

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B VIRUS: Guidelines

on antiviral prophylaxis in pregnancy

July 2020

Web Annex B: Systematic review of the performance of hepatitis B e antigen test, as an alternative to HBV DNA, to assess eligibility for initiating antiviral therapy during pregnancy

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Table of Contents

1.	BAC	CKGROUND	9
2.	OB.	IECTIVES	.11
	2.1.	Primary objective	. 11
	2.2.	Secondary objectives	. 12
	2.3.	Post-hoc analyses	. 13
3	MF'	THODS	14
5.	3.1.	Narrative review question	.14
	3.2.	PICO questions	. 14
	3.3.	Post-hoc analyses	. 17
	3.4.	Search strategy	. 17
	3.5.	Conduct of the review	. 17
	3.6.	Quality appraisal	. 18
	3.7.	Data extraction	. 18
	3.8.	Data synthesis	. 19
	3.9.	GRADE review process	. 21
4.	RES	SULTS	.23
	4.1.	Flowchart for PICO questions	. 23
	4.2.	PICO2A: Performance of HBeAg to identify women with high HBV DNA viral loads	. 25
	4.2.1	. Summary of included studies	31
	4.2.2	Risk of bias assessment	33
	4.2.3	Primary analysis, narrative descriptions and forest plots	35
	4.2	2.3.1. Overall performance of HBeAg to identify pregnant women with high HBV DNA levels	35
	4	2.3.2. Performance of HBeAg to identify pregnant women with HBV DNA $\geq 5 \log 10 \text{ IU/mL}$	37 1.0
	4.2	2.3.4. Performance of HBeAg to identify pregnant women with HBV DNA >7 log10 IU/mL	
	4.2.4	. GRADE evidence profile for PICO2A	70
	4.3.	PICO2B: Performance of HBeAg to predict MTCT	. 71
	4.3.1	. Summary of included studies	73
	4.3.2	Risk of bias assessment	76
	4.3.3	Primary analysis, narrative descriptions and forest plots	78
	4.3.4	GRADE evidence profile for PICO2B	83
	4.4.	PICO2C: Performance of HBV DNA to predict MTCT	. 85
	4.4.1	. Summary of included studies	87
	4.4.2	. Risk of bias assessment	90
	4.4.3	•. Primary analysis, narrative descriptions and forest piols	92
	4.4	4.3.2. Performance of HBV DNA >5 log10 IU/mL during pregnancy to predict MTCT	94
	4.4	4.3.3. Performance of HBV DNA \geq 7 log10 IU/mL during pregnancy to predict MTCT	97
	4.4.4	GRADE evidence profile for PICO2C	99
	4.5.	Post-hoc analysis	101
	4.5.1	. HBV DNA level during pregnancy from which the MTCT risk increases despite infant's	
	imm	unoprophylaxis	101
	4.5.2	Performance of HBeAg to identify pregnant women with HBV DNA \geq 5.3 log10 IU/mL	104

5. CO	NCLUSION	107
5.1.	Implications for practice	
5.2.	Implications for research	111
6. AC	KNOWLEDGEMENT	113
7. REI	FERENCES	
8. API	PENDICES	
8.1.	Appendix A: Search strategies	
8.2.	Appendix B: QUADAS2 protocol	
8.3.	Appendix C: Data extraction sheet protocol	
8.4.	Appendix D: Detailed QUADAS2 results for studies included in PICO2A	
8.5.	Appendix E: Detailed QUADAS2 results for studies included in PICO2B	
8.6.	Appendix F: Detailed QUADAS2 results for studies included in PICO2C	
8.7.	Appendix G: Funnel plots for publication bias	147

List of Tables

Table 1. PICO questions for this systematic review	14
Table 2. Characteristics of the 82 studies included for the PICO2A	25
Table 3. Characteristics of studies included in PICO2A	32
Table 4. Performance of HBeAg to identify pregnant women with high viral load, stratified by	
HBV DNA threshold	35
Table 5. Post-test probabilities of having high viral load depending on HBeAg test results in	
pregnant women	35
Table 6. Performance of HBeAg to identify pregnant women with HBV viral load $\geq 5 \log 10$	
IU/mL, stratified by potential sources of heterogeneity	40
Table 7. Results of the sensitivity analysis for the performance of HBeAg to identify pregnant	
women with HBV DNA \geq 5 log10 IU/mL	48
Table 8. Performance of HBeAg to identify pregnant women with HBV viral load ≥6 log10	
IU/mL, stratified by potential sources of heterogeneity	51
Table 9. Results of the sensitivity analysis for the performance of HBeAg to identify pregnant	
women with HBV DNA $\geq 6 \log 10 \text{ IU/mL}$	58
Table 10. Performance of HBeAg to identify pregnant women with HBV viral load $\geq 7 \log 10$	
IU/mL, stratified by potential sources of heterogeneity	62
Table 11. Results of sensitivity analysis for the performance of HBeAg to identify pregnant	
women with HBV DNA \geq 7 log10 IU/mL	69
Table 12. GRADE evidence profile table of the performance of HBeAg to identify pregnant	
women with a HBV viral load $\geq 5 \log IU/mL$, and $\geq 6 \log IU/mL$, $\geq 7 \log IU/mL$	70
Table 13. Characteristics of the 15 studies included for the PICO2B	71
Table 14. Characteristics of studies included in the PICO2B	74
Table 15. Performance of HBeAg during pregnancy to predict MTCT of HBV, stratified by HI	ΒV
MTCT prevention strategy	78
Table 16. Post-test probabilities of having MTCT of HBV after positive or negative maternal	
HBeAg result	79
Table 17. Results of sensitivity analysis for the performance of HBeAg during pregnancy to	
predict MTCT	82
Table 18. GRADE evidence profile table of the performance of HBeAg during pregnancy to	
predict MTCT, stratified by prevention strategy for MTCT	83
Table 19. Characteristics of 13 studies included in the PICO2C	85
Table 20. Characteristics of studies included in the PICO2C	88
Table 21. Performance of HBV DNA during pregnancy to predict MTCT, stratified by HBV	
DNA threshold and prevention of MTCT strategy	92
Table 22. Post-test probabilities of MTCT if pregnant women have high or low HBV viral load	1,
according to various HBV DNA thresholds and prevention of MTCT strategies	93
Table 23. Results of sensitivity analysis for the performance of HBV DNA \geq 5 log10 IU/mL	
during pregnancy to predict MTCT of HBV	96
Table 24. Results of sensitivity analysis for the performance of HBV DNA \geq 7 log10 IU/mL	
during pregnancy to predict MTCT	98

List of Figures

Fig. 1. PRISMA diagram	24
Fig. 2. Risk of bias results for PICO2A	34
Fig. 3. Concerns about applicability results for PICO2A	34
Fig. 4. Coupled forest plot of the performance of HBeAg to identify pregnant women with HB	V
viral load \geq 5 log10 IU/mL	38
Fig. 5. Summary scatter plot of the performance of HBeAg to identify maternal HBV DNA ≥5	,
log10 IU/mL	39
Fig. 6. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 5	
log10 IU/mL by WHO region	42
Fig. 7. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 5	
log10 IU/mL by type of HBeAg assay	43
Fig. 8. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 5	
log10 IU/mL by HBeAg assay commercial name	44
Fig. 9. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 5	
log10 IU/mL by type of HBV DNA assay	45
Fig. 10. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 5	
log10 IU/mL by mean or median maternal age	46
Fig. 11. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 5	
log10 IU/mL by maternal HIV status	47
Fig. 12. Coupled forest plot for all studies included in the meta-analysis of the performance of	
HBeAg to identify maternal HBV DNA $\geq 6 \log 10 \text{ IU/mL}$	49
Fig. 13. Summary scatter plot of the performance of HBeAg to identify maternal HBV DNA \geq	<u>:</u> 6
log10 IU/mL	50
Fig. 14. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥ 6	
log10 IU/mL by WHO region	53
Fig. 15. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥ 6	
log10 IU/mL by type of HBeAg assay	54
Fig. 16. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥ 6	
10g10 IU/mL by HBeAg assay commercial name	55
Fig. 17. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥ 6	
10 full holds for a start	56
Fig. 18. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥ 6	F 7
10g10 IU/mL by maternal age	57
Fig. 19. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥ 6	- 7
Fig. 20. Coupled forest plot for all studies included in the mote analysis of the performance of	57
Fig. 20. Coupled forest plot for all studies included in the meta-analysis of the performance of UD_{2} A stability is the statement UDX DNA >7.1 s 10 H J/mJ	<u> </u>
IDEAS TO IDENTIFY MATERIAL HBV DIA \geq / 10g10 IU/mL	00
Fig. 21. Summary scatter plot of the performance of HBeAg to identify maternal HBV DNA \geq	:/ (1
10g10 10/111L	01
Fig. 22. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA $\geq 10 \times 10 \times 10^{-10}$	61
log 10 10/111L by WHO region	04

Fig. 23. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 7	
log10 IU/mL by HBeAg assay type	5
Fig. 24. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 7	
log10 IU/mL by HBeAg assay commercial name	6
Fig. 25. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥7	
log10 IU/mL by HBV DNA assay type	7
Fig. 26. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥7	
log10 IU/mL by mean or median maternal age	7
Fig. 27. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 7	
log10 IU/mL by maternal HIV status	8
Fig. 28. Risk of bias results for PICO2B	6
Fig. 29. Concerns about applicability results for PICO2B7	7
Fig. 30. Coupled forest plot of the performance of HBeAg during pregnancy to predict MTCT or	f
HBV by prevention strategy for MTCT	9
Fig. 31. Coupled forest plot of the performance of HBeAg during pregnancy to predict MTCT or	f
HBV by HBeAg assay	0
Fig. 32. Summary scatter plot with SROC curve of the performance of HBeAg during pregnancy	у
to predict MTCT	1
Fig. 33. Risk of bias results for PICO2C	0
Fig. 34. Concerns about applicability results for PICO2C9	1
Fig. 35. Coupled forest plot of the performance of HBV DNA ≥5 log10 IU/mL during pregnance	y
to predict MTCT of HBV by type of prevention of MTCT strategy	4
Fig. 36. Coupled forest plot of the performance of HBV DNA ≥5 log10 IU/mL during pregnance	у
to predict MTCT of HBV by type of HBV DNA assay94	4
Fig. 37. Summary scatter plot and SROC curve of the performance of HBV DNA \geq 5 log10	
IU/mL during pregnancy to predict MTCT9	5
Fig. 38. Coupled forest plot of the performance of HBV DNA ≥7 log10 IU/mL during pregnance	у
to predict MTCT of HBV by type of prevention of MTCT strategy9	7
Fig. 39. Coupled forest plot of the performance of HBV DNA ≥7 log10 IU/mL during pregnance	y
to predict MTCT of HBV by type of HBV DNA assay9	7
Fig. 40. Risk of HBV MTCT according to maternal HBV DNA level during pregnancy10	2
Fig. 41. Forest plot of the risk of HBV MTCT according to maternal HBV DNA level during	
pregnancy10	3
Fig. 42. Coupled forest plot for all studies included in the meta-analysis of the performance of	
HBeAg to identify maternal HBV DNA \geq 5.3 log10 IU/mL	4

List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AFR	African Region
AMR	Region of the Americas
APASL	Asian Pacific Association for the Study of the Liver
ВСР	basal core promoter
СНВ	chronic hepatitis B virus infection
CIA	counting immunoassay
CLIA	chemiluminescence immunoassay
CNKI	China National Knowledge Infrastructure
EASL	European Association for the Study of the Liver
EIA	enzyme immunoassay
EMR	Eastern Mediterranean Region
ESS	effective sample size
EUR	European Region
FIA	fluoroimmunoassay
FN	false negative
FP	false positive
GHSS	Global Health Sector Strategy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
НСС	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
InDOR	log diagnostic odds ratio
МТСТ	mother-to-child transmission
N/A	not applicable

NAT	nucleic acid test
NLR	negative likelihood ratio
N/R	not reported
PC	precore
PCR	(real-time) polymerase chain reaction
PLR	positive likelihood ratio
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
RDT	rapid diagnostic test
RIA	radioimmunoassay
Se	sensitivity
SEAR	South-East Asia Region
Sp	specificity
SROC	summary receiver operating characteristic curve
TBD	timely birth dose of hepatitis B vaccine
TN	true negative
TP	true positive
VL	viral load
WPR	Western Pacific Region
WHO	World Health Organization
95% CI	95% confidence interval

1. BACKGROUND

Currently, the World Health Organization (WHO) estimates that chronic hepatitis B virus (HBV) infection affects close to 260 million persons and causes an estimated 900 000 deaths annually through manifestations of chronic liver disease, such as cirrhosis or hepatocellular carcinoma (HCC). The regions with the highest prevalence of chronic HBV infection (CHB) are the Western Pacific and Africa (1). In 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis, which calls for an elimination of HBV worldwide as a public health threat by 2030, to be accomplished through reducing the incidence of CHB by 90%, and its mortality by 65% (2).

Chronic infection is more likely to develop when HBV is acquired early in life, and therefore, perinatal mother-to-child transmission (MTCT) is a major contributor to the incidence of CHB (3). Moreover, the risk of developing chronic liver disease, including HCC, may be higher in those who acquired CHB through MTCT compared to those who ended up with CHB through horizontal transmission later in life (4,5).

In order to achieve the WHO's global hepatitis elimination plan, it is imperative to prevent MTCT of HBV (6). Since 2009, WHO makes a universal recommendation to administer timely hepatitis B vaccines to all newborn babies within 24 hours of birth to prevent MTCT and early childhood transmission (7). Although the birth dose vaccines alone should be enough to prevent MTCT from mothers with CHB who have low HBV viral replication (8,9), 20–30% of women with high viral load infect their newborns despite timely birth dose vaccination (9,10). Therefore, in resource-rich countries, pregnant women are screened for hepatitis B surface antigen (HBsAg), and subsequently for hepatitis B e antigen (HBeAg), to identify high-risk infants who would benefit from hepatitis B immunoglobulin (HBIG) in addition to timely birth dose vaccination (11). However, despite this active and passive immunoprophylaxis, a substantial proportion of infants are still infected when their mothers have a very high viral load, particularly when the serum HBV DNA level exceeds 200 000 IU/mL (12). Consequently, in high-income countries, HBV DNA quantification has become a part of antenatal HBV testing to identify highly viraemic women who have a residual

risk of MTCT despite administration of both hepatitis B vaccine and HBIG to neonates at birth (12-14), and who thus require antiviral therapy during pregnancy for minimizing its risk (15).

However, in low- and middle-income countries, such additional measures to prevent MTCT have rarely been implemented (16). Following antenatal screening for HBsAg, it is essential to quantify serum HBV DNA levels using the nucleic acid test (NAT) to decide whom to treat and not to treat during pregnancy to prevent MTCT. However, access to NAT is severely limited in these countries. The current standard NAT assay, which is real-time polymerase chain reaction (PCR), is hardly accessible due to its high cost (US\$ 60–200/assay) and its need for a sophisticated laboratory with highly skilled laboratory staff (1). Alternatively, detection of HBeAg using laboratory-based immunoassays, such as enzyme immunoassay (EIA) and chemiluminescence immunoassay (CLIA), or rapid diagnostic test (RDT) with lateral flow immunochromatographic assay, may largely overcome these limitations, because these tests may be more readily available and affordable (US\$ 1–30/assay) than HBV DNA NAT in such settings (17).

2. OBJECTIVES

2.1. Primary objective

To provide a summary estimate of the performance (sensitivity and specificity) of HBeAg tests in pregnant women with CHB with the purpose of diagnosing high HBV DNA levels for the assessment of eligibility for antiviral treatment during pregnancy to prevent HBV MTCT

The definition of high maternal HBV DNA levels that warrant antiviral therapy during pregnancy varies substantially according to the regional/national guidelines as below:

0	EASL & AASLD	200 000 IU/mL (13,14)
0	China	2 000 000 IU/mL (18)
0	APASL	1 000 000–10 000 000 IU/mL (19)
0	Australia & New Zealand	10 000 000 IU/mL

Abbreviations: AASLD (American Association for the Study of Liver Diseases); APASL (Asian Pacific Association for the Study of the Liver); EASL (European Association for the Study of the Liver)

The general eligibility criteria for initiating the immediate antiviral therapy in people with CHB set the HBV DNA thresholds much lower, but also require the presence of other disease parameters (i.e. liver inflammation and/or liver fibrosis):

WHO 20 000 IU/mL (20)
 EASL, AASLD & APASL 2000 IU/mL (13,14,19)

Because of the variability in the definition of high HBV DNA levels as an eligibility criterion for antiviral therapy, in this systematic review we defined high HBV DNA levels to be any value greater than or equal to 20 000 IU/mL.

The summary estimates (sensitivity and specificity) were reported at each of the different HBV DNA thresholds used in the included studies. In addition, the following subgroup analyses were considered whenever there were at least three studies:

- Type of HBeAg assay
- Type of HBV DNA assay
- Mean/median maternal age
- Maternal coinfection with HIV, HCV or HDV
- Maternal HBV genotypes
- WHO region
- Study's risk of bias (high vs low)

2.2. Secondary objectives

The secondary objectives were:

• Secondary Objective 1

To provide a summary estimate of the performance (sensitivity and specificity) of HBeAg tests in pregnant women with CHB to predict the risk of HBV MTCT, by type of HBeAg assay and type of preventive measures

• Secondary Objective 2

To provide a summary estimate of the performance (sensitivity and specificity) of different serum HBV DNA thresholds in pregnant women with CHB to predict the risk of HBV MTCT, by type of preventive measure

These secondary objectives were assessed within the studies included for the primary objective; no additional systematic review was conducted to respond specifically to these secondary objectives.

We also provided a Grading of Recommendations Assessment, Development and Evaluation (GRADE) review, and identified gaps in research.

2.3. Post-hoc analyses

Following the Guidelines Development Group meeting held in Geneva on 9–10 October 2019, we conducted post-hoc analyses:

- Post-hoc analysis 1:

To assess the maternal HBV DNA threshold during pregnancy at which the risk of HBV MTCT starts to increase despite infant's immunoprophylaxis (timely birth dose vaccine with or without HBIG)

- Post-hoc analysis 2:

To provide a summary estimate of the performance (sensitivity and specificity) of HBeAg tests in pregnant women with CHB to diagnose HBV DNA threshold specifically defined by the analysis above

3. METHODS

3.1. Narrative review question

Can HBeAg test be used instead of NAT to diagnose high HBV DNA levels in order to assess eligibility for antiviral therapy initiation in pregnant women with CHB to prevent MTCT?

3.2. PICO questions

We obtained evidence to answer the following questions (Table 1).

Table 1. PICO questions for this systematic review

	PICO2A	PICO2B	PICO2C
	What is the performance of HBeAg to diagnose high HBV DNA levels in pregnant women with CHB?	What is the performance of HBeAg in pregnant women with CHB to predict the risk of MTCT?	What is the performance of different HBV DNA thresholds in pregnant women with CHB to predict the risk of MTCT?
P opulation	Pregnant women with CHB ^{*1} without concomitant anti- HBV therapy	Same as PICO2A	Same as PICO2A
Intervention	Maternal HBeAg test during pregnancy ^{*2}	Same as PICO2A	 Maternal HBV DNA levels during pregnancy^{*4} Dichotomized into high and low using the following thresholds: ≥20,000, 10^5, 10^6, 10^7 and 10^8 IU/mL
Comparison	 Maternal HBV DNA levels during pregnancy*^{3,4} Dichotomized into high and low using the following thresholds: ≥20 000, 10^5, 10^6, 10^7, & 10^8 IU/mL 	 MTCT defined as: HBsAg positivity or HBV DNA positivity in infants aged 6–12 months Extended to 6–24 months in infants who received three doses of HBV vaccine 	Same as PICO2B

Outcomes	Sensitivity and specificity of HBeAg tests ^{*5} to diagnose each of different HBV DNA thresholds	Sensitivity and specificity of HBeAg tests to predict MTCT ^{*6}	Sensitivity and specificity of HBV DNA test to predict MTCT ^{*6}
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^{*1} CHB was defined as HBsAg seropositivity on two occasions at least 6 months apart. However, because new HBV infections in adults are uncommon in highly endemic areas where the vast majority of HBsAg-positive people acquired the infection perinatally or during childhood, HBsAg positivity on only one occasion (at antenatal care) in women living in highly prevalent countries was assumed to reflect CHB (*21*).

^{*2} Maternal HBeAg test performed after child delivery was not considered. The test result should be reported positive or negative; an indeterminate result was not considered for the meta-analysis. Instead, the frequency of the indeterminate result in each study was extracted and reported. The following HBeAg immunoassays were considered:

- Lateral flow immunochromatographic rapid diagnostic test (RDT)
- Enzyme immunoassay (EIA)
- Chemiluminescence immunoassay (CLIA)
- Radioimmunoassay (RIA)
- Counting immunoassay (CIA)
- Fluoroimmunoassay (FIA)

^{*3} It is ideal to have both HBeAg and HBV DNA measurements from the same sample, or at least from a sampling done at the same time. However, a study was still considered whenever both markers were measured during the same period of pregnancy, even if they were not measured using samples collected on the same day.

^{*4} There are two types of NAT: qualitative (undetectable or detectable) and quantitative. When NAT provided a continuous value through quantification of HBV DNA levels, the value was dichotomized into high and low according to a threshold used in each included study. In order to have a wide range of estimations, the HBV DNA threshold used in each included study to dichotomize HBV DNA levels into high and low should have been greater than or equal to 20 000 IU/mL. Similarly, when NAT provided only a qualitative binary result (detectable or

undetectable), the limit of detection of the qualitative NAT should have been greater than or equal to 20 000 IU/mL.

^{*5} For example, in the case of HBV DNA levels of \geq 200 000 IU/mL, the sensitivity and specificity were defined as below:

- sensitivity = $\frac{No. of women with HBV DNA \ge 200 000 IU/mL who tested positive for HBeAg}{Total no. of women with HBV DNA \ge 200 000 IU/mL}$
- specificity = $\frac{No. of women with HBVDNA < 200 000IU/mL who tested negative for HBeAg}{Total no. of women with HBV DNA < 200 000 IU/mL}$

In order to have these estimates, a study needed to provide sufficient data for us to draw a 2x2 or 2x1 table with the cross-classification of the reference test results (high vs low HBV DNA levels) and the index test results (positive vs negative HBeAg serostatus).

^{*6} The outcome was stratified by the type of preventive measures: timely birth dose vaccine (yes or no); and HBIG at birth (yes or no). We only considered studies in which sensitivity and specificity estimates could be stratified by the type of preventive measure provided to the mother–child pairs. We did not consider studies that provided antiviral therapy to mothers during pregnancy, since our objective is to evaluate these HBV markers as a tool to identify pregnant women who would benefit from antiviral therapy during pregnancy.

Other inclusion and exclusion criteria: study design, languages, dates of publication

We included studies with any design, published in any language, which used an HBV DNA threshold to dichotomize HBV DNA levels into high and low. This threshold needed to be at least higher than 20 000 IU/mL. Moreover, studies needed to provide sufficient data to draw a 2x1 or 2x2 table with the cross-classification of the reference test results (high vs low HBV DNA levels) and the index test results (positive vs negative HBeAg serostatus) in pregnant women with CHB without concomitant anti-HBV therapy. We excluded studies that selected participants based on the index test (i.e. maternal HBeAg status) to avoid verification bias (22). Studies published between 1 January 2000 and 3 April 2019 were considered.

3.3. Post-hoc analyses

For the post-hoc analyses, we included studies evaluating mother–child pairs, in which child outcomes could be stratified by different maternal HBV DNA levels during pregnancy with a narrow range ($\leq 1.0 \log IU/mL$; such as <4.0, 4.0–4.9, 5.0–5.9, 6.0–6.9, and $\geq 7.0 \log IU/mL$). At each stratum defined by maternal viral load, there should be ≥ 10 infants assessed for MTCT. We excluded studies that selected participants based on maternal HBeAg status or maternal viral load to avoid verification bias (22). Studies published between 1 January 2000 and 3 April 2019 were considered.

3.4. Search strategy

The search terms employed covered "hepatitis B infection" AND "viral load" AND "pregnancy" and their variations. The databases searched included: four English-language databases (PubMed, EMBASE, Scopus, and CENTRAL (the Cochrane Library)); and two Chinese-language databases (the China National Knowledge Infrastructure [CNKI] and the Wanfang database). The search strategies used for each of the databases are presented in **Appendix A**.

A manual search through the references of the included studies, as well as through those of relevant systematic reviews identified through the literature search, was undertaken to identify any further eligible studies. Expert opinion was also sought to include other relevant studies.

3.5. Conduct of the review

Titles and abstracts for all of the publications identified by the search strategy were independently screened for relevance by two reviewers (PB and KY). Following selection of potentially eligible studies, full-text reading and reviewing was independently performed. Finally, the two reviewers discussed the list of eventually eligible studies, and if discrepancies existed that could not be resolved between the two reviewers, a third reviewer (YS) was consulted in order to make the final decision. For the Chinese databases, the same procedure was followed by two independent Chinese

reviewers (YL and TZ).

For all potentially eligible studies, if information was lacking within the full-text article that limited the ability to make a final decision on whether or not the study should be included, the corresponding author of that study was contacted by mail or phone.

The final protocol for this review was registered on the international prospective register of systematic reviews (PROSPERO) with the registration number: CRD42019138227 prior to starting the data analysis.

3.6. Quality appraisal

The quality of included studies was assessed independently by two reviewers. Risk of bias and applicability of population, index and reference tests to the main review questions were evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (23). A list of the signalling questions used for QUADAS2 are presented in **Appendix B**.

3.7. Data extraction

The data were extracted from the selected studies by the two independent reviewers for each of the English (PB and KY) and Chinese articles (YL and TZ), using a pre-piloted data extraction form (**Appendix C**). In case of disagreement in the data extracted between the two reviewers, a deliberation that involved a third person (YS) was carried out.

During data extraction, articles from the same study sites with overlapping recruitment periods, enrolment criteria, and treatment types were considered as being part of one study. The lead reviewer for both English (PB) and Chinese (YL) articles then followed up with the corresponding author(s) from each of the article groups in order to understand if there was any patient overlap. If the authors explicitly stated in their article that there is overlap, or if the authors responded to the email inquiry confirming overlap, or if the author did not respond, then only the data extracted from the most recently published article was used in data analysis. If authors denied any patient overlap between articles then data extracted from all the articles within the group were used. In the

case of a group of articles from the same study where some articles were published in Chinese and some in English, the latest English article was included in the data analysis sheet, unless a direct communication with the study authors directed the reviewers to use a different article in the group.

3.8. Data synthesis

All statistical analyses were performed using STATA 14.2 (Stata Corp LP, College Station, TX).

Sensitivity and specificity were estimated at each of different HBV DNA thresholds used in the included studies ($\geq 20\ 000\ IU/mL$, $\geq 5\ log_{10}\ IU/mL$, $\geq 6\ log_{10}\ IU/mL$, $\geq 7\ log_{10}\ IU/mL$ and $\geq 8\ log_{10}\ IU/mL$). In case a single study presented the results at multiple HBV DNA thresholds, all the different thresholds were used. In addition, for PICO2B and 2C, sensitivity and specificity were estimated specifically for each measure of prevention for HBV MTCT. The summary statistics were pooled only when there were at least three studies.

We performed bivariate analysis for studies allowing estimation of both sensitivity and specificity. Study-specific estimates of sensitivity and specificity along with their 95% CI were graphically presented in coupled forest plots. When there were at least three studies, the summary estimates for sensitivity and specificity along with their 95% CI were obtained using the DerSimonian–Laird bivariate random effects model. Positive and negative likelihood ratios (PLR, NLR) with 95% CIs were obtained from the pooled sensitivity and specificity. When there were <3 studies, the range of sensitivity, specificity, PLR, and NLR, were presented. Pre-test probabilities were estimated by pooling the proportion of pregnant women with CHB who had high viral loads. After the variance of the proportions was stabilized using Freeman–Tukey double arcsine transformation, these estimates were pooled using the DerSimonian–Laird random-effects model (24). Post-test probabilities were computed using the pre-test probabilities and the pooled PLR and NLR.

Heterogeneity in the estimates across the studies was visually assessed using: (i) coupled forest plots displaying study-specific estimates of sensitivity and specificity, and (ii) summary scatter plots. The summary scatter plots were presented without a summary receiver operating characteristic (SROC) curve for PICO2A and with a SROC curve for PICO2B and 2C.

Characteristics of the outlier studies were narratively described. A sensitivity analysis was also performed after excluding these outlier studies.

Heterogeneity was also assessed statistically, by considering the following variables as a priori potential sources of heterogeneity: type of HBeAg assay, type of reference standard (commercial PCR vs other/not reported), mean/median maternal age, maternal virological characteristics (HIV/HCV/HDV coinfection status and HBV genotypes), WHO region, and study's risk of bias (high vs low). In addition, for PICO2B and 2C, the measures of prevention for HBV MTCT were considered. Models fitted with and without the covariate were compared using likelihood ratio tests assuming equal variances. When there was good evidence (P<0.05) to support the heterogeneity, another model was fitted with separate variances and compared to the model with equal variances to understand if the heterogeneity observed could be due to the differences in variances between studies within a category rather than differences between categories of variables identified as potential sources of heterogeneity.

To integrate estimates from studies that provided data only for sensitivity or specificity, we performed univariate analyses using the DerSimonian–Laird univariate random effects model. When the study estimates could not be pooled (<3 studies), the range of sensitivity and specificity was presented.

Publication bias was assessed using Deeks' test, which was developed specifically for diagnostic accuracy reviews and is the method recommended in the Cochrane Handbook for Diagnostic Test Accuracy Reviews (25). It tests the asymmetry of the plot of log diagnostic odds ratio (lnDOR) against 1/effective sample size (ESS)^{1/2}. The ESS is a function of the number of diseases (n₁) and non-diseased participants (n₂) ((4n₁*n₂)/(n₁ + n₂)) and this takes into account the numbers of diseased and non-diseased participants (26,27).

The post-hoc analysis 1 was conducted as below. For the studies using "IU/mL" as a unit for HBV DNA levels, MTCT risk was estimated for the following maternal HBV DNA levels during pregnancy: <4.00; 4.00–4.99; 5.00–5.99; 6.00–6.99; and \geq 7.00 log₁₀ IU/mL. For those using "copies/mL", the maternal viral load was transformed into "IU/mL" (by dividing by the factor of 5) and risk was estimated for the following HBV DNA levels: <4.30; 4.30–5.29; 5.30–6.29; 6.30–

7.29; and \geq 7.30 log₁₀ IU/mL. In case a single study presented the results at multiple HBV DNA thresholds, all different thresholds were used.

Once the HBV DNA level where the risk of MTCT was identified despite infants' immunoprophylaxis, post-hoc analysis 2 was conducted. The sensitivity and specificity of the HBeAg test to diagnose this HBV DNA threshold were estimated using the method described above.

3.9. GRADE review process

For each examined PICO question, the quality of the evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation methodology (GRADE) (28). We used this tool to evaluate: (i) the risk of bias; (ii) inconsistency (high heterogeneity); (iii) imprecision (confidence intervals); (iv) indirectness (use of surrogate outcomes); (v) reporting and publication bias; and (vi) other factors; for each of the outcomes. This eventually gave a score of high (further research is very unlikely to change the effect estimate), moderate, low or very low (all estimates are very uncertain). Decisions for the complex judgements within the GRADE table were made through study group consensus. The study group reviewers were supported in the process of completing this GRADE template through discussion and advice from a WHO-designated methodological expert, Professor Roger Chou (Oregon Health & Science University, USA). For this specific meta-analysis, the following rules were used to determine whether or not a group of studies had no serious, serious, or very serious issues with regard to GRADE criteria:

- GRADE scoring system:

As cohorts and cross-sectional studies can provide reliable evidence for diagnostic accuracy, strength of evidence was initially rated as high quality (29). Then, strength of evidence was lowered by one degree if there was "serious" and by two degrees if there was "very serious" risk of bias, inconsistency, indirectness or imprecision. The strength of evidence was similarly lowered by one degree if publication bias was "likely" and by two degrees if the bias was "very likely" (30).

- Risk of bias:

A study was considered as "high" overall risk of bias when multiple QUADAS-2

domains were rated as "high risk of bias". Then, for each outcome, the number of studies with "high risk of bias" was counted. The risk of bias for the outcome was rated as "very serious", "serious" or "not serious" when the proportion of studies rated as "high risk of bias" was >75%, >50-75% or $\le50\%$, respectively.

- Indirectness:

Indirectness is linked with the level of applicability of the study population, index test or reference standard to the review question. A study was considered as "high" overall concern about applicability when at least one out of the three QUADAS-2 domains was rated as "high concern about applicability". Then, for each outcome, the number of studies with "high concern about applicability" was counted. Indirectness for the outcome was rated as "very serious", "serious" or "not serious" when the proportion of studies rated as "high concern about applicability" was >75%, >50-75% or $\le 50\%$, respectively (29).

- Imprecision:

Imprecision was considered "not serious" when an absolute range in the 95% confidence intervals (95% CI) for a pooled sensitivity or specificity was $\leq 20\%$. Imprecision was "serious" or "very serious" when the range was 20–40% or >40%. Moreover, when the cumulated sample size for all included studies was <30, it was categorized as "very serious".

- Inconsistency:

Inconsistency was considered "not serious" when $\geq 75\%$ of studies' estimates were within $\pm -20\%$ of the pooled estimate for an outcome. Inconsistency was considered "serious" or "very serious" when this proportion was 50–75% or <50%.

- Publication bias:

This was not assessed as part of the GRADE, because none of the studies, except one, was designed to assess diagnostic accuracy. Therefore, the analysis based on the diagnostic odds ratio seemed irrelevant.

4. RESULTS

4.1. Flowchart for PICO questions

The search strategy identified a total of 9001 papers. After excluding 3784 articles in duplicate, 5217 were screened, and 1341 papers potentially eligible for the study were fully assessed. Finally, 82 papers were included in this review (Fig. 1). Reasons for exclusion are presented in Fig. 1.

Fig. 1. PRISMA diagram



4.2. PICO2A: Performance of HBeAg to identify women with high HBV DNA viral loads

Detailed characteristics of each included study are presented in Table 2.

