latthaphasavang V, 2019 ⁵⁹	Laos	Prospective cohort	Q2, Q3	PCR (Fast-track Diagnostics)	EIA (Monolisa PLUS, Bio-Rad)	153	1/153 (0.7%)	HepB-BD only	HBsAg (+)	6	NA (Q1) 120 (Q3)
Lee L, 2015 ²⁹	Singapore	Prospective cohort	Q1, Q3	PCR (Artus, Qiagen)	CLIA (Architect, Abbott)	161	NR	HepB-BD & HBIG at birth	HBV DNA (+) & anti-HBs <10 IU/mL	9	54 (Q1) 154 (Q3)
Li X, 2018 ⁶⁰	China	Retrospective cohort	Q2	PCR (Fosun Pharmaceutical Group)	CLIA (Architect, Abbott)	716	0/716 (0%)	NA	NA	NA	NA
Lin J, 2002 ⁶¹	China	Retrospective cohort	Q2	PCR (Biotromics technologies)	EIA (WB-2496, Wantai)	69	NR	NA	NA	NA	NA
Lu Y, 2017 ⁶²	China	Prospective cohort	Q1, Q3	PCR (RealTime, Abbott)	CLIA (Architect, Abbott)	NA	NR	HepB-BD & HBIG at birth	HBsAg (+)	7	484 (Q1) 1177 (Q3)
Lu H, 2009 ⁶³	China	Prospective cohort	Q2	PCR (PG Biotech)	FIA (Anytest, SYM-BIO)	33	NR	NA	NA	NA	NA
Lunel-Fabiani F, 2018 ⁶⁴	Cameroon	Prospective cohort	Q2, Q3	PCR (Aptima, Hologic)	EIA (ETI-EBK PLUS, Diasorin)	594	1/592 (0.2%)	HepB-BD only	HBsAg (+)	6-24	NA (Q1) 133 (Q3)
Makhlouf N, 2014 ⁶⁵	Egypt	Prospective cohort	Q3	PCR (Kehua Bio-Engineering)	EIA (AxSYM, Abbott)	NA	NR	HepB-BD & HBIG at birth	HBsAg (+)	9	NA (Q1) 14 (Q3)
Onakewhor J, 2013 ⁶⁶	Nigeria	Prospective cohort	Q3	NA	RDT (HBV-5 panel, LumiQuick)	NA	2/65 (3.1%)	-Group 1: HepB-BD & HBIG -Group 2: HepB-BD only -Group 3: Delayed birth dose	HBsAg (+)	9	NA (Q1) -Group 1: 16 (Q3) -Group 2: 12 (Q3) -Group 3: 11 (Q3)
Pan C, 2013 ⁶⁷	China	Retrospective cohort	Q1, Q3	PCR (Kehua Bio-Engineering)	CLIA (Architect, Abbott or Elecsys, Roche) or EIA (WB, Wantai)	1401	0/1401 (0%)	HepB-BD & HBIG at birth and at 2 wk	HBsAg (+)	7-12	541 (Q1) 1409 (Q3)
Peng N, 2012 ⁶⁸	China	Cross-sectional	Q2	PCR (Kehua Bio-Engineering)	CLIA (Architect, Abbott)	410	NR	NA	NA	NA	NA
Peng S, 2019 ⁶⁹	China	Prospective cohort	Q3	PCR (Da'an Gene)	EIA (Kehua Bio-Engineering)	NA	0/1219 (0%)	HepB-BD & HBIG at birth	HBsAg (+)	At birth & 7 mo	NA (Q1) 1219 (Q3)
Pirillo M, 2007 ⁷⁰	Uganda & Rwanda	Cross-sectional	Q2	PCR (in-house)	EIA (Murex, Murex Biotech)	7	7/7 (100%)	NA	NA	NA	NA
Pirillo M, 2015 ⁷¹	Malawi	Prospective cohort	Q2	PCR (Versant, Siemens)	CLIA (Architect, Abbott)	21	27/27 (100%)	NA	NA	NA	NA
Rouet F, 2004 ²⁴	Côte d'Ivoire	Cross-sectional	Q2	bDNA (Quantiplex HBV DNA, Bayer)	EIA (Murex, Abbott)	77	45/77 (58.4%)	NA	NA	NA	NA