Author, year	PICO2A	Countr y	Original study design	HBV DNA thresho ld(s) (IU/mL)	HBV DNA assay	HBeAg assay	MTC T clinic al endpo int	Particip ants with both index and referen ce standar d test, n	Matern al age (years)	HIV, n (%)	Childr en tested, n
Bai H, 2010 <i>(31)</i>	Bivariate	China	Retrospe ctive cohort	5 log10	PCR Da'an Gene	FIA (Anytest SYM- BIO)	No	120	Mean (SD): 27.2 (3.2)	Unkn own	N/A
Bissinger A, 2013 (32)	Bivariate	Germa ny	Cross- sectional	5 log10	PCR COBAS Taqman (Roche)	ELISA (ETI-EBK PLUS Diasorin)	No	183	Median : 31	Unkn own	N/A
Cai J, 2005 <i>(33)</i>	Bivariate	China	Cross- sectional	5 log10	Real-Time Fluorescence quantitative PCR (PG Biotech)	ELISA (WB-2496 HBeAg Wantai)	No	709	Unkno wn	Unkn own	N/A
Cai S, 2009 <i>(34)</i>	Bivariate	China	Cross- sectional	20,000	Real-Time Fluorescence quantitative PCR (Kelong Bio-hightech)	ELISA (Intec HBeAg)	No	198	Unkno wn	Unkn own	N/A
Carey I, 2017 <i>(35)</i>	Univaria te (Specific ity)	UK	Cross- sectional	5 log10	PCR COBAS Taqman (Roche)	CLIA (Architect Abbott)	No	238	Unkno wn	Unkn own	N/A
Carey I, 2018 <i>(36)</i>	Bivariate	UK	Cross- sectional	5 log10	PCR COBAS Taqman (Roche)	CLIA (Architect Abbott)	No	514	Median : 31	Unkn own	N/A
Chang C, 2017 <i>(37)</i>	Univaria te (Sensitiv ity)	USA	Retrospe ctive cohort	5 log10	PCR (unknown manufacturer)	Unknown	No	32	Mean (SD): 29 (4)	Unkn own	N/A
Chen T, 2018 (38)	Bivariate	China	Prospecti ve cohort	6 log10	PCR Da'an Gene	CLIA (Architect Abbott)	Yes	499	Median (Range): 27 (19-42) (n=951)	Unkn own	499
Chen T, 2018 (39)	Univaria te (Sensitiv ity)	China	Prospecti ve cohort	6 log10	PCR Da'an Gene	CLIA (Architect Abbott)	Yes	48	Median (Range): 24.25 (19-38)	0/48 (0.0%)	48
Chen Z, 2017 (40)	Bivariate	China	Prospecti ve cohort	5 log10	Real-Time Fluorescence quantitative PCR (Kehua Bio- engineering)	ELISA (AxSYM Abbott)	Yes	211	Mean: 26.96	0/211 (0.0%)	168
Cheng S, 2006 (41)	Bivariate	China	Prospecti ve cohort	20,000	PCR (unknown manufacturer)	ELISA (Unknown	No	110	Unkno wn	Unkn own	N/A

Table 2. Characteristics of the 82 studies included for the PICO2A

						manufactu					
Cheung K, 2019 (42)	Bivariate	China	Cross- sectional	6, 7 & 8 log10	PCR COBAS Taqman (Roche)	CLIA (Elecsys Roche)	No	325	Median (IQR): 32 (26- 38)	Unkn own	N/A
Chotun N, 2017 <i>(43)</i>	Bivariate	South Africa	Prospecti ve cohort	20,000 & 5 log10	PCR COBAS Taqman (Roche)	CLIA (Architect Abbott)	Yes	6	Mean (Range): 27 (21-34)	0/6 (0.0%)	4
Dervisevic S, 2007 (44)	Bivariate	UK	Prospecti ve cohort	5 log10	PCR COBAS Taqman (Roche)	Unknown	No	114	Unkno wn	Unkn own	N/A
Ding Y, 2013 (45)	Bivariate	China	Prospecti ve cohort	7 log10	PCR COBAS Taqman (Roche)	CLIA (Architect Abbott)	Yes	249	Unkno wn (Range : 16- 45) (n=453 6)	Unkn own	249
Dolman G, 2018 <i>(46)</i>	Bivariate	UK	Cross- sectional	5 log10	Unknown	CLIA (Architect Abbott)	No	423	Median (IQR): 30 (28- 35)	Unkn own	N/A
Dopico E, 2013 (47)	Bivariate	Spain	Cross- sectional	7 log10	PCR Abbott	CLIA (Ortho Vitros)	No	4	Unkno wn	Unkn own	N/A
Dyson J, 2014 <i>(48)</i>	Bivariate	UK	Retrospe ctive cohort	20,000 & 7 log10	Unknown	Unknown	No	56	Median (Range): 28 (18-40) (n=81)	2/81 (2.5%)	N/A
Eilard A, 2019 <i>(49)</i>	Bivariate	Swede n	Prospecti ve cohort	7 log10	PCR COBAS Taqman (Roche)	CLIA (Architect Abbott)	Yes	42	Mean: 32.3	0/42 (0.0%)	44
Elefsinioti s I, 2007 (50)	Bivariate	Greece	Cross- sectional	7 log10	PCR Amplicor HBV Monitor test (Roche)	ELISA (AxSYM Abbott)	No	63	Unkno wn	Unkn own	N/A
Foaud HM, 2019 (51)	Bivariate	Egypt	Prospecti ve cohort	5 log10	Real-time PCR MX 400	ELISA (ETI-EBK PLUS Diasorin)	Yes	41	Mean: 27.3	0/41 (0.0%)	39
Fujiko M, 2015 <i>(52)</i>	Bivariate	Indone sia	Cross- sectional	6 log10	PCR COBAS Taqman (Roche)	ELISA (Monolisa HBeAg- Ab PLUS Bio-Rad)	No	64	Median (Range): 29 (Range : 18- 42)	0/64 (0.0%)	N/A
Godbole G, 2013 (53)	Bivariate	UK	Cross- sectional	6 & 7 log10	PCR Abbott	CLIA (Elecsys Roche or Architect Abbott)	No	293	Median (Range): 29 (15-46)	Unkn own	N/A
Guo F, 2007 <i>(54)</i>	Bivariate	China	Cross- sectional	6 log10	Real-Time Fluorescence quantitative PCR (PG Biotech)	ELISA (Intec HBeAg)	No	319	Unkno wn	Unkn own	N/A
Han Y, 2007 (55)	Bivariate	China	Prospecti ve cohort	20,000	PCR (Haoyuan Biotech)	CLIA (Elecsys Roche)	No	69	Mean (Range): 26 (22-38)	Unkn own	N/A
Hao X, 2015 (56)	Bivariate	China	Prospecti ve cohort	5 log10	Real-Time Fluorescence quantitative PCR (Shanghai Fosun	ELISA (Kehua HBeAg test)	No	154	Mean (SD): 27.4 (4.3)	Unkn own	N/A

					Pharmaceutic						
Hu O	Diversiete	China	Cross	20.000	al Group)	ELICA	No	420	Moon	0/420	NI/A
2007(57)	Divariate	China	sectional	20,000 & 7	Fluorescence	(Robio	INO	420	(Range	(0.0%)	IN/A
2007 (07)				log10	quantitative	RongShen): 25)	
				U	PCR (PG	g)			(18-37)	,	
					Biotech)				(n=365		
	D: : : /	CI.	D (51 10	TT 1		N	22.4	8)	XX 1	NT/A
Huang L, $2014(58)$	Bivariate	China	Retrospe	$5 \log 10$	Unknown	ELISA	No	324	Unkno	Unkn	N/A
2014 (36)			cohort			(Dayou HBeAg			(Range	own	
			conort			Dakewe)			: 20-		
									36)		
Jackson V,	Univaria	Ireland	Retrospe	6 log10	Real-Time	CLIA	Yes	36	Median	Unkn	21
2015 (59)	te		ctive		Fluorescence	(Architect			(Range	own	
	(Sensitiv		cohort		quantitative	Abbott)): 26		
	ity)				PCR (Kehua				(16-40)		
					engineering)						
Jin C.	Bivariate	China	Cross-	6 log10	PCR Da'an	Unknown	No	204	Unkno	Unkn	N/A
2007 (60)			sectional	*8-*	Gene				wn	own	
Johanness	Bivariate	Ethiopi	Prospecti	6 log10	PCR Abbott	ELISA	No	63	Median	Unkn	N/A
en A, 2017		а	ve cohort			(Vidas			(Range	own	
(61)						HBeAg/an): 28		
						ti-Hbe Biomóriou			(18-41) (n-121)		
						x))		
Köse S,	Bivariate	Turkey	Retrospe	20,000	PCR COBAS	ELISA	No	7	Mean	0/7	N/A
2011 (62)		-	ctive	& 5,6,7	Taqman	(Liaison			26.5	(0.0%	
			cohort	log10	(Roche)	Diasorin)			(4.0))	
Kubo A,	Bivariate	USA	Retrospe	5 &7	Real-Time	ELISA	Yes	835	Mean	Unkn	835
2014 (63)			ctive	log10	Fluorescence	(Unknown			(SD):	own	
			conort		PCP (Kebua	manulaciu			31(3.3) (n=444		
					Bio-	ici)			(II +++ 6)		
					engineering)				0)		
Lao PDR	Bivariate	China	Cross-	8 log10	PCR COBAS	Unknown	No	56	Mean:	Unkn	N/A
T, 2012			sectional		Taqman				31.95	own	
(64)	Disconists	Tee	Duranati	5110	(Roche)		Vee	152	Malian	1/152	120
avang V	Divariate	PDR	ve cohort	5 log10	PCR (Fast-	(Monolisa	ies	155	(IOR).	(0.7%)	120
2019(65)		TDR	ve conort		track	HBeAg-			28 (24-)	
(00)					Diagnostics)	Ab PLUS			30)	,	
						Bio-Rad)			-		
Lee L,	Bivariate	Singap	Prospecti	20,000	PCR artus	CLIA	Yes	161	Mean	Unkn	154
2015 (66)		ore	ve cohort		HBV PCR	(Architect			(SD):	own	
					Kits, OIAGEN	Abbott)			32.4 (4.7)		
Li X. 2018	Bivariate	China	Retrospe	20,000	Real-Time	CLIA	No	716	Unkno	0/716	N/A
(67)			ctive	& 5, 6,	Fluorescence	(Architect			wn	(0.0%	
			cohort	7 log10	quantitative	Abbott))	
					PCR						
					(Shanghai						
					Phormacoutie						
					al Group)						
Li Y, 2013	Bivariate	China	Prospecti	20,000	Real-Time	ELISA	No	140	Unkno	0/140	N/A
(68)			ve cohort	& 7	Fluorescence	(Unknown			wn	(0.0%	
				log10	quantitative	manufactu)	
					PCR	rer)					
Liong D	Divoriata	China	Cross	5 10~10	(loyobo)	CLIA	Nc	201	Unima	0/201	NI/A
2017 (60)	Divariate	Cinina	sectional	5 10810	real-time	(Architect	110	371	wn	(0.0%	1N/2A
2017 (09)			sectional		PCR system	Abbott)			***1)	
					(Applied	,				,	
					Biosystems)						
Lin J,	Bivariate	China	Retrospe	20,000	Real-Time	ELISA	No	69	Unkno	Unkn	N/A
2002 (70)			ctive	& 5, 6	Fluorescence	(WB-2496			wn	own	
1		1	conort	logiu	quantitative	1	1	1	1	1	1

					PCR	HBeAg					
					(Biotromics technologies)	Wantai)					
Liu CP,	Univaria	China	Retrospe	6 log10	PCR Da'an	ELISA	Yes	256	Mean:	0/256	256
2015 (71)	te (Sensitiv		ctive		Gene	(HBeAg Santa-			25.7	(0.0%	
	(Sensitiv ity)		conort			Cruz))	
Liu H,	Bivariate	China	Case-	5 log10	PCR Da'an	CLIA	No	259	Mean	Unkn	N/A
2013 (72)			control		Gene	(Elecsys			(SD):	own	
Lin V	T.I	China	Duranti	(110	A.D.L. 7500	Roche)	V	110	28 (4)	0/110	70
2016(73)	te	China	ve cohort	0 log10	real-time	(Architect	ies	110	27 7	(0.0%)	/0
2010 (75)	(Sensitiv		ve conore		PCR system	Abbott)			27.7)	
	ity)				(Applied					· ·	
x x	Dist	G1 :	D	5 0 0	Biosystems)	TT A	N	22	X	XX 1	27/4
Lu H, $2009(74)$	Bivariate	China	Prospecti ve cohort	5 & 8	Real-lime	FIA (Anytest	No	33	Mean (Range	Unkn	N/A
2009 (74)			ve conort	10510	quantitative	SYM-): 26.2	0.011	
					PCR (PG	BIO)			(21-34)		
					Biotech)						
Lunel-	Bivariate	Camer	Prospecti	20,000	HBV Aptima,	Unknown	Yes	594	Median	1/592	133
2018(75)		oun	ve conort	$\begin{array}{c} \alpha & 3, 0, \\ 7 & 8 \end{array}$	Hologic				(1QK): 24 (20-	(0.2%)	
2010 (75)				log10					30))	
Ma Y,	Bivariate	China	Prospecti	20,000	PCR	ELISA	No	675	Mean	Unkn	N/A
2014 (76)			ve cohort		(unknown	(Unknown			(SD):	own	
					manufacturer)	manufactu			26.5		
Michitaka	Bivariate	Japan	Prospecti	6 log10	Real-Time	CLIA	No	21	(2.0) Median	Unkn	N/A
K, 2012	Difunate	vapan	ve cohort	0 10 51 0	Fluorescence	(Unknown	110		(IQR):	own	
(77)					quantitative	manufactu			34		
					PCR (Kehua	rer)			(IQR:		
					B10- engineering)				25-40)		
Peng N,	Bivariate	China	Cross-	5 log10	Real-Time	CLIA	No	410	Unkno	Unkn	N/A
2012 (78)			sectional	0	Fluorescence	(Architect		-	wn	own	
					quantitative	Abbott)					
					PCR (Kehua						
					engineering)						
Peng S,	Bivariate	China	Prospecti	6 log10	PCR Da'an	ELISA	Yes	1219	Mean:	0/121	93
2019 (79)			ve cohort		Gene	(Kehua			29.17	9	
						HBeAg)				(0.0%	
Pirillo M	Bivariate	Uganda	Cross-	6 10910	In-house PCR	ELISA	No	7	Unkno) 7/7	N/A
2007 (80)	Divariate	and	sectional	0 10510	in nouse i cit	(Murex	110	,	wn	(100.	1071
		Rwand				HBeAg/an				0%)	
D::11 M	Diana 1 d	a M-1	Dress (*	20.000	Verse (1DCD	ti-Hbe)	V-	21	M- 1	27/27	17
PITIIO M, 2015 (81)	Bivariate	Malawi	Prospecti ve.cohort	20,000	HRV DNA	CLIA (Architect	res	21	(IOR).	(100	1/
2013 (01)				7, 8	1.0 (Siemens)	Abbott)			27 (23-	0%)	
				log10	· · · · ·	,			30)	,	
D 1	D	LICA	D (71 10	TT 1	TT 1	N	200	(n=27)	11.1	200
Punzalan	Bivariate	USA	Retrospe	7 log10	Unknown	Unknown	Yes	200	Unkno	Unkn	200
(82)			cohort						WII	Owli	
Rouet F,	Bivariate	Ivory	Cross-	5 log10	Non-PCR	ELISA	No	77	Mean:	45/77	N/A
2004 (83)		Coast	sectional		(Quantiplex	(Murex			25	(58.4	
					HBV DNA, Boyer)	HBeAg/an			(n=501	%)	
Samadi	Bivariate	Canada	Prospecti	7 10910	PCR CORAS	CLIA	No	99) Median	0/99	N/A
Kochaksar	Divariate	Cunudu	ve cohort	, 10510	Taqman	(Architect	1.5		(IQR):	(0.0%	1.11.1
aei G,					(Roche)	Abbott)			32 (29-)	
2016 (84)	D	0.1	D	50 (0	DCD (DDT (CD	N	100	35)	11.1	NT/A
Segeral O, 2018 (85)	Bivariate	Cambo	Prospecti ve cohort	5 & 6 & 7 log10	PCR targeting	KDI (SD Bioline	No	128	(IOP)	Unkn	N/A
2010 (05)		uia	ve conort	/ 10g10	HBV (PUMA	HBeAg			29 (25-	Own	
					HBV kit,	test)			32)		
					Omunis)			1			

									(n=250		
Sellier P, 2017 (86)	Univaria te (Sensitiv ity)	France	Prospecti ve cohort	5 log10	PCR COBAS Taqman (Roche)	CLIA (Architect Abbott)	No	27) Mean (SD): 28.2 (4.7)	0/27 (0.0%)	N/A
Seo K, 2018 <i>(87)</i>	Univaria te (Sensitiv ity)	DR Korea	Retrospe ctive cohort	6 log10	PCR COBAS Taqman (Roche)	RIA (Abbott- Hbe Abbott)	No	41	Median (Range): 32 (22-40)	0/41 (0.0%)	N/A
Shao Z, 2011 (88)	Bivariate	China	Prospecti ve cohort	5 & 8 log10	PCR Amplicor HBV Monitor test (Roche)	ELISA (AxSYM Abbott)	Yes	212	Unkno wn	Unkn own	158
Sheng Q, 2018 (89)	Bivariate	China	Prospecti ve cohort	6 log10	PCR COBAS Taqman (Roche)	CLIA (Architect Abbott)	No	441	Mean (SD): 31.1 (4.5) (n=143 14)	Unkn own	N/A
Shi Y, 2012 <i>(90)</i>	Bivariate	China	Cross- sectional	20,000 & 7 log10	Real-Time Fluorescence quantitative PCR (Kehua Bio- engineering)	ELISA (Suzhou Sym-Bio)	No	452	Unkno wn	Unkn own	N/A
Söderströ m A, 2003 <i>(91)</i>	Bivariate	Swede n	Retrospe ctive cohort	5,6 & 7 log10	PCR Amplicor HBV Monitor test (Roche)	ELISA (AxSYM Abbott)	Yes	46	Unkno wn	Unkn own	264
Tang A, 2018 <i>(92)</i>	Univaria te (Sensitiv ity)	USA	Cross- sectional	5 log10	Real-Time Fluorescence quantitative PCR (Kehua Bio- engineering)	CLIA or ELISA (ELISA: Quest and BioRefere nce; CLIA: LabCorp)	No	203	Mean (Range): 29.2 (18-55) (n=978)	Unkn own	N/A
Tang Y, 2013 <i>(93)</i>	Bivariate	China	Cross- sectional	5 &7 log10	Real-Time Fluorescence quantitative PCR (Kehua Bio- engineering)	ELISA (Kehua HBeAg test)	No	500	Mean (Range): 27.8 (18-40)	Unkn own	N/A
Thilakanat han C, 2018 <i>(94)</i>	Bivariate	Austral ia	Retrospe ctive cohort	5 & 6 log10	PCR COBAS Taqman (Roche)	CLIA (Architect Abbott)	Yes	642	Median (Range): 30 (15-44)	Unkn own	469
Van Zonneveld M, 2003 (95)	Univaria te (Sensitiv ity)	The Netherl ands	Prospecti ve cohort	6 log10	Non-PCR (Digene Hybrid Capture I/II assay)	Unknown	Yes	8	Median (Range): 20 (17-25)	0/8 (0.0%)	8
Wang F, 2009 <i>(96)</i>	Bivariate	China	Retrospe ctive cohort	5 log10	Real-Time Fluorescence quantitative PCR (Sangon)	ELISA (Kehua HBeAg test)	No	1237	Unkno wn	Unkn own	N/A
Wang J, 2015 <i>(97)</i>	Univaria te (Sensitiv ity)	China	Prospecti ve cohort	6 log10	PCR Da'an Gene	CLIA (Architect Abbott)	Yes	48	Mean (SD): 29.31 (3.82)	0/48 (0.0%)	48
Wang J, 2018 <i>(98)</i>	Bivariate	China	Cross- sectional	6 log10	Real-Time Fluorescence quantitative PCR (Kehua Bio- engineering)	Unknown	No	567	Mean (SD): 27.27 (3.35) (n=141 32)	Unkn own	N/A

Wang L, 2016 (99)	Bivariate	China	Randomi zed controlle d trial	20,000 & 5,6, 7 log10	PCR Abbott	FIA (Anytest SYM- BIO)	No	31	Median (Range): 28.52 (19-39)	31/31 (100. 0%)	N/A
Wang M, 2018 (100)	Bivariate	China	Retrospe ctive cohort	5 log10	PCR Abbott	Unknown	No	76	Unkno wn (Range : 20- 40)	0/76 (0.0%)	N/A
Wang X, 2015 (101)	Bivariate	China	Prospecti ve cohort	5 log10	Real-Time Fluorescence quantitative PCR (Shanghai Fosun Pharmaceutic al Group)	CLIA (Architect Abbott)	No	409	Unkno wn	0/409 (0.0%)	N/A
Wang X, 2015 (102)	Bivariate	China	Case- control	5 log10	PCR COBAS Taqman (Roche)	ELISA (Unknown manufactu rer)	No	120	Unkno wn	Unkn own	N/A
Wang Z, 2018 (103)	Bivariate	China	Cross- sectional	6 log10	Unknown	Unknown	No	253	Mean (SD): 29.38 (4.77)	Unkn own	N/A
Wei K, 2017 (104)	Bivariate	China	Cross- sectional	5, 6, 7 & 8 log10	PCR Abbott	CLIA (Architect Abbott)	No	1741	Median (Range): 26 (15-43) (n=174 1)	0/174 1 (0.0%)	N/A
Wiseman, E, 2009 (105)	Bivariate	Austral ia	Prospecti ve cohort	5 & 8 log10	PCR Amplicor HBV Monitor test (Roche)	CLIA or ELISA (AxSYM Abbott or Architect Abbott)	Yes	313	Unkno wn	0/313 (0.0%)	138
Xu C, 2018 (106)	Bivariate	China	Cross- sectional	6 log10	Real-time fluorescence quantitative PCR reagents (Shenyou Biotechnolog y)	CLIA or ELISA (Kehua HBeAg or Architect Abbott)	No	214	Median (IQR): 25.3 (22.7- 30.2)	0/214 (0.0%)	N/A
Xu H, 2008 (107)	Bivariate	China	Cross- sectional	20,000 & 6 log10	Real-Time Fluorescence quantitative PCR (PG Biotech)	ELISA (Intec HBeAg)	No	198	Unkno wn	Unkn own	N/A
Yin Yu- zhu, 2013 (108)	Bivariate	China	Retrospe ctive cohort	5 &7 log10	PCR Da'an Gene	ELISA (Intec HBeAg)	Yes	1355	Mean (SD): 28.83 (3.92)	Unkn own	1360
Zhang L, 2017 <i>(109)</i>	Bivariate	China	Cross- sectional	20,000 & 5, 6, 7, 8 log10	Real-Time Fluorescence quantitative PCR (Sansure Biotech)	ELISA (Unknown manufactu rer)	No	491	Unkno wn	Unkn own	N/A
Zhang Q, 2009 (110)	Bivariate	China	Retrospe ctive cohort	20,000	PCR (unknown manufacturer)	ELISA (Unknown manufactu rer)	No	80	Unkno wn	Unkn own	N/A
Zheng H, 2010 (111)	Bivariate	China	Case- control	6 log10	Real-Time Fluorescence quantitative PCR (Kehua Bio- engineering)	ELISA (Kehua HBeAg test)	No	478	Mean (SD): 27 (6.2)	0/478 (0.0%)	N/A

Zhu	B,	Bivariate	China	Retrospe	5 log10	PCR COBAS	CLIA	Yes	53	Mean	0/53	53
2013 (112)			ctive	-	Taqman	(Elecsys			(SD):	(0.0%	
				cohort		(Roche)	Roche)			26 (4.1))	

4.2.1. Summary of included studies

There were 82 original studies, including 71 allowing estimation of both sensitivity and specificity, using bivariate analysis, and 11 that can be only used for the univariate analysis to estimate sensitivity only (n=10) or specificity only (n=1). Except for one randomized controlled trial, all were observational studies: 28 cross-sectional, 50 cohorts (31 prospective and 19 retrospective) and 3 case–control studies (Table 2).

Table 3 summarizes the characteristics of studies included in the PICO2A. Across all 82 studies, recruitment took place as early as 1989 and up until 2018. Most studies took place in the WHO Western Pacific Region (n=54); including China (n=47), Cambodia (n=1), Democratic Republic of Korea (n=1), Japan (n=1), Lao People's Democratic Republic (n=1), Singapore (n=1) and Australia (n=2). Fifteen studies took place in the WHO European Region: the United Kingdom (n=6), Sweden (n=2), France (n=1), Germany (n=1), Ireland (n=1), the Netherlands (n=1), Greece (n=1), Spain (n=1) and Turkey (n=1). Six studies took place in the WHO African Region: Ivory Coast (n=1), Uganda and Rwanda (n=1), Ethiopia (n=1), Malawi (n=1), South Africa (n=1), and Cameroon (n=1). Five studies took place in WHO region of the Americas: United States of America (n=4) and Canada (n=1). One study took place in the WHO South-East Asia Region in Indonesia, and one study took place in the WHO Eastern Mediterranean Region in Egypt (Table 2).

Of 82 studies, 52 reported maternal age; mean/median maternal age was higher in EUR/AMR regions (7/10 studies reporting a mean/median maternal age \geq 28 years in EUR and 4/4 in AMR) and lower in the AFR Region (only n=1/4 reporting mean/median maternal age \geq 28 years). EIA was most frequently used to assess pregnant women's HBeAg status (n=35/72, 48.6%) followed by CLIA (n=29/72, 40.3%) for all WHO regions except EUR where CLIA was more frequently used than EIA (8 using CLIA vs 4 using EIA). FIA (time-resolved fluoroimmunoassay) was used only in Chinese studies (n=3/72, 4.2%). Only 1 study (1.4%) used a rapid diagnostic test (*Ségéral O et al., 2018*). Most studies exclusively included women without coinfection: n=40/60 (66.7%)

for HIV, n=41/50 (82.0%) for HCV and n=26/30 (86.7%) for HDV). Only a few studies reported HBV genotypes (n=24/82) and, of this, the majority had mixed genotypes (n=18/24, 75.0%). Only two studies reported the frequency of indeterminate HBeAg results: *Kubo A et al.*, 2014 (n=4/835 (0.5%)) and *Tang A et al.*, 2018 (n=3/200 (1.5%)).

Subgroup variables	Subgroup category	Studies (N)	%
Overall		82	100.0
WHO region (n=82)	WPR	54	65.9
	SEAR	1	1.2
	EUR	15	18.3
	EMR	1	1.2
	AFR	6	7.3
	AMR	5	6.1
HBeAg assay type (n=72)	EIA	35	48.6
	FIA	3	4.2
	CLIA	29	40.3
	RDT	1	1.4
	Multiple	3	4.2
	CIA/RIA	1	1.4
Mean / median maternal age (n=52)	<28 years	24	46.2
	≥28 years	28	53.8
HIV status (n=60)	All uninfected	40	66.7
	All infected	11	18.3
	Mixed population	9	15.0
HCV status (n=50)	All uninfected	41	82.0
	All infected	0	0.0
	Mixed population	9	18.0
HDV status (n=30)	All uninfected	26	86.7
	All infected	0	0.0

Table 3. Characteristics of studies included in PICO2A

	Mixed population	4	13.3
Genotype (n=24)	Genotype A	2	8.3
	Genotype B	0	0.0
	Genotype C	1	4.2
	Genotype D	3	12.5
	Genotype E	0	0.0
	Mixed population	18	75.0

4.2.2. Risk of bias assessment

The risk of bias assessment is presented in Fig. 2 and 3 (full details are provided in **Appendix D**). Only one study was designed to evaluate the diagnostic performance of an HBeAg test in pregnant women, and had the same objective as that of the PICO2A (85). Therefore, for the other diagnostic studies included, essential information was often missing. Except for the one study that shared the same objectives as PICO2A (85), all were rated as having an unclear risk of bias for both the reference standard and the index tests due to the fact that they did not state whether or not blinding was performed (Fig. 2). The risk of selection bias was high in most studies (n=54/82, 65.9%), mainly due to restrictive exclusion criteria (e.g. exclusion of HIV-, HCV-, or HDV-coinfected pregnant women).

Concerns about applicability were low for most studies (Fig. 3). There was high concern for patient selection applicability in 13 studies (15.9%), due to the enrolment of pregnant women based on their HBV viral load. For two studies there was concern regarding the applicability of the index test, because HBeAg status was not systematically ascertained during the pregnancy. This was unclear for a further 14 studies (17.1%) that did explicitly report the timing of HBeAg testing or type of HBeAg assay test used.

Fig. 2. Risk of bias results for PICO2A



Fig. 3. Concerns about applicability results for PICO2A


4.2.3. Primary analysis, narrative descriptions and forest plots

4.2.3.1. Overall performance of HBeAg to identify pregnant women with high HBV DNA levels

Tables 4 and 5 present detailed performance results for PICO2A. Detailed results of the performance of HBeAg to identify pregnant women with high viral load \geq 5, 6 and 7 log IU/mL are presented in the following sections.

HBV DNA threshold (IU/mL)	Meta- analysis	Studies (N)	Subjects (N)	TP (N)	FN (N)	TN (N)	FP (N)	Se (95% CI) or Range Se	Sp (95% CI) or Range Sp
20,000	Bivariate	19	4506	1121	224	2598	563	91.0 (79.2-96.4)	91.8 (83.6-96.1)
	Univariate	-	-	-	-	-	-	-	-
5 log10	Bivariate	38	13734	3486	669	8684	895	84.2 (80.2-87.4)	92.3 (89.5-94.5)
	Univariate	42	14231	3719	695	8917	900	82.5 (79.0-85.5)	91.4 (88.9-93.5)
6 log10	Bivariate	27	9651	2109	160	6691	691	92.0 (88.2-94.6)	92.7 (90.3-94.5)
	Univariate	34	10196	2514	300	6691	691	88.9 (84.0-92.4)	91.7 (89.5-93.5)
7 log10	Bivariate	24	8825	1416	62	5972	1375	98.0 (93.3-99.4)	88.5 (80.7-93.4)
	Univariate	-	-	-	-	-	-	-	-
8 log10	Bivariate	9	3786	575	7	2578	626	98.5 (88.1-99.8)	83.9 (77.0-89.1)
	Univariate	-	-	-	-	-	-	-	-

Table 4. Performance of HBeAg to identify pregnant women with high viral load, stratified by HBV DNA threshold

Table 5. Post-test probabilities of having high viral load depending on HBeAg test results in pregnant women

HBV DNA threshold (IU/mL)	WHO region	Studies, N	Pre-test probability (%)	PLR (95% CI)	Post-test probability of having high viral load after positive HBeAg result (%)	NLR (95% CI)	Post-test probabilit y of having high viral load after negative HBeAg result (%)
20,000	Overall	19	34	11.1 (5.7-21.7)	79.1	0.10 (0.04-0.23)	3.2
	WPR	14	36	8.9 (4.3-18.6)	76.2	0.08 (0.03-0.24)	3.0
	AFR	3	21	31.4 (18.3-53.9)	86.8	0.15 (0.10-0.22)	3.1
5 log10	Overall	38	31	11.0 (7.9-15.3)	77.3	0.17 (0.14-0.22)	5.0
	WPR	26	37	7.9 (5.7-10.8)	74.4	0.18 (0.14-0.24)	6.3
	AFR	4	19	26.0 (14.5-46.8)	83.2	0.12 (0.05-0.33)	2.3
6 log10	Overall	27	22	12.6 (9.5-16.7)	73.5	0.09 (0.06-0.13)	1.9

	WPR	19	24	10.4 (8.0-13.6)	71.4	0.08 (0.05-0.13)	1.9
	AFR	4	16	24.90 (16.3-38.0)	79.9	0.07 (0.03-0.13)	1.0
7 log10	Overall	24	14	8.5 (5.0-14.6)	54.4	0.02 (0.01-0.08)	0.3
	WPR	12	14	4.6 (2.6-8.3)	39.3	0.03 (0.01-0.10)	0.4
	AFR	2	18	5.7-19.3	50.5-77.7	0.00-0.05	0.0-21.6
8 log10	Overall	9	11	6.1 (4.2-9.0)	40.3	0.02 (0.00-0.16)	0.2
	WPR	7	11	5.7 (3.7-8.6)	38.4	0.01 (0.00-0.49)	0.1
	AFR	2	13	4.5-11.1	36.9-59.0	0.00-0.03	0.0-10.5

4.2.3.2. Performance of HBeAg to identify pregnant women with HBV DNA \geq 5 log10 IU/mL

- Overall pooled sensitivity = 84.2% (95% CI: 80.2–87.4)
- Overall pooled specificity = 92.3% (95% CI: 89.5–94.5)

There was no evidence of publication bias (P=0.48) (Appendix G.1). However, the funnel plots for the assessment of publication bias were thought to be not very informative because only one study had the same objective as that of the PICO2A (85). We identified one outlier study (*Lin J, 2002*) through visual assessment of the overall coupled forest plot (Fig. 4) and the summary scatter plot (Fig. 5). This retrospective cohort study from China reported low sensitivity (40.5%) and high specificity (95.6%) of HBeAg to identify women with HBV viral load \geq 5 log10 IU/mL. Recruitment was from 1999 to 2000. HBV DNA was measured using a commercial PCR (real-time fluorescence quantitative PCR [Biotromics technologies]). HBeAg was determined by the ELISA test (WB-2496 Wantai). Maternal age and HIV status were not reported.

Author, year	TP/(TP+FN)	TN/(TN+FP)		Sensitivity (95% CI)	Specificity (95% CI)	
Lin J, 2002	17/42	25/27		0.40 (0.26, 0.57)		99)
Wang M, 2018	22/34	26/42	_	0.65 (0.46, 0.80)		76)
Rouet F, 2004	10/15	59/62		0.67 (0.38, 0.88)	- 0.95 (0.87, 0.9	99)
Carey I, 2018	50/72	430/442		0.69 (0.57, 0.80)	0.97 (0.95, 0.9	99)
Wang F, 2009	123/177	859/1060	-#-	0.69 (0.62, 0.76)	0.81 (0.79, 0.8	83)
Bissinger A, 2013	12/17	158/166		0.71 (0.44, 0.90)	0.95 (0.91, 0.9	98)
Cai J, 2005	181/244	428/465	+	0.74 (0.68, 0.80)	0.92 (0.89, 0.9	94)
Tang Y, 2013	156/210	248/300	+	0.74 (0.68, 0.80)	0.83 (0.78, 0.8	87)
Köse S, 2011	3/4	4/4		- 0.75 (0.19, 0.99)	——— 1.00 (0.40, 1.0	00)
Wang X, 2015	47/62	47/58	-8-	0.76 (0.63, 0.86)		90)
Ségéral O, 2018	26/34	91/94		0.76 (0.59, 0.89)	- 0.97 (0.91, 0.9	99)
Shao Z, 2011	33/43	155/169		0.77 (0.61, 0.88)	- 0.92 (0.86, 0.9	95)
Peng N, 2012	165/215	162/195	-	0.77 (0.71, 0.82)	- 0.83 (0.77, 0.8	88)
Latthaphasavang V, 2019	51/65	79/88	-8-	0.78 (0.67, 0.88)	- 0.90 (0.81, 0.9	95)
Chen Z, 2017	104/132	57/79	-=-	0.79 (0.71, 0.85)		82)
Hao X, 2015	30/37	106/117		0.81 (0.65, 0.92)	0.91 (0.84, 0.9	95)
Dolman G, 2018	26/32	384/391		0.81 (0.64, 0.93)	■ 0.98 (0.96, 0.9	99)
Wang L, 2016	9/11	20/20		- 0.82 (0.48, 0.98)	—= 1.00 (0.83, 1.0	00)
Söderström A, 2003	9/11	35/35		- 0.82 (0.48, 0.98)	- 1.00 (0.90, 1.0	00)
Zhang L, 2017	143/172	281/319	-	0.83 (0.77, 0.88)	0.88 (0.84, 0.9	91)
Liu H, 2013	138/165	77/94	-	0.84 (0.77, 0.89)		89)
Wiseman E, 2009	82/98	205/215	-8-	0.84 (0.75, 0.90)	0.95 (0.92, 0.9	98)
Yin Yu-zhu, 2013	435/512	810/848		0.85 (0.82, 0.88)	0.96 (0.94, 0.9	97)
Kubo A, 2014	127/147	652/688	-=	0.86 (0.80, 0.91)	0.95 (0.93, 0.9	96)
Lu H, 2009	7/8	21/25		- 0.88 (0.47, 1.00)		95)
Li X, 2018	150/171	524/545	-	0.88 (0.82, 0.92)	0.96 (0.94, 0.9	98)
Thilakanathan C, 2018	168/185	433/457	4	0.91 (0.86, 0.95)	0.95 (0.92, 0.9	97)
Lunel-Fabiani F, 2018	112/123	456/471	-	0.91 (0.85, 0.95)	0.97 (0.95, 0.9	98)
Liang P, 2017	131/143	220/248	-	0.92 (0.86, 0.96)	• 0.89 (0.84, 0.9	92)
Huang L, 2014	122/132	125/192	-	0.92 (0.87, 0.96)		72)
Wei K, 2017	568/606	1058/1135		0.94 (0.91, 0.96)	0.93 (0.92, 0.9	95)
Bai H, 2010	44/46	73/74	_	0.96 (0.85, 0.99)	 0.99 (0.93, 1.0 	00)
Wang X, 2015	133/138	203/271		 0.96 (0.92, 0.99) 	- 0.75 (0.69, 0.8	80)
Dervisevic S, 2007	13/13	101/101		1 .00 (0.75, 1.00)	■ 1.00 (0.96, 1.0	00)
Chotun N, 2017	1/1	5/5		1.00 (0.03, 1.00)		00)
Pirillo M, 2015	7/7	14/14		1.00 (0.59, 1.00)	—— 1.00 (0.77, 1.0	00)
Zhu B, 2013	24/24	26/29	-	■ 1.00 (0.86, 1.00)		98)
Foaud HM, 2019	7/7	27/34		1.00 (0.59, 1.00)		91)
			0.00 0.50	1.00 0.00	0.50 1.00	

Fig. 4. Coupled forest plot of the performance of HBeAg to identify pregnant women with HBV viral load \geq 5 log10 IU/mL



Fig. 5. Summary scatter plot of the performance of HBeAg to identify maternal HBV DNA \geq 5 log10 IU/mL

Subgroup analysis

Of the variables predefined as potential sources of heterogeneity, it was not possible to do a subgroup analysis by HCV- or HDV-coinfection status, nor by maternal HBV genotype as too few studies reported information on these factors.

Table 6 and Fig. 6 to 11 present detailed results of the performance of HBeAg to identify pregnant women with HBV DNA \geq 5 log10 IU/mL, stratified by the potential sources of heterogeneity.

There was some evidence of interaction by maternal age (P=0.02), with a higher sensitivity and lower specificity in studies of young mean/median maternal age (<28 years) (Fig. 10). There was strong evidence that the performance of HBeAg to identify pregnant women with HBV DNA ≥5 log IU/mL varied according to the WHO region (P=0.001), some evidence for HBeAg assay type (P=0.02), weak evidence for maternal HIV status (P=0.09) and no evidence for HBV DNA type of assay.

Subgroup	Subgroup	Studies	Se (95% CI) or	Sp (95% CI) or	P-value
variables	category	(N)	Range Se	Range Sp	
Overall		38	84.2 (80.2-87.4)	92.3 (89.5-94.5)	N/A
WHO	WPR	26	83.9 (79.2-87.7)	89.3 (85.6-92.1)	0.001*
region	SEAR	0	N/A	N/A	
	EUR	6	79.9 (65.4-89.3)	98.2 (95.7-99.3)	
	EMR	1	100.0	79.4	
	AFR	4	88.0 (70.9-95.7)	96.6 (94.3-98.0)	
	AMR	1	86.4	94.8	
HBeAg	EIA	19	79.4 (74.0-84.0)	90.4 (86.3-93.3)	0.02**
assay type	FIA	3	91.4 (78.5-96.9)	96.6 (81.2-99.5)	
	CLIA	12	89.1 (83.2-93.0)	92.8 (88.1-95.8)	
	RDT	1	76.5	96.8	
	Multiple	1	83.7	95.3	
	Commercial PCR	34	83.7 (79.5-87.1)	91.9 (89.0-94.0)	0.58

Table 6. Performance of HBeAg to identify pregnant women with HBV viral load \geq 5 log10 IU/mL, stratified by potential sources of heterogeneity

HBV DNA	In-house or	4	87.8 (76.4-94.2)	95.0 (80.4-98.9)	
assay type	unknown test				
Mean /	<28 years	12	89.7 (83.6-93.7)	91.8 (86.1-95.3)	0.02
median maternal age	≥28 years	10	82.3 (77.6-86.2)	95.3 (92.8-97.0)	
HIV status	All uninfected	12	89.4 (82.7-93.7)	89.0 (81.7-93.6)	0.09***
	All infected	3	82.6 (55.8-94.7)	98.2 (74.7-99.9)	
	Mixed population	3	83.6 (71.8-91.0)	94.5 (89.9-97.1)	

*comparison of WPR/EUR/AFR

**comparison CLIA/EIA/FIA

*** comparison all HIV uninfected vs all HIV infected

Fig.	6. Coupled	l forest	plot of the	performance	of HBeAg	to identify	/ maternal	HBV	DNA
≥5 1	og10 IU/m	L by W	HO region						

WHO region and				Sensitivity	Specificity	y
Author, year	TP/(TP+FN)	TN/(TN+FP)		(95% CI)	(95% CI)	
WPRO						
Lin J, 2002	17/42	25/27		0.40 (0.26, 0.57)		6, 0.99)
Wang M, 2018	22/34	26/42		0.65 (0.46, 0.80)		6, 0.76)
Wang F, 2009	123/177	859/1060		- 0.69 (0.62, 0.76)	0.81 (0.79	9, 0.83)
Cai J, 2005	181/244	428/465		- - 0.74 (0.68, 0.80)	0.92 (0.89	9, 0.94)
Tang Y, 2013	156/210	248/300		- 0.74 (0.68, 0.80)	0.83 (0.78	3, 0.87)
Wang X, 2015	47/62	47/58				9, 0.90)
Ségéral O, 2018	26/34	91/94			· D 0.97 (0.91	1, 0.99)
Shao Z, 2011	33/43	155/169			- 0.92 (0.86	6, 0.95)
Peng N, 2012	165/215	162/195		■ 0.77 (0.71, 0.82)	- 0.83 (0.77	7, 0.88)
Latthaphasavang V, 2019	51/65	79/88			- 0.90 (0.81	1, 0.95)
Chen Z, 2017	104/132	57/79				1, 0.82)
Hao X, 2015	30/37	106/117		0.81 (0.65, 0.92)	- 0.91 (0.84	4, 0.95)
Wang L, 2016	9/11	20/20		0.82 (0.48, 0.98)		3, 1.00)
Zhang L, 2017	143/172	281/319		- 0.83 (0.77, 0.88)	0.88 (0.84	4, 0.91)
Liu H, 2013	138/165	77/94				3, 0.89)
Wiseman E. 2009	82/98	205/215			■ 0.95 (0.92	2. 0.98)
Yin Yu-zhu, 2013	435/512	810/848		0.85 (0.82, 0.88)	• 0.96 (0.94	1. 0.97)
Lu H. 2009	7/8	21/25		0.88 (0.47, 1.00)		4, 0, 95)
Li X. 2018	150/171	524/545		■ 0.88 (0.82, 0.92)	0.96 (0.94	4. 0.98)
Thilakanathan C. 2018	168/185	433/457		 0.91 (0.86, 0.95) 	0.95 (0.92	2. 0.97)
Liang P. 2017	131/143	220/248		- 0.92 (0.86, 0.96)	0.89 (0.84	4. 0.92)
Huang L. 2014	122/132	125/192		• 0.92 (0.87, 0.96)		3. 0.72)
Wei K. 2017	568/606	1058/1135		0.94 (0.91, 0.96)	0.93 (0.92	2. 0.95)
Bai H. 2010	44/46	73/74		- 0.96 (0.85, 0.99)	- 0.99 (0.93	3. 1.00)
Wang X. 2015	133/138	203/271		0.96 (0.92, 0.99)	- 0.75 (0.69	9. 0.80)
Zhu B, 2013	24/24	26/29		— 1.00 (0.86, 1.00)		3, 0.98)
EURO						
Carev I. 2018	50/72	430/442			• 0.97 (0.95	5. 0.99)
Bissinger A, 2013	12/17	158/166		0.71 (0.44, 0.90)	■ 0.95 (0.91	1. 0.98)
Köse S, 2011	3/4	4/4	_	0.75 (0.19, 0.99)	——— 1.00 (0.40), 1.00)
Dolman G, 2018	26/32	384/391			■ 0.98 (0.96	6, 0.99)
Söderström A, 2003	9/11	35/35		0.82 (0.48, 0.98)	- 1.00 (0.90), 1.00)
Dervisevic S, 2007	13/13	101/101		—— 1.00 (0.75, 1.00)	■ 1.00 (0.96	6, 1.00)
EMRO						
Foaud HM, 2019	7/7	27/34		─── 1.00 (0.59, 1.00)		2, 0.91)
AFRO						
Rouet F, 2004	10/15	59/62		<u> </u>	- 0.95 (0.87	7, 0.99)
Lunel-Fabiani F, 2018	112/123	456/471		0.91 (0.85, 0.95)	0.97 (0.95	5, 0.98)
Chotun N, 2017	1/1	5/5		■ 1.00 (0.03, 1.00)	—— 1.00 (0.77	7, 1.00)
Pirillo M, 2015	7/7	14/14		1.00 (0.59, 1.00)	1.00 (0.48	3, 1.00)
AMRO						
Kubo A, 2014	127/147	652/688		0.86 (0.80, 0.91)	■ 0.95 (0.93	3, 0.96)
			0.00			
			0.00	0.00 1.00	0.00 0.30 1.00	

Type of HBeAg assay			Sensitivity	Specificity
and Author, year	TP/(TP+FN)	TN/(TN+FP)	(95% CI)	(95% CI)
FIΔ				
Lin J. 2002	17/42	25/27	0.40 (0.26, 0.57)	
Rouet F. 2004	10/15	59/62	0.67 (0.38, 0.88)	- 0.95 (0.87, 0.99)
Wang F. 2009	123/177	859/1060		0.81 (0.79, 0.83)
Bissinger A 2013	12/17	158/166		■ 0.95 (0.91 0.98)
Cai J 2005	181/244	428/465	- 0.74 (0.68, 0.80)	
Tang Y 2013	156/210	248/300	- 0.74 (0.68, 0.80)	
Köse S 2011	3/4	240/000		
Wang X 2015	47/62	47/58		
Shao 7 2011	33/43	155/169		- 0.92 (0.86, 0.95)
Latthanhasavang V 2019	51/65	79/88		
Chen 7 2017	104/132	57/79		
Hao X 2015	30/37	106/117		- 0.91 (0.84 0.95)
Söderström A 2003	9/11	35/35		- 1 00 (0 90 1 00)
Zhang L 2017	1/13/172	281/310		
	/35/512	810/8/8		
Kubo A 2014	127/147	652/699		
Lunel-Eabiani E 2018	127/147	456/471		
	12/123	430/47 1		
Found HM 2010	7/7	123/192		
F0auu Hivi, 2019	///	21/34	■ 1.00 (0.39, 1.00)	
FIA				
Wang L 2016	9/11	20/20	0.82 (0.48, 0.98)	— 1 00 (0 83 1 00)
Lu H 2009	7/8	21/25		
Bai H. 2010	44/46	73/74	- 0.96 (0.85, 0.99)	■ 0.99 (0.93, 1.00)
				(,)
CLIA				
Carey I, 2018	50/72	430/442		 0.97 (0.95, 0.99)
Peng N, 2012	165/215	162/195	■ 0.77 (0.71, 0.82)	0.83 (0.77, 0.88)
Dolman G, 2018	26/32	384/391		0.98 (0.96, 0.99)
Liu H, 2013	138/165	77/94	- 0.84 (0.77, 0.89)	
Li X, 2018	150/171	524/545	0.88 (0.82, 0.92)	 0.96 (0.94, 0.98)
Thilakanathan C, 2018	168/185	433/457	 0.91 (0.86, 0.95) 	 0.95 (0.92, 0.97)
Liang P, 2017	131/143	220/248	- 0.92 (0.86, 0.96)	 0.89 (0.84, 0.92)
Wei K, 2017	568/606	1058/1135	0.94 (0.91, 0.96)	 0.93 (0.92, 0.95)
Wang X, 2015	133/138	203/271	0.96 (0.92, 0.99)	• 0.75 (0.69, 0.80)
Pirillo M, 2015	7/7	14/14	——— 1.00 (0.59, 1.00)	—— 1.00 (0.77, 1.00)
Chotun N, 2017	1/1	5/5	——— 1.00 (0.03, 1.00)	——— 1.00 (0.48, 1.00)
Zhu B, 2013	24/24	26/29	—1 .00 (0.86, 1.00)	
RDT				
Ségéral O, 2018	26/34	91/94		■ 0.97 (0.91, 0.99)
Multiple				
Wiseman E, 2009	82/98	205/215		 0.95 (0.92, 0.98)
			0.00 0.50 1.00 0.00	0.50 1.00

Fig. 7. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 5 log10 IU/mL by type of HBeAg assay