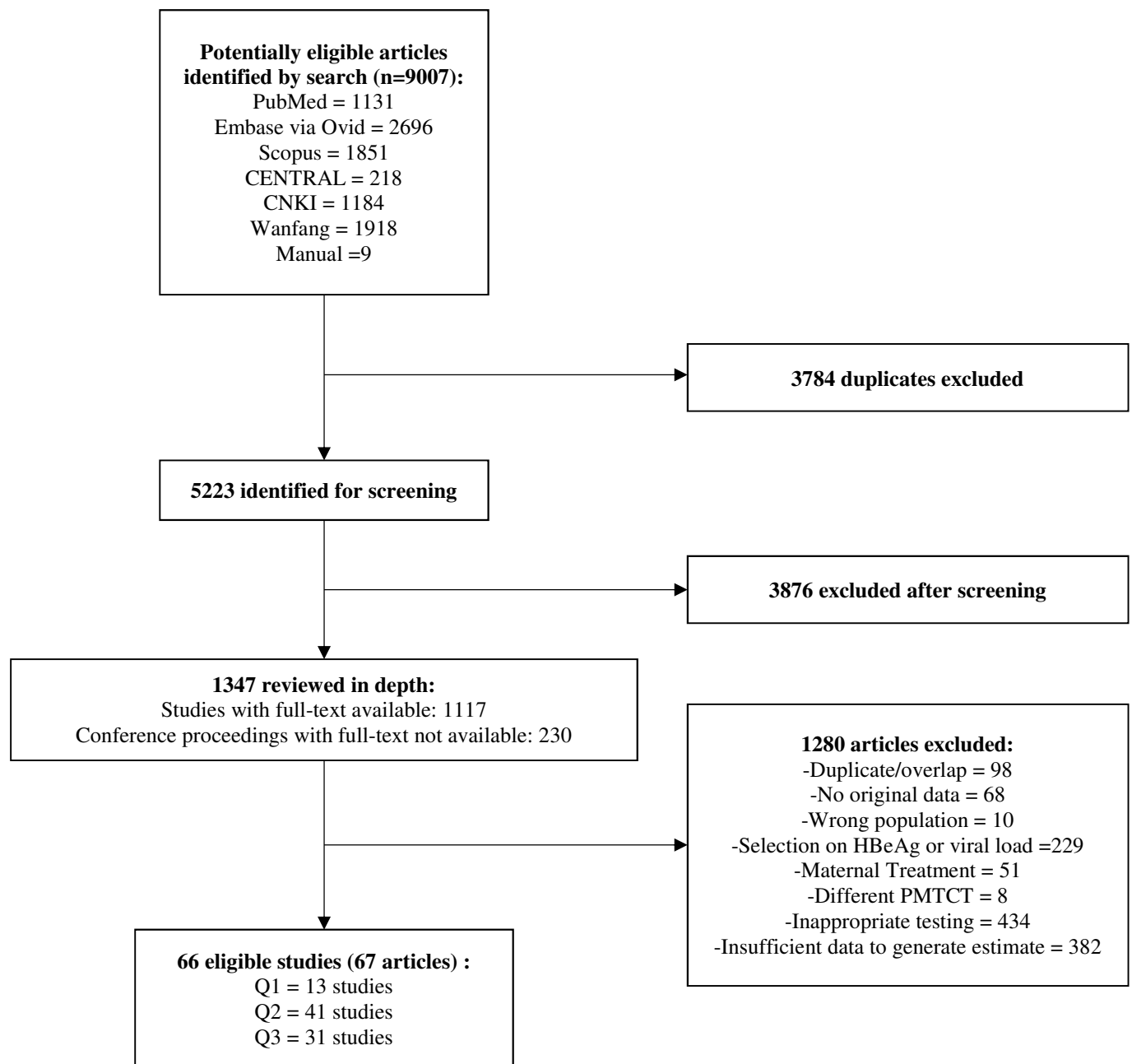
Ségéral O, 2018 ²⁸	Cambodia	Prospective cohort	Q2	PCR (PUMA, Omunis)	RDT (SD Bioline, Standard Diagnostics)	128	NR	NA	NA	NA	NA
Sheng Q, 2018 ⁷²	China	Prospective cohort	Q1, Q3	PCR (Cobas TaqMan, Roche)	CLIA (Architect, Abbott)	441	NR	HepB-BD & HBIG at birth	HBsAg (+) & HBV DNA (+)	7	278 (Q1) 375 (Q3)
Singh A, 2011 ⁷³	Canada	Case-control	Q3	PCR (Artus, Qiagen)	EIA (AxSYM, Abbott)	NA	0/64 (0%)	HepB-BD only	HBsAg (+) & anti-HBs (-)	12	NA (Q1) 61 (Q3)
Söderström A, 2003 ⁷⁴	Sweden	Retrospective cohort	Q2	PCR (Cobas Amplicor, Roche)	EIA (AxSYM, Abbott)	46	NR	NA	NA	NA	NA
Thilakanathan C, 2018 ⁷⁵	Australia	Retrospective cohort	Q1, Q2	PCR (Cobas TaqMan, Roche)	CLIA (Architect, Abbott)	642	NR	HepB-BD & HBIG at birth	HBsAg (+)	9-18	14 (Q1) NA (Q3)
Virine B, 2015 ⁷⁶	Canada	Prospective cohort	Q3	PCR (RealTime, Abbott)	CLIA (Architect, Abbott)	N/A	0/21 (0%)	HepB-BD & HBIG at birth	HBsAg (+) & anti-HBs <10 IU/mL	6-12	NA (Q1) 12 (Q3)
Wang C, 2016 ⁷⁷	China	Prospective cohort	Q3	NA	CLIA (Architect, Abbott)	N/A	0/863 (0%)	HepB-BD & HBIG at birth	HBsAg (+)	7	NA (Q1) 871 (Q3)
Wang F, 2009 ⁷⁸	China	Retrospective cohort	Q2	PCR (Sangon)	EIA (Kehua Bio-Engineering)	1237	NR	NA	NA	NA	NA
Wang J, 2018 ⁷⁹	China	Cross-sectional	Q2	PCR (Kehua Bio-Engineering)	N/R	567	NR	NA	NA	NA	NA