Table and continue table TP(TP+FN) TN(TN+FP) Derivative Section of the content of the conten of the content of the content of the content of the content o						Constitute :			On a sifi site :	
Inite at Control, res IF (11, 11, 11, 11) IF (11, 11, 11, 11) IF (11, 11, 11, 11, 11) Weag (5, 2005 123, 117, 153, 115, 12, 12, 12, 12, 12, 12, 12, 12, 12, 12	HBeAg assay commercial					Sensitivity			Specificity	
Besch gehne Bio-Engloering Construction Consteteset set set set set set set set set	hame and Author, year	1F/(1F + FIN)				(93%01)			(95 % 01)	
mark 2: 2000 mark 2: 2001	HBeAg Kebus Bio-Engin	eering								
Trang Y: 2013 155210 266/20 0.71 (0.56, 0.50) 0.72 (0.56, 0.50) Hao X, 2015 30037 100/117 - - 0.81 (0.56, 0.32) 0.91 (0.54, 0.02) Shoz, 2011 33/43 159/169 - 0.77 (0.51, 0.85) - 0.82 (0.76, 0.02) Shoz, 2011 33/43 159/169 - 0.77 (0.51, 0.85) - 0.82 (0.56, 0.02) Shoz, 2017 10/113 35/55 - 0.82 (0.46, 0.08) - 0.82 (0.46, 0.08) Shoz, 2013 435/57.12 81/0/48 0.85 (0.82, 0.88) - 0.98 (0.87, 0.08) There HeAp, ELSA Thin 10/15 59/62 - 0.67 (0.36, 0.88) 0.98 (0.87, 0.08) Morolia HisAp, Samoli 11 59/62 - 0.67 (0.36, 0.88) 0.98 (0.87, 0.98) Cill 2005 18/12/44 42/8/465 - 0.74 (0.86, 0.80) 0.93 (0.76, 0.80) EFLEK/PLUS Diasofn 158/167 100/15 - 0.97 (0.26, 0.57) - 0.93 (0.76, 0.80) 0.93 (0.76, 0.80) 0.93 (0.76, 0.80) 0.93 (0.76, 0.80) 0.93 (0.76, 0.80) 0.93 (0.76, 0.80) 0.93 (0.76, 0.80) 0.93 (0.76, 0.80)	Wang E 2000	102/177	950/1060		-	0.60 (0.62, 0.76)		-	0.91 (0.70.0	021
Ing 7, 2013 106210 240.30 0.43 (0.5, 0.6) 0.53 (0.5, 0.6) ASYM Abbott 500.2, 2017 1041117 0.57 (0.5, 0.6) 0.57 (0.5, 0.6) 0.57 (0.5, 0.6) Sho Z, 2017 134/33 155/169 0.77 (0.51, 0.8) 0.57 (0.5, 0.6) 0.57 (0.5, 0.6) Sho Z, 2017 104112 57/79 0.57 (0.5, 0.6) 0.77 (0.61, 0.8) 0.57 (0.5, 0.6) Soberston A, 2003 9111 3555 0.58 (0.82, 0.80) 0.99 (0.94, 0.9) Morcitle HEsAgatt HEB 0.85 (0.82, 0.80) 0.99 (0.94, 0.9) 0.99 (0.94, 0.9) Warest HEsAgatt HEB 0.85 (0.82, 0.80) 0.99 (0.94, 0.9) 0.99 (0.94, 0.9) Warest HEsAgatt HEB 0.87 (0.67, 0.80) 0.99 (0.94, 0.9) 0.99 (0.94, 0.9) Warest HEsAgatt HEB 0.99 (0.27, 0.4) 0.99 (0.97, 0.9) 0.99 (0.97, 0.9) Un J. 2005 1742 2527 0.47 (0.66, 0.80) 0.99 (0.87, 0.9) Un J. 2005 1747 150/168 0.71 (0.44, 0.90) 0.97 (0.85, 0.9) Stand MA 2019 77 774 0.91 (0.56, 0.95) 0.97 (0.85, 0.9) Dayou HEBAG Dateve 1.92/192 0.92 (0.87, 0.90) <td< td=""><td></td><td>123/117</td><td>0.10/200</td><td></td><td>_</td><td>0.09 (0.02, 0.70)</td><td></td><td>-</td><td>0.81 (0.79, 0</td><td>.03)</td></td<>		123/117	0.10/200		_	0.09 (0.02, 0.70)		-	0.81 (0.79, 0	.03)
Tab. A. 2015 30.37 108117 0.51 (0.85, 0.02) 0.01 (0.84, 0.95) Shaz S2 2011 33.43 155/169 0.77 (0.61, 0.85) 0.22 (0.85, 0.85) Sdd#sbfm A. 2003 9111 35/03 0.85 (0.82, 0.85) 0.82 (0.86, 0.99) 1.00 (0.80, 1.02) Hec Hedg ELSA Yin Ya-Ju, 2013 43/5512 #10.848 0.85 (0.82, 0.86) 0.96 (0.87, 0.89) 0.90 (0.81, 0.89) Murcx Hedg ELSA Yin Ya-Ju, 2014 1015 59/92 0.87 (0.38, 0.89) 0.90 (0.81, 0.8) Murcx Hedg ELSA Yin Ya-Ju, 2014 1015 59/92 0.87 (0.85, 0.89) 0.90 (0.81, 0.8) Mircx Hedg ELSA Yin Ya-Ju, 2014 1015 59/92 0.97 (0.85, 0.8) 0.93 (0.75, 0.8) Disaling A. 2013 11742 25/27 0.47 (0.88, 0.89) 0.93 (0.75, 0.8) Disaling A. 2013 1217 158/168 0.74 (0.68, 0.80) 0.92 (0.87, 0.90) 0.95 (0.81, 0.9) Disaline A.2019 122/132 122/132	Tang Y, 2013	156/210	248/300		-	0.74 (0.68, 0.80)		•	0.83 (0.78, 0	1.87)
SSTM 22.2017 33/43 155/169 → 0.77 (0.51, 0.63) → 0.92 (0.66, 0.67) Chen 2.2017 104/132 57/73 → 0.79 (0.71, 0.63) → 0.72 (0.61, 0.63) Chen 2.2017 104/132 57/73 → 0.82 (0.46, 0.89) → 1.00 (0.00, 1.0 Ince HBAG BLISA Yn Yu-Ju, 2013 430/512 810/843 0.85 (0.82, 0.88) 0.96 (0.94, 0.9 Mondits HBAG AS PLUS Bio-Rad Instrumptexemmenty 2.015 510/55 75/88 → 0.67 (0.36, 0.89) → 0.99 (0.87, 0.89) Witzek PBAG Marti-HEe Rocuf F. 2001 101/5 59/62 → 0.67 (0.36, 0.89) → 0.93 (0.76, 0.9 Witzek PLUE Dissofts T1/24 25/27 → 0.40 (0.26, 0.57) → 0.83 (0.76, 0.9 Call 2005 112/123 45/84 → 0.71 (0.44, 0.90) → 0.97 (0.85, 0.9 Call 2005 112/123 45/84 → 0.71 (0.44, 0.90) → 0.77 (0.82, 0.9 Call 2005 132/14 4/4 → 0.76 (0.18, 0.99) → 0.79 (0.85, 0.9 0.77 (0.50, 0.9) → 0.77	Hao X, 2015	30/37	106/117			- 0.81 (0.65, 0.92)			0.91 (0.84, 0	1.95)
Abs/m Absorti Smar, 2, 2017 S3/43 155/160										
Shao Z. 2011 3343 156169 - 0.77 (0.81.0.88) 0.22 (0.86.0.99) - 1.00 (0.81.0.89) 1.00 (0.81.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.84.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.96 (0.81.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.92 (0.85.0.99) 0.93 (0.85.	AxSYM Abbott				_				_	
Chen Z, 2017 104/132 67/79 6.79 (0.71, 0.85) 72 (0.71, 0.85) 72 (0.71, 0.85) 73 (0.71, 0.75) 73 (0.72, 0.75) 7	Shao Z, 2011	33/43	155/169			- 0.77 (0.61, 0.88)		_	0.92 (0.86, 0	.95)
Sodesrofn A. 2003 9/11 35/35 - 0.82 (0.48, 0.99) 1 100 (0.50, 1.0 Inter HBAg ELSA Yn Yu-zhu. 2013 435/512 510/848 0.85 (0.82, 0.88) 0.56 (0.82, 0.88) 0.56 (0.84, 0.99) Iter HBAg ELSA Yn Yu-zhu. 2015 51/65 79/88 - 0.78 (0.67, 0.89) 0.09 (0.81, 0.9 Warcx HBAg Allella Rouel F. 2004 10/15 59/62 0.67 (0.86, 0.89) 0.05 (0.87, 0.9 Warcx HBAg Allella Rouel F. 2004 10/15 59/62 0.07 (0.86, 0.89) 0.05 (0.87, 0.9 Warcx HBAg Allella Rouel F. 2004 10/15 59/62 0.07 (0.86, 0.89) 0.05 (0.87, 0.9 Warcx HBAg Allella Hardel Lathone Allella Rouel F. 2004 10/15 59/62 0.07 (0.86, 0.89) 0.05 (0.87, 0.9 Warcx HBAg Allella Hardel Lathone Allella Hardel Lat	Chen Z, 2017	104/132	57/79		-8	0.79 (0.71, 0.85)		-8-	0.72 (0.61, 0	.82)
Intic HBsAg ELSA Yn Yu-Ju, 2013 435/512 B10/848 0.85 (0.82, 0.88) 0.06 (0.94, 0.9 Mondias HBsAg-Ab PLUS Bio-Rad Lathightaswame Yu Yu-Ju 2015 51/52 70/88 0.76 (0.57, 0.88) 0.09 (0.81, 0.9 Murce HBsAg-ant-HBs Coart F, 2004 10/15 50/62 0.67 (0.38, 0.89) 0.09 (0.87, 0.9 Wa-2469 HBsAg Yu-HBs Coart F, 2004 10/15 50/62 0.67 (0.38, 0.89) 0.09 (0.87, 0.9 ETHEBK-Plant 0.09 (0.87, 0.9 0.39 (0.76, 0.9 0.09 (0.87, 0.9 0.03 (0.76, 0.9 ETHEBK-Plant 0.09 (0.81, 0.9 0.09 (0.81, 0.9 0.03 (0.76, 0.9 0.03 (0.76, 0.9 ETHEBK-Plant 0.09 (0.81, 0.9 0.03 (0.76, 0.9 0.03 (0.76, 0.9 0.03 (0.76, 0.9 ETHEBK-Plant 12/17 128/165 0.01 (0.85, 0.95) 0.03 (0.76, 0.9 0.03 (0.82, 0.9 Evand M, 2019 12/17 128/165 0.03 (0.85, 0.95) 0.03 (0.82, 0.9 0.03 (0.82, 0.9 Evand M, 2014 12/12 27/34 0.03 (0.85, 0.9) 0.03 (0.85, 0.9) 0.03 (0.85, 0.8) Uname Submit R, 2015 12/17 22/16 0.077 (0.71, 0.8) 0.	Söderström A, 2003	9/11	35/35			0.82 (0.48, 0.98)			- 1.00 (0.90, 1	.00)
Inter HEAg ELSA Constrained and the second and the secon										
Yin Yu-zhu. 2013 456/512 810/648 0.85 (0.82, 0.88) 0.05 (0.81, 0.9 Monolisa HBAAg-AD PUS Bio-Rad Lathaphaseximoly 2019 51/65 78/88 - 0.76 (0.67, 0.88) 0.03 (0.81, 0.9 Murex HBAAg/ant HBa Roue F, 2004 10/15 50/62 - 0.67 (0.38, 0.88) 0.03 (0.81, 0.9 W2-2496 HBAAg Wantai Lu, 2002 17/42 25/27 - 0.40 (0.26, 0.57) - 0.39 (0.76, 0.9 Cai J, 2005 191/244 428/465 0.71 (0.44, 0.90) 0.95 (0.81, 0.9 0.95 (0.81, 0.9 Cai J, 2005 191/244 428/465 0.71 (0.44, 0.90) 0.95 (0.81, 0.9 0.95 (0.81, 0.9 Cai J, 2005 777 27/74 - 0.92 (0.87, 0.98) 0.95 (0.81, 0.9 0.97 (0.85, 0.9 0.97 (0.85, 0.9 Dayou HBAAg Dakwe Huang L, 2014 122/132 122/132 126/192 0.92 (0.87, 0.98) - 1.00 (0.40, 1.0 Arylets SVM-BIO Yang L, 2016 911 20/20 - 0.88 (0.87, 1.09) - 1.00 (0.83, 1.0) 0.97 (0.55, 0.9) 0.97 (0.55, 0.9) 0.94 (0.40, 0.9) 0.94 (0.40, 0.9) 0.94 (0.40, 0.9) 0.94 (0.40, 0.9) 0.94 (0.40, 0.9)	Intec HBeAg ELISA									
Monolita HBcAg-AD PUS Bio-Rad Latthaphaswang V, 2019 51/65 79/86 0.78 (0.67, 0.88) 0.39 (0.81, 0.9 Murce HBcAgarint-HBc Rouel F, 2004 10/15 59/62 0.67 (0.38, 0.88) 0.95 (0.87, 0.9 WB-2496 HBcAg Wantai Lin J, 2005 11/124 25/27 0.40 (0.26, 0.57) 0.20 (0.87, 0.9 ET-EBK-PLUS Diasorin Bissinger A, 2013 12/17 158/166 0.71 (0.44, 0.90) 0.93 (0.76, 0.9 ET-EBK-PLUS Diasorin Bissinger A, 2013 12/17 158/166 0.71 (0.44, 0.90) 0.93 (0.85, 0.95) Fauel HM, 2019 7/7 27/34 0.91 (0.85, 0.95) 0.97 (0.85, 0.95) Fauel MM, 2019 7/7 27/34 0.92 (0.87, 0.96) 0.95 (0.97, 0.96) Dayou HBcAg Dakewe Hwang L, 2016 9/11 20/20 0.92 (0.48, 0.86) 0.96 (0.67, 0.96) Wang L, 2016 9/11 20/20 0.92 (0.48, 0.98) 0.97 (0.65, 0.97) Wang L, 2016 9/11 20/20 0.96 (0.57, 0.90) 0.99 (0.93, 1.0 Carwy L, 2018 50/72 430/442 0.96 (0.57, 0.80) 0.97 (0.65, 0.9 Carwy L, 2018 50/72 430/442 0.96 (0.57, 0.80) 0.93 (0.62, 0.9) Carwy	Yin Yu-zhu, 2013	435/512	810/848		1	0.85 (0.82, 0.88)			0.96 (0.94, 0	.97)
Nonolis HBsAg-AP PLUS Bio-Rad Lathaphaswang V. 2019 51/65 79/68 - 0.78 (0.67, 0.88) 0.09 (0.81, 0.9 Murax HBsAg/smi-HBs Rouel F. 2004 10/15 59/62 - 0.67 (0.38, 0.88) 0.09 (0.81, 0.9 Murax HBsAg/smi-HBs Rouel F. 2004 11/142 25/27 - 0.40 (0.26, 0.57) - 0.39 (0.67, 0.9 Cail J. 2002 11/142 428/455 0.71 (0.44, 0.20) 0.05 (0.85, 0.9) 0.05 (0.85, 0.9) ETHEBK-PLUS Discorin Baanger A. 2018 12/17 158/165 - 0.71 (0.44, 0.20) 0.05 (0.56, 0.7) Caul HB-AQ Dakwet Huang L. 2014 12/132 456/471 - 0.32 (0.87, 0.96) - 0.57 (0.50, 0.6) Dayou HB-AQ Dakwet Huang L. 2014 12/132 125/192 0.32 (0.87, 0.96) - 0.06 (0.56, 0.7) Arytest SYM-BIO 3/4 4/4 - 0.75 (0.19, 0.99) - 1.00 (0.83, 1.0 Arytest SYM-BIO 3/4 4/4 - 0.56 (0.57, 0.80) - 0.97 (0.50, 0.9 Sait 7, 2018 50/71 430/442 - 0.68 (0.87, 0.80) - 0.98 (0.87, 0.80) 0.93 (0.87, 0.9 0.93 (0.87, 0.9 0.93 (0.87									•	
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Dayou HBeAg Dakewe Huang L, 2014 122/132 125/192 0.92 (0.87, 0.96) ● 0.65 (0.58, 0.7) Liaison Diasorin Köse S, 2011 3/4 4/4 ● 0.75 (0.19, 0.99) ● 1.00 (0.83, 0.0) Anytest SYM-BIO Wang L, 2016 9/11 20/20 ● 0.82 (0.48, 0.98) ● 1.00 (0.83, 0.0) Lu H, 2009 7/8 21/25 ● 0.88 (0.47, 1.00) ● 0.89 (0.57, 0.80) ● 0.99 (0.93, 0.0) Architect Abbott Carey I, 2018 50/72 430/42 ● 0.69 (0.57, 0.80) ● 0.97 (0.95, 0.9) Doima G, 2018 26/32 38/4/911 ● 0.81 (0.64, 0.93) ● 0.89 (0.96, 0.9) ● 0.89 (0.96, 0.9) LiX, 2018 150/171 524/545 ● 0.81 (0.64, 0.93) ● 0.89 (0.96, 0.9) ● 0.89 (0.96, 0.9) ● 0.89 (0.96, 0.9) ● 0.89 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.89 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9) ● 0.98 (0.96, 0.9)										
Huang L, 2014 122/132 125/192 $0.92 (0.87, 0.96)$ \bullet $0.65 (0.58, 0.7)$ Liaison Diasorin Kose S, 2011 $3/4$ $4/4$ \bullet $0.75 (0.19, 0.99)$ \bullet $1.00 (0.40, 1.0)$ Anytest SYM-BIO Wang L, 2016 $9/11$ $20/20$ \bullet $0.82 (0.48, 0.98)$ \bullet $1.00 (0.43, 1.0)$ Lu H, 2009 $7/8$ $21/25$ \bullet $0.86 (0.47, 1.00)$ \bullet $0.99 (0.93, 1.0)$ Architest SMM-BIO Carey I, 2013 $50/72$ $430/442$ \bullet $0.96 (0.85, 0.99)$ \bullet $0.99 (0.93, 1.0)$ Architest Abbott Carey I, 2018 $150/71$ $430/442$ \bullet $0.69 (0.57, 0.80)$ \bullet $0.97 (0.95, 0.9)$ Dolman G, 2018 $26/22$ $344/391$ \bullet $0.88 (0.82, 0.9)$ $0.98 (0.96, 0.9)$ $0.98 (0.96, 0.9)$ $0.98 (0.96, 0.9)$ $0.98 (0.96, 0.9)$ $0.95 (0.92, 0.9)$ Ua K, 2018 $150/171$ $524/455$ $0.88 (0.82, 0.92)$ $0.96 (0.96, 0.9)$ $0.95 (0.92, 0.9)$ $0.95 (0.92, 0.9)$ $0.95 (0.92, 0.9)$ $0.95 (0.92, 0.9)$ $0.95 (0.92, 0.9)$ $0.95 (0.92, 0.9)$ $0.98 (0.84, 0.9)$ $0.$	Dayou HBeAg Dakewe									
Liaison Diasorin Kose S, 2011 3/4 4/4	Huang L, 2014	122/132	125/192			0.92 (0.87, 0.96)		-	0.65 (0.58, 0	.72)
Laison Dissorin Kese S, 2011 $3/4$ $4/4$ \bullet 0.75 (0.19, 0.99) \bullet 1.00 (0.40, 1.0 Anytest SYM-BIO \bullet \bullet 0.82 (0.48, 0.98) \bullet 1.00 (0.81, 1.0 Vang L, 2016 9/11 20/20 \bullet 0.82 (0.48, 0.98) \bullet 1.00 (0.84, 0.9 Bai H, 2010 44/46 73/74 \bullet 0.88 (0.47, 1.00) \bullet 0.84 (0.64, 0.9 Architect Abbott Carey I, 2018 $50/72$ 430/442 \bullet 0.66 (0.57, 0.80) \bullet 0.97 (0.95, 0.9 Peng N, 2012 165/215 152/195 \bullet 0.77 (0.71, 0.82) \bullet 0.88 (0.84, 0.93) \bullet 0.88 (0.84, 0.93) \bullet 0.88 (0.96, 0.96) Dolman G, 2018 26/32 384/391 \bullet \bullet 0.81 (0.64, 0.9) \bullet 0.88 (0.92, 0.9) \bullet 0.98 (0.96, 0.95) \bullet 0.98 (0.96, 0.95) \bullet 0.98 (0.96, 0.95) \bullet 0.98 (0.96, 0.96) \bullet 0.88 (0.92, 0.9) \bullet 0.75 (0.69, 0.89) \bullet 0.98 (0.98, 0.96) \bullet 0.89 (0.94, 0.92) \bullet 0.98 (0.84, 0.92) \bullet 0.75 (0.69, 0.89) \bullet 0.98 (0.84, 0.92) \bullet 0.75 (0.69, 0.89) \bullet 0.97 (0.91, 0.92) \bullet 0.98 (0.77, 0.89) \bullet 0.97 (0.91, 0.92) \bullet 0.98 (0.77, 0.89)									· · ·	,
Kese S, 2011 3/4 4/4	Liaison Diasorin									
Anytest SYM-BIO	Köse S. 2011	3/4	4/4	-		0.75 (0.19, 0.99)			1.00 (0.40, 1	.00)
Anytest SYM-BIO Wang L, 2016 9/11 20/20 $-$ 0.82 (0.48, 0.98) $-$ 1.00 (0.83, 1.0) Bai H, 2010 44/46 73/74 $-$ 0.96 (0.85, 0.99) 0.99 (0.93, 1.0) Architect Abbott Carey I, 2018 50/72 430/442 $-$ 0.69 (0.57, 0.80) $0.97 (0.95, 0.9)$ Peng N, 2012 165/215 162/195 $0.77 (0.71, 0.82)$ $0.38 (0.97, 0.8)$ Dolman G, 2018 26/32 384/391 $ 0.81 (0.64, 0.93)$ $0.88 (0.86, 0.93)$ Li X, 2018 150/171 524/545 $0.81 (0.64, 0.93)$ $0.98 (0.96, 0.96)$ $0.99 (0.94, 0.9)$ U X, 2018 150/171 524/545 $0.91 (0.86, 0.95)$ $0.93 (0.92, 0.9)$ U Wai X, 2017 58/606 1055/1135 $0.94 (0.91, 0.96)$ $0.93 (0.92, 0.9)$ Wai X, 2015 7/7 14/14 $ 0.96 (0.59, 0.89)$ $0.97 (0.95, 0.9)$ Pirilio M, 2015 7/7 14/14 $ 0.00 (0.59, 1.00)$ $0.97 (0.91, 0.9)$ Spéral O, 2018 26/34 91/94 $ 0.84 (0.77, 0.89)$ $ 0.97 (0.91, 0.9)$ <td></td> <td></td> <td></td> <td></td> <td>_</td> <td></td> <td></td> <td></td> <td></td> <td>,</td>					_					,
Wang L 2016 9/11 $20/20$ \bullet $0.82 (0.48, 0.98)$ \bullet $0.84 (0.64, 0.9)$ Lu H, 2009 7/8 $21/25$ \bullet $0.88 (0.47, 1.00)$ \bullet $0.44 (0.64, 0.9)$ Bai H, 2010 $44/46$ 73/74 \bullet $0.96 (0.85, 0.99)$ $0.99 (0.93, 1.0)$ Architect Abbott Carey I, 2018 $50/72$ $430/442$ \bullet $0.69 (0.57, 0.80)$ $0.97 (0.95, 0.9)$ Dolman G, 2018 $28/32$ $38/391$ \bullet $0.81 (0.64, 0.93)$ $0.83 (0.76, 0.8)$ Li X, 2013 $150/171$ $524/545$ $0.88 (0.82, 0.92)$ $0.96 (0.94, 0.9)$ Diang P, 2017 $131/143$ $220/248$ $0.92 (0.86, 0.96)$ $0.98 (0.84, 0.9)$ Uaing P, 2017 $133/138$ $203/271$ $0.96 (0.92, 0.99)$ $0.75 (0.69, 0.8)$ Wang X, 2015 $133/138$ $203/271$ $0.96 (0.92, 0.99)$ $0.75 (0.69, 0.8)$ Wang X, 2015 $138/165$ $77/94$ $0.84 (0.77, 0.89)$ $-0.76 (0.63, 0.86)$ Elecsys Roche Lu H, 2013 $28/98$ $205/215$ $-0.76 (0.63, 0.86)$ $-0.98 (0.73, 0.8)$ $0.97 (0.91, 0.9)$	Anytest SYM-BIO									
Lu H, 2009 7/8 21/25 ■ 0.88 (0.47, 1.00) ● 0.84 (0.47, 1.00) Bai H, 2010 44/46 73/74 ■ 0.96 (0.85, 0.99) ● 0.97 (0.95, 0.9) Architect Abbott Carey I, 2018 50/72 430/442 ● 0.69 (0.57, 0.80) ● 0.97 (0.95, 0.9) Dolman G, 2018 26/32 384/391 ● 0.81 (0.64, 0.93) ● 0.83 (0.67, 0.80) Dolman G, 2018 26/32 384/391 ● 0.81 (0.64, 0.93) ● 0.88 (0.87, 0.80) U X, 2018 150/171 524/545 ● 0.81 (0.64, 0.93) ● 0.98 (0.94, 0.9 U X, 2018 150/171 524/545 ● 0.88 (0.87, 0.90) ● 0.96 (0.92, 0.99) U X, 2018 150/171 524/545 ● 0.96 (0.92, 0.99) ● 0.75 (0.69, 0.80) U Age Z, 2017 568/606 1058/1135 ● 0.94 (0.91, 0.96) ● 0.93 (0.27, 0.9 Vang X, 2015 133/138 203/271 ● 0.86 (0.92, 0.99) ● 0.75 (0.66, 0.80) Spedral O, 2013 24/24 26/29 ● <td>Wang L 2016</td> <td>9/11</td> <td>20/20</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>—1 00 (0.83, 1</td> <td>00)</td>	Wang L 2016	9/11	20/20						—1 00 (0.83, 1	00)
Lu n, 2009 1/8 21/23 ■ 0.08 (0.47, 1.00) ■ 0.08 (0.47, 1.00) Architect Abbott ■ 0.96 (0.85, 0.99) 0.99 (0.93, 1.0 Carey I, 2018 50/72 430/442 ■ 0.69 (0.57, 0.80) 0.97 (0.95, 0.9 Peng N, 2012 165/215 162/195 ■ 0.77 (0.71, 0.82) ■ 0.83 (0.37, 0.80) Dolman G, 2018 26/32 384/391 ■ ■ 0.81 (0.46, 0.93) ■ 0.98 (0.82, 0.92) Li X, 2018 150/171 524/545 ■ 0.81 (0.86, 0.95) ■ 0.98 (0.84, 0.9 Liarg P, 2017 131/143 220/248 ■ 0.92 (0.86, 0.96) ■ 0.93 (0.82, 0.92) Waig X, 2015 133/138 220/271 ■ 0.94 (0.91, 0.96) ■ 0.93 (0.92, 0.9) Pirillo M, 2015 7/7 14/14 ■ 1.00 (0.03, 1.00) ■ 1.00 (0.7, 1.0) Chotun N, 2017 1/1 5/5 ■ 0.94 (0.97, 0.89) ■ 0.82 (0.73, 0.8 Sub Bioline HBeAg test Segeral O, 2018 26/34 91/94 ■ ● 0.76 (0.63, 0.86) ● 0.81 (0.		7/9	20/20		-					.00)
Lai H, 2010 44/46 73/74 - 0.96 (0.85, 0.99) 0.99 (0.93, 1.0 Architect Abbott Carey I, 2018 50/72 430/442 - 0.69 (0.57, 0.80) 0.97 (0.95, 0.9 Peng N, 2012 165/215 162/195 0.77 (0.71, 0.82) 0.83 (0.77, 0.80) Dolman G, 2018 26/32 384/391 - 0.81 (0.64, 0.93) 0.98 (0.96, 0.9, 0.9) Li X, 2018 150/171 524/445 0.81 (0.86, 0.95) 0.95 (0.92, 0.9) 0.96 (0.94, 0.9) Liang P, 2017 131/143 220/248 0.92 (0.86, 0.96) 0.98 (0.82, 0.9) 0.95 (0.82, 0.9) Wei K, 2017 568/606 1058/1135 0.94 (0.91, 0.86) 0.93 (0.82, 0.9) 0.75 (0.69, 0.8) Wang X, 2015 133/138 203/271 0.96 (0.92, 0.99) 0.75 (0.69, 0.8) 0.89 (0.87, 0.8) Pirtilo M, 2015 7/7 14/14 - 1.00 (0.03, 1.00) - 1.00 (0.48, 1.0) Chourn N, 2017 1/1 5/5 - 1.00 (0.86, 1.00) - 0.93 (0.73, 0.8) Zhu B, 2013 24/24 26/29 - 1.00 (0.86, 1.00) - 0.95 (0.92, 0.9)	Lu H, 2009	7/8	21/25						0.84 (0.64, 0	.95)
Architect Abbott Carey I, 2018 50/72 430/442 - - 0.69 (0.57, 0.80) 0.97 (0.95, 0.9) Peng N, 2012 165/215 162/195 0.77 (0.71, 0.82) 0.83 (0.77, 0.8) Dolman G, 2018 26/32 384/391 - 0.81 (0.64, 0.93) 0.98 (0.94, 0.9) Li X, 2018 150/171 524/545 0.88 (0.82, 0.92) 0.96 (0.94, 0.9) Liag P, 2017 131/143 220/248 0.92 (0.86, 0.96) 0.89 (0.84, 0.9) Wait X, 2017 568/606 1056/1135 0.94 (0.91, 0.96) 0.93 (0.92, 0.9) Wang X, 2015 133/138 203/271 0.96 (0.94, 0.9, 1.00) - 1.00 (0.77, 1.0) Pirilo M, 2015 7/7 14/14 1.00 (0.59, 1.00) - 1.00 (0.77, 1.0) Chorun N, 2017 1/1 5/5 1.00 (0.03, 1.00) - 0.98 (0.84, 0.9) Systematic 2/2/24 2/9 - 1.00 (0.03, 1.00) - 0.90 (0.73, 0.8) Distribut N, 2017 1/1 5/5 - 0.84 (0.75, 0.89) 0.97 (0.91, 0.9) Systematic 2/9/8 205/215 - 0	Bai H, 2010	44/46	73/74			0.96 (0.85, 0.99)			0.99 (0.93, 1	.00)
Architect Abbott Carey I, 2018 50/72 430/442 - - 0.69 (0.57, 0.80) 0.97 (0.57, 0.8) Peng N, 2012 165/215 162/195 0.77 (0.71, 0.82) 0.83 (0.77, 0.8) Dolman G, 2018 26/32 384/391 - 0.81 (0.64, 0.93) 0.98 (0.96, 0.9 Li X, 2018 150/171 524/545 0.88 (0.82, 0.92) 0.96 (0.94, 0.9) 0.95 (0.92, 0.9) Thilkanathan C, 2018 168/185 433/457 0.99 (0.86, 0.96) 0.98 (0.96, 0.92, 0.9) Liang P, 2017 131/143 220/248 0.92 (0.86, 0.96) 0.93 (0.92, 0.9) Wei K, 2017 568/606 1056/1135 0.94 (0.91, 0.96) 0.93 (0.92, 0.9) Wai X, 2015 7/7 14/14 - 1.00 (0.80, 1.00) - 0.91 (0.04, 1.0) Pirillo M, 2015 7/7 14/14 - 1.00 (0.03, 1.00) - 1.00 (0.73, 0.8) Zhu B, 2013 138/165 77/94 0.84 (0.77, 0.89) 0.97 (0.91, 0.9) Sb Bioline HBeAg test Segeral O, 2018 26/34 91/94 - - 0.76 (0.59, 0.89) 0.97 (0.91, 0.9) 0.95 (0.92, 0.9)										
Carey I, 2018 50/72 430/442 → 0.69 (0.57, 0.80) 0.97 (0.95, 0.9) Peng N, 2012 165/215 162/195 0.77 (0.71, 0.82) 0.83 (0.77, 0.8) 0.83 (0.77, 0.8) Dolman G, 2018 26/32 384/391 → 0.81 (0.64, 0.93) 0.98 (0.94, 0.9) Li X, 2018 166/165 433/457 0.91 (0.86, 0.95) 0.95 (0.82, 0.9) Liag P, 2017 131/143 220/248 0.92 (0.86, 0.96) 0.89 (0.84, 0.9) Wei K, 2017 568/606 1058/1135 0.94 (0.91, 0.96) 0.93 (0.92, 0.9) Wang X, 2015 133/138 203/271 0.96 (0.92, 0.99) 0.75 (0.66, 0.80) Wang X, 2015 133/138 203/271 0.96 (0.92, 0.99) 0.75 (0.66, 0.80) Pirillo M, 2015 7/7 14/14	Architect Abbott				_				—	
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Dolman G, 2018 26/32 384/391 → 0.81 (0.64, 0.93) 0.98 (0.96, 0.93) Li X, 2018 150/171 524/545 0.88 (0.82, 0.92) 0.96 (0.94, 0.9) Thilakanathan C, 2018 168/185 433/457 0.91 (0.86, 0.95) 0.99 (0.92, 0.9) Viait X, 2017 568/606 1058/1135 0.94 (0.91, 0.96) 0.93 (0.92, 0.9) Wait X, 2015 133/138 203/271 0.96 (0.92, 0.99) 0.75 (0.69, 0.8) Wait X, 2017 568/606 1058/1135 0.94 (0.91, 0.96) 0.93 (0.92, 0.9) Wait X, 2017 133/138 203/271 0.96 (0.92, 0.9) 0.75 (0.69, 0.8) Wait X, 2017 1/1 5/5 1.00 (0.59, 1.00) - 1.00 (0.77, 1.0 Chotun N, 2017 1/1 5/5 1.00 (0.03, 1.00) - 0.82 (0.73, 0.8 Zhu B, 2013 24/24 26/29 - 1.00 (0.86, 1.00) - 0.97 (0.91, 0.9 Segeral O, 2018 26/34 91/94 - - 0.76 (0.59, 0.89) 0.97 (0.91, 0.9 Wiseman E, 2009 82/98 205/215 - 0.84 (0.75, 0.90) 0.95 (0.92, 0.9	Peng N, 2012	165/215	162/195			0.77 (0.71, 0.82)			0.83 (0.77, 0	.88)
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Thilakanathan C, 2018 168/185 433/457 ● 0.91 (0.86, 0.95) ● 0.95 (0.92, 0.9) Liang P, 2017 131/143 220/248 ● 0.92 (0.86, 0.96) ● 0.89 (0.84, 0.9) Wei K, 2017 568/606 1058/1135 ● 0.94 (0.91, 0.96) ● 0.93 (0.92, 0.9) Wang X, 2015 133/138 203/271 ● 0.96 (0.92, 0.99) ● 0.75 (0.69, 0.8) Pirillo M, 2015 7/7 14/14 ● 0.96 (0.92, 0.99) ● 0.76 (0.69, 0.8) Chotun N, 2017 1/1 5/5 ● 1.00 (0.59, 1.00) ● 1.00 (0.77, 1.0 Chotun N, 2017 1/1 5/5 ● 1.00 (0.03, 1.00) ● 0.82 (0.73, 0.8 Zhu B, 2013 24/24 26/29 ● 1.00 (0.86, 1.00) ● 0.90 (0.73, 0.9 Sb Bioline HBeAg test Ségéral O, 2018 26/34 91/94 ● 0.76 (0.59, 0.89) ● 0.97 (0.91, 0.9 Multiple Wiseman E, 2009 82/98 205/215 ● 0.76 (0.63, 0.86) ● 0.81 (0.69, 0.9 Vias Mag X, 2015 47/62 47/58 ● 0.76 (0.63, 0.86) ● 0.81 (0.69, 0.9 ● 0.88 (0.84, 0.9 Vias Mag X, 2014 127/147 652/688 ● 0.86 (0.80, 0.91) ● 0.88 (0.84, 0.9 ● 0.82	Li X, 2018	150/171	524/545			0.88 (0.82, 0.92)			0.96 (0.94, 0	.98)
Liang P, 2017 131/143 220/248 0.92 (0.86, 0.96) 0.89 (0.84, 0.9 Wei K, 2017 568/606 1058/1135 0.94 (0.91, 0.96) 0.93 (0.92, 0.99) Wang X, 2015 133/138 203/271 0.96 (0.92, 0.99) 0.75 (0.69, 0.8 Prillo M, 2015 7/7 14/14 0.00 (0.3, 1.00) 0.00 0.50 1.00 (0.77, 1.0 Chotun N, 2017 1/1 5/5 0.08 (0.92, 0.99) 0.75 (0.69, 0.8 Chotun N, 2017 1/1 5/5 0.08 (0.92, 0.99) 0.082 (0.73, 0.8 Zhu B, 2013 24/24 26/29 0.84 (0.77, 0.89) 0.90 (0.73, 0.9 SD Bioline HBeAg test Ségéral O, 2018 26/34 91/94 0.76 (0.59, 0.89) 0.97 (0.91, 0.9 Multiple Wiseman E, 2009 82/98 205/215 0.084 (0.77, 0.89) 0.95 (0.92, 0.9 Unknown Wang X, 2015 47/62 47/58 0.84 (0.77, 0.88) 0.95 (0.92, 0.9 Kubo A, 2014 127/147 652688 0.86 (0.80, 0.91) 0.88 (0.84, 0.9 Kubo A, 2014 127/147 652688 0.86 (0.80, 0.91) 0.86 (0.80, 0.91) Wang Wang V1018 22/34 26/42 0.65 (0.46, 0.80) 0.05 (0.46, 0.80) 0.95 (0.92, 0.9 Unknown Wang X, 2015 47/62 47/58 0.86 (0.80, 0.91) 0.88 (0.84, 0.9 Chotu A, 2014 127/147 652688 0.068 (0.46, 0.80) 0.91 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 0.091) 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 0.091) 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 (0.80, 0.91) 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 0.080 0.91) 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 0.080 0.91) 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 0.080 0.91) 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 0.080 0.91) 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 0.080 0.91) 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 0.080 0.91) 0.95 (0.92, 0.9 Chotu A, 2014 127/147 652688 0.068 0.080 0.91) 0.95 (0.93, 0.9 Chotu A, 2014 127/147 652688 0.068 0.080 0.91) 0.95 (0.93, 0.9 Chotu A, 2014 1207/147 143/172 10.06 0.75, 1.00) 0.05 (0.46, 0.78) 0.95 (0.93, 0.9 Chotu A, 2014 1207/147 143/172 10.06 0.75, 1.00) 0.05 (0.46, 0.78) 0.95 (0.93, 0.9 Chotu A, 2014 1.00 (0.75, 1.00) 0.05 (0.46, 0.78) 0.95 (0.93, 0.9 Chotu A, 2014 1.00 (0.96, 1.0 Chotu A, 2014 1.00 (0.96, 1.0 Chotu A, 2014 1.00 (0.96, 1.0 Cho	Thilakanathan C, 2018	168/185	433/457			0.91 (0.86, 0.95)			0.95 (0.92, 0	.97)
Wei K, 2017 568/606 1058/1135 0.94 (0.91, 0.96) 0.93 (0.92, 0.9 Wang X, 2015 133/138 203/271 0.96 (0.92, 0.99) 0.75 (0.69, 0.8 Pirillo M, 2015 7/7 14/14 1.00 (0.59, 1.00) 1.00 (0.77, 1.0) Chotun N, 2017 1/1 5/5 1.00 (0.03, 1.00) 1.00 (0.48, 1.0) Elecsys Roche 1.04 (0.97, 0.89) 0.84 (0.77, 0.89) 0.82 (0.73, 0.8 Zhu B, 2013 24/24 26/29 1.00 (0.86, 1.00) 0.90 (0.73, 0.9 Sb Bioline HBeAg test Ségéral O, 2018 26/34 91/94 - 0.76 (0.59, 0.89) 0.97 (0.91, 0.9 Multiple Wiseman E, 2009 82/98 205/215 - 0.84 (0.75, 0.90) 0.95 (0.92, 0.9 Unknown Wang X, 2015 47/62 47/58 - 0.76 (0.63, 0.86) - 0.88 (0.84, 0.9 Wang M, 2018 22/34 26/42 - 0.76 (0.63, 0.86) - 0.88 (0.84, 0.9 Ubanown Wang M, 2018 22/34 26/42 - 0.76 (0.63, 0.86) - 0.88 (0.84, 0.9 Wang M, 2018 22/34 26/42 -	Liang P. 2017	131/143	220/248			0.92 (0.86, 0.96)			0.89 (0.84, 0	.92)
Wang X, 2015 133/138 203/271 0.96 (0.92, 0.99) 0.75 (0.69, 0.8 Pirillo M, 2015 7/7 14/14 1.00 (0.59, 1.00) 1.00 (0.77, 1.0 Chotun N, 2017 1/1 5/5 1.00 (0.03, 1.00) 0.96 (0.92, 0.99) 0.75 (0.69, 0.8 Elecsys Roche 1.00 (0.77, 1.0 0.98 (0.77, 0.89) 0.75 (0.69, 0.8 0.75 (0.69, 0.8 SD Bioline HBeAg test 56géral O, 2018 26/34 91/94 0.84 (0.77, 0.89) 0.97 (0.91, 0.9 Multiple Wiseman E, 2009 82/98 205/215 0.84 (0.75, 0.90) 0.95 (0.92, 0.9 Unknown Wang X, 2015 47/62 47/58 - 0.76 (0.63, 0.86) - 0.81 (0.69, 0.9 Vang X, 2015 47/62 47/58 - 0.76 (0.63, 0.86) - 0.88 (0.84, 0.9 Vus A, 2014 127/147 652/688 0.83 (0.77, 0.88) 0.83 (0.77, 0.80) 0.95 (0.92, 0.9 Unknown 0.091 0.950 1.00 0.091 0.95 (0.93, 0.9 0.95 (0.93, 0.9 0.95 (0.93, 0.9 Uak do the dot	Wei K 2017	568/606	1058/1135						0.93 (0.92 0	95)
Margin 2010 100/100 200211 0.30 (0.59, 0.59) 0.73 (0.89, 0.5) Prillo N, 2015 7/7 14/14 1.00 (0.59, 1.00)	Wang X 2015	133/138	203/271					_	0.75 (0.60 0	1.801
Chotun N, 2017 1/1 5/5 1.00 (0.39, 1.00) 1.00 (0.77, 1.0 Chotun N, 2017 1/1 5/5 1.00 (0.03, 1.00) 1.00 (0.48, 1.00) Elecsys Roche 1.01 (0.77, 0.89) 0.84 (0.77, 0.89) 0.82 (0.73, 0.8 Zhu B, 2013 24/24 26/29 1.00 (0.66, 1.00) 0.90 (0.73, 0.9 SD Bioline HBeAg test 5/5 0.76 (0.59, 0.89) 0.97 (0.91, 0.9 Multiple Wiseman E, 2009 82/98 205/215 0.84 (0.75, 0.90) 0.95 (0.92, 0.9 Unknown Wang X, 2015 47/62 47/58 0.76 (0.63, 0.86) 0.95 (0.92, 0.9 Vang X, 2015 47/62 47/58 0.76 (0.63, 0.86) 0.95 (0.92, 0.9 Vang X, 2015 47/62 47/58 0.76 (0.63, 0.86) 0.95 (0.92, 0.9 Wang X, 2015 47/62 47/58 0.76 (0.63, 0.86) 0.95 (0.92, 0.9 Wang M, 2018 22/34 26/42 0.86 (0.80, 0.91) 0.95 (0.93, 0.9 Wang M, 2018 22/34 26/42 0.65 (0.46, 0.80) 0.62 (0.46, 0.7 Dervisevic S, 2007 13/13 101/101 1.00 (0.75, 1.00) 1.00 (0.96, 1.0	Pirillo M 2015	7/7	14/14					_		
Circuit N, 2017 1/1 5/5 1.00 (0.03, 1.00) 1.00 (0.03, 1.00) Elecsys Roche 1.01 (0.13, 1.00) 0.84 (0.77, 0.89) 0.82 (0.73, 0.8 Zhu B, 2013 24/24 26/29 - 1.00 (0.66, 1.00) 0.90 (0.73, 0.9 SD Bioline HBeAg test 5/5 - 0.76 (0.59, 0.89) 0.97 (0.91, 0.9 Multiple Wiseman E, 2009 82/98 205/215 - 0.84 (0.75, 0.90) 0.95 (0.92, 0.9 Unknown - - 0.76 (0.63, 0.86) - - 0.81 (0.69, 0.9 Zhang L, 2017 143/172 281/319 - 0.86 (0.80, 0.91) 0.95 (0.92, 0.9 Wang M, 2018 22/34 26/42 - - 0.65 (0.46, 0.80) - - 0.81 (0.69, 0.9 Dervisevic S, 2007 13/13 101/101 - - 0.65 (0.46, 0.80) - - 0.62 (0.46, 0.7	Chotup N 2017	1/1	14/14 5/5							.00)
Elecsys Roche Liu H, 2013 138/165 77/94 ● 0.84 (0.77, 0.89) ● 0.82 (0.73, 0.8 Zhu B, 2013 24/24 26/29 ● 1.00 (0.86, 1.00) ● 0.90 (0.73, 0.9 SD Bioline HBeAg test Ségéral O, 2018 26/34 91/94 ● 0.76 (0.59, 0.89) ● 0.97 (0.91, 0.9 Multiple Wiseman E, 2009 82/98 205/215 ● 0.84 (0.75, 0.90) ● 0.95 (0.92, 0.9 Unknown Wang X, 2015 47/62 47/58 ● 0.76 (0.63, 0.86) ● ● 0.81 (0.69, 0.9 Zhang L, 2017 143/172 281/319 ● 0.83 (0.77, 0.88) ● 0.88 (0.84, 0.9 Wang M, 2018 22/34 26/42 ● 0.65 (0.46, 0.80) ● 0.62 (0.46, 0.7 Dervisevic S, 2007 13/13 101/101 ● 0.00 0.50 1.00		17.1	0/0			 1.00 (0.03, 1.00) 			1.00 (0.48, 1	.00)
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Zhu B, 2013 24/24 26/29 - 1.00 (0.86, 1.00) - - 0.90 (0.73, 0.9) SD Bioline HBeAg test Ségéral O, 2018 26/34 91/94 - - 0.76 (0.59, 0.89) 0.97 (0.91, 0.9) Multiple Wiseman E, 2009 82/98 205/215 - 0.84 (0.75, 0.90) 0.95 (0.92, 0.9) Unknown Wang X, 2015 47/62 47/58 - 0.76 (0.63, 0.86) - - 0.81 (0.69, 0.9) Zhang L, 2017 143/172 281/319 - 0.83 (0.77, 0.88) 0.88 (0.84, 0.9) Wang M, 2018 22/34 26/42 - - 0.65 (0.46, 0.80) - - 0.62 (0.46, 0.7) Dervisevic S, 2007 13/13 101/101 - 1.00 (0.75, 1.00) 1.00 (0.96, 1.0)	Liu H, 2013	138/165	77/94		1	0.84 (0.77, 0.89)		-	• 0.82 (0.73, 0	.89)
SD Bioline HBeAg test Ségéral O, 2018 26/34 91/94 - - 0.76 (0.59, 0.89) 0.97 (0.91, 0.9 Multiple Wiseman E, 2009 82/98 205/215 - 0.84 (0.75, 0.90) 0.95 (0.92, 0.9 Unknown Wang X, 2015 47/62 47/58 - - 0.76 (0.63, 0.86) - - 0.81 (0.69, 0.9 Zhang L, 2017 143/172 281/319 - 0.83 (0.77, 0.88) 0.88 (0.84, 0.9 Kubo A, 2014 127/147 652/688 - 0.86 (0.80, 0.91) - 0.95 (0.93, 0.9 Wang M, 2018 22/34 26/42 - 0.65 (0.46, 0.80) - 0.62 (0.46, 0.7 Dervisevic S, 2007 13/13 101/101 - 1.00 (0.75, 1.00) 1.00 (0.96, 1.0	Zhu B, 2013	24/24	26/29			— 1.00 (0.86, 1.00)			0.90 (0.73, 0	.98)
SD Bioline HBeAg test Ségéral O, 2018 26/34 91/94 - - 0.76 (0.59, 0.89) 0.97 (0.91, 0.9 Multiple Wiseman E, 2009 82/98 205/215 - 0.84 (0.75, 0.90) 0.95 (0.92, 0.9 Unknown Wang X, 2015 47/62 47/58 - - 0.76 (0.63, 0.86) - - 0.81 (0.69, 0.9 Zhang L, 2017 143/172 281/319 0.83 (0.77, 0.88) 0.88 (0.84, 0.9 Kubo A, 2014 127/147 652/688 - 0.86 (0.80, 0.91) 0.95 (0.93, 0.9 Wang M, 2018 22/34 26/42 - 0.65 (0.46, 0.80) - - 0.62 (0.46, 0.7 Dervisevic S, 2007 13/13 101/101 - 1.00 (0.75, 1.00) 1.00 (0.96, 1.0										
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Multiple Wiseman E, 2009 82/98 205/215 - 0.84 (0.75, 0.90) 0.95 (0.92, 0.9) Unknown Wang X, 2015 47/62 47/58 - - 0.76 (0.63, 0.86) - - 0.81 (0.69, 0.9) Zhang L, 2017 143/172 281/319 - 0.83 (0.77, 0.88) 0.88 (0.84, 0.9) Kubo A, 2014 127/147 652/688 - 0.86 (0.80, 0.91) 0.95 (0.93, 0.9) Wang M, 2018 22/34 26/42 - - 0.65 (0.46, 0.80) - - 0.62 (0.46, 0.7) Dervisevic S, 2007 13/13 101/101 - - 1.00 (0.75, 1.00) 1.00 (0.96, 1.0)	Ségéral O, 2018	26/34	91/94			- 0.76 (0.59, 0.89)			0.97 (0.91, 0	.99)
Multiple Wiseman E, 2009 82/98 205/215 - 0.84 (0.75, 0.90) 0.95 (0.92, 0.9 Unknown Wang X, 2015 47/62 47/58 - - 0.76 (0.63, 0.86) - - 0.81 (0.69, 0.9 Zhang L, 2017 143/172 281/319 - 0.83 (0.77, 0.88) 0.88 (0.84, 0.9 Kubo A, 2014 127/147 652/688 - 0.86 (0.80, 0.91) 0.95 (0.93, 0.9 Wang M, 2018 22/34 26/42 - 0.65 (0.46, 0.80) - 0.62 (0.46, 0.7 Dervisevic S, 2007 13/13 101/101 - 1.00 (0.75, 1.00) 1.00 (0.96, 1.0										
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Unknown Wang X, 2015 47/62 47/58 -■ 0.76 (0.63, 0.86) -■ 0.81 (0.69, 0.9) Zhang L, 2017 143/172 281/319 ■ 0.83 (0.77, 0.88) ■ 0.88 (0.84, 0.9) Kubo A, 2014 127/147 652/688 ■ 0.86 (0.80, 0.91) ■ 0.95 (0.93, 0.9) Wang M, 2018 22/34 26/42 -■ 0.65 (0.46, 0.80) -■ 0.62 (0.46, 0.7) Dervisevic S, 2007 13/13 101/101 -■ 1.00 (0.75, 1.00) ■ 1.00 (0.96, 1.0)										
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Zhang L, 2017 143/172 281/319 0.83 (0.77, 0.88) 0.83 (0.84, 0.9 Kubo A, 2014 127/147 652/688 0.86 (0.80, 0.91) 0.85 (0.46, 0.80) 0.65 (0.46, 0.80) 0.62 (0.46, 0.7 <	Wang X, 2015	47/62	47/58		=	- 0.76 (0.63. 0.86)			- 0.81 (0.69. 0	.90)
Kubo A, 2014 127/147 652/688	Zhang L. 2017	143/172	281/319		-	0,83 (0.77. 0.88)		_	0,88 (0.84 0	.91)
Wang M, 2018 22/34 26/42 Image: Constraint of the state of the sta	Kubo A 2014	127/1/7	652/699						0.95 (0.02.0	
Wang W, 2010 22/34 20/42 ■ 0.05 (0.40, 0.80) ■ 0.62 (0.40, 0.7) Dervisevic S, 2007 13/13 101/101 ■ 1.00 (0.75, 1.00) ■ 1.00 (0.96, 1.0) 0.00 0.50 1.00 0.00 0.50 1.00	Wang M 2019	121/141	002/000							
Dervisevic S, 2007 13/13 101/101	Damianuia C. 0007	22/34	20/42						0.62 (0.46, 0	. (0)
	Dervisevic S, 2007	13/13	101/101		_	1.00 (0.75, 1.00)			1.00 (0.96, 1	.00)
0.00 0.50 1.00 0.00 0.50 1.00										
				0.00	0.50	1.00	0.00	0.50	1.00	

Fig. 8. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥5 log10 IU/mL by HBeAg assay commercial name

HBV DNA type of assay and Author, year	TP/(TP+FN)	TN/(TN+FP)			Sensitivity (95% CI)			Specificity (95% CI)
Commercial PCR								
Lin J. 2002	17/42	25/27			0.40 (0.26, 0.57)	_	
Wang M, 2018	22/34	26/42			0.65 (0.46, 0.80)		0.62 (0.46, 0.76
Carev I. 2018	50/72	430/442		-8-	0.69 (0.57, 0.80			0.97 (0.95, 0.99
Wang F, 2009	123/177	859/1060		-	0.69 (0.62, 0.76)	=	0.81 (0.79, 0.83
Bissinger A, 2013	12/17	158/166			- 0.71 (0.44, 0.90)		0.95 (0.91, 0.98
Cai J, 2005	181/244	428/465		-	0.74 (0.68, 0.80)		■ 0.92 (0.89, 0.94
Tang Y, 2013	156/210	248/300		-	0.74 (0.68, 0.80)	-	0.83 (0.78, 0.87
Köse S, 2011	3/4	4/4	_		- 0.75 (0.19, 0.99)		—1 .00 (0.40, 1.00
Wang X, 2015	47/62	47/58		-8-	0.76 (0.63, 0.86))	=	- 0.81 (0.69, 0.90
Ségéral O, 2018	26/34	91/94			- 0.76 (0.59, 0.89))		- 0.97 (0.91, 0.99
Shao Z, 2011	33/43	155/169			- 0.77 (0.61, 0.88))		• 0.92 (0.86, 0.95
Peng N, 2012	165/215	162/195		-	0.77 (0.71, 0.82))	-8	e 0.83 (0.77, 0.88
Latthaphasavang V, 2019	51/65	79/88		-8	- 0.78 (0.67, 0.88))	-	0.90 (0.81, 0.95
Chen Z, 2017	104/132	57/79		-8	0.79 (0.71, 0.85)	-8-	0.72 (0.61, 0.82
Hao X, 2015	30/37	106/117			- 0.81 (0.65, 0.92))	-	 0.91 (0.84, 0.95
Söderström A, 2003	9/11	35/35			─ 0.82 (0.48, 0.98))		- 1.00 (0.90, 1.00
Wang L, 2016	9/11	20/20			─ 0.82 (0.48, 0.98))	-	—1 .00 (0.83, 1.00
Zhang L, 2017	143/172	281/319		-	0.83 (0.77, 0.88))	4	0.88 (0.84, 0.91
Liu H, 2013	138/165	77/94		-	0.84 (0.77, 0.89))	-8	- 0.82 (0.73, 0.89
Wiseman E, 2009	82/98	205/215		-	► 0.84 (0.75, 0.90))		0.95 (0.92, 0.98
Yin Yu-zhu, 2013	435/512	810/848			0.85 (0.82, 0.88)			0.96 (0.94, 0.97
Kubo A, 2014	127/147	652/688		-)	_	0.95 (0.93, 0.96
Lu H, 2009	//8	21/25			■ 0.88 (0.47, 1.00)			■ 0.84 (0.64, 0.95
Li X, 2018	150/171	524/545		-	0.88 (0.82, 0.92))		0.96 (0.94, 0.98
Thilakanathan C, 2018	168/185	433/457			 0.91 (0.86, 0.95) 0.01 (0.85, 0.95))		0.95 (0.92, 0.97
Lunel-Fabiani F, 2018	112/123	456/471			 0.91 (0.85, 0.95) 0.00 (0.00, 0.00) 			0.97 (0.95, 0.98
	131/143	220/248)	,	 0.89 (0.84, 0.92 0.02 (0.02, 0.05
Werk, 2017	568/606	1058/1135)	-	0.93 (0.92, 0.95)
Wang X, 2015	133/138	203/271			 0.96 (0.92, 0.99) 1.00 (0.02, 1.00))	-	0.75 (0.69, 0.80
Dorvisovic S 2007	1/1	5/5 101/101		_	■ 1.00 (0.03, 1.00)			1.00 (0.77, 1.00
Dervisevic 3, 2007	7/7	14/14			■ 1.00 (0.75, 1.00)			
7 millo M, 2013	24/24	26/20						
Enaud HM 2019	24/24 7/7	20/29						- 0.79 (0.62 0.91
1 0400 1101, 2013	1/1	21/04			- 1.00 (0.00, 1.00)		-	0.75 (0.02, 0.01
In-house or unknown HB	V DNA test							
Rouet F, 2004	10/15	59/62			- 0.67 (0.38, 0.88))		- 0.95 (0.87, 0.99
Dolman G, 2018	26/32	384/391			- 0.81 (0.64, 0.93))		0.98 (0.96, 0.99
Huang L, 2014	122/132	125/192			■ 0.92 (0.87, 0.96))		0.65 (0.58, 0.72
Bai H, 2010	44/46	73/74			- 0.96 (0.85, 0.99))		• 0.99 (0.93, 1.00
			0.00	0.50	1 00	0.00	0.50	1 00
			0.00	0.00	1.00	0.00	0.00	1.00

Fig. 9. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 5 log10 IU/mL by type of HBV DNA assay

Maternal age and					Sensitivity			Specificity
Author, year	TP/(TP+FN)	TN/(TN+FP)			(95% CI)			(95% CI)
Mean/median age < 28 ye	ars old							
Tang Y, 2013	156/210	248/300		-	0.74 (0.68, 0.80)		ł	0.83 (0.78, 0.87)
Köse S, 2011	3/4	4/4	-		0.75 (0.19, 0.99)			1.00 (0.40, 1.00)
Chen Z, 2017	104/132	57/79		-8-	0.79 (0.71, 0.85)		-8-	- 0.72 (0.61, 0.82)
Hao X, 2015	30/37	106/117			0.81 (0.65, 0.92)			- 0.91 (0.84, 0.95)
Lu H, 2009	7/8	21/25		8	0.88 (0.47, 1.00)			 0.84 (0.64, 0.95)
Lunel-Fabiani F, 2018	112/123	456/471		-8	0.91 (0.85, 0.95)			 0.97 (0.95, 0.98)
Wei K, 2017	568/606	1058/1135			0.94 (0.91, 0.96)			 0.93 (0.92, 0.95)
Bai H, 2010	44/46	73/74		-8	0.96 (0.85, 0.99)			 0.99 (0.93, 1.00)
Chotun N, 2017	1/1	5/5			1.00 (0.03, 1.00)			1.00 (0.48, 1.00)
Pirillo M, 2015	7/7	14/14		8	1.00 (0.59, 1.00)		-	1.00 (0.77, 1.00)
Zhu B, 2013	24/24	26/29		8	1.00 (0.86, 1.00)		-	
Foaud HM, 2019	7/7	27/34		8	1.00 (0.59, 1.00)			- 0.79 (0.62, 0.91)
Mean/median age ≥ 28 ye	ars old							
Carey I, 2018	50/72	430/442		-8-	0.69 (0.57, 0.80)			0.97 (0.95, 0.99)
Bissinger A, 2013	12/17	158/166			0.71 (0.44, 0.90)			0.95 (0.91, 0.98)
Ségéral O, 2018	26/34	91/94			0.76 (0.59, 0.89)			 0.97 (0.91, 0.99)
Latthaphasavang V, 2019	51/65	79/88			0.78 (0.67, 0.88)			- 0.90 (0.81, 0.95)
Dolman G, 2018	26/32	384/391			0.81 (0.64, 0.93)			0.98 (0.96, 0.99)
Wang L, 2016	9/11	20/20			0.82 (0.48, 0.98)			—1 .00 (0.83, 1.00)
Liu H, 2013	138/165	77/94		-	0.84 (0.77, 0.89)		-	■ 0.82 (0.73, 0.89)
Yin Yu-zhu, 2013	435/512	810/848			0.85 (0.82, 0.88)			0.96 (0.94, 0.97)
Kubo A, 2014	127/147	652/688		-	0.86 (0.80, 0.91)			0.95 (0.93, 0.96)
Thilakanathan C, 2018	168/185	433/457		-	0.91 (0.86, 0.95)			• 0.95 (0.92, 0.97)
			0.00	0.50 1.0	0	0.00	0.50	l 1.00

Fig. 10. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 5 log10 IU/mL by mean or median maternal age

HIV status and					Sensitivity			Specificity
Author, year	TP/(TP+FN)	TN/(TN+FP)			(95% CI)			(95% CI)
All uninfected								
Wang M, 2018	22/34	26/42			- 0.65 (0.46, 0.80	1		0.62 (0.46, 0.76)
Köse S, 2011	3/4	4/4	-		0.75 (0.19, 0.99	1		■ 1.00 (0.40, 1.00)
Chen Z, 2017	104/132	57/79		-	■ 0.79 (0.71, 0.85	1		0.72 (0.61, 0.82)
Wiseman E, 2009	82/98	205/215				1		0.95 (0.92, 0.98)
Li X, 2018	150/171	524/545			- 0.88 (0.82, 0.92	1		0.96 (0.94, 0.98)
Liang P, 2017	131/143	220/248			- 0.92 (0.86, 0.96	1		0.89 (0.84, 0.92)
Wei K, 2017	568/606	1058/1135			■ 0.94 (0.91, 0.96	1	I	0.93 (0.92, 0.95)
Wang X, 2015	133/138	203/271			■ 0.96 (0.92, 0.99	1	-	0.75 (0.69, 0.80)
Chotun N, 2017	1/1	5/5			■ 1.00 (0.03, 1.00	1		■ 1.00 (0.48, 1.00)
Zhu B, 2013	24/24	26/29				1		► 0.90 (0.73, 0.98)
Foaud HM, 2019	7/7	27/34			■ 1.00 (0.59, 1.00	1		0.79 (0.62, 0.91)
All infected								
Wang L, 2016	9/11	20/20			0.82 (0.48, 0.98	1	-	■ 1.00 (0.83, 1.00)
Pirillo M, 2015	7/7	14/14			■ 1.00 (0.59, 1.00	1		■ 1.00 (0.77, 1.00)
Mixed population								
Rouet F, 2004	10/15	59/62				1	-	0.95 (0.87, 0.99)
Latthaphasavang V, 2019	51/65	79/88		_	■ 0.78 (0.67, 0.88	1	-4	0.90 (0.81, 0.95)
Lunel-Fabiani F, 2018	112/123	456/471			-■ 0.91 (0.85, 0.95	1		0.97 (0.95, 0.98)
			0.00	0.50	l 1.00	0.00	0.50	1.00

Fig. 11. Coupled forestplot of the performance of HBeAg to identify maternal HBV DNA ≥5 log10 IU/mL by maternal HIV status

Sensitivity analysis for the performance of HBeAg to identify pregnant women with HBV DNA ≥5 log10 IU/mL (Table 7)

Sensitivity and specificity were slightly lower in univariate analysis compared to the bivariate analysis. However, there was no evidence of a statistically significant difference between the bivariate and univariate analysis estimates as 95% CI overlapped. Results were unchanged when the outlier study (*Lin J, 2002*) was excluded from the bivariate analysis or when studies with an overall "high" risk of bias as per QUADAS-2 assessment were excluded.