Wang L, 2016 ⁸⁰	China	Cross-sectional	Q2	PCR (RealTime, Abbott)	FIA (Anytest, SYM-BIO)	31	31/31 (100%)	NA	NA	NA	NA
Wang M, 2018 ²⁵	China	Retrospective cohort	Q2	PCR (RealTime, Abbott)	N/R	76	0/76 (0%)	NA	NA	NA	NA
Wang X, 2015 ⁸¹	China	Case-control	Q2	PCR (Cobas TaqMan, Roche)	EIA (unknown)	120	NR	NA	NA	NA	NA
Wang X, 2015 ⁸²	China	Prospective cohort	Q2	PCR (Fosun Pharmaceutical Group)	CLIA (Architect, Abbott)	409	0/409 (0%)	NA	NA	NA	NA
Wang Z, 2003 ⁸³	China	Prospective cohort	Q3	NA	EIA (AxSYM, Abbott)	NA	NR	Delayed birth dose & HBIG at birth and 1 mo	HBsAg (+)	12	NA (Q1) 95 (Q3)
Wang Z, 2018 ⁸⁴	China	Cross-sectional	Q2	NR	N/R	253	NR	NA	NA	NA	NA
Wei K, 2017 ⁸⁵	China	Cross-sectional	Q2	PCR (RealTime, Abbott)	CLIA (Architect, Abbott)	1741	0/1741 (0%)	NA	NA	NA	NA
Wen W, 2013 ⁸⁶	China	Prospective cohort	Q2	PCR (RealTime, Abbott)	EIA (AxSYM, Abbott)	303	0/347 (0%)	NA	NA	NA	NA
White H, 2015 ⁸⁷	UK	Retrospective cohort	Q2	NR	N/R	123	2/140 (1.4%)	NA	NA	NA	NA
Wiseman E, 2009 ⁸⁸	Australia	Prospective cohort	Q1, Q3	PCR (Cobas Amplicor/Cobas TaqMan, Roche)	CLIA (AxSYM, Abbott) or EIA (Architect, Abbott)	313	0/313 (0%)	HepB-BD & HBIG at birth	HBsAg (+) & anti-HBs (-)	9	47 (Q1) 138 (Q3)
Xu C, 2018 ⁸⁹	China	Cross-sectional	Q2	PCR (Shenyou Biotechnology)	CLIA (Architect, Abbott) or EIA (Kehua Bio-Engineering)	214	0/214 (0%)	NA	NA	NA	NA

Yi W, 2014 ⁹⁰	China	Case-control	Q1, Q3	PCR (Kehua Bio-Engineering)	CLIA (Architect, Abbott)	261	0/642 (0%)	HepB-BD & HBIG at birth and at 1 mo	HBsAg (+)	7-12	120 (Q1) 261 (Q3)
Yin Y, 2013 ⁹¹	China	Retrospective cohort	Q1, Q3	PCR (Da'an Gene)	EIA (Intec)	1360	NR	HepB-BD & HBIG at birth	HBsAg (+) or HBV DNA (+)	12	1004 (Q1) 1360 (Q3)
Zhang L, 2014 ⁹²	China	Prospective cohort	Q3	NA	EIA (Kehua Bio-Engineering)	NA	NR	-Group 1: HepB-BD & HBIG -Group 2: HepB-BD only	HBsAg (+) & HBeAg (+) & HBcAb (+)	8-12	NA (Q1) -Group1: 1014 (Q3) -Group2: 188 (Q3)
Zhang L, 2017 ⁹³	China	Cross-sectional	Q2	PCR (Sansure Biotech)	EIA (unknown)	491	NR	NA	NA	NA	NA
Zhang Z, 2014 ⁹⁴	China	Prospective cohort	Q1, Q3	PCR (Kehua Bio-Engineering)	EIA (Sino-American Biotechnology)	212	NR	HepB-BD & HBIG at birth	HBsAg (+)	At 24h or 1 mo & 6 mo	147 (Q1) 176 (Q3)
Zhang L, 2016 ⁹⁵	China	Prospective cohort	Q1, Q3	PCR (Kehua Bio-Engineering)	CLIA (Elecsys, Roche)	NA	NR	HepB-BD & HBIG at birth	HBsAg (+) & HBV DNA (+) & HBeAg (+)	8-12	332 (Q1) 385 (Q3)
Zheng H, 2010 ⁹⁶	China	Case-control	Q2	PCR (Kehua Bio-Engineering)	EIA (Kehua Bio-Engineering)	478	0/478 (0%)	NA	NA	NA	NA
Zhu Y, 2010 ⁹⁷	China	Prospective cohort	Q3	NA	EIA (AxSYM, Abbott)	NA	NR	HepB-BD & HBIG at birth	HBsAg (+)	9-15	NA (Q1) 6 (Q3)
Zhu B, 2013 ⁹⁸	China	Case-control	Q2, Q3	PCR (Cobas TaqMan, Roche)	CLIA (Elecsys, Roche)	53	0/53 (0%)	HepB-BD & HBIG at birth	HBsAg (+)	12	NA (Q1) 53 (Q3)
Zou H, 2011 ⁹⁹	China	Retrospective cohort	Q3	NA	CLIA (Architect, Abbott or Elecsys, Roche) or EIA (WB, Wantai)	NA	0/621 (0%)	HepB-BD & HBIG at birth and at 2 wk	HBsAg (+) & anti-HBs (-)	7	NA (Q1) 621 (Q3)
Zou H, 2012 ¹⁰⁰	China	Retrospective cohort	Q1, Q3	PCR (Kehua Bio-Engineering)	CLIA (Architect, Abbott or Elecsys, Roche) or EIA (WB, Wantai)	NA	0/864 (0%)	HepB-BD & HBIG at birth	HBsAg (+)	7-12	443 (Q1) 869 (Q3)