Sensitivity analysis	Studies,	Se (95% CI) or	Sp (95% CI) or
	Ν	Range Se	Range Sp
Overall bivariate	38	84.2 (80.2-87.4)	92.3 (89.5-94.5)
Overall univariate	42	82.5 (79.0-85.5)	91.4 (88.9-93.5)
Bivariate without outlier study	37	84.8 (81.4-87.7)	92.4 (89.4-94.5)
Bivariate without studies with an overall "high" risk of bias	28	85.0 (79.9-89.0)	93.0 (89.5-95.4)

Table 7. Results of the sensitivity analysis for the performance of HBeAg to identify pregnant women with HBV DNA \geq 5 log10 IU/mL

4.2.3.3. Performance of HBeAg to identify pregnant women with HBV DNA ≥6 log10 IU/mL

- Overall pooled sensitivity = 92.0% (95% CI: 88.2-94.6)
- Overall pooled specificity = 92.7% (95% CI: 90.3-94.5)

There was no evidence of publication bias (p=0.15) (Appendix G.2). We did not identify any outlier study through visual assessment of the overall coupled forest plot (Fig. 12) and the summary scatter plot (Fig. 13).

Fig. 12. Coupled forestplot for all studies included in the meta-analysis of the performance of HBeAg to identify maternal HBV DNA $\geq 6 \log 10 \text{ IU/mL}$

Author, year	TP/(TP+FN)	TN/(TN+FP)			Sensitivity (95% CI)			Specificity (95% CI)
Johannessen A, 2017	1/2	59/61		-	0.50 (0.01, 0.9	9)		- 0.97 (0.89, 1.00)
Lin J, 2002	15/28	37/41			0.54 (0.34, 0.7	2)		
Michitaka K, 2012	4/6	15/15			0.67 (0.22, 0.9	6)		1.00 (0.78, 1.00)
Godbole G, 2013	20/26	261/267			► 0.77 (0.56, 0.9	1)		 0.98 (0.95, 0.99)
Ségéral O, 2018	26/33	92/95		—	0.79 (0.61, 0.9	1)		- 0.97 (0.91, 0.99)
Wang Z, 2018	43/54	171/199		-	■ 0.80 (0.66, 0.8	9)		- 0.86 (0.80, 0.90)
Fujiko M, 2015	8/10	50/54			0.80 (0.44, 0.9	7)		- 0.93 (0.82, 0.98)
Zhang L, 2017	121/142	289/349			- 0.85 (0.78, 0.9	1)		 0.83 (0.78, 0.87)
Peng S, 2019	124/143	977/1076			- 0.87 (0.80, 0.9	2)		0.91 (0.89, 0.92)
Xu H, 2008	8/9	145/189			0.89 (0.52, 1.0	0)	+	0.77 (0.70, 0.83)
Söderström A, 2003	9/10	36/36				0)		- 1.00 (0.90, 1.00)
Wang L, 2016	9/10	21/21				0)		—1 .00 (0.84, 1.00)
Guo F, 2007	95/102	201/217			- 0.93 (0.86, 0.9	7)		• 0.93 (0.88, 0.96)
Cheung K, 2019	68/73	239/252			- 0.93 (0.85, 0.9	8)		 0.95 (0.91, 0.97)
Lunel-Fabiani F, 2018	110/117	460/477			- 0.94 (0.88, 0.9	8)		0.96 (0.94, 0.98)
Thilakanathan C, 2018	158/168	440/474			■ 0.94 (0.89, 0.9	7)		 0.93 (0.90, 0.95)
Zheng H, 2010	86/91	343/387			- 0.95 (0.88, 0.9	8)		 0.89 (0.85, 0.92)
Li X, 2018	141/149	537/567			■ 0.95 (0.90, 0.9	8)		0.95 (0.93, 0.96)
Sheng Q, 2018	107/112	285/329			- 0.96 (0.90, 0.9	9)		 0.87 (0.82, 0.90)
Wei K, 2017	540/559	1077/1182			0.97 (0.95, 0.9	8)		0.91 (0.89, 0.93)
Chen T, 2018	160/165	305/334			0.97 (0.93, 0.9	9)		0.91 (0.88, 0.94)
Xu C, 2018	66/68	140/146			- 0.97 (0.90, 1.0	0)		• 0.96 (0.91, 0.98)
Jin C, 2007	38/39	155/165			- 0.97 (0.87, 1.0	0)		 0.94 (0.89, 0.97)
Wang J, 2018	141/142	334/425			0.99 (0.96, 1.0	0)		0.79 (0.74, 0.82)
Köse S, 2011	3/3	4/4			1.00 (0.29, 1.0	0)		1.00 (0.40, 1.00)
Pirillo M, 2015	6/6	14/15			1.00 (0.54, 1.0	0)	_	0.93 (0.68, 1.00)
Pirillo M, 2007	2/2	4/5	-		■ 1.00 (0.16, 1.0	0)		■ 0.80 (0.28, 0.99)
			0.00	0.50	1.00	0.00	0.50	l 1.00



Fig. 13. Summary scatter plot of the performance of HBeAg to identify maternal HBV DNA $\geq 6 \log 10 \text{ IU/mL}$

Subgroup analysis

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Table 8 and Fig. 14 to 19 present detailed results of the performance of HBeAg to identify pregnant women with HBV DNA \geq 6 log10 IU/mL stratified by the potential sources of heterogeneity.

There was strong evidence that the performance differed according to mean/median maternal age; higher sensitivity and lower specificity were observed in younger age group (P=0.001) (Fig. 18). There was some evidence that performance of HBeAg varied according to the WHO region (P=0.04), weak evidence for HBeAg assay type (P=0.08), and no evidence for HIV status.

Table 8.	Performance	of HBeAg to ident	tify pregnant won	nen with HBV	viral load ≥6 log1	0
IU/mL,	stratified by p	otential sources of	fheterogeneity		_	

		-				
Subgroup	Subgroup	Studies	Se (95% CI) or	Sp (95% CI) or	P-	
variables	category	(N)	Range Se	Range Sp	value	
Overall		27	92.0 (88.2-94.6)	92.7 (90.3-94.5)	N/A	
WHO	WPR	19	92.6 (88.4-95.3)	91.1 (88.4-93.2)	0.04*	
region	SEAR	1	80.0	92.6		
	EUR	3	82.1 (66.9-91.2)	98.0 (95.7-99.1)		
	EMR	0	N/A	N/A		
	AFR	4	93.7 (87.9-96.8)	96.2 (94.3-97.5)		
	AMR	0	N/A	N/A		
HBeAg	EIA	12	88.2 (80.9-93.0)	91.5 (87.0-94.6)	0.08**	
assay type	FIA	1	90.0	100.0		
	CLIA	9	94.0 (89.9-96.5)	93.9 (90.9-95.9)		
	RDT	1	78.8	96.8		
	Multiple	1	97.1	95.9		
	RIA/CIA	0	N/A	N/A		
Type of HBV	Commercial PCR	25	92.3 (88.4-94.9)	93.1 (90.7-94.9)	N/A	
DNA assay	In-house or unknown test	2	79.6-100.0	80.0-85.9		
Mean /	<28 years	8	96.6 (94.8-97.8)	91.7 (87.0-94.8)	0.001	
median	≥28 years	11	86.9 (80.2-91.6)	94.1 (90.9-96.3)		

maternal age					
HIV	All	7	94.2 (90.3-96.6)	92.2 (89.9-94.0)	0.77**
status	uninfected				*
	All infected	3	95.2 (56.3-99.7)	95.2 (80.1-99.0)	
	Mixed	1	94.0	96.4	
	population				

*comparison of WPR/EUR/AFR **comparison CLIA/EIA ***comparison all uninfected vs all infected

WHO region and						Sensitivity			Specificity
Author, year	TP/(TP+FN)	TN/(TN+FP)				(95% CI)			(95% CI)
Lin L 2002	15/28	37/41				0.54 (0.34 0.72)			
Michitaka K 2012	15/20	15/15				0.54 (0.54, 0.72)			- 1 00 (0.77, 0.97)
Sógóral O 2019	4/0	02/05		_	_	0.07 (0.22, 0.90)			
Segeral 0, 2010	20/33	92/90				0.79 (0.01, 0.91)		_	
Wang 2, 2010	43/34	171/199				0.00 (0.00, 0.09)			0.66 (0.60, 0.90)
Znang L, 2017	121/142	289/349			-	0.85 (0.78, 0.91)			0.83 (0.78, 0.87)
Peng S, 2019	124/143	977/1076			-	0.87 (0.80, 0.92)			0.91 (0.89, 0.92)
Xu H, 2008	8/9	145/189			-	0.89 (0.52, 1.00)			0.77 (0.70, 0.83)
Wang L, 2016	9/10	21/21			-	0.90 (0.55, 1.00)			■ 1.00 (0.84, 1.00)
Guo F, 2007	95/102	201/217			-	0.93 (0.86, 0.97)			0.93 (0.88, 0.96)
Cheung K, 2019	68/73	239/252			-	0.93 (0.85, 0.98)		1	0.95 (0.91, 0.97)
Thilakanathan C, 2018	158/168	440/474			-	0.94 (0.89, 0.97)			0.93 (0.90, 0.95)
Zheng H, 2010	86/91	343/387			-	0.95 (0.88, 0.98)			0.89 (0.85, 0.92)
Li X, 2018	141/149	537/567			-	0.95 (0.90, 0.98)		I	0.95 (0.93, 0.96)
Sheng Q, 2018	107/112	285/329			-	0.96 (0.90, 0.99)		-	0.87 (0.82, 0.90)
Wei K, 2017	540/559	1077/1182				0.97 (0.95, 0.98)			0.91 (0.89, 0.93)
Chen T, 2018	160/165	305/334				0.97 (0.93, 0.99)			0.91 (0.88, 0.94)
Xu C, 2018	66/68	140/146			-	0.97 (0.90, 1.00)			 0.96 (0.91, 0.98)
Jin C, 2007	38/39	155/165			-8	0.97 (0.87, 1.00)		1	0.94 (0.89, 0.97)
Wang J, 2018	141/142	334/425				0.99 (0.96, 1.00)		-	0.79 (0.74, 0.82)
SEAR									
Fujiko M, 2015	8/10	50/54				0.80 (0.44, 0.97)		-	■ 0.93 (0.82, 0.98)
EUR									
Godbole G, 2013	20/26	261/267			-	0.77 (0.56, 0.91)			0.98 (0.95, 0.99)
Söderström A, 2003	9/10	36/36			-8-	0.90 (0.55, 1.00)		-	■ 1.00 (0.90, 1.00)
Köse S, 2011	3/3	4/4				1.00 (0.29, 1.00)			■ 1.00 (0.40, 1.00)
AFR									
Johannessen A, 2017	1/2	59/61				0.50 (0.01, 0.99)		-	0.97 (0.89, 1.00)
Lunel-Fabiani F, 2018	110/117	460/477			-	0.94 (0.88, 0.98)			 0.96 (0.94, 0.98)
Pirillo M. 2015	6/6	14/15				1.00 (0.54, 1.00)			■ 0.93 (0.68, 1.00)
Pirillo M, 2007	2/2	4/5	_		-	1.00 (0.16, 1.00)	—		- 0.80 (0.28, 0.99)
			0.00	0.50	1.00)	0.00	0.50	1.00

Fig. 14. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥6 log10 IU/mL by WHO region

EIA Johannessen A, 2017 1/2 Lin J, 2002 15/ Fujiko M, 2015 8/1 Zhang L, 2017 12' Peng S, 2019 12' Xu H, 2008 8/9 Söderström A, 2003 9/1 Guo F, 2007 95/	2 5/28 10 11/142 14/143 3 10 /102 0/147	59/61 37/41 50/54 289/349 977/1076 145/189 36/36 	0.50 (0.01, 0.99) -■ 0.54 (0.34, 0.72) -■ 0.80 (0.44, 0.97) -■ 0.85 (0.78, 0.91) ■ 0.87 (0.80, 0.92) ■	0.97 (0.89, 1.00) 0.90 (0.77, 0.97) 0.93 (0.82, 0.98) 0.83 (0.78, 0.87)
EIA Johannessen A, 2017 1/2 Lin J, 2002 15/ Fujiko M, 2015 8/1 Zhang L, 2017 12' Peng S, 2019 12' Xu H, 2008 8/9 Söderström A, 2003 9/1 Guo F, 2007 95/	2 5/28 10 11/142 14/143 3 10 /102 0/117	59/61 ■ 37/41 ■ 50/54 ■ 289/349 ■ 977/1076 ■ 145/189 ■ 36/36 ■	0.50 (0.01, 0.99) -■ 0.54 (0.34, 0.72) -■ 0.80 (0.44, 0.97) -■ 0.85 (0.78, 0.91) ■ 0.87 (0.80, 0.92) ■	0.97 (0.89, 1.00) 0.90 (0.77, 0.97) 0.93 (0.82, 0.98) 0.83 (0.78, 0.87)
Johannessen A, 2017 1/2 Lin J, 2002 15/ Fujiko M, 2015 8/1 Zhang L, 2017 12' Peng S, 2019 12' Xu H, 2008 8/9 Söderström A, 2003 9/1 Guo F, 2007 95/	2 5/28 10 11/142 5/4/143 3 10 7/102 0/417	59/61 37/41 50/54 289/349 977/1076 145/189 36/36	0.50 (0.01, 0.99) -■ 0.54 (0.34, 0.72) -■ 0.80 (0.44, 0.97) -■ 0.85 (0.78, 0.91) ■ 0.87 (0.80, 0.92) ■	0.97 (0.89, 1.00) 0.90 (0.77, 0.97) 0.93 (0.82, 0.98) 0.83 (0.78, 0.87)
Lin J, 2002 15/ Fujiko M, 2015 8/1 Zhang L, 2017 12 ⁻ Peng S, 2019 12 ⁻ Xu H, 2008 8/9 Söderstöm A, 2003 9/1 Guo F, 2007 95/	5/28 10 11/142 14/143 3 10 /102	37/41	0.54 (0.34, 0.72) -∎ 0.80 (0.44, 0.97) -∎ 0.85 (0.78, 0.91) ∎ 0.87 (0.80, 0.92) ∎	0.90 (0.77, 0.97) 0.93 (0.82, 0.98) 0.83 (0.78, 0.87)
Fujiko M, 2015 8/1 Zhang L, 2017 12' Peng S, 2019 12' Xu H, 2008 8/9 Söderström A, 2003 9/1 Guo F, 2007 95/	10 11/142 24/143 9 10 /102	50/54 ■ 289/349 ■ 977/1076 ■ 145/189 ■ 36/36 ■	0.80 (0.44, 0.97) -∎ 0.85 (0.78, 0.91) ∎ 0.87 (0.80, 0.92) ∎	0.93 (0.82, 0.98) 0.83 (0.78, 0.87)
Zhang L, 2017 12' Peng S, 2019 12' Xu H, 2008 8/9 Söderström A, 2003 9/1 Guo F, 2007 95/	21/142 24/143 9 10 /102	289/349 -∎ 977/1076 -∎ 145/189 -∎ 36/36 -∎	0.85 (0.78, 0.91) 0.87 (0.80, 0.92)	0.83 (0.78, 0.87)
Peng S, 2019 12- Xu H, 2008 8/9 Söderström A, 2003 9/1 Guo F, 2007 95/	24/143 9 10 /102	977/1076 -	0.87 (0.80, 0.92)	0.01 (0.00 0.00)
Xu H, 2008 8/9 Söderström A, 2003 9/1 Guo F, 2007 95/	9 10 //102	145/189 — — — — — — — — — — — — — — — — — — —		0.91 (0.09, 0.92)
Söderström A, 2003 9/1 Guo F, 2007 95/	10 /102	36/36	0.89 (0.52, 1.00)	0.77 (0.70, 0.83)
Guo F, 2007 95/	0/102		0.90 (0.55, 1.00) -	1.00 (0.90, 1.00)
	0/117	201/217 -	0.93 (0.86, 0.97)	0.93 (0.88, 0.96)
Lunel-Fabiani F, 2018 110	0/11/	460/477	0.94 (0.88, 0.98)	0.96 (0.94, 0.98)
Zheng H, 2010 86/	/91	343/387 -	0.95 (0.88, 0.98)	0.89 (0.85, 0.92)
Köse S, 2011 3/3	3	4/4	1.00 (0.29, 1.00)	1.00 (0.40, 1.00)
Pirillo M, 2007 2/2	2	4/5	1.00 (0.16, 1.00)	0.80 (0.28, 0.99)
FIA				
Wang L, 2016 9/1	10	21/21 —	0.90 (0.55, 1.00) —	1.00 (0.84, 1.00)
CLIA				
Michitaka K, 2012 4/6	6	15/15	0.67 (0.22, 0.96)	1.00 (0.78, 1.00)
Godbole G, 2013 20/	1/26	261/267	0.77 (0.56, 0.91)	0.98 (0.95, 0.99)
Cheung K, 2019 68/	/73	239/252	0.93 (0.85, 0.98)	0.95 (0.91, 0.97)
Thilakanathan C, 2018 158	8/168	440/474	0.94 (0.89, 0.97)	0.93 (0.90, 0.95)
Li X, 2018 14-	1/149	537/567	0.95 (0.90, 0.98)	0.95 (0.93, 0.96)
Sheng Q, 2018 107	7/112	285/329	0.96 (0.90, 0.99)	0.87 (0.82, 0.90)
Wei K, 2017 540	0/559	1077/1182	0.97 (0.95, 0.98)	0.91 (0.89, 0.93)
Chen T, 2018 160	0/165	305/334	0.97 (0.93, 0.99)	0.91 (0.88, 0.94)
Pirillo M, 2015 6/6	3	14/15	1.00 (0.54, 1.00)	0.93 (0.68, 1.00)
RDT				
Ségéral O, 2018 26/	/33	92/95	0.79 (0.61, 0.91) -	0.97 (0.91, 0.99)
Multiple				
Xu C, 2018 66/	/68	140/146 -	0.97 (0.90, 1.00)	0.96 (0.91, 0.98)

Fig. 15. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA $\geq 6 \log 10 \text{ IU/mL}$ by type of HBeAg assay

Fig. 16. Coupled forestplot of the performance of HBeAg to identify maternal HBV DNA ≥6 log10 IU/mL by HBeAg assay commercial name

HBeAg assay				Constitute			Onesidiaite
commercial name				Sensitivity			Specificity
and Author, year				(95% CI)			(95% CI)
HBeAg Kehua Bio-Eng	gineering	0	_			_	
Peng S, 2019	124/143	977/1076	-	0.87 (0.80, 0.92)		_	0.91 (0.89, 0.92)
Zheng H, 2010	86/91	343/387	-	0.95 (0.88, 0.98)			0.89 (0.85, 0.92)
AxSYM Abbott							
Söderström A, 2003	9/10	36/36		0.90 (0.55, 1.00)		-	1.00 (0.90, 1.00)
Intec HBeAg ELISA							
Xu H, 2008	8/9	145/189		0.89 (0.52, 1.00)		-	0.77 (0.70, 0.83)
Guo F, 2007	95/102	201/217	-	0.93 (0.86, 0.97)			0.93 (0.88, 0.96)
Monolisa HBeAg-Ab P	LUS Bio-Rad						
Fujiko M, 2015	8/10	50/54		0.80 (0.44, 0.97)		-	0.93 (0.82, 0.98)
Murex HBeAg/anti-HB	e						
Pirillo M, 2007	2/2	4/5		1.00 (0.16, 1.00)	_		0.80 (0.28, 0.99)
WB-2496 HBeAg Want	ai						
Lin J, 2002	15/28	37/41		0.54 (0.34, 0.72)			0.90 (0.77, 0.97)
ETI-EBK-PLUS Diasor	in						
Lunel-Fabiani F, 2018	110/117	460/477	-	0.94 (0.88, 0.98)			0.96 (0.94, 0.98)
Liaison Diasorin							
Köse S, 2011	3/3	4/4		1.00 (0.29, 1.00)			1.00 (0.40, 1.00)
Vidas HBe/anti-HBe Bi	iomérieux						
Johannessen A 2017	1/2	59/61		0.50 (0.01 0.99)			0.97 (0.89, 1.00)
	172	00/01	-	0.00 (0.01, 0.00)		-	0.07 (0.00, 1.00)
Anytest SYM-BIO	0/10	01/01	-	0.00 (0.55, 1.00)		_	1.00 (0.04, 1.00)
wang L, 2016	9/10	21/21		0.90 (0.55, 1.00)			1.00 (0.84, 1.00)
Architect Abbott			_			_	
Thilakanathan C, 2018	158/168	440/474	-	0.94 (0.89, 0.97)		_	0.93 (0.90, 0.95)
Li X, 2018	141/149	537/567		0.95 (0.90, 0.98)		_	0.95 (0.93, 0.96)
Sheng Q, 2018	107/112	285/329	1 1	0.96 (0.90, 0.99)			0.87 (0.82, 0.90)
Wei K, 2017	540/559	1077/1182		0.97 (0.95, 0.98)			0.91 (0.89, 0.93)
Chen T, 2018	160/165	305/334		0.97 (0.93, 0.99)			0.91 (0.88, 0.94)
Pirillo M, 2015	6/6	14/15		1.00 (0.54, 1.00)			0.93 (0.68, 1.00)
Elecsys Roche							
Cheung K, 2019	68/73	239/252	-	0.93 (0.85, 0.98)			0.95 (0.91, 0.97)
SD Bioline HBeAg test	t						
Ségéral O, 2018	26/33	92/95		0.79 (0.61, 0.91)		-	0.97 (0.91, 0.99)
Multiple							
Godbole G, 2013	20/26	261/267		0.77 (0.56, 0.91)			0.98 (0.95, 0.99)
Xu C, 2018	66/68	140/146	-	0.97 (0.90, 1.00)			0.96 (0.91, 0.98)
Unknown							
Zhang L, 2017	121/142	289/349	-	0.85 (0.78, 0.91)			0.83 (0.78, 0.87)
Michitaka K, 2012	4/6	15/15	_	0.67 (0.22, 0.96)			1.00 (0.78, 1.00)
Wang Z, 2018	43/54	171/199		0.80 (0.66, 0.89)		-	0.86 (0.80, 0.90)
Jin C, 2007	38/39	155/165	-	0.97 (0.87, 1.00)			0.94 (0.89, 0.97)
Wang J, 2018	141/142	334/425	-	0.99 (0.96, 1.00)			0.79 (0.74, 0.82)
			0.00 0.50 1.0	00	0.00	0.50 1.0	0

HBV DNA type of assay and Author, year	TP/(TP+FN)	TN/(TN+FP)			Sensitivity (95% CI)			S (Specificity 95% CI)
Commercial PCR									
Johannessen A, 2017	1/2	59/61			0.50 (0.01, 0.99))		- 0	0.97 (0.89, 1.00)
Lin J, 2002	15/28	37/41			0.54 (0.34, 0.72	2)		 (0.90 (0.77, 0.97)
Michitaka K, 2012	4/6	15/15			0.67 (0.22, 0.96	5)		—— ∎ 1	.00 (0.78, 1.00)
Godbole G, 2013	20/26	261/267			0.77 (0.56, 0.91)			.98 (0.95, 0.99)
Ségéral O, 2018	26/33	92/95		\neg	■ 0.79 (0.61, 0.91)		-	0.97 (0.91, 0.99)
Fujiko M, 2015	8/10	50/54			0.80 (0.44, 0.97	7)			0.93 (0.82, 0.98)
Zhang L, 2017	121/142	289/349			- 0.85 (0.78, 0.91)		e 0	0.83 (0.78, 0.87)
Peng S, 2019	124/143	977/1076			- 0.87 (0.80, 0.92	2)			0.91 (0.89, 0.92)
Xu H, 2008	8/9	145/189			0.89 (0.52, 1.00))	-	- 0	0.77 (0.70, 0.83)
Söderström A, 2003	9/10	36/36))		-∎ 1	.00 (0.90, 1.00)
Wang L, 2016	9/10	21/21))		∎ 1	.00 (0.84, 1.00)
Guo F, 2007	95/102	201/217			- 0.93 (0.86, 0.97	7)		e 0	0.93 (0.88, 0.96)
Cheung K, 2019	68/73	239/252			- 0.93 (0.85, 0.98	3)		a (.95 (0.91, 0.97)
Lunel-Fabiani F, 2018	110/117	460/477			- 0.94 (0.88, 0.98	3)			0.96 (0.94, 0.98)
Thilakanathan C, 2018	158/168	440/474			• 0.94 (0.89, 0.97)			0.93 (0.90, 0.95)
Zheng H, 2010	86/91	343/387			- 0.95 (0.88, 0.98	3)		a c	0.89 (0.85, 0.92)
Li X, 2018	141/149	537/567			■ 0.95 (0.90, 0.98	3)			0.95 (0.93, 0.96)
Sheng Q, 2018	107/112	285/329			- 0.96 (0.90, 0.99))		•	0.87 (0.82, 0.90)
Wei K, 2017	540/559	1077/1182			0.97 (0.95, 0.98	3)		• 0	0.91 (0.89, 0.93)
Chen T, 2018	160/165	305/334			0.97 (0.93, 0.99))			0.91 (0.88, 0.94)
Xu C, 2018	66/68	140/146			- 0.97 (0.90, 1.00))		= (0.96 (0.91, 0.98)
Jin C, 2007	38/39	155/165			- 0.97 (0.87, 1.00))		-	0.94 (0.89, 0.97)
Wang J, 2018	141/142	334/425			0.99 (0.96, 1.00)))		• 0	0.79 (0.74, 0.82)
Köse S, 2011	3/3	4/4			1.00 (0.29, 1.00))		1	.00 (0.40, 1.00)
Pirillo M, 2015	6/6	14/15			■ 1.00 (0.54, 1.00))	-	-	0.93 (0.68, 1.00)
In-house or unknown H	BV DNA test								
Wang Z, 2018	43/54	171/199		-	0.80 (0.66, 0.89))		-	0.86 (0.80, 0.90)
Pirillo M, 2007	2/2	4/5	-		1.00 (0.16, 1.00))		• (0.80 (0.28, 0.99)
			0.00	0.50	1.00	0.00	0.50	1.00	

Fig. 17. Coupled forestplot of the performance of HBeAg to identify maternal HBV DNA ≥6 log10 IU/mL by type of HBV DNA assay

Maternal age and					Sensitivity			:	Specificity
Author, year	TP/(TP+FN)	TN/(TN+FP)			(95% CI)			((95% CI)
Mean/median age < 28	years old								
Lunel-Fabiani F, 2018	110/117	460/477			- 0.94 (0.88, 0.98)			0.96 (0.94, 0.98)
Zheng H, 2010	86/91	343/387			- 0.95 (0.88, 0.98)			0.89 (0.85, 0.92)
Wei K, 2017	540/559	1077/1182			0.97 (0.95, 0.98)			0.91 (0.89, 0.93)
Chen T, 2018	160/165	305/334			0.97 (0.93, 0.99)			0.91 (0.88, 0.94)
Xu C, 2018	66/68	140/146			- 0.97 (0.90, 1.00)		-	0.96 (0.91, 0.98)
Wang J, 2018	141/142	334/425			0.99 (0.96, 1.00)		•	0.79 (0.74, 0.82)
Köse S, 2011	3/3	4/4			1.00 (0.29, 1.00)		·	1.00 (0.40, 1.00)
Pirillo M, 2015	6/6	14/15			■ 1.00 (0.54, 1.00)	-		0.93 (0.68, 1.00)
Mean/median age ≥ 28	years old								
Johannessen A, 2017	1/2	59/61			0.50 (0.01, 0.99)		- 🔳 (0.97 (0.89, 1.00)
Michitaka K, 2012	4/6	15/15	-		0.67 (0.22, 0.96)		·	1.00 (0.78, 1.00)
Godbole G, 2013	20/26	261/267			0.77 (0.56, 0.91)			0.98 (0.95, 0.99)
Ségéral O, 2018	26/33	92/95			0.79 (0.61, 0.91)		- 🔳 (0.97 (0.91, 0.99)
Wang Z, 2018	43/54	171/199			■- 0.80 (0.66, 0.89)		- 🖶 🛛	0.86 (0.80, 0.90)
Fujiko M, 2015	8/10	50/54			0.80 (0.44, 0.97)			0.93 (0.82, 0.98)
Peng S, 2019	124/143	977/1076			- 0.87 (0.80, 0.92)			0.91 (0.89, 0.92)
Wang L, 2016	9/10	21/21)		B '	1.00 (0.84, 1.00)
Cheung K, 2019	68/73	239/252			- 0.93 (0.85, 0.98)			0.95 (0.91, 0.97)
Thilakanathan C, 2018	158/168	440/474			0.94 (0.89, 0.97)			0.93 (0.90, 0.95)
Sheng Q, 2018	107/112	285/329			• 0.96 (0.90, 0.99)		-	0.87 (0.82, 0.90)
			0.00	0.50	1 00	0.00	0.50	1.00	
			0.00	0.50	1.00	0.00	0.50	1.00	

Fig. 18. Coupled forestplot of the performance of HBeAg to identify maternal HBV DNA $\geq 6 \log 10 \text{ IU/mL}$ by maternal age

Fig. 19. Coupled forestplot of the performance of HBeAg to identify maternal HBV DNA $\geq 6 \log 10 \text{ IU/mL}$ by maternal HIV status

HIV status and						Sensitivity				Specificity
Author, year	TP/(TP+FN)	TN/(TN+FP)				(95% CI)				(95% CI)
All uninfected					_				_	
Fujiko M, 2015	8/10	50/54				0.80 (0.44, 0.97)				0.93 (0.82, 0.98)
Peng S, 2019	124/143	977/1076			-	0.87 (0.80, 0.92)				0.91 (0.89, 0.92)
Zheng H, 2010	86/91	343/387			-	0.95 (0.88, 0.98)				0.89 (0.85, 0.92)
Li X, 2018	141/149	537/567			-	0.95 (0.90, 0.98)				0.95 (0.93, 0.96)
Wei K, 2017	540/559	1077/1182				0.97 (0.95, 0.98)				0.91 (0.89, 0.93)
Xu C, 2018	66/68	140/146			-	0.97 (0.90, 1.00)			-	0.96 (0.91, 0.98)
Köse S, 2011	3/3	4/4			-	1.00 (0.29, 1.00)			-	1.00 (0.40, 1.00)
All infected										
Wang L, 2016	9/10	21/21				0.90 (0.55, 1.00)				1.00 (0.84, 1.00)
Pirillo M, 2015	6/6	14/15			-	1.00 (0.54, 1.00)		_		0.93 (0.68, 1.00)
Pirillo M, 2007	2/2	4/5	_		-	1.00 (0.16, 1.00)				0.80 (0.28, 0.99)
Mixed population										
Lunel-Fabiani F, 2018	110/117	460/477			-	0.94 (0.88, 0.98)				0.96 (0.94, 0.98)
			0.00	0.50	1.0)	0.00	0.50	1 O	n

Sensitivity analysis for the performance of HBeAg to identify pregnant women with HBV DNA ≥6 log10 IU/mL (Table 9)

As there was no outlier study identified for this HBV DNA threshold, we did not perform sensitivity analysis on this factor.

When excluding from the analysis studies with an overall "high" risk of bias as per QUADAS-2 assessment or performing univariate analysis, there was no evidence of a difference in pooled sensitivity and specificity compared with those of the main bivariate analysis (95% CI overlapped).

Table 9. Results of the sensitivity analysis for the performance of HBeAg to identify pregnant women with HBV DNA $\geq 6 \log 10 \text{ IU/mL}$

Sensitivity analysis	Studies,	Se (95% CI) or	Sp (95% CI) or
	Ν	Range Se	Range Sp
Overall bivariate	27	92.0 (88.2-94.6)	92.7 (90.3-94.5)
Overall univariate	34	89.2 (83.9-92.8)	91.7 (89.5-93.5)
Bivariate without studies with an	21	90.5 (85.8-93.7)	93.6 (91.0-95.5)
overall "high" risk of bias			

4.2.3.4. Performance of HBeAg to identify pregnant women with HBV DNA \geq 7 log10 IU/mL

- Overall pooled sensitivity = 98.0% (95% CI: 93.3-99.4)
- Overall pooled specificity = 88.5% (95% CI: 80.7-93.4)

There was no evidence of publication bias (*P*=0.25) (Appendix G.3). We identified three outliers (*Elefsiniotis I, 2007; Ding Y, 2013* and *Li Y, 2013*) through visual assessment of the overall coupled forest plot (Fig. 20) and the summary scatter plot (Fig. 21).

The first outlier (*Elefsiniotis I*, 2007) was a cross-sectional study in Greece that reported a very low sensitivity (12.5%) and high specificity (100.0%). Recruitment was from 2003 to 2005. HBV DNA was measured using a commercial PCR (COBAS Amplicor HBV Monitor test (Roche Diagnostics)). HBeAg was tested using an ELISA (AxSYM Abbott). Maternal age and HIV status were unknown, and all women were HCV negative.