Abbreviations: bDNA, branched DNA; CLIA, chemiluminescent immunoassay; EIA, enzyme immunoassay; FIA, fluorescent immunoassay; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HepB-BD, birth dose of hepatitis B vaccine; NA, not applicable; NR, not reported; PCR, polymerase chain reaction; RDT, rapid diagnostic test

FIGURES

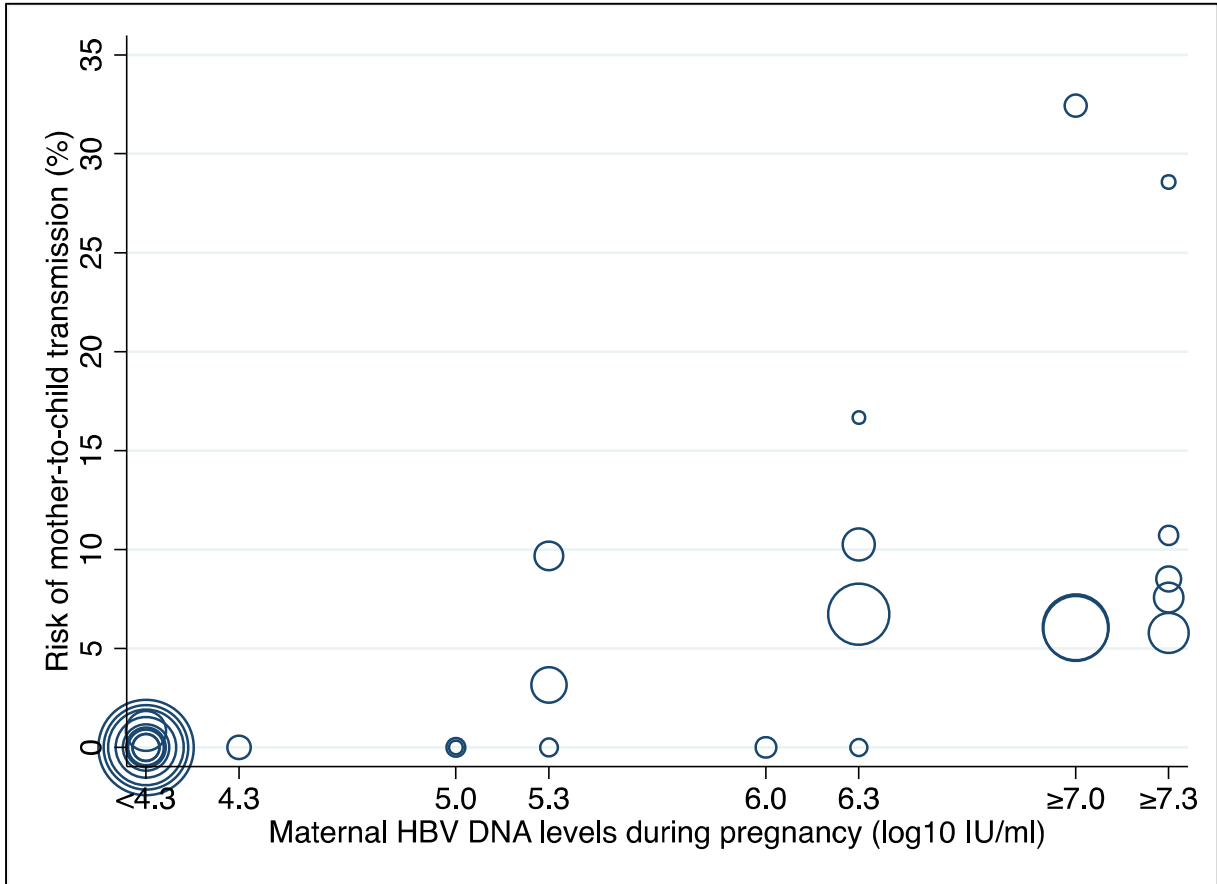
Figure 1. Study selection



Abbreviations: HBeAg, hepatitis B e antigen; PMTCT, prevention of mother-to-child transmission

Figure 2. Risk of infant passive-active immunoprophylaxis failure according to maternal viral load during pregnancy

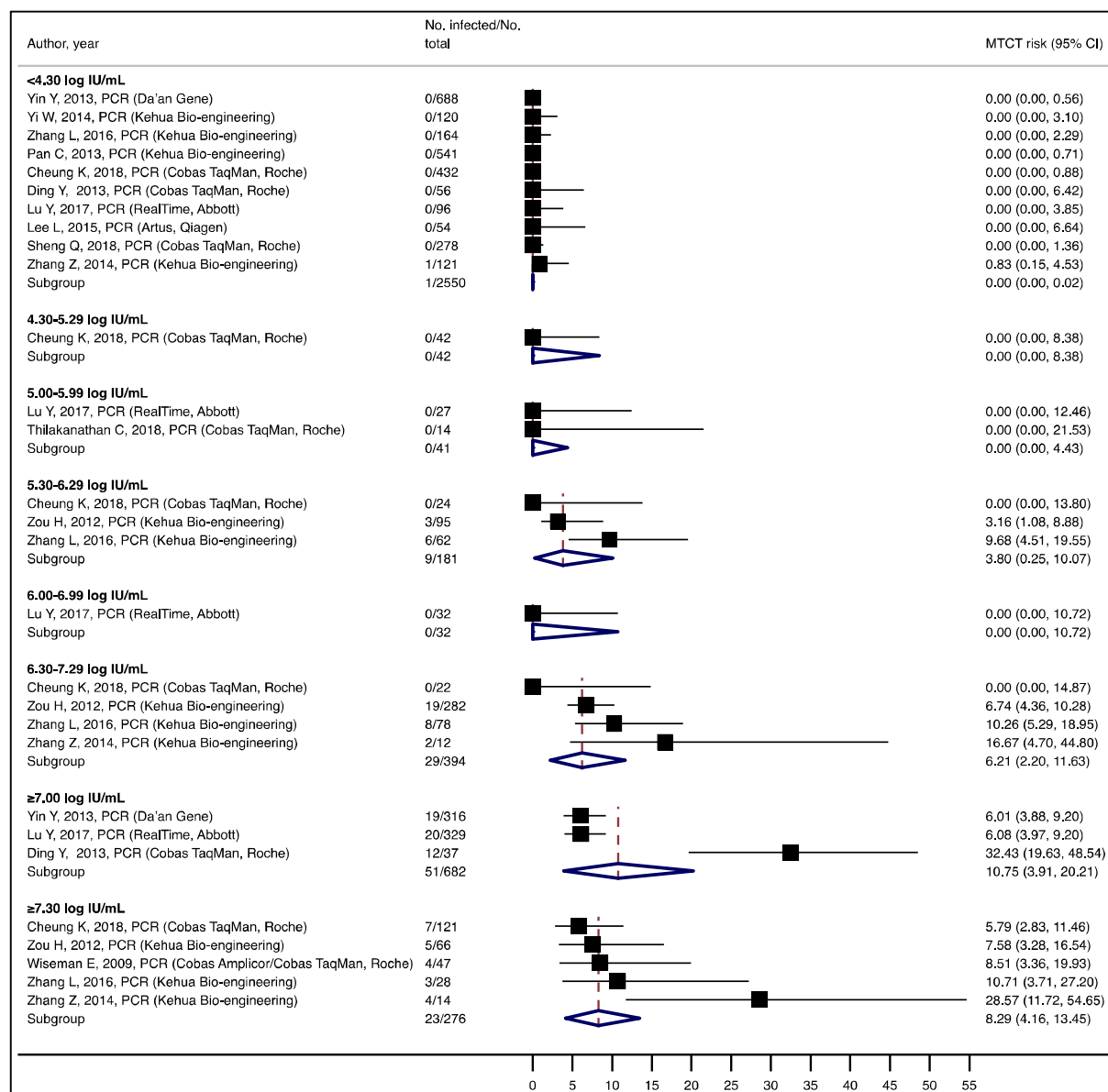
Figure 2A. Scatter plot of the relationship between maternal HBV DNA levels (horizontal axis) and MTCT risk (vertical axis) reported at each viral load category in each study*