The second outlier (*Ding Y, 2013*) was a prospective cohort in China that reported a low specificity (38.7%) and high sensitivity (100.0%). Recruitment was from 2010 to 2011. HBV DNA was measured using a commercial PCR (COBAS Taqman (Roche Diagnostics). HBeAg was tested using a CLIA (Architect Abbott). Maternal age was unknown, but 2/249 women were younger than 20 years and 247/249 women were older than 20 years. Maternal HIV status was unknown.

The third outlier (*Li Y, 2013*) was a prospective cohort in China that reported a low specificity (25.4%) and high sensitivity (100.0%). Recruitment was in 2006. HBV DNA was measured using a commercial PCR (Real-Time Fluorescence quantitative PCR (Toyobo)). HBeAg was tested using an ELISA (manufacturer not stated). Maternal age was unknown, and all recruited women were HIV negative.

Fig. 20. Coupled forestplot for all studies included in the meta-analysis of the performance of HBeAg to identify maternal HBV DNA \geq 7 log10 IU/mL

Author, year	TP/(TP+FN)	TN/(TN+FP)		Sensitivity (95% CI)		Specificity (95% CI)
Elefsiniotis I, 2007	1/8	55/55		0.13 (0.00, 0.53)		1.00 (0.94, 1.00)
Zhang L, 2017	32/40	302/451		0.80 (0.64, 0.91)	-	0.67 (0.62, 0.71)
Shi Y, 2012	17/21	286/431	————— —	0.81 (0.58, 0.95)	-	0.66 (0.62, 0.71)
Godbole G, 2013	15/18	264/275		0.83 (0.59, 0.96)	-	0.96 (0.93, 0.98)
Ségéral O, 2018	25/28	96/100		0.89 (0.72, 0.98)	-8	0.96 (0.90, 0.99)
Yin Yu-zhu, 2013	295/316	866/1044		0.93 (0.90, 0.96)		0.83 (0.81, 0.85)
Tang Y, 2013	33/35	300/475		0.94 (0.81, 0.99)	-	0.63 (0.59, 0.68)
Lunel-Fabiani F, 2018	103/108	462/486	-	0.95 (0.90, 0.98)	•	0.95 (0.93, 0.97)
Wei K, 2017	496/504	1088/1237		0.98 (0.97, 0.99)	•	0.88 (0.86, 0.90)
Kubo A, 2014	75/76	671/759	-	0.99 (0.93, 1.00)	•	0.88 (0.86, 0.91)
Söderström A, 2003	9/9	37/37		1.00 (0.66, 1.00)	-	1.00 (0.91, 1.00)
Dopico E, 2013	2/2	2/2		1.00 (0.16, 1.00)		1.00 (0.16, 1.00)
Köse S, 2011	3/3	4/4		1.00 (0.29, 1.00)		1.00 (0.40, 1.00)
Wang L, 2016	9/9	22/22		1.00 (0.66, 1.00)	-	1.00 (0.85, 1.00)
Samadi Kochaksaraei G, 2016	19/19	76/80		1.00 (0.82, 1.00)	-8	0.95 (0.88, 0.99)
Eilard A, 2019	6/6	36/38		1.00 (0.54, 1.00)		0.95 (0.82, 0.99)
Cheung K, 2019	58/58	244/267	-	1.00 (0.94, 1.00)	-	0.91 (0.87, 0.94)
Dyson J, 2014	6/6	44/50		1.00 (0.54, 1.00)		0.88 (0.76, 0.95)
Li X, 2018	71/71	545/645	-	1.00 (0.95, 1.00)	=	0.84 (0.81, 0.87)
Punzalan C, 2012	38/38	136/162	-8	1.00 (0.91, 1.00)	-	0.84 (0.77, 0.89)
Hu Q, 2007	48/48	308/372	-8	1.00 (0.93, 1.00)		0.83 (0.79, 0.86)
Pirillo M, 2015	4/4	14/17		1.00 (0.40, 1.00)		0.82 (0.57, 0.96)
Ding Y, 2013	37/37	82/212	-8	1.00 (0.91, 1.00)	-	0.39 (0.32, 0.46)
Li Y, 2013	14/14	32/126		1.00 (0.77, 1.00)		0.25 (0.18, 0.34)
			0.00 0.50 1.0	00 0.0	ا 00 0.50 1.0	00



Fig. 21. Summary scatter plot of the performance of HBeAg to identify maternal HBV DNA \geq 7 log10 IU/mL

Subgroup analysis

Of the variables predefined as potential sources of heterogeneity, it was not possible to do a subgroup analysis by HCV- or HDV-coinfection status, nor by maternal HBV genotype as too few studies reported information on these factors. Additionally, as all studies had an important risk of bias, we did not perform a subgroup analysis on risk of bias.

Table 10 and Fig. 22 to 27 present detailed results of the performance of HBeAg to identify pregnant women with HBV DNA \geq 7 log10 IU/mL stratified by the potential sources of heterogeneity identified.

There was some evidence that performance of HBeAg to identify pregnant women with HBV DNA \geq 7 log IU/mL varied according to the WHO region (*P*=0.01), and weak evidence that it varied with HBeAg assay type (*P*=0.07). There was no evidence that its performance differed according to maternal age.

Subgroup variables	Subgroup category	Studies (N)	Se (95% CI) or Range Se	Sp (95% CI) or Range Sp	P value
Overall		24	98.0 (93.3-99.4)	88.5 (80.7-93.4)	N/A
WHO region	WPR	12	97.6 (92.2-99.3)	78.9 (64.2-88.6)	0.01*
	SEAR	0	-	-	
	EUR	7	96.7 (36.7-99.9)	95.6 (91.2-97.8)	
	EMR	0	-	-	
	AFR	2	95.0-100.0	82.0-95.0	
	AMR	3	99.2 (94.9-99.9)	88.2 (86.1-90.1)	
HBeAg assay	EIA	11	94.4 (81.3-98.5)	86.9 (67.9-95.4)	0.07**
type	FIA	1	100.0	100.0	
	CLIA	9	98.8 (94.8-99.7)	87.9 (77.2-94.0)	
	RDT	1	89.3	96.0	
	Multiple	0	-	-	
Type of HBV	Commercial	22	97.5 (92.2-99.2)	89.0 (80.3-94.1)	N/A
DNA assay	PCR				
	In-house or	2	100.0	83.4-88.0	
	unknown test				

Table 10. Performance of HBeAg to identify pregnant women with HBV viral load \geq 7 log10 IU/mL, stratified by potential sources of heterogeneity

Mean /	<28 years	6	98.0 (96.3-98.9)	85.9 (74.7-92.7)	0.16
median	≥28 years	9	96.8 (89.5-99.1)	92.5 (88.5-95.2)	
maternal age					
HIV status	All uninfected	7	98.9 (97.0-99.6)	85.3 (66.4-94.4)	N/A
	All infected	2	100.0	82.4-100.0	
	Mixed	2	95.4-100.0	88.0-95.1	
	population				

*comparison of WPR/EUR/AMR

**comparison of CLIA/EIA

WHO region and					Sensitivity				Specificity
Author, year	TP/(TP+FN)	TN/(TN+FP)			(95% CI)				(95% CI)
WPRO									
Zhang L, 2017	32/40	302/451			0.80 (0.64, 0.91)		-		0.67 (0.62, 0.71)
Shi Y, 2012	17/21	286/431		—	0.81 (0.58, 0.95)		-		0.66 (0.62, 0.71)
Ségéral O, 2018	25/28	96/100			0.89 (0.72, 0.98)			-8	0.96 (0.90, 0.99)
Yin Yu-zhu, 2013	295/316	866/1044			0.93 (0.90, 0.96)				0.83 (0.81, 0.85)
Tang Y, 2013	33/35	300/475			- 0.94 (0.81, 0.99)		-		0.63 (0.59, 0.68)
Wei K, 2017	496/504	1088/1237			0.98 (0.97, 0.99)				0.88 (0.86, 0.90)
Wang L, 2016	9/9	22/22			1.00 (0.66, 1.00)				1.00 (0.85, 1.00)
Cheung K, 2019	58/58	244/267			— 1.00 (0.94, 1.00)				0.91 (0.87, 0.94)
Li X, 2018	71/71	545/645			1.00 (0.95, 1.00)				0.84 (0.81, 0.87)
Hu Q, 2007	48/48	308/372			- 1.00 (0.93, 1.00)				0.83 (0.79, 0.86)
Ding Y, 2013	37/37	82/212			- 1.00 (0.91, 1.00)		-		0.39 (0.32, 0.46)
Li Y, 2013	14/14	32/126		-	1.00 (0.77, 1.00)	-	∎-		0.25 (0.18, 0.34)
EURO									
Elefsiniotis I, 2007	1/8	55/55	-8-		0.13 (0.00, 0.53)			-8	1.00 (0.94, 1.00)
Godbole G, 2013	15/18	264/275			0.83 (0.59, 0.96)				0.96 (0.93, 0.98)
Söderström A, 2003	9/9	37/37			—1 .00 (0.66, 1.00)	_			1.00 (0.16, 1.00)
Dopico E, 2013	2/2	2/2	_		—1 .00 (0.16, 1.00)				1.00 (0.40, 1.00)
Köse S, 2011	3/3	4/4			1.00 (0.29, 1.00)			-8	1.00 (0.91, 1.00)
Eilard A, 2019	6/6	36/38			— 1.00 (0.54, 1.00)				0.95 (0.82, 0.99)
Dyson J, 2014	6/6	44/50			1.00 (0.54, 1.00)				0.88 (0.76, 0.95)
AFRO									
Lunel-Fabiani F, 2018	103/108	462/486			• 0.95 (0.90, 0.98)				0.95 (0.93, 0.97)
Pirillo M, 2015	4/4	14/17			1.00 (0.40, 1.00)			-	0.82 (0.57, 0.96)
AMRO									
Kubo A, 2014	75/76	671/759			 0.99 (0.93, 1.00) 				0.88 (0.86, 0.91)
Samadi Kochaksaraei G, 2016	19/19	76/80						-8	0.95 (0.88, 0.99)
Punzalan C, 2012	38/38	136/162			- 1.00 (0.91, 1.00)			-	0.84 (0.77, 0.89)
								1	
			0.00	0.50	1.00	0.00	0.50	1.00)

Fig. 22. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 7 log10 IU/mL by WHO region

Type of HBeAg assay					Sensitivity			Specificity
and Author, year	TP/(TP+FN)	TN/(TN+FP)			(95% CI)			(95% CI)
EIA								
Elefsiniotis I, 2007	1/8	55/55	-8-		0.12 (0.00, 0.53)			- 1.00 (0.94, 1.00)
Zhang L, 2017	32/40	302/451			0.80 (0.64, 0.91)			0.67 (0.62, 0.71)
Shi Y, 2012	17/21	286/431			0.81 (0.58, 0.95)		-	0.66 (0.62, 0.71)
Yin Yu-zhu, 2013	295/316	866/1044			0.93 (0.90, 0.96)			0.83 (0.81, 0.85)
Tang Y, 2013	33/35	300/475			- 0.94 (0.81, 0.99)		-	0.63 (0.59, 0.68)
Lunel-Fabiani F, 2018	103/108	462/486			- 0.95 (0.90, 0.98)			0.95 (0.93, 0.97)
Kubo A, 2014	75/76	671/759			- 0.99 (0.93, 1.00)			0.88 (0.86, 0.91)
Söderström A, 2003	9/9	37/37			1.00 (0.66, 1.00)			- 1.00 (0.91, 1.00)
Köse S, 2011	3/3	4/4			1.00 (0.29, 1.00)			1.00 (0.40, 1.00)
Hu Q, 2007	48/48	308/372			- 1.00 (0.93, 1.00)			0.83 (0.79, 0.86)
Li Y, 2013	14/14	32/126			1.00 (0.77, 1.00)	-	-	0.25 (0.18, 0.34)
FIA								
Wang L, 2016	9/9	22/22		_	1.00 (0.66, 1.00)			— ■ 1.00 (0.85, 1.00)
CLIA								
Godbole G, 2013	15/18	264/275			0.83 (0.59, 0.96)			0.96 (0.93, 0.98)
Wei K, 2017	496/504	1088/1237			0.98 (0.97, 0.99)			0.88 (0.86, 0.90)
Dopico E, 2013	2/2	2/2	_		1.00 (0.16, 1.00)			1.00 (0.16, 1.00)
Samadi Kochaksaraei G, 2016	19/19	76/80			1.00 (0.82, 1.00)			- 0.95 (0.88, 0.99)
Eilard A, 2019	6/6	36/38			1.00 (0.54, 1.00)			
Cheung K, 2019	58/58	244/267			- 1.00 (0.94, 1.00)			0.91 (0.87, 0.94)
Li X, 2018	71/71	545/645			1.00 (0.95, 1.00)			0.84 (0.81, 0.87)
Pirillo M, 2015	4/4	14/17			1.00 (0.40, 1.00)			0.82 (0.57, 0.96)
Ding Y, 2013	37/37	82/212			- 1.00 (0.91, 1.00)		-	0.39 (0.32, 0.46)
RDT								
Ségéral O, 2018	25/28	96/100		-	0.89 (0.72, 0.98)			- 0.96 (0.90, 0.99)
			0.00	0.50	1 00	0.00	0.50	1 00
			0.00	0.50	1.00	0.00	0.00	1.00

Fig. 23. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥7 log10 IU/mL by HBeAg assay type

HBeAg assay commercial					Sensitivity			Specificity
name and Author, year	TP/(TP+FN)	TN/(TN+FP)			(95% Cl)			(95% Cl)
HBeAg Kehua Bio-Engineerin	g							
Tang Y, 2013	33/35	300/475			- 0.94 (0.81, 0.99)		-	0.63 (0.59, 0.68)
AxSYM Abbott								
Elefsiniotis I. 2007	1/8	55/55			0.12 (0.00, 0.53)			1.00 (0.94, 1.00)
Söderström A, 2003	9/9	37/37		_	1.00 (0.66, 1.00)			- 1.00 (0.91, 1.00)
Intec HBeAg ELISA								
Yin Yu-zhu, 2013	295/316	866/1044			0.93 (0.90, 0.96)			0.83 (0.81, 0.85)
EII-EBK-PLUS Diasonin	102/108	460/496						
Lunel-Fabiani F, 2018	103/108	462/486			■ 0.95 (0.90, 0.98)			0.95 (0.93, 0.97)
Robio HBeAg Rongsheng					_			_
Hu Q, 2007	48/48	308/372			- 1.00 (0.93, 1.00)			0.83 (0.79, 0.86)
Liaison Diasorin								
Köse S, 2011	3/3	4/4			1.00 (0.29, 1.00)			1.00 (0.40, 1.00)
Anytest SYM-BIO								
Wang L, 2016	9/9	22/22			1.00 (0.66, 1.00)			—1 .00 (0.85, 1.00)
Architect Abbott								
Wei K 2017	496/504	1088/1237			0.98 (0.97 0.99)			0.88 (0.86, 0.90)
Samadi Kochaksaraei G. 2016	19/19	76/80			1.00 (0.82, 1.00)			- 0.95 (0.88, 0.99)
Filard A 2019	6/6	36/38						
	71/71	545/645			■ 1.00 (0.05, 1.00) ■ 1.00 (0.95, 1.00)			
Birillo M 2015	A 1A	14/17			1 1.00 (0.30, 1.00)			0.82 (0.57, 0.96)
Ding V 2012	4/4	90/010			■ 1.00 (0.40, 1.00)		_	0.32 (0.37, 0.90)
Ding 1, 2013	3//3/	02/212			- 1.00 (0.91, 1.00)		-	0.39 (0.32, 0.46)
Elecsys Roche								
Cheung K, 2019	58/58	244/267			- 1.00 (0.94, 1.00)			0.91 (0.87, 0.94)
Ortho Vitros								
Dopico E, 2013	2/2	2/2	_		1.00 (0.16, 1.00)	-		1.00 (0.16, 1.00)
SD Bioline HBeAg test								
Ségéral O, 2018	25/28	96/100		-	0.89 (0.72, 0.98)			0.96 (0.90, 0.99)
Multiple								
Godbole G, 2013	15/18	264/275			0.83 (0.59, 0.96)			0.96 (0.93, 0.98)
Unknown								
Zhang L, 2017	32/40	302/451		_	0.80 (0.64, 0.91)		-	0.67 (0.62, 0.71)
Shi Y, 2012	17/21	286/431			0.81 (0.58, 0.95)			0.66 (0.62, 0.71)
Kubo A, 2014	75/76	671/759			0.99 (0.93, 1.00)			0.88 (0.86, 0.91)
Li Y, 2013	14/14	32/126			1.00 (0.77, 1.00)	-	-	0.25 (0.18, 0.34)
Dyson J. 2014	6/6	44/50			1.00 (0.54, 1.00)			
Punzalan C, 2012	38/38	136/162			-■ 1.00 (0.91, 1.00)			-■ 0.84 (0.77, 0.89)
			0.00	0.50	1.00	0.00	0.50	1.00

Fig. 24. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥7 log10 IU/mL by HBeAg assay commercial name

HBV DNA type of assay					Sensitivity			Spe	cificity
and Author, year	TP/(TP+FN)	TN/(TN+FP)			(95% CI)			(95%	6 CI)
Commercial PCR									
Elefsiniotis I, 2007	1/8	55/55	-8-		0.13 (0.00, 0.53)			- 1.00	(0.94, 1.00)
Zhang L, 2017	32/40	302/451			0.80 (0.64, 0.91)		-	0.67	(0.62, 0.71)
Shi Y, 2012	17/21	286/431			0.81 (0.58, 0.95)		-	0.66	(0.62, 0.71)
Godbole G, 2013	15/18	264/275			0.83 (0.59, 0.96)			0.96	(0.93, 0.98)
Ségéral O, 2018	25/28	96/100		-	0.89 (0.72, 0.98)			- 0.96	(0.90, 0.99)
Yin Yu-zhu, 2013	295/316	866/1044			0.93 (0.90, 0.96)			0.83	(0.81, 0.85)
Tang Y, 2013	33/35	300/475					-	0.63	(0.59, 0.68)
Lunel-Fabiani F, 2018	103/108	462/486			- 0.95 (0.90, 0.98)			0.95	(0.93, 0.97)
Wei K, 2017	496/504	1088/1237			0.98 (0.97, 0.99)			0.88	(0.86, 0.90)
Kubo A, 2014	75/76	671/759			- 0.99 (0.93, 1.00)			0.88	(0.86, 0.91)
Köse S, 2011	3/3	4/4			1.00 (0.29, 1.00)			- 1.00	(0.91, 1.00)
Söderström A, 2003	9/9	37/37			1.00 (0.66, 1.00)			1.00	(0.40, 1.00)
Wang L, 2016	9/9	22/22			1.00 (0.66, 1.00)			—1 .00	(0.85, 1.00)
Dopico E, 2013	2/2	2/2	-		1.00 (0.16, 1.00)	-		1.00	(0.16, 1.00)
Samadi Kochaksaraei G, 2016	19/19	76/80			—1 .00 (0.82, 1.00)			- 0.95	(0.88, 0.99)
Eilard A, 2019	6/6	36/38			1.00 (0.54, 1.00)				(0.82, 0.99)
Cheung K, 2019	58/58	244/267			- 1.00 (0.94, 1.00)			0.91	(0.87, 0.94)
Li X, 2018	71/71	545/645			1.00 (0.95, 1.00)			0.84	(0.81, 0.87)
Hu Q, 2007	48/48	308/372			- 1.00 (0.93, 1.00)			0.83	(0.79, 0.86)
Pirillo M, 2015	4/4	14/17			1.00 (0.40, 1.00)			0.82	(0.57, 0.96)
Ding Y, 2013	37/37	82/212			- 1.00 (0.91, 1.00)			0.39	(0.32, 0.46)
Li Y, 2013	14/14	32/126			1.00 (0.77, 1.00)	-		0.25	(0.18, 0.34)
In-house or unknown HBV DN	A test								
Dyson J, 2014	6/6	44/50			1.00 (0.54, 1.00)				(0.76, 0.95)
Punzalan C, 2012	38/38	136/162			- 1.00 (0.91, 1.00)			- 0.84	(0.77, 0.89)
				1					
			0.00	0.50	1.00	0.00	0.50	1.00	

Fig. 25. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 7 log10 IU/mL by HBV DNA assay type

Fig. 26. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA \geq 7 log10 IU/mL by mean or median maternal age

Maternal age and			Sensitivity	Specificity
Author, year	TP/(TP+FN)	TN/(TN+FP)	(95% CI)	(95% CI)
Mean/median age < 28 years ol	d			
Tang Y, 2013	33/35	300/475	0.94 (0.81, 0.99)	• 0.63 (0.59, 0.68)
Lunel-Fabiani F, 2018	103/108	462/486	- 0.95 (0.90, 0.98)	• 0.95 (0.93, 0.97)
Wei K, 2017	496/504	1088/1237	0.98 (0.97, 0.99)	0.88 (0.86, 0.90)
Köse S, 2011	3/3	4/4	1.00 (0.29, 1.00)	■ 1.00 (0.40, 1.00)
Hu Q, 2007	48/48	308/372	-■ 1.00 (0.93, 1.00)	0.83 (0.79, 0.86)
Pirillo M, 2015	4/4	14/17	1.00 (0.40, 1.00)	0.82 (0.57, 0.96)
Mean/median age ≥ 28 years ol	d			
Godbole G, 2013	15/18	264/275	0.83 (0.59, 0.96)	• 0.96 (0.93, 0.98)
Ségéral O, 2018	25/28	96/100		- 0.96 (0.90, 0.99)
Yin Yu-zhu, 2013	295/316	866/1044	0.93 (0.90, 0.96)	0.83 (0.81, 0.85)
Kubo A, 2014	75/76	671/759	- 0.99 (0.93, 1.00)	0.88 (0.86, 0.91)
Wang L, 2016	9/9	22/22	1.00 (0.66, 1.00)	—1 .00 (0.85, 1.00)
Samadi Kochaksaraei G, 2016	19/19	76/80	—— 1.00 (0.82, 1.00)	- 0.95 (0.88, 0.99)
Eilard A, 2019	6/6	36/38	1.00 (0.54, 1.00)	
Cheung K, 2019	58/58	244/267	- 1.00 (0.94, 1.00)	0.91 (0.87, 0.94)
Dyson J, 2014	6/6	44/50	1.00 (0.54, 1.00)	
			0.00 0.50 1.00 0.00	0.50 1.00

Fig. 27. Coupled forest plot of the performance of HBeAg to identify maternal HBV DNA ≥7 log10 IU/mL by maternal HIV status

HIV status and					Sensitivity			S	Specificity
Author, year	TP/(TP+FN)	TN/(TN+FP)			(95% CI)			(95% CI)
All uninfected									
Wei K, 2017	496/504	1088/1237			0.98 (0.97, 0.99)			D 0	.88 (0.86, 0.90)
Köse S, 2011	3/3	4/4			1.00 (0.29, 1.00)			1	.00 (0.40, 1.00)
Samadi Kochaksaraei G, 2016	19/19	76/80			—1 .00 (0.82, 1.00)			- B 0	0.95 (0.88, 0.99)
Eilard A, 2019	6/6	36/38			1.00 (0.54, 1.00)			—— 0	0.95 (0.82, 0.99)
Li X, 2018	71/71	545/645			■ 1.00 (0.95, 1.00)			■ 0	0.84 (0.81, 0.87)
Hu Q, 2007	48/48	308/372			- 1.00 (0.93, 1.00)			■ 0	0.83 (0.79, 0.86)
Li Y, 2013	14/14	32/126			1.00 (0.77, 1.00)	-1	┣─	C	0.25 (0.18, 0.34)
All infected									
Wang L, 2016	9/9	22/22		_	1.00 (0.66, 1.00)			—= 1	.00 (0.85, 1.00)
Pirillo M, 2015	4/4	14/17			1.00 (0.40, 1.00)		_	— 0	0.82 (0.57, 0.96)
Mixed population									
Lunel-Fabiani F, 2018	103/108	462/486			- 0.95 (0.90, 0.98)			D 0	0.95 (0.93, 0.97)
Dyson J, 2014	6/6	44/50			1.00 (0.54, 1.00)			∎- 0	0.88 (0.76, 0.95)
			0.00	0.50	1 00	0.00	0.50	1.00	

Sensitivity analysis for the performance of HBeAg to identify pregnant women with HBV DNA ≥7 log10 IU/mL (Table 11)

As all the included studies provided sufficient data to conduct bivariate analysis, univariate analysis was not conducted.

When excluding the three outlier studies from the analysis or those with an overall "high" risk of bias as per QUADAS-2 assessment, there was no evidence of a difference in pooled sensitivity and specificity compared with those of the main bivariate analysis (95% CI overlapped).

Table 11. Results of sensitivity analysis for the performance of HBeAg to identify pregnant women with HBV DNA \geq 7 log10 IU/mL

Sensitivity analysis	Studies,	Se (95% CI) or	Sp (95% CI) or
	Ν	Range Se	Range Sp
Overall bivariate	24	98.0 (93.3-99.4)	88.5 (80.7-93.4)
Bivariate without outlier studies	21	97.6 (94.1-99.0)	89.3 (84.3-92.9)
Bivariate without studies with an overall "high" risk of bias	20	98.6 (92.3-99.8)	90.2 (81.3-95.1)

4.2.4. GRADE evidence profile for PICO2A

Table 12. GRADE evidence profile table of the performance of HBeAg to identify pregnant women with an HBV viral load \geq 5 log IU/mL, and \geq 6 log IU/mL, \geq 7 log IU/mL

Test	Reference	Studies, n	Risk of bias	Inconsistency	Indirectness	Imprecision	Patients,	Strength
performance	standard						n	of
								evidence ^a
HBeAg	HBV DNA	Sens: 41	No serious	No serious	No serious	No serious	Sens:	Sens: High
	5 log10	Spec: 39					4414	Spec: High
	IU/mL	_					Spec:	
							9817	
HBeAg	HBV DNA	Sens: 34	No serious	No serious	No serious	No serious	Sens:	Sens: High
	6 log10	Spec: 27					2814	Spec: High
	IU/mL	-					Spec:	
							7382	
HBeAg	HBV DNA	Sens: 24	No serious	No serious	No serious	No serious	Sens:	Sens: High
	7 log10	Spec: 24					1478	Spec: High
	IU/mL						Spec:	
							7347	

^a Although there was no evidence of publication bias, we did not take this factor into account to grade the strength of evidence because most studies were not designed to assess the diagnostic accuracy and there are no reliable methods to assess publication bias in such a context.
4.3. PICO2B: Performance of HBeAg to predict MTCT

Detailed characteristics of each included study are presented in Table 13 below.

Author, year	PICO2B	Country	Original study design	HBeAg assay	Maternal age (years)	Maternal HIV, n (%)	Measure of prevention for MTCT	Children tested, n	Children age at testing (months)	Marker tested in children
Chen Z, 2017 (40)	Bivariate	China	Prospective cohort	ELISA (AxSYM Abbott)	Mean: 26.96	0/211 (0.0%)	TBD + HBIg	168	7	HBsAg & HBV DNA
Chotun N, 2017 (43)	Univariate (specificity)	South Africa	Prospective cohort	CLIA (Architect Abbott)	Mean (Range): 27 (21-34)	0/6 (0.0%)	TBD only	4	7	HBsAg
Ding Y, 2013 (45)	Bivariate	China	Prospective cohort	CLIA (Architect Abbott)	Unknown (Range: 16-45) (n=4536)	Unknown	TBD + HBIg	249	7	HBsAg & HBV DNA
Foaud HM, 2019 (51)	Univariate (Specificity)	Egypt	Prospective cohort	ELISA (ETI-EBK PLUS Diasorin)	Mean: 27.3	0/41 (0.0%)	TBD + HBIg	39	12	HBV DNA
Latthaphasavang V, 2019 (65)	Bivariate	Lao PDR	Prospective cohort	ELISA (Monolisa HBeAg-Ab PLUS Bio-Rad)	Median (IQR): 28 (24-30)	1/153 (0.7%)	TBD only	120	6	HBsAg
Lee L, 2015 (66)	Bivariate	Singapore	Prospective cohort	CLIA (Architect Abbott)	Mean (SD): 32.4 (4.7)	Unknown	TBD + HBIg	154	9	HBsAg & HBV DNA
Liu CP, 2015 (71)	Univariate (Sensitivity)	China	Retrospective cohort	ELISA (HBeAg Santa-Cruz)	Mean: 25.7	0/256 (0.0%)	TBD + HBIg	256	6	HBsAg
Liu Y, 2016 (73)	Bivariate	China	Prospective cohort	CLIA (Architect Abbott)	Mean 27.7	0/110 (0.0%)	TBD + HBIg	78	12	HBsAg & HBV DNA
Lunel-Fabiani F, 2018 (75)	Bivariate	Cameroon	Prospective cohort	Unknown	Median (IQR): 24 (20-30)	1/592 tested (0.2%)	TBD only	133	24	HBsAg
Peng S, 2019 (79)	Bivariate	China	Prospective cohort	ELISA (Kehua HBeAg)	Mean: 29.17	0/1219 (0.0%)	TBD + HBIg	93	7	HBsAg
Shao Z, 2011 (88)	Univariate (Sensitivity)	China	Prospective cohort	ELISA (AxSYM Abbott)	Unknown	Unknown	TBD + HBIg	158	7	HBsAg
Thilakanathan C, 2018 (94)	Univariate (Sensitivity)	Australia	Retrospective cohort	CLIA (Architect Abbott)	Median (Range): 30 (15-44)	Unknown	TBD + HBIg	469	9	HBsAg
Wiseman, E, 2009 (105)	Bivariate	Australia	Prospective cohort	CLIA or ELISA (AxSYM Abbott or Architect Abbott)	Unknown	0/313 (0.0%)	TBD + HBIg	138	9	HBsAg

Yin Y, 2013 (108)	Bivariate	China	Retrospective cohort	ELISA HBeAg)	(Intec	Mean (SD): 28.83 (3.92)	Unknown	TBD + HBIg	1360	12	HBsAg & HBV DNA
Zhu B, 2013 (112)	Univariate (Specificity)	China	Retrospective cohort	CLIA Roche)	(Elecsys	Mean (SD): 26 (4.1)	0/53 (0.0%)	TBD + HBIg	53	12	HBsAg

4.3.1. Summary of included studies

There were 15 original studies, including 9 that allowed for the estimation of both sensitivity and specificity using bivariate analysis, and for the remaining 6, only univariate analysis was possible to estimate sensitivity (n=3) or specificity (n=3). All were observational cohort studies (11 prospective and 4 retrospective) (Table 13).

Recruitment took place from 2002 (*Shao Z, 2011 and Wiseman E, 2009*) to 2017 (*Latthaphasavang V, 2019*). Most studies took place in the Western Pacific Region (n=12); including China (n=8), Lao People's Democratic Republic (n=1), Singapore (n=1) and Australia (n=2). Two studies took place in WHO African Region: Cameroon (n=1) and South Africa (n=1); and one study in the WHO Eastern Mediterranean Region in Egypt (Table 13). No study took place in WHO South-East Asian, European or American regions.

Table 14 describes the characteristics of studies included in PICO2B. Of 15 studies, 12 reported maternal age: 7 (58.3%) with a mean/median maternal age below 28 years; and 5 (41.7%) with \geq 28 years. EIA and CLIA were most frequently used to assess HBeAg (8/15=53.3% and 6/15=40.0, respectively). No study reported the use of a rapid diagnostic test. Most studies included women not infected with HIV, HCV or HDV (n=7/9 (77.8%)), n=5/6 (83.3%) and n=2/2 (100.0%), respectively). Four studies reported HBV genotypes: one with genotype D only and 3 with mixed genotypes. Among studies included in PICO2B. All studies reported giving timely birth dose of HBV vaccine and 12 studies (80.0%) reported giving HBIG to infants. Lastly, all 15 studies reported that infants had received at least 3 doses of HBV vaccine.

PICO2B		Overall (n=1	5)	TBD + HBIG	(n=12)	TBD only	(n=3)
Subgroup variables	Subgroup category	Studies (N)	%	Studies (N)	%	Studies (N)	%
WHO region	WPRO	12	80.0	11	91.7	1	33.3
(n=15)	SEARO	0	0.0	0	0.0	0	0.0
	EURO	0	0.0	0	0.0	0	0.0
	EMRO	1	6.7	0	0.0	0	0.0
	AFRO	2	13.3	1	8.3	2	66.7
	AMRO	0	0.0	0	0.0	0	0.0
HBeAg assay type	EIA	8	53.3	6	50.0	2	66.7
(n=15)	FIA	0	0.0	0	0.0	0	0.0
	CLIA	6	40.0	5	41.7	1	33.3
	RDT	0	0.0	0	0.0	0	0.0
	Multiple	1	6.7	1	8.3	0	0.0
Maternal age	<28 years	7	58.3	5	55.6	2	66.7
(n=12)	≥28 years	5	41.7	4	44.4	1	33.3
HBIg at birth	No	3	20.0	0	0.0	3	100.0
(n=15)	Yes	12	80.0	12	100.0	0	0.0
First dose of HBV vaccine (n=15)	Timely birth dose	15	100.0	12	100.0	3	100.0
, , , , , , , , , , , , , , , , , , ,	Delayed	0	0.0	0	0.0	0	0.0
Three doses of	No	0	0.0	0	0.0	0	0.0
HBV vaccine (n=15)	Yes	15	100.0	12	100.0	3	100.0
HIV status (n=9)	All uninfected	7	77.8	6	100.0	1	33.3
	All infected	0	0.0	0	0.0	0	0.0

Table 14. Characteristics of studies included in the PICO2B

	Mixed	2	22.2	0	0.0	2	66.7
	population						
HCV status (n=6)	All uninfected	5	83.3	5	83.3	0	0.0
	All infected	0	0.0	0	0.0	0	0.0
	Mixed	1	16.7	1	16.7	0	0.0
	population						
HDV status (n=2)	All uninfected	2	100.0	2	100.0	0	0.0
	All infected	0	0.0	0	0.0	0	0.0
	Mixed	0	0.0	0	0.0	0	0.0
	population						
Genotype (n=4)	Genotype A	0	0.0	0	0.0	0	0.0
	Genotype B	0	0.0	0	0.0	0	0.0
	Genotype C	0	0.0	0	0.0	0	0.0
	Genotype D	1	0.0	0	0.0	1	50.0
	Genotype E	0	0.0	0	0.0	0	0.0
	Genotype F	0	0.0	0	0.0	0	0.0
	Genotype I	0	0.0	0	0.0	0	0.0
	Mixed	3	100.0	2	100.0	1	50.0
	population						

4.3.2. Risk of bias assessment

The risk of bias assessment is presented in Fig. 28 & 29 (and details in Appendix E).

None of the studies had the same objective as that of the PICO2B. Therefore, the essential information for the diagnostic studies were often missing. All studies were rated as unclear risk of bias for the reference standard and for the index tests because whether blinding was performed was not mentioned (Fig. 28). Risk of selection bias was high in most studies (n=12/15, 80.0%), mainly due to restrictive exclusion criteria (e.g. exclusion of HIV-, HCV-, or HDV-coinfected pregnant women).

Concerns about applicability were low for most studies (Fig. 29). There was high concern for patient selection applicability in 3 studies (20.0%), due to the enrolment of pregnant women based on their HBV viral load. There was no concern about the applicability of the index test or about the reference standard.







Fig. 29. Concerns about applicability results for PICO2B

4.3.3. Primary analysis, narrative descriptions and forest plots

Overall performance of HBeAg to identify pregnant women at high risk of mother-to-child transmission of HBV, stratified by prevention of MTCT strategy, was as below.

- Overall pooled sensitivity = 99.1 (95% CI: 61.8-100.0)
- Overall pooled specificity = 55.7 (95% CI: 34.0-75.5)

Tables 15 and 16 present detailed performance results for PICO2B. There was no evidence of publication bias (P=0.97) (Appendix G.4). We identified one outlier study (*Liu Y*, 2016) through visual assessment of the coupled forest plots (Fig. 30 and 31) and the summary scatter plot with SROC curve (Fig. 32).