Abbreviations: HBV, hepatitis B virus

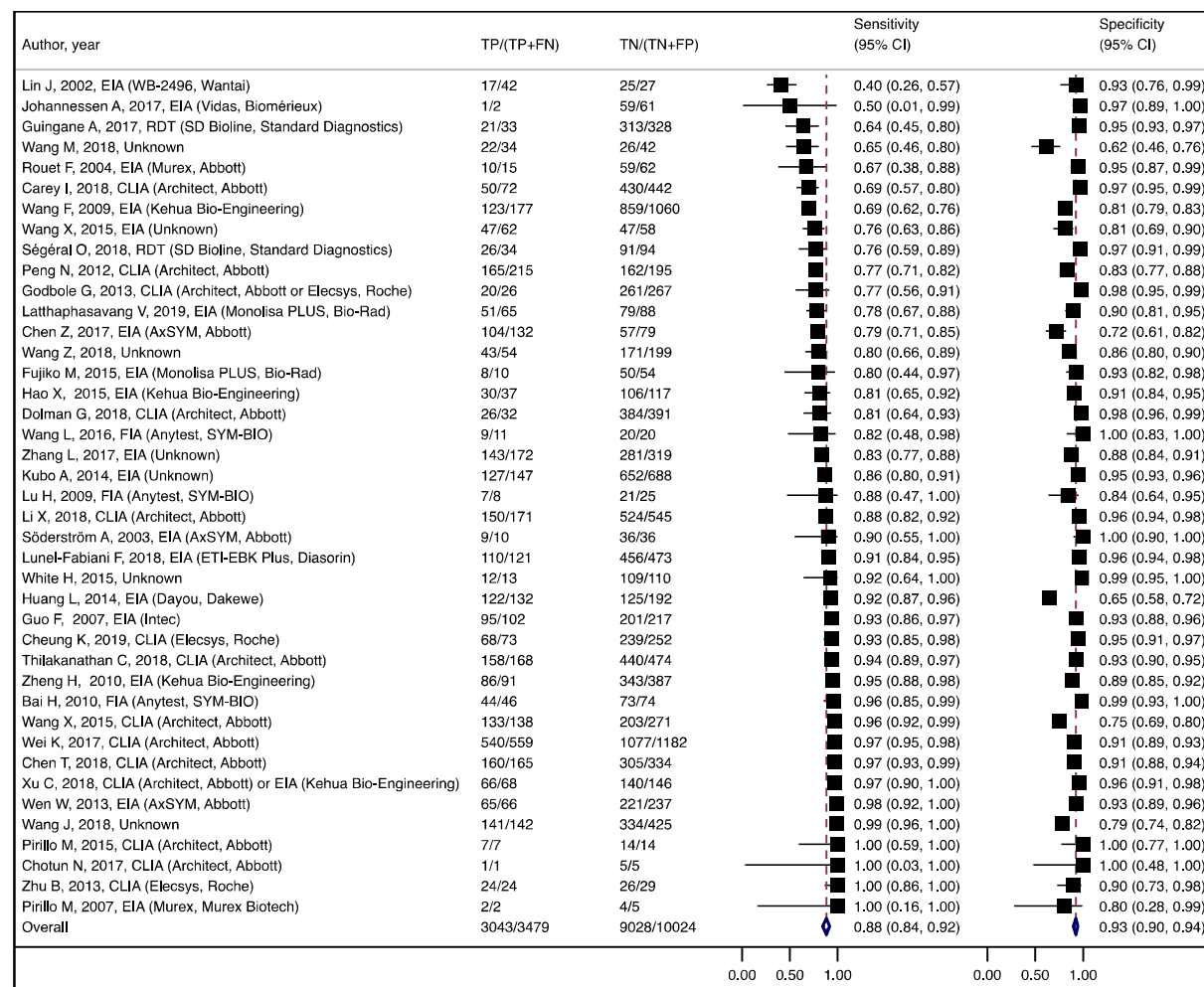
* The size of the dot was proportional to the sample size.

Figure 2B. Forest plots of the risk of infant passive-active immunoprophylaxis failure according to maternal viral load during pregnancy