The outlier study was a prospective cohort in China that reported high sensitivity (100.0%) and very low specificity (3.0%) that recruited high viral load (HBV DNA \geq 6 log IU/mL) pregnancy women from 2010 to 2013. HBeAg status in pregnant women was determined using CLIA (Architect Abbott). Mean maternal age was 27.7 years and all enrolled women were HIV negative. In this study, infants received a timely birth dose vaccine, HBIg at birth and 2 subsequent doses of infant vaccine at 1 month and 6 months of age.

Prevention of MTCT strategy	Meta- analysis	Studies (N)	Subjects (N)	TP (N)	FN (N)	TN (N)	FP (N)	Se (95% CI) or Range Se	Sp (95% CI) or Range Sp
Overall	Bivariate	9	3619	92	9	2401	1117	99.1 (61.8-100.0)	55.7 (34.0-75.5)
	Univariate	15	3720	106	9	2454	1151	84.8 (74.8-91.3)	59.9 (48.0-70.7)
TBD +	Bivariate	7	3366	84	9	2220	1053	98.8 (52.0-100.0)	49.2 (25.1-73.7)
IIDIg	Univariate	12	3465	98	9	2271	1087	86.5 (74.3-93.4)	55.2 (41.4-68.2)
TBD only	Bivariate	2	253	8	0	181	64	100.0	60.0-86.2
	Univariate	3	255	8	0	183	64	100.0	76.1 (47.8-91.7)

Table 15. Performance of HBeAg during pregnancy to predict MTCT of HBV, stratified by HBV MTCT prevention strategy

HBeAg to identify MTCT	Studies, N	Pretest probability (%)	PLR (95% CI) or Range PLR	Posttest probability of having MTCT of HBV after positive HBeAg result (%)	NLR (95% CI) or Range NLR	Post-test probability of having MTCT of HBV after positive HBeAg result (%)
Overall	9	4	2.2 (1.4-3.7)	8.2	0.02 (0.00-1.0)	0.07
TBD + HBIG	2	3	2.5-7.2	7.0-17.8	0.00	0.00
TBD only	9	4	2.2 (1.4-3.7)	8.2	0.02 (0.00-1.0)	0.07

Table 16. Post-test probabilities of having MTCT of HBV after positive or negative maternal HBeAg result

Fig. 30. Coupled forest plot of the performance of HBeAg during pregnancy to predict MTCT of HBV by prevention strategy for MTCT

Prevention strategy for MTCT of HBV and Author, year	TP/(TP+FN)	TN/(TN+FP)			Sensitivity (95% CI)			Specificity (95% CI)
TBD + HBlg								
Lee L, 2015	2/4	111/150			- 0.50 (0.07, 0.93)		-8	- 0.74 (0.66, 0.81)
Chen Z, 2017	21/28	65/140			0.75 (0.55, 0.89)		-8-	0.46 (0.38, 0.55)
Peng S, 2019	11/11	996/1208			1 .00 (0.72, 1.00)			0.82 (0.80, 0.85)
Yin Yu-zhu, 2013	21/21	887/1339			■ 1.00 (0.84, 1.00)			0.66 (0.64, 0.69)
Wiseman E, 2009	4/4	77/134			- ■ 1.00 (0.40, 1.00)		-8-	0.57 (0.49, 0.66)
Ding Y, 2013	12/12	82/237		_	1 .00 (0.74, 1.00)		•	0.35 (0.29, 0.41)
Liu Y, 2016	13/13	2/65		_	1 .00 (0.75, 1.00)	(-)		0.03 (0.00, 0.11)
						\smile		
TBD only								
Lunel-Fabiani F, 2018	3/3	112/130			1.00 (0.29, 1.00)			
Latthaphasavang V, 2019	5/5	69/115			■ 1.00 (0.48, 1.00)		-8-	0.60 (0.50, 0.69)
			l 0.00	0.50	l 1.00	l 0.00	l 0.50	l 1.00

HBeAg assay commercial					Sensitivity			Specificity
name and Author, year	TP/(TP+FN)	TN/(TN+FP)			(95% CI)			(95% CI)
HBeAg Kehua Bio-Engine	eering							
Peng S, 2019	11/11	996/1208		_	1.00 (0.72, 1.00)		I	0.82 (0.80, 0.85)
AxSYM Abbott								
Chen Z, 2017	21/28	65/140			- 0.75 (0.55, 0.89)		-	0.46 (0.38, 0.55)
Intec HBeAg ELISA								
Yin Yu-zhu, 2013	21/21	887/1339			—1 .00 (0.84, 1.00)			0.66 (0.64, 0.69)
Monolisa HBeAg-Ab PLU	S Bio-Rad							
Latthaphasavang V, 2019	5/5	69/115			1.00 (0.48, 1.00)			0.60 (0.50, 0.69)
ETI-EBK-PLUS Diasorin								
Lunel-Fabiani F, 2018	3/3	112/130			1.00 (0.29, 1.00)			0.86 (0.79, 0.92)
Architect Abbott								
Lee L, 2015	2/4	111/150			- 0.50 (0.07, 0.93)		-	- 0.74 (0.66, 0.81)
Ding Y, 2013	12/12	82/237		-	1.00 (0.74, 1.00)	- +	-	0.35 (0.29, 0.41)
Liu Y, 2016	13/13	2/65		-	1.00 (0.75, 1.00)	⊕		0.03 (0.00, 0.11)
Multiple								
Wiseman E, 2009	4/4	77/134			1.00 (0.40, 1.00)		-8-	0.57 (0.49, 0.66)
					1			
			0.00	0.50	1.00	0.00	0.50	1.00

Fig. 31. Coupled forest plot of the performance of HBeAg during pregnancy to predict MTCT of HBV by HBeAg assay

Fig. 32. Summary scatter plot with SROC curve of the performance of HBeAg during pregnancy to predict MTCT



Subgroup analysis

As the number of studies was low, we were not able to perform subgroup analysis of the performance of HBeAg during pregnancy to predict MTCT.

Sensitivity analysis for the performance of HBeAg to predict MTCT (Table 17)

When performing univariate analysis and excluding the outlier study from the analysis or those with an overall "high" risk of bias, results remained unchanged compared with that of the main bivariate analysis (95% CI overlapped).

	Studies,	Se (95% CI) or	Sp (95% CI) or
	Ν	Range Se	Range Sp
Overall bivariate	9	99.1 (61.8-100.0)	55.7 (34.0-75.5)
Overall univariate	15	84.8 (74.8-91.3)	59.9 (48.0-70.7)
Bivariate without outlier studies	8	98.6 (59.0-100.0)	65.1 (52.2-76.2)
Bivariate without studies with	6	100.0	34.6-86.2
an overall "high" risk of bias			

Table 17.	Results	of sensitivity	analysis for	r the pe	erformance	e of HBeAg	during pr	egnancy
to predict	MTCT							

4.3.4. GRADE evidence profile for PICO2B

Table 18. GRADE evidence profile table of the performance of HBeAg during pregnancy to predict MTCT, stratified by prevention strategy for MTCT

Test performance	Reference standard	Prevention strategy for MTCT	Studies, n	Risk of bias	Inconsistency	Indirectness	Imprecision	Patients , n	Strength of evidence ^a
HBeAg	МТСТ	Overall	Sens: 12 Spec: 12	Serious	No serious	No serious	Serious	Sens: 115 Spec: 3605	Sens: Low ^b Spec: Low ^b
HBeAg	MTCT	TBD + HBIg	Sens: 10 Spec: 9	Serious	No serious	No serious	Serious	Sens: 107 Spec: 3358	Sens: Low ^c Spec: Low ^c
HBeAg	МТСТ	TBD only	Sens: 2 Spec: 3	Serious	Serious	No serious	Serious	Sens: 8 Spec: 247	Sens: Insufficient data ^d Spec: Very low ^d

^a Although there was no evidence of publication bias, we did not take this factor into account to grade the strength of evidence because none of the included studies was designed to assess the diagnostic accuracy and there are no reliable methods to assess publication bias in such a context.

^b Downgraded from high to low strength of evidence because 7/12 studies that evaluated sensitivity and 8/12 studies that allowed estimation of specificity had an overall high risk of bias, and there was serious imprecision because 95% confidence range for pooled specificity was 22.7%.

^c Downgraded from high to low strength of evidence because 6/10 studies that allowed estimation of sensitivity and 6/9 studies that evaluated specificity had an overall high risk of bias, and there was serious imprecision in pooled specificity estimate (95% CI range was 26.8%);

^d We did not rate evidence for sensitivity because there were only two studies available and results could not be pooled. Concerning specificity, we downgraded from high to very low the strength of evidence because 2/3 studies that allowed estimation of specificity had an overall high risk of bias, there was serious inconsistency as 1/3 study was not within 20% of the pooled estimate, and there was serious imprecision in pooled specificity estimate (95% CI range was 40.0%);

4.4. PICO2C: Performance of HBV DNA to predict MTCT

Detailed characteristics of each included study are presented in Table 19 below.

Author, year	PICO2C	Country	Original study design	HBV DNA threshold(s) (IU/mL)	HBV DNA assay	Maternal age (years)	Maternal HIV, n (%)	Measure of prevention for MTCT	Children tested, n	Children age at testing (months)	Marker tested in children
Chen Z, 2017 (40)	Bivariate	China	Prospective cohort	5 log10	Unknown	Mean: 26.96	0/211 (0.0%)	TBD + HBIg +	168	7	HBsAg & HBV DNA
Chotun N, 2017 (43)	Univariate (Specificity)	South Africa	Prospective cohort	20,000 & 5 log10	PCR Amplicor HBV Monitor test (Roche)	Mean (Range): 27 (21-34)	0/6 (0.0%)	TBD only	4	7	HBsAg
Ding Y, 2013 (45)	Bivariate	China	Prospective cohort	7 log10	Real-Time Fluorescence quantitative PCR (Kehua Bio- engineering)	Unknown (Range: 16-45) (n=4536)	Unknown	TBD + HBIg	249	7	HBsAg & HBV DNA
Latthaphasava ng V, 2019 (65)	Bivariate	Lao PDR	Prospective cohort	5 log10	PCR Amplicor HBV Monitor test (Roche)	Median (IQR): 28 (24-30)	1/153 (0.7%)	TBD only	120	6	HBsAg
Lee L, 2015 (66)	Bivariate	Singapore	Prospective cohort	20,000	PCR COBAS Taqman (Roche)	Mean (SD): 32.4 (4.7)	Unknown	TBD + HBIg	154	9	HBsAg & HBV DNA
Liu CP, 2015 (71)	Univariate (Sensitivity)	China	Retrospective cohort	6, 7 & 8 log10	PCR COBAS Taqman (Roche)	Mean: 25.7	0/256 (0.0%)	TBD + HBIg	256	6	HBsAg
Lunel-Fabiani F, 2018 (75)	Bivariate	Cameroun	Prospective cohort	8 log10	PCR Da'an Gene	Median (IQR): 24 (20-30)	1/592 tested (0.2%)	TBD only	133	24	HBsAg
Peng S, 2019 (79)	Bivariate	China	Prospective cohort	6 log10	Real-Time Fluorescence quantitative PCR (Kehua Bio- engineering)	Mean: 29.17	0/1219 (0.0%)	TBD + HBIg	93	7	HBsAg
Shao Z, 2011 (88)	Univariate (Sensitivity)	China	Prospective cohort	5 & 8 log10	Real-time PCR (Fast-track Diagnostics)	Unknown	Unknown	TBD + HBIg +	158	7	HBsAg
Thilakanathan C. 2018 (94)	Bivariate	Australia	Retrospective	5 & 6 log10	PCR COBAS Tagman (Roche)	Median (Range): 30 (15-44)	Unknown	TBD + HBIg	469	9	HBsAg

Table 19. Characteristics of 13 studies included in the PICO2C

Wiseman, E,	Bivariate	Australia	Prospective	8 log10	PCR artus HBV	Unknown	0/313	TBD -	138	9	HBsAg
2009 (105)			cohort		PCR Kits, QIAGEN		(0.0%)	HBIg			
Yin Yu-zhu, 2013 (108)	Bivariate	China	Retrospective cohort	5 &7 log10	PCR Da'an Gene	Mean (SD): 28.83 (3.92)	Unknown	TBD - HBIg	1360	12	HBsAg & HBV DNA
Zhu B, 2013 (112)	Univariate (Specificity)	China	Retrospective cohort	5 log10	PCR COBAS Tagman (Roche)	Mean (SD): 26 (4.1)	0/53 (0.0%)	TBD - HBIg	53	12	HBsAg

4.4.1. Summary of included studies

There were 13 original studies, including 9 for which bivariate analysis was performed, and 4 for which only univariate analysis to estimate sensitivity (n=2) or specificity (n=2) was possible. All were observational cohort studies (9 prospective and 4 retrospective) (Table 19).

Recruitment took place from 2002 (*Shao Z, 2011* and *Wiseman E, 2009*) to 2017 (*Latthaphasavang V, 2019*). Most studies took place in the Western Pacific Region (n=11); including China (n=7), Lao People's Democratic Republic (n=1), Singapore (n=1) and Australia (n=2). Two studies took place in the African Region: Cameroon (n=1) and South Africa (n=1). None of the studies took place in AMR, EUR, EMR or SEAR (Table 20).

Among studies included in PICO2C, 10/13 studies (76.9%) reported giving HBIg at birth, and all gave timely birth dose of HBV vaccine to infants. Table 20 describes the characteristics of studies included in the PICO2C.

		Overall (n=13)		TBD + HBIG (n=10)	TBD only (n=3)	
Subgroup variables	Subgroup category	Studies (N)	%	Studies (N)	%	Studies (N)	%
WHO region (n=13)	WPR	11	84.6	10	100.0	1	33.3
	SEAR	0	0.0	0	0.0	0	0.0
	EUR	0	0.0	0	0.0	0	0.0
	EMR	0	0.0	0	0.0	0	0.0
	AFR	2	15.4	0	0.0	2	66.7
	AMR	0	0.0	0	0.0	0	0.0
HBeAg assay type (n=13)	EIA	7	53.8	5	50.0	2	66.7
	FIA	0	0.0	0	0.0	0	0.0
	CLIA	5	38.5	4	40.0	1	33.3
	RDT	0	0.0	0	0.0	0	0.0
	Multiple	1	7.7	1	10.0	0	0.0
Maternal age (n=10)	<28 years	5	50.0	3	42.9	2	66.7
	≥28 years	5	50.0	4	57.1	1	33.3
HBIg at birth (n=13)	No	3	23.1	0	0.0	3	100.0
	Yes	10	76.9	10	100.0	0	0.0
First dose of HBV	Timely birth dose	13	100.0	10	100.0	3	100.0
vaccine (n=15)	Delayed	0	0.0	0	0.0	0	0.0
Three doses of HBV	No	0	0.0	0	0.0	0	0.0
vaccine (n=15)	Yes	13	100.0	10	100.0	3	100.0
HIV status (n=11)	All uninfected	9	81.8	7	100.0	2	50.0
	All infected	0	0.0	0	0.0	0	0.0
	Mixed population	2	18.2	0	0.0	2	50.0
HCV status (n=7)	All uninfected	6	85.7	6	85.7	0	0.0
	All infected	0	0.0	0	0.0	0	0.0

Table 20. Characteristics of studies included in the PICO2C

	Mixed population	1	14.3	1	14.3	0	0.0
HDV status (n=3)	All uninfected	3	100.0	3	42.9	0	0.0
	All infected	0	0.0	0	0.0	0	0.0
	Mixed population	0	0.0	0	0.0	0	0.0
Genotype (n=3)	Genotype A	0	0.0	0	0.0	0	0.0
	Genotype B	0	0.0	0	0.0	0	0.0
	Genotype C	0	0.0	0	0.0	0	0.0
	Genotype D	0	0.0	0	0.0	0	0.0
	Genotype E	0	0.0	0	0.0	0	0.0
	Mixed population	3	100.0	1	100.0	2	100.0

4.4.2. Risk of bias assessment

The risk of bias assessment is presented in Fig. 33 & 34 (and details in Appendix F).

Overall, none of the studies included had the same objective as that of the PICO2C, and therefore, essential information was often missing. All studies were rated as having an unclear risk of bias for the reference standard and for the index tests because they did not mention whether or not blinding was performed (Fig. 33). Risk of selection bias was high in most studies (n=10/13, 76.9%), mainly due to restrictive exclusion criteria (e.g. exclusion of HIV-, HCV-, or HDV-coinfected pregnant women).

Concerns about applicability were low for most studies (Fig. 34). There was high concern for patient selection applicability for two studies (15.4%), due to the enrolment of pregnant women based on their HBV viral load. There was no concern about applicability of index test or HBV DNA assay test used.



Fig. 33. Risk of bias results for PICO2C



Fig. 34. Concerns about applicability results for PICO2C

4.4.3. Primary analysis, narrative descriptions and forest plots

4.4.3.1. Overall performance of HBV DNA during pregnancy to predict MTCT

Tables 21 and 22 present detailed performance results for the PICO2C. In the following sections, we present detailed results of the performance of HBV DNA \geq 5 and 7 log IU/mL to predict MTCT.

		-	1								
HBV I	DNA threshol	d Prevention of MTCT	Meta-	Studies,	Subjects	TP	FN	TN	FP	Se (95% CI) or Range	Sp(95% CI) or Range
(IU/mL)		strategy	analysis	Ν	(N)	(N)	(N)	(N)	(N)	Se	Sp
≥5 log		Overall	Bivariate	4	1999	46	10	1298	645	97.7 (42.9-100.0)	68.4 (48.6-83.2)
			Univariate	7	2056	48	10	1329	669	81.5 (62.4-92.1)	66.6 (51.3-79.0)
		TBD + HBIg	Bivariate	3	1879	41	10	1231	597	97.9 (30.3-100.0)	71.1 (46.0-87.7)
			Univariate	5	1934	43	10	1260	621	81.1 (57.8-93.1)	67.5 (47.8-82.6)
		TBD only	Bivariate	1	120	5	0	67	48	100.0	58.3
			Univariate	2	122	5	0	69	48	100.0	58.3-100.0
≥6 log		Overall (All TBD + HBIG)	Bivariate	2	1570	13	0	1404	153	100.0	89.1-94.0
			Univariate	3	1580	23	0	1404	153	93.3 (72.5-98.7)	89.1-94.0
≥7 log		Overall (All TBD + HBIG)	Bivariate	2	1609	31	2	1254	322	90.5 -100.0	77.8-89.5
			Univariate	3	1619	37	6	1254	322	84.4 (52.0-96.4)	77.8-89.5
≥8 log		Overall	Bivariate	2	271	7	0	210	54	100.0	67.9-91.5
			Univariate	4	283	9	10	210	54	57.8 (13.3-92.4)	82.1 (49.0-95.6)
		TBD + HBIg	Bivariate	1	138	4	0	91	43	100.0	67.9
			Univariate	3	150	6	10	91	43	45.9 (6.1-91.7)	67.9
		TBD only	Bivariate	1	133	3	0	119	11	100.0	91.5

Table 21. Performance of HBV DNA during pregnancy to predict MTCT, stratified by HBV DNA threshold and prevention of MTCT strategy

	Univariate	-	-	-	-	-	-	-	-

Table 22. Post-test probabilities of MTCT if pregnant women have high or low HBV viral load, according to various HBV DNA thresholds and prevention of MTCT strategies

HBV DNA threshold (IU/mL)	HBV DNA to diagnose MTCT	Studies, N	Pre-test probability (%)	LR+ (95% CI) or Range LR+	Post-test probability of having MTCT after high viral load result for HBV DNA test (%)	LR- (95% CI) or Range LR-	Post-test probability of MTCT after low viral load result for HBV DNA test (%)
5 log10	Overall	4	4	3.1 (1.6-5.8)	11.0	0.03 (0.00-2.1)	0.13
	TBD + HBIg	3	4	3.4 (1.5-7.8)	11.9	0.03 (0.00-3.6)	0.12
	TBD only	1	4	2.4	8.7	0.00	0.00
6 log10	Overall	2	1	9.2-16.6	9.2-16.6	0.00	0.00
7 log10	Overall (All TBD + HBIg)	2	2	4.1-9.5	4.1-9.5	0.00-0.12	0.00-0.24
8 log10	Overall	2	3	3.1-11.8	3.1-11.8	0.00	0.00
	TBD + HBIg	1	3	3.1	3.1	0.00	0.00
	TBD only	1	2	11.8	11.8	0.00	0.00

4.4.3.2. Performance of HBV DNA \geq 5 log10 IU/mL during pregnancy to predict MTCT

- Overall pooled sensitivity = 97.7 (95% CI: 42.9-100.0)
- Overall pooled specificity = 68.4 (95% CI: 48.6-83.2)

There was no evidence of publication bias (p=0.63) (Appendix G.5). We did not identify any outlier through visual assessment (Fig. 35 and 36) and summary scatter plot with the SROC curve (Fig. 37).

Fig. 35. Coupled forest plot of the performance of HBV DNA \geq 5 log10 IU/mL during pregnancy to predict MTCT of HBV by type of prevention of MTCT strategy

Prevention strategy for MTCT of HBV and Author, year	TP/(TP+FN)	TN/(TN+FP)			Sensitivity (95% CI)			Specificity (95% CI)
TBD + HBlg								
Chen Z, 2017	19/28	70/140			- 0.68 (0.48	, 0.84)	-8-	0.50 (0.41, 0.5
Yin Yu-zhu, 2013	20/21	847/1339				, 1.00)		0.63 (0.61, 0.6
Thilakanathan C, 2018	2/2	314/349	_		1.00 (0.16	, 1.00)		■ 0.90 (0.86, 0.9
TBD only								
Latthaphasavang V, 2019	5/5	67/115			1.00 (0.48	, 1.00)	-8-	0.58 (0.49, 0.6
			0.00	0.50	1.00	0.00	0.50	1.00

Fig. 36. Coupled forest plot of the performance of HBV DNA \geq 5 log10 IU/mL during pregnancy to predict MTCT of HBV by type of HBV DNA assay

HBV DNA type of assay and Author, year	TP/(TP+FN)	TN/(TN+FP)			Sensit (95% (ivity CI)		S (9	pecificity 95% CI)
Commercial PCR									
Chen Z, 2017	19/28	70/140			- 0.68 (0	0.48, 0.84)	-8-	0.	.50 (0.41, 0.59)
Yin Yu-zhu, 2013	20/21	847/1339				0.76, 1.00)		0.	.63 (0.61, 0.66)
Thilakanathan C, 2018	2/2	314/349	-		1.00 (0	0.16, 1.00)			.90 (0.86, 0.93)
Latthaphasavang V, 2019	5/5	67/115			1.00 (0	0.48, 1.00)		0.	.58 (0.49, 0.67)
						I	I	1	
			0.00	0.50	1.00	0.00	0.50	1.00	

Fig. 37. Summary scatter plot and SROC curve of the performance of HBV DNA \geq 5 log10 IU/mL during pregnancy to predict MTCT



Subgroup analysis

The number of included studies was very low. Therefore, we were not able to perform subgroup analysis of the performance of HBV DNA \geq 5 log10 IU/mL to predict MTCT of HBV.

Sensitivity analysis for the performance of HBV DNA ≥5 log10 IU/mL to predict MTCT

As no outlier study was identified, we did not conduct sensitivity analysis on this factor Results of sensitivity analysis are presented in Table 23. Sensitivity was lower in univariate analysis compared with bivariate analysis and the specificity remained unchanged. However, there was no evidence of a statistical difference between the bivariate and univariate analysis because the 95% CIs overlapped. Moreover, results remained unchanged when excluding studies with a high risk of bias.

	Studies, N	Se (95% CI) or Range Se	Sp (95% CI) or Range Sp
Overall bivariate	4	97.7 (42.9-100.0)	68.4 (48.6-83.2)
Overall univariate	7	81.5 (62.4-92.1)	66.6 (51.3-79.0)
Bivariate without studies with	3	97.3 (34.7-100.0)	73.6 (52.2-87.7)
overall "high" risk of bias			

Table 23. Results of sensitivity analysis for the performance of HBV DNA \geq 5 log10 IU/mL during pregnancy to predict MTCT of HBV

4.4.3.3. Performance of HBV DNA \geq 7 log10 IU/mL during pregnancy to predict MTCT

- Range sensitivity = 90.5 100.0
- Range specificity = 77.8–89.5

As the number of studies was too low (n=2), we could not assess publication bias or present a summary scatter plot with SROC curve. The coupled forest plots (Fig. 38 and 39) are presented below. Both included studies reported giving timely birth dose of HBV vaccine and HBIG at birth to infants.

Fig. 38. Coupled forest plot of the performance of HBV DNA \geq 7 log10 IU/mL during pregnancy to predict MTCT of HBV by type of prevention of MTCT strategy



Fig. 39. Coupled forest plot of the performance of HBV DNA ≥7 log10 IU/mL during pregnancy to predict MTCT of HBV by type of HBV DNA assay

HBV DNA type of assay and Author, year	TP/(TP+FN)	TN/(TN+FP)			Sensitiv (95% C	ity I)			Specificity (95% CI)
Commercial PCR									
Yin Yu-zhu, 2013	19/21	1042/1339		-	0.90 (0.	70, 0.99)			0.78 (0.75, 0.80)
Ding Y, 2013	12/12	212/237			1.00 (0.	74, 1.00)			0.89 (0.85, 0.93)
			ا 0.00	0.50	l 1.00	l 0.00	l 0.50	l 1.00	I

Subgroup analysis

As per the HBV DNA threshold \geq 5 log10 IU/mL, we were not able to perform subgroup analysis of the performance of HBV DNA \geq 7 log10 IU/mL during pregnancy to predict MTCT, given the small number of included studies.

Sensitivity analysis for the performance of HBV DNA ≥7 log10 IU/mL during pregnancy to predict MTCT (Table 24)

As no study had an overall "high" risk of bias, we did not perform sensitivity analysis on this factor. When performing univariate analysis, the results remained unchanged.

Table 24. Results o	of sensitivity analysis for the pe	erformance of HBV	DNA ≥7 log10 IU/mL
during pregnancy t	o predict MTCT		

	Studies, N	Se (95% CI) or Range Se	Sp (95% CI) or Range Sp
Overall bivariate	2	90.5 -100.0	77.8–89.5
Overall univariate	3	84.4 (52.0–96.4)	77.8-89.5

4.4.4. GRADE evidence profile for PICO2C

Table 25. GRADE evidence profile table of the performance of HBV DNA \geq 5 log10 IU/mL during pregnancy to predict MTCT, stratified by prevention strategy for MTCT

Test performance	Reference standard	Prevention strategy for	Studies, n	Risk of bias	Inconsistency	Indirectness	Imprecision	Patients, n	Strength of
1		MTCT							evidence ^a
HBV DNA 5 log 10 IU/mL	МТСТ	Overall	Sens: 5 Spec: 6	No serious	Serious	No serious	Serious	Sens: 58 Spec: 1998	Sens: Low ^b Spec: Low ^b
HBV DNA 5 log 10 IU/mL	МТСТ	TBD + HBIg	Sens: 4 Spec: 4	No serious	Serious	No serious	Serious	Sens: 53 Spec: 1881	Sens: Low ^c Spec: Low ^c
HBV DNA 5 log 10 IU/mL	МТСТ	TBD only	Sens: 1 Spec: 2	Insuff. data	Insuff. data	Insuff. data	Insuff. data	Sens: 5 Spec: 117	Sens: Insufficient data ^d Spec: Insufficient data ^d

^a Publication bias was not considered because none of the included studies was designed to evaluate diagnostic accuracy, and the assessment of publication bias in such a context may not be reliable.

^b Downgraded from high to low strength of evidence because of serious inconsistency (8/11 studies were within 20% of the pooled estimate) and serious imprecision (the range in 95% CI was 29.7% for sensitivity and 27.7% for specificity)

^cDowngraded from high to low strength of evidence because of serious inconsistency (3/4 studies were within 20% of the pooled estimate) and serious imprecision (the range in 95% CI was 35.3% for sensitivity and 34.8% for specificity)

^dThere was not enough data to rate the evidence for the timely birth dose only group because the number of studies was too low (n=2)

Table 26. GRADE evidence profile table of the performance of HBV DNA \geq 7 log10 IU/mL during pregnancy to predict MTCT, stratified by prevention strategy for MTCT

Test	Reference	Prevention	Studies,	Risk of	Inconsistency	Indirectness	Imprecision	Patients,	Strength of
performance	standard	strategy	n	bias				n	evidence ^a
_		for MTCT							
		of HBV							
HBV DNA 7	MTCT	Overall	Sens: 3	No	No serious	No serious	Very serious	Sens: 43	Sens: Low ^b
log 10 IU/mL		(All TBD +	Spec: 2	serious			-	Spec:	Spec:
_		HBIg)	_					1576	Insufficient
									data ^a

^a We did not rate publication bias because there were too few studies and its assessment may not be reliable

^b Downgraded from high to low strength of evidence because of very serious imprecision in pooled sensitivity (95% CI range was 44.4%)

4.5. Post-hoc analysis

4.5.1. HBV DNA level during pregnancy from which the MTCT risk increases despite infant's immunoprophylaxis

Thirteen studies were included in this analysis (45,66,89,94,105,108,113–119). All these studies provided timely birth dose and HBIG at birth. Fig. 40 and 41 show that the risk of HBV MTCT starts to increase from a maternal HBV DNA level during pregnancy of 5.3 log IU/mL (200 000 IU/mL), despite passive–active immunoprophylaxis. There were three studies that examined the risk of MTCT from pregnant women with a viral load of 5.3–6.2 log IU/mL; the risk of passive–active immunoprophylaxis failure was 0% (0/24) in the study of Cheung K et al., 3.2% (3/95) in Zou H et al., and 9.7% (6/62) in Zhang L et al. The pooled risk was 3.8% (95%CI: 0.3–10.1, Fig. 41). The exact viral loads (log IU/mL) of pregnant women who transmitted the virus to their infants despite passive–active immunoprophylaxis in this viral load range (5.3–6.2 log IU/mL) were: 5.7, 6.1, and 6.2 in the study by Zou H et al.; and 5.8, 5.8, 5.9, 5.9, 6.1, and 6.2 in the study by Zhang L et al. Both studies used PCR assay of Kehua Bio-engineering to quantify HBV DNA levels (*115,116*).



Fig. 40. Risk of HBV MTCT according to maternal HBV DNA level during pregnancy

Fig. 41. Forest plot of the risk of HBV MTCT according to maternal HBV DNA level during pregnancy

	No. infected/No.		
Author, year	tota		MTCT risk (95% CI)
<4.30 log IU/mL			
Yin Y, 2013, PCR (Da'an Gene)	0/688		0.00 (0.00, 0.56)
Yi W, 2014, PCR (Kehua Bio-engineering)	0/120		0.00 (0.00, 3.10)
Zhang L, 2016, PCR (Kehua Bio-engineering)	0/164		0.00 (0.00, 2.29)
Pan C, 2013, PCR (Kehua Bio-engineering)	0/541		0.00 (0.00, 0.71)
Cheung K, 2018, PCR (Cobas TaqMan, Roche)	0/432		0.00 (0.00, 0.88)
Ding Y, 2013, PCR (Cobas TagMan, Roche)	0/56		0.00 (0.00, 6.42)
Lu Y, 2017, PCR (RealTime, Abbott)	0/96		0.00 (0.00, 3.85)
Lee L. 2015, PCR (Artus, Qiagen)	0/54		0.00 (0.00, 6.64)
Sheng Q. 2018, PCR (Cobas TagMan, Roche)	0/278		0.00 (0.00, 1.36)
Zhang Z. 2014, PCB (Kehua Bio-engineering)	1/121		0.83 (0.15, 4.53)
Subaroup	1/2550		0.00 (0.00, 0.02)
Cabgroup	1/2000	•	0.00 (0.00, 0.02)
4,30-5.29 log IU/mL		-	
Cheung K, 2018, PCR (Cobas TaqMan, Roche)	0/42		0.00 (0.00, 8.38)
Subgroup	0/42		0.00 (0.00, 8.38)
5.00-5.99 log IU/mL			
Lu Y, 2017, PCR (RealTime, Abbott)	0/27		0.00 (0.00, 12.46)
Thilakanathan C, 2018, PCR (Cobas TaqMan, Roche)	0/14		0.00 (0.00, 21.53)
Subaroup	0/41	\triangleright	0.00 (0.00, 4.43)
			,
5.30-6.29 log IU/mL			
Cheung K, 2018, PCR (Cobas TaqMan, Roche)	0/24		0.00 (0.00, 13.80)
Zou H, 2012, PCR (Kehua Bio-engineering)	3/95	-∰	3.16 (1.08, 8.88)
Zhang L, 2016, PCR (Kehua Bio-engineering)	6/62		9.68 (4.51, 19.55)
Subgroup	9/181	\diamond	3.80 (0.25, 10.07)
6.00-6.99 log IU/mL			
Lu Y 2017, PCB (BealTime Abbott)	0/32		0.00 (0.00, 10.72)
Subgroup	0/32		0.00 (0.00, 10.72)
	0,02		0.00 (0.000, 10112)
6.30-7.29 log IU/mL			
Cheung K, 2018, PCR (Cobas TaqMan, Roche)	0/22		0.00 (0.00, 14.87)
Zou H, 2012, PCR (Kehua Bio-engineering)	19/282		6.74 (4.36, 10.28)
Zhang L, 2016, PCR (Kehua Bio-engineering)	8/78		10.26 (5.29, 18.95)
Zhang Z, 2014, PCR (Kehua Bio-engineering)	2/12	<u> </u>	16.67 (4.70, 44.80)
Subgroup	29/394	>	6.21 (2.20, 11.63)
≥7.00 log IU/mL			
Cheung K, 2018, PCR (Cobas TagMan, Roche)	7/121	- -	5.79 (2.83, 11.46)
Yin Y, 2013, PCR (Da'an Gene)	19/316		6.01 (3.88, 9.20)
Lu Y, 2017, PCR (RealTime, Abbott)	20/329		6.08 (3.97, 9.20)
Zou H. 2012, PCR (Kehua Bio-engineering)	5/66		7.58 (3.28, 16.54)
Wiseman E, 2009, PCR (Cobas Amplicor/Cobas TagMan, Boche)	4/47		8.51 (3.36, 19.93)
Zhang L. 2016, PCB (Kehua Bio-engineering)	3/28		10.71 (3.71, 27.20)
Zhang Z. 2014, PCB (Kehua Bio-engineering)	4/14		28 57 (11 72 54 65)
Ding Y 2013 PCB (Cobas TagMan Boche)	12/37		32 43 (19 63 48 54)
Subgroup	74/958		9.32 (5.40 14.04)
	, 1000		0.02 (0.40, 14.04)
		0 5 10 15 20 25 30 35 40 45 50 55	

4.5.2. Performance of HBeAg to identify pregnant women with HBV DNA ≥5.3 log10 IU/mL

A total of 41 studies were included for this meta-analysis (Fig. 42).