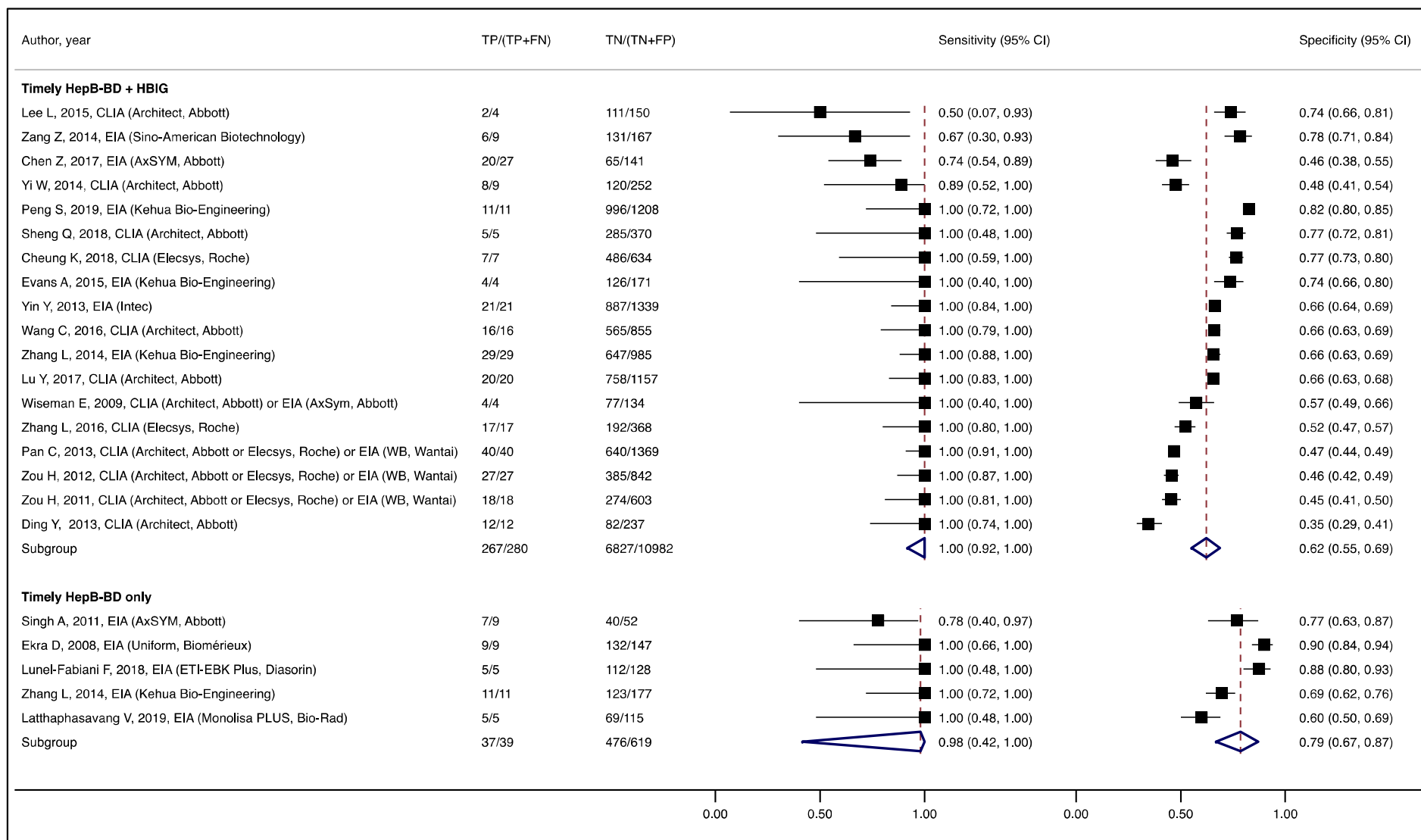
Abbreviations: CI, confidence intervals; IU, international units; MTCT, mother-to-child transmission; PCR, polymerase chain reaction

Figure 3. Sensitivity and specificity of an HBeAg test to diagnose pregnant women with high viral load $\geq 200,000$ IU/mL (≥ 5.30 log IU/mL)



Abbreviations: CLIA, chemiluminescent immunoassay; CI, confidence intervals; EIA, enzyme immunoassay; FIA, fluorescent immunoassay; FN, false negative; FP, false positive; HBeAg, hepatitis B e antigen; RDT, rapid diagnostic test; TN, true negative; TP, true positive

Figure 4. Sensitivity and specificity of an HBeAg test during pregnancy to predict MTCT by type of infant immunoprophylaxis



Abbreviations: CLIA, chemiluminescent immunoassay; CI, confidence intervals; EIA, enzyme immunoassay; FN, false negative; FP, false positive; HBeAg, hepatitis B e antigen; HepB-BD, birth dose of hepatitis B vaccine; HBIG, hepatitis B immune globulin; MTCT, mother-to-child transmission; TN, true negative; TP, true positive