- Overall pooled sensitivity = 88.2% (95% CI: 83.9-91.5)
- Overall pooled specificity = 92.6% (95% CI: 90.0-94.5)

Fig	42.	Coupled	forest plot for	all studies	included in	the meta	-analysis of	f the perform	nance
of H	IBe	Ag to ide	ntify maternal	HBV DN	A ≥5.3 log1	0 IU/mL			

			Sensitivity	Specificity
Author, year	TP/(TP+FN)	TN/(TN+FP)	(95% CI)	(95% C I)
Lin J, 2002, EIA (WB-2496, Wantai)	17/42	25/27		0.93 (0.76, 0.99)
Johannessen A, 2017, EIA (Vidas, Biomérieux)	1/2	59/61		0.97 (0.89, 1.00)
Guingane A, 2017, RDT (SD Bioline, Standard Diagnostics)	21/33	313/328	- 0.64 (0.45, 0.80)	0.95 (0.93, 0.97)
Wang M, 2018, Unknown	22/34	26/42		0.62 (0.46, 0.76)
Rouet F, 2004, EIA (Murex, Abbott)	10/15	59/62		0.95 (0.87, 0.99)
Carey I, 2018, CLIA (Architect, Abbott)	50/72	430/442	0.69 (0.57, 0.80)	0.97 (0.95, 0.99)
Wang F, 2009, EIA (Kehua Bio-Engineering)	123/177	859/1060	0.69 (0.62, 0.76)	0.81 (0.79, 0.83)
Wang X, 2015, EIA (Unknown)	47/62	47/58	- 0.76 (0.63, 0.86) - Hi	0.81 (0.69, 0.90)
Ségéral O, 2018, RDT (SD Bioline, Standard Diagnostics)	26/34	91/94	0.76 (0.59, 0.89)	0.97 (0.91, 0.99)
Peng N, 2012, CLIA (Architect, Abbott)	165/215	162/195	0.77 (0.71, 0.82)	0.83 (0.77, 0.88)
Godbole G, 2013, CLIA (Architect, Abbott or Elecsys, Roche)	20/26	261/267	- 0.77 (0.56, 0.91)	0.98 (0.95, 0.99)
Latthaphasavang V, 2019, EIA (Monolisa PLUS, Bio-Rad)	51/65	79/88	0.78 (0.67, 0.88)	0.90 (0.81, 0.95)
Chen Z, 2017, EIA (AxSYM, Abbott)	104/132	57/79	0.79 (0.71, 0.85)	0.72 (0.61, 0.82)
Wang Z, 2018, Unknown	43/54	171/199	0.80 (0.66, 0.89)	0.86 (0.80, 0.90)
Fujiko M, 2015, EIA (Monolisa PLUS, Bio-Rad)	8/10	50/54		0.93 (0.82, 0.98)
Hao X, 2015, EIA (Kehua Bio-Engineering)	30/37	106/117	0.81 (0.65, 0.92)	0.91 (0.84, 0.95)
Dolman G. 2018, CLIA (Architect, Abbott)	26/32	384/391	0.81 (0.64, 0.93)	0.98 (0.96, 0.99)
Wang L. 2016, FIA (Anytest, SYM-BIO)	9/11	20/20		1.00 (0.83, 1.00)
Zhang L, 2017, EIA (Unknown)	143/172	281/319	0.83 (0.77, 0.88)	0.88 (0.84, 0.91)
Kubo A. 2014, EIA (Unknown)	127/147	652/688	0.86 (0.80, 0.91)	0.95 (0.93, 0.96)
Lu H. 2009, FIA (Anvtest, SYM-BIO)	7/8	21/25	0.88 (0.47, 1.00)	0.84 (0.64, 0.95)
Li X. 2018. CLIA (Architect, Abbott)	150/171	524/545	0.88 (0.82, 0.92)	0.96 (0.94, 0.98)
Söderström A. 2003. EIA (AxSYM, Abbott)	9/10	36/36	0.90 (0.55, 1.00)	1.00 (0.90, 1.00)
Lunel-Fabiani F. 2018. EIA (ETI-EBK Plus, Diasorin)	110/121	456/473	0.91 (0.84, 0.95)	0.96 (0.94, 0.98)
White H. 2015. Unknown	12/13	109/110	0.92 (0.64, 1.00)	0.99 (0.95, 1.00)
Huang L 2014 EIA (Dayou Dakewe)	122/132	125/192	0.92 (0.87, 0.96)	0.65 (0.58, 0.72)
Guo E. 2007. FIA (Intec)	95/102	201/217		0.93 (0.88, 0.96)
Cheung K 2019 CLIA (Elecsys Boche)	68/73	239/252	0.93 (0.85, 0.98)	0.95 (0.91 0.97)
Thilakanathan C. 2018. CLIA (Architect, Abbott)	158/168	440/474		0.93 (0.90, 0.95)
Zheng H 2010 EIA (Kebua Bio Engineering)	86/91	343/387		0.89 (0.85, 0.92)
Bai H 2010 FIA (Apytest SYM-BIO)	44/46	73/74		0.99 (0.93, 1.00)
Wang X 2015, CLIA (Architect Abbott)	133/138	203/271		0.75 (0.69, 0.80)
Wei K 2017, CLIA (Architect, Abbott)	540/559	1077/1182		0.91 (0.89, 0.93)
Chen T 2018 CLIA (Architect Abbott)	160/165	305/334		0.01 (0.88, 0.94)
Yu C 2018, CLIA (Architect, Abbott) or EIA (Kebus Bio-Engineering)	66/68	140/146		0.91 (0.00, 0.94)
Web W 2013 EIA (ArSYM Abbett)	65/66	221/227	0.98 (0.93, 1.00)	0.90 (0.91, 0.98)
Wang L 2019, Linknown	141/149	221/207		0.33 (0.03, 0.30)
Pirille M 2015, CLIA (Architect Abbett)	7/7	14/14		1.00 (0.77, 1.00)
Chotun N. 2017, CLIA (Architect, Abbott)	1/1	5/5		1.00 (0.48, 1.00)
Zhu B. 2012. CLIA (Elegano, Beche)	1/1	06/00		0.00 (0.48, 1.00)
Dirille M. 2007. EIA (Murey, Murey Biotech)	24/24	20/29		0.90 (0.73, 0.96)
Chorall	2/2	4/3		0.00 (0.28, 0.99)
	3043/34/9	9026/10024	V 0.00 (0.04, 0.92)	0.85 (0.80, 0.94)
			0.00 0.50 1.00 0.00 0.50 1.00	

Subgroup analysis

Of the variables predefined as potential sources of heterogeneity, it was not possible to do a subgroup analysis by HCV- or HDV-coinfection status, or by maternal HBV genotype as too few studies reported information on these factors.

Table 27 present detailed results of the performance of HBeAg to identify pregnant women with HBV DNA \geq 5.3 log10 IU/mL stratified by the potential sources of heterogeneity.

Subgroup	Subgroup	Studies	Se (95% CI) or	Sp (95% CI) or	P value
variables	category	(N)	Range Se	Range Sp	
Overall		41	88.2 (83.9-91.5)	92.6 (90.0-94.5)	N/A
WHO	WPR	27	90.0 (85.0-93.5)	89.1 (85.6-91.8)	< 0.0001*
region	AFR	7	82.0 (65.1-91.7)	96.0 (94.4-97.1)	
(N=41)	EUR	5	78.9 (67.3-87.1)	98.0 (96.8-98.8)	
	AMR	1	86.4 (79.8-91.5)	94.8 (92.8-96.3)	
	SEAR	1	80.0 (44.4-97.5)	92.6 (82.1-97.9)	
	EMR	0	-	-	
HBeAg	EIA	18	84.6 (77.4-89.8)	90.5 (86.4-93.4)	0.11**
assay type	CLIA	13	91.4 (85.2-95.1)	93.9 (90.2-96.3)	
(N=36)	FIA	3	91.4 (78.5-96.9)	96.6 (81.2-99.5)	
	RDT	2	70.1 (58.2-79.9)	95.7 (93.3-97.3)	
Mean /	<28 years	14	94.2 (88.8-97.1)	91.9 (87.8-94.8)	0.02
median	≥28 years	14	85.3 (79.0-90.0)	95.6 (93.6-97.0)	
maternal					
age					
(N=28)					
HBV	Commercial	35	88.1 (83.3-91.8)	92.5 (90.0-94.4)	0.98
DNA	PCR	_			
assay	In-house or	6	88.8 (78.6-94.5)	93.5 (79.8-98.1)	
(N=41)	unknown test				
HIV	All uninfected	11	93.5 (87.2-96.9)	89.2 (82.4-93.6)	0.30***
status	All infected	4	95.1 (50.7-99.7)	96.6 (82.8-99.4)	
(1N=22)	Mixed	7	82.7 (70.5-90.6)	95.6 (94.3-96.6)	
	population				

Table 27. Performance of HBeAg to identify pregnant women with HBV viral load \geq 5.3 log10 IU/mL, stratified by potential sources of heterogeneity

*comparison of WPR/EUR/AMR

**comparison of CLIA/EIA

***comparison of uninfected/infected
5. CONCLUSION

To our knowledge, this systematic review is the first to examine the diagnostic accuracy of the HBeAg test to diagnose high HBV DNA levels in pregnant women. Our results suggest that the risk of HBV MTCT, despite passive–active immunoprophylaxis, starts to increase at a maternal viral load of 5.3 log IU/mL (i.e. 200 000 IU/mL). The pooled sensitivity and specificity of HBeAg, obtained by the bivariate analyses, were: 84.2% (95% CI: 80.2–87.4%) and 92.3% (89.5–94.5%) to diagnose viral load of \geq 5 log10 IU/mL; 92.0% (88.2–94.6%) and 92.7% (90.3–94.5%) for \geq 6 log10 IU/mL; and 98.0% (93.3–99.4%) and 88.5% (80.7–93.4%) for \geq 7 log10 IU/mL, respectively. We evaluated the performance of HBeAg for three other different HBV DNA thresholds (\geq 20 000, \geq 200 000 and \geq 8 log10 IU/mL). Irrespective of these different HBV DNA cut-off levels, pooled sensitivity and specificity were constantly higher than 80%, with the lower boundary of the 95% CI exceeding 75%. The univariate analyses provided similar results, supporting the robustness of these estimates. As expected, the sensitivity improved with increasing HBV DNA threshold whereas the specificity decreased.

We found evidence that the performance of HBeAg during pregnancy to identify pregnant women with a high viral load differed according to the WHO region, type of HBeAg and maternal age. However, there was no evidence that its performance varied according to HBV DNA NAT or maternal HIV status.

The performance of HBeAg differed significantly between lower (<28 years) and higher (\geq 28 years) mean/median maternal age reported in each study; younger maternal age was associated with higher sensitivity and lower specificity to diagnose HBV DNA levels of \geq 5 and \geq 6 log10 IU/mL, compared to higher maternal age (\geq 28 years). Although the difference was not significant, a similar tendency was observed for the cut-off of \geq 7 log10 IU/mL. Since spontaneous loss of HBeAg occurs over time, the prevalence of HBeAg is higher in younger HBsAg-positive women than in older HBsAg-positive women (*120*), and this may explain the difference in performance of HBeAg according to maternal age.

The natural history of CHB varies according to geographical area, particularly between Asia and sub-Saharan Africa, which both carry a high HBV-related disease burden. Historically in both areas, the majority of CHB occurs during childhood either perinatally from infectious mothers or horizontally from household members. In Asia, a substantial proportion (about 40%) of children who are chronically infected with HBV continue to carry HBeAg and high viral load beyond their adolescence (121) while in Africa, spontaneous HBeAg loss often occurs at younger age and only 10-20% of HBV-infected women of childbearing age carry HBeAg (122). This difference might be due to varying frequency of emerging basal core promoter (BCP) or precore (PC) variants, which abolish or reduce HBeAg production without affecting the capacity of HBV to replicate (123). We found a similar high sensitivity of HBeAg to diagnose high viraemia in both regions: 83.9% (79.2-87.7%) in Asia and 88.0% (70.9-95.7%) in Africa for HBV DNA levels $\geq 5 \log 10$ IU/mL, respectively; 92.6% (88.4–95.3%) and 93.7% (87.9–96.8%) for HBV DNA levels \geq 6 log10 IU/mL, respectively. However, the specificity of HBeAg to diagnose high maternal viral loads tended to be lower in Asia (Western Pacific) compared with Africa: 89.3% (85.6–92.1%) and 96.6% (94.3–98.0%) for HBV DNA levels \geq 5 log10 IU/mL; 91.1% (88.4–93.2%) and 96.2% (94.3–97.5%) for HBV DNA levels ≥6 log10 IU/mL, respectively.

More recent types of HBeAg assays such as CLIA tended to have a higher sensitivity for diagnosing viraemia than EIA: 89.1% (95% CI: 83.2–93.0%) and 79.4% (74.0–84.0%) to diagnose viral load \geq 5 log10 IU/mL; and 94.4% (81.3–98.5%) and 98.8% (93.7–99.8%) to diagnose viraemia \geq 7 log10 IU/ml, respectively. This might be related to improved analytical sensitivity of CLIA, in comparison with EIA, to detect HBeAg. Although there was only one study that evaluated RDT, this had lower clinical sensitivity compared to the laboratory-based immunoassays (76.5% and 89.3% to diagnose high HBV DNA levels of \geq 5 log10 and \geq 7 log10 IU/mL, respectively). Low clinical sensitivity of commercially available HBeAg RDT was also found to be related to its low analytical sensitivity compared to CLIA (*17*).

A few outlying studies were identified: one study for $\geq 5 \log 10$ IU/mL and three studies for $\geq 7 \log 10$ IU/mL. Compared to other studies, these outliers tended to have either "lower sensitivity and higher specificity" (50,70), or "lower specificity with higher sensitivity" (45,68). Although we did not perform further assessment, this might be related to multiple factors such as low HBeAg prevalence (1.6%) in HBsAg-positive pregnant women in a Greek study (50) or the difference in analytical sensitivity of the HBeAg tests used in these outlier studies (68,70). The sensitivity analyses excluding these outliers did not alter the interpretation of these results.

The systematic review addressed two additional questions: the performance of HBeAg detection and HBV DNA quantification during pregnancy to predict an MTCT event, defined as HBsAg positivity in infants aged 6–12 months. These analyses were stratified by the type of preventive measures provided to mother–child pairs. We found that the pooled sensitivity and specificity of maternal HBeAg during pregnancy to predict MTCT despite infant immunoprophylaxis were 99.1% (95% CI: 61.8–100%) and 55.7% (34.0–75.5%). The pooled sensitivity and specificity of maternal HBV DNA levels \geq 5 log IU/mL was 97.7% (95% CI: 42.9–100.0%) and 68.4% (95% CI: 48.6–83.2%); and the sensitivity and specificity range of maternal HBV DNA levels \geq 7 log IU/mL were 90.5% to 100.0% and 77.8% to 89.5%, respectively. Although no formal assessment was performed, these results might indicate that: (i) both HBeAg and high HBV DNA levels, measured during pregnancy, have high sensitivity to predict the risk of immunoprophylaxis failure; and (ii) the specificity is low for HBeAg and moderate for high HBV DNA levels.

The strength of the evidence for the performance of HBeAg to identify pregnant women with viral loads \geq 5, \geq 6, and \geq 7 log 10 IU/mL were high. Although most studies had excluded women coinfected with either HIV, HCV or HDV, this did not constitute a serious risk of bias. There was no evidence of publication bias; however, only one study was designed to evaluate diagnostic accuracy, which might have made the conventional assessment of publication bias, through assessing small sample effects, less meaningful. Moreover, since essential information for diagnostic studies (e.g. blinding) were missing in the majority of studies, the assessment of the quality of studies was difficult for the index test and reference standard sections of the QUADAS2.

For the performance of HBeAg to predict MTCT, the strength of evidence was low due to high risk of bias in most studies and serious imprecision of the pooled estimates, probably due to the small number of included studies. When stratified by prevention of MTCT regimen, evidence was low for the timely birth dose plus HBIG regimen and could not be graded for timely birth dose only regimen (without HBIG) because there was not enough data available.

The strength of evidence for the overall performance of maternal HBV DNA levels \geq 5 log 10 IU/mL was low due to inconsistency in the estimates and serious imprecision in the pooled estimates. When stratifying by prevention of MTCT strategy, evidence was low for timely birth dose plus HBIG for the same reasons as stated above, and there was not enough data to grade the evidence for the timely birth dose only strategy. For maternal HBV DNA levels \geq 7 log 10 IU/mL, all included studies reported using the timely birth dose plus HBIG strategy and there was not enough data to grade evidence for specificity. Concerning sensitivity, evidence was low because of very serious imprecision in the pooled estimate, which may be due to the low number of studies included to answer this objective.

As a strength of this study, the literature was systematically searched through both Englishand Chinese-language databases, and independently reviewed by two investigators for each language (a total of four reviewers). Duplicate publications were carefully checked and excluded from the analysis to avoid biased estimates.

As a limitation, this systematic review was primarily designed to accomplish the primary objective (PICO2A); we thus included only studies that measured both HBeAg and HBV DNA during pregnancy to answer the secondary objectives. Of the studies eligible for the PICO2A, we further selected those that followed infants to ascertain MTCT end-points to answer two additional questions (PICO2B and PICO2C). Consequently, we might have missed a few of the eligible studies for PICO2B (e.g. a study evaluating maternal HBeAg

during pregnancy and infant HBsAg at 6 months without doing maternal HBV DNA) or PICO2C (e.g. a study evaluating maternal HBV DNA and infant MTCT end-point, without assessing HBeAg during pregnancy). Because of these limitations, care must be taken when interpreting PICO2B and PICO2C.

5.1. Implications for practice

This study suggests that risk of HBV MTCT, despite passive–active immunoprophylaxis, starts to increase at a maternal viral load of 5.3 log IU/mL. This threshold should be theoretically lower when the PMTCT strategy does not include HBIG (e.g. timely birth dose alone).

With the high strength of the evidence observed, this study suggests that HBeAg might be a good alternative marker to HBV DNA NAT to diagnose high HBV viral load during pregnancy. Moreover, although the strength of the evidence was low, the systematic review found high sensitivity (99.1% (95% CI: 61.8–100%)) of HBeAg during pregnancy to predict immunoprophylaxis failure in infants (MTCT despite administration of birth dose vaccine and HBIG), with a poor specificity of around 55%.

The findings are particularly relevant in countries where there is limited access to HBV DNA NAT. Even though the HBeAg test may perform less well than HBV DNA NAT to identify pregnant women with an elevated risk of MTCT, other parameters (lower costs, improved access to testing and uptake, better linkage to care, and greater feasibility) may favour its use in certain contexts.

5.2. Implications for research

The vast majority of the included studies were from the Western Pacific Region (WPR: 65.9%), followed by the European Region (EUR: 18.3%), African Region (AFR: 7.3%), the Americas (AMR: 6.1%), and only one study each from South-East Asia (SEAR: 1.2%) and Eastern Mediterranean Region (EMR: 1.2%). We need additional research, particularly

outside East Asia. There was no study that included only HCV- or HDV-coinfected women. Only a few studies provided the estimates for HIV-coinfected mothers; we did not find any difference in performance of HBeAg to diagnose high viraemia according to HIV status. As there were only a few studies that assessed viral genotype, we could not investigate the performance of HBeAg during pregnancy in different HBV genotypes.

The use of RDT is more attractive than laboratory-based immunoassays, because the former may be less expensive, faster, easier to perform, and thus more feasible than the latter in a peripheral laboratory in resource-limited contexts. We identified only one study evaluating the performance of RDT during pregnancy, and its sensitivity tended to be lower than that of EIA or CLIA. We need additional studies to evaluate the performance of RDT in pregnant women; but we may also need improvement of analytical sensitivity of RDT to detect HBeAg. The development and evaluation of other low-cost molecular assays or serological markers (e.g. hepatitis B core-related antigen (HBcrAg)) is also highly warranted (*124*).

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7. REFERENCES

- 1. World Health Organization. Global Hepatitis Report 2017 [Internet]. Geneva; 2017. Available from: https://apps.who.int/iris/handle/10665/255016
- World Health Organization. Combating hepatitis B and C to reach elimination by 2030 [Internet]. World Health Organization. Geneva: World Health Organization; 2016. Available from: https://www.who.int/hepatitis/publications/hep-eliminationby-2030-brief/en/
- 3. Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. Proc R Soc B Biol Sci. 1993 Aug;253(1337):197–201.
- 4. Shimakawa Y, Yan H-J, Tsuchiya N, Bottomley C, Hall AJ. Association of early age at establishment of chronic hepatitis B infection with persistent viral replication, liver cirrhosis and hepatocellular carcinoma: a systematic review. PLoS One. 2013;8(7):e69430.
- 5. Chang M-H. Natural history and clinical management of chronic hepatitis B virus infection in children. Hepatol Int. 2008 May;2(Supplement 1):28–36.
- Nayagam S, Thursz M, Sicuri E, Conteh L, Wiktor S, Low-Beer D, et al. Requirements for global elimination of hepatitis B: a modelling study. Lancet Infect Dis [Internet]. 2016 Dec [cited 2019 Aug 28];16(12):1399–408. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27638356
- 7. World Health Organization. Hepatitis B vaccines: WHO position paper. Wkly Epidemiol Rec [Internet]. 2009;84(40):405–20. Available from: http://www.who.int/we
- 8. Machaira M, Papaevangelou V, Vouloumanou EK, Tansarli GS, Falagas ME. Hepatitis B vaccine alone or with hepatitis B immunoglobulin in neonates of HBsAg+/HBeAg- mothers: a systematic review and meta-analysis. J Antimicrob Chemother. 2015 Feb;70(2):396–404.
- 9. Keane E, Funk AL, Shimakawa Y. Systematic review with meta-analysis: the risk of mother-to-child transmission of hepatitis B virus infection in sub-Saharan Africa. Aliment Pharmacol Ther [Internet]. 2016 Nov;44(10):1005–17. Available from: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2036
- Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database Syst Rev [Internet]. 2006 Apr 19 [cited 2019 Aug 28];(2):Art. No.: CD004790. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16625613
- 11. Chen H, Lin L, Hu F, Lee J, Lin W, Yang Y, et al. Effects of Maternal Screening and Universal Immunization to Prevent Mother-to-Infant Transmission of HBV. Gastroenterology. 2012 Apr;142(4):773-781.e2.
- 12. Wen W-H, Chang M-H, Zhao L-L, Ni Y-H, Hsu H-Y, Wu J-F, et al. Mother-toinfant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol. 2013 Jul;59(1):24–30.
- 13. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol.

2017;67(2):370-398.

- 14. Terrault N, Lok A, McMahon B, Chang K, Hwang J, Jonas M, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.
- Visvanathan K, Dusheiko G, Giles M, Wong M-L, Phung N, Walker S, et al. Managing HBV in pregnancy. Prevention, prophylaxis, treatment and follow-up: position paper produced by Australian, UK and New Zealand key opinion leaders. Gut. 2016;65(2):340–50.
- 16. Lemoine M, Thursz MR. Battlefield against hepatitis B infection and HCC in Africa. Journal of Hepatology. 2017.
- 17. Seck A, Ndiaye F, Maylin S, Ndiaye B, Simon F, Funk AL, et al. Poor Sensitivity of Commercial Rapid Diagnostic Tests for Hepatitis B e Antigen in Senegal, West Africa. Am J Trop Med Hyg [Internet]. 2018 Aug;99(2):428–34. Available from: http://www.ajtmh.org/docserver/fulltext/14761645/99/2/tpmd180116.pdf?expires= 1533364940&id=id&accname=12015&checksum=F3723E8693D99CAC3AC9DC 5E712FD2C1
- Chinese Society of Hepatology CMA. Consensus on clinical management of hepatitis B virus- infected women of childbearing age. Zhonghua Gan Zang Bing Za Zhi [Internet]. 2018 Mar 20 [cited 2019 Sep 13];26(3):204–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29804394
- 19. Yuen MF, Hou JL, Chen CJ, Locarnini S, Al Mahtab M, Jafri W, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Vol. 10, Hepatology International. Springer India; 2015. 1–98 p.
- World Health Organization. Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. World Health Organisation. Geneva; 2015. 1–134 p.
- Evans AA, O'Connell AP, Pugh JC, Mason WS, Shen FM, Chen GC, et al. Geographic variation in viral load among hepatitis B carriers with differing risks of hepatocellular carcinoma. Cancer Epidemiol Biomarkers Prev. 1998 Jul;7(7):559– 65.
- 22. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis C a, Glasziou PP, Irwig LM, et al. The STARD Statement for Reporting Studies of Diagnostic Accuracy : Ann Intern Med. 2003;138(1):1–12.
- 23. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med [Internet]. 2011 Oct 18 [cited 2019 Aug 28];155(8):529. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22007046
- 24. Nyaga VN, Arbyn M, Aerts M. Metaprop: A Stata command to perform metaanalysis of binomial data. Arch Public Heal. 2014;72(1):1–10.
- 25. Macaskill P, Gatsonis C, Deeks J, Harbord R, Takwoingi Y. Analysing and Presenting Results. In: Deeks J, Bossuyt P, Gatsonis C, editors. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 10 The Cochrane Collaboration [Internet]. 2010. Available from: http://srdta.cochrane.org/
- 26. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol. 2005;58(9):882–93.

- van Enst WA, Ochodo E, Scholten RJPM, Hooft L, Leeflang MM. Investigation of publication bias in meta-analyses of diagnostic test accuracy: a meta-epidemiological study. BMC Med Res Methodol [Internet]. 2014 May 23 [cited 2019 Sep 13];14:70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24884381
- 28. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun;328(7454):1490.
- 29. Chou R, Easterbrook P, Hellard M. Methodological challenges in appraising evidence on diagnostic testing for WHO guidelines on hepatitis B and hepatitis C virus infection. BMC Infect Dis. 2017;17(Suppl 1).
- Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–6.
- 31. Bai H, Yan H, Shang H, Sun J, Luo H. Clinical study on HBV infection and intrauterine vertical transmission. J Foshan Univ. 2010;28(3):76–8.
- Bissinger A, Enders G, Schalasta G, Vergopoulos A. Frequency of hepatitis B antigen positive pregnant women with high viral loads detected during routine antenatal care in Germany. J Hepatol [Internet]. 2013;58(SUPPL. 1):S398. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=IS&PAGE=reference&D=emed14&NE

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS =N&AN=71055240

- 33. Cai J, Jin Q, Lu M. Real-time PCR analysis of serum HBV DNA in 1018 pregnant women. Matern Child Heal Care China. 2005;20(14):1739–41.
- 34. Cai S, Zhao L. Discuss on relative factors of maternal-infant vertical transmission of hepatitis B virus. Mod Diagn Treat. 2009;20(1):23–4.
- 35. Carey I, McLeod M-A, Bruce M, Horner M, Wang B, Spaan M, et al. Does postdelivery ALT flare modulate the natural course of hepatitis B infection? J Hepatol [Internet]. 2017;66(1 Supplement 1):S246. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01469201/full
- 36. Carey I, Bruce M, Mcleod M, Bowyer T, Horner M, Byrne R, et al. A new utility of HBcrAg-a pan-genotypic predictor of mother to child HBV transmission. J Hepatol [Internet]. 2018;68 (suppl(Supplement 1):S490-S491 (abstr). Available from:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS= N&AN=621859043

- 37. Chang C, Chang M, Jeong D, Aziz N, Lau D, Trinh H. Characterization and statistical modeling to estimate timing and duration of antiviral therapy to achieve target HBV DNA <=200,000 IU/mL at delivery to reduce risk of mother to child transmission (MTCT) in pregnant women with chronic hepatitis B (CHB). Gastroenterology [Internet]. 2017;152(5 Supplement 1):S1087. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18&NEWS =N&AN=618671664
- 38. Chen T, Wang J, Qiu H, Yu Q, Yan T, Qi C, et al. Different interventional criteria for chronic hepatitis B pregnant women with HBeAg(+) or HBeAg(-). Med [Internet]. 2018;97(27):e11406. Available from:

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85049944318&doi=10.1097%2FMD.00000000011406&partnerID=40&md5=d 0bac31a8f8f57226ad9c8a3242fd88c

- 39. Chen T, Liu J, Yu Q, Yao N, Yang Y, Wu Y, et al. Tenofovir plus hepatitis B immunoglobulin treatment resulted in a rapid HBV DNA load decline in high-risk pregnant women who missed the optimal time window of antiviral prophylaxis. Antivir Ther. 2018 Dec;
- 40. Chen Z-X, Gu G-F, Bian Z-L, Cai W-H, Shen Y, Hao Y-L, et al. Clinical course and perinatal transmission of chronic hepatitis B during pregnancy: A real-world prospective cohort study. J Infect [Internet]. 2017 Aug;75(2):146–54. Available from: http://www.elsevier.com/inca/publications/store/6/2/3/0/5/4/index.htt
- 41. Cheng S, Liao Z, Cui T, Cao H, Zeng X. The relationship between HBV infections status in pregnant women and intrauterine infection of fetus. Chinese J Eugen Genet. 2006;14(11):73–4.
- 42. Cheung KW, Seto MTY, So PL, Wong D, Mak ASL, Lau WL, et al. Optimal timing of hepatitis B virus DNA quantification and clinical predictors for higher viral load during pregnancy. Acta Obstet Gynecol Scand. 2019;98(10):1301–6.
- 43. Chotun N, Preiser W, van Rensburg CJ, Fernandez P, Theron GB, Glebe D, et al. Point-of-care screening for hepatitis B virus infection in pregnant women at an antenatal clinic: A South African experience. PLoS One [Internet]. 2017;12(7):e0181267. Available from: http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0181267&typ e=printable
- 44. Dervisevic S, Ijaz S, Chaudry S, Tedder RS. Non-A hepatitis B virus genotypes in antenatal clinics, United Kingdom. Emerg Infect Dis [Internet]. 2007 Nov;13(11):1689–93. Available from: http://www.cdc.gov/eid/content/13/11/pdfs/1689.pdf
- 45. Ding Y, Sheng Q, Ma L, Dou X. Chronic HBV infection among pregnant women and their infants in Shenyang, China. Virol J [Internet]. 2013 Jan;10:17. Available from:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS= N&AN=369370728

- 46. Dolman G, Saleh H, Kemos P. Quantitative hepatitis B surface antigen (qHBsAg) has poor performance as a marker of high risk antenatal chronic hepatitis B (CHB) in a multi-ethnic population. Hepatology [Internet]. 2018;68 (suppl(Supplement 1):1187A-1188A (abstr). Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS= N&AN=624566411
- 47. Dopico E, Navarro R, Allende B, Faith S, Moure Z, Guerrero L. Chronic hepatitis B virus infection in pregnant Chinese women living in Barcelona (Spain). Trop Med Int Heal [Internet]. 2013;18(SUPPL. 1):140. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS =N&AN=71540307
- 48. Dyson JK, Waller J, Turley A, Michael E, Moses S, Valappil M, et al. Hepatitis B in pregnancy. Frontline Gastroenterol [Internet]. 2014 Apr;5(2):111–7. Available from: http://fg.bmj.com/content/5/2/111.full.pdf+html

- 49. Eilard A, Andersson M, Ringlander J, Wejstal R, Norkrans G, Lindh M. Vertically acquired occult hepatitis B virus infection may become overt after several years. J Infect [Internet]. 2019 Mar;78(3):226–31. Available from: http://www.elsevier.com/inca/publications/store/6/2/3/0/5/4/index.htt
- 50. Elefsiniotis IS, Glynou I, Brokalaki H, Magaziotou I, Pantazis KD, Fotiou A, et al. Serological and virological profile of chronic HBV infected women at reproductive age in Greece. A two-year single center study. Eur J Obstet Gynecol Reprod Biol [Internet]. 2007 Jun;132(2):200–3. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS =N&AN=46817719
- 51. Foaud HM, Maklad S, Gmal El Din A, Mahmoud F. Lamivudine use in pregnant HBsAg-females effectively reduces maternal viremia. Arab J Gastroenterol [Internet]. 2019 Mar;20(1):8–13. Available from: http://www.arabjg.eg.net/
- 52. Fujiko M, Chalid MT, Turyadi, Ie SI, Maghfira, Syafri, et al. Chronic hepatitis B in pregnant women: Is hepatitis B surface antigen quantification useful for viral load prediction? Int J Infect Dis [Internet]. 2015 Dec;41:83–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed16&NEWS =N&AN=607132330
- 53. Godbole G, Irish D, Basarab M, Mahungu T, Fox-Lewis A, Thorne C, et al. Management of hepatitis B in pregnant women and infants: A multicentre audit from four London hospitals. BMC Pregnancy Childbirth [Internet]. 2013;13:222. Available from: http://www.biomedcentral.com/1471-2393/13/222
- 54. Guo F, Liu X, Jiang B, Liu J. Analysis of hepatitis B virus markers in the serum and viral load of 4461 pregnant woman. Chinese J Soc Med. 2007;24(4):284–6.
- 55. Han Y, Liu Z, Pan F, Wang X. Study on HBV infection and intrauterine infection in pregnant women. Matern Child Heal Care China. 2007;22(1):29–30.
- 56. Hao X, Li Z, Ding Y, Du Y, Zhao Y. Study on risk factors in trans-placental transmission of hepatitis B virus. Shanghai J Prev Med. 2015;27(7):387–91.
- 57. Hu Q, Wang Y. Results in detection of perinatal infectious disease markers in 3658 lying-in women. China Trop Med. 2007;7(8):1350–2.
- 58. Huang L, Wang C. Investigation on the safety of breastfeeding among mothers chronically infected with hepatitis B virus. Matern Child Heal Care China. 2014;29(33):5389–90.
- 59. Jackson V, Ferguson W, Kelleher TB, Lawless M, Eogan M, Nusgen U, et al. Lamivudine treatment and outcome in pregnant women with high hepatitis B viral loads. Eur J Clin Microbiol Infect Dis [Internet]. 2015 Mar;34(3):619–23. Available from: http://link.springer.de/link/service/journals/10096/index.htm
- 60. Jin C, Li P, Zhu T. Analysis of HBV DNA quantitative testing results in pregnant women with different patterns of HBV serological markers. Chinese J Eugen Genet. 2007;15(6):62,116.
- 61. Johannessen A, Stene-Johansen K, Mekasha B, N. B. Mother-to-child transmission of hepatitis B virus in Ethiopia. J Hepatol [Internet]. 2017;66 (suppl)(1):S470 (abstr). Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS= N&AN=621222629
- 62. Köse S, Türken M, Devrim I, Taner C. Efficacy and safety of lamivudine treatment

in late pregnancy with high HBV DNA: A perspective for mother and infants. J Infect Dev Ctries [Internet]. 2011 Apr;5(4):303–6. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-79955855125&partnerID=40&md5=9e71b041054564ecc6d3437e307eb4f8

- Kubo A, Shlager L, Marks AR, Lakritz D, Beaumont C, Gabellini K, et al. Prevention of vertical transmission of hepatitis B: An observational study. Ann Intern Med [Internet]. 2014 Jun;160(12):828–35. Available from: http://annals.org/data/Journals/AIM/930364/0000605-201406170-00004.pdf
- 64. Lao T, Leung T, Suen S, Chung M, Chim S, Cheung T, et al. Maternal HBeAg status and hepatitis B viral activity in HBsAg positive mothers. Am J Obstet Gynecol [Internet]. 2012;206(1 SUPPL. 1):S273. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS =N&AN=70633356
- 65. Latthaphasavang V, Vanhems P, Ngo-Giang-Huong N, Sibounlang P, Paboriboune P, Malato L, et al. Perinatal hepatitis B virus transmission in Lao PDR: A prospective cohort study. PLoS One. 2019;14(4):1–14.
- 66. Lee LY, Aw M, Rauff M, Loh K-S, Lim SG, Lee GH. Hepatitis B immunoprophylaxis failure and the presence of hepatitis B surface gene mutants in the affected children. J Med Virol [Internet]. 2015 Aug;87(8):1344–50. Available from: http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1096-9071
- 67. Li X, Zhang J, Wang C. Analysis on association between HBV markers in pregnant women with hepatitis B and neonatal infection. Int J Lab Med. 2018;39(4):495–8.
- 68. Li Y. The study of the relationship between HBV infection status in pregnant women and maternal-infant transmission. Front Med. 2013;(3):86–7.
- 69. Liang P, Sun C, Wang J, Luo Y, Wang J. Analysis on testing results of 4 infectious diseases in 6930 pregnant women. Int J Lab Med. 2017;38(19):2753–5.
- 70. Lin J, Liao S, Guo G, Huang W, Wang C, Zhou M. Significance of hepatitis B virus DNA quantity in transmission between mothers and infants. Chin J Pediatr. 2002;40(2):84–7.
- 71. Liu C-P, Zeng Y-L, Zhou M, Chen L-L, Hu R, Wang L, et al. Factors associated with mother-to-child transmission of hepatitis B virus despite immunoprophylaxis. Intern Med [Internet]. 2015;54(7):711–6. Available from: https://www.jstage.jst.go.jp/article/internalmedicine/54/7/54 54.3514/ pdf
- 72. Liu H, Li J, Peng J, Chen Q, Yang Z, Ying R. Clinical features of pregnant women with hepatitis B virus infection. Chin J Clin. 2013;23(7):10473–6.
- 73. Liu Y, Wang M, Yao S, Yuan J, Lu J, Li H, et al. Efficacy and safety of telbivudine in different trimesters of pregnancy with high viremia for interrupting perinatal transmission of hepatitis B virus. Hepatol Res [Internet]. 2016 Mar;46(3):E181–8. Available from: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1872-034X
- 74. Lu H, Jin W, Huang X, Zhao Q, Mao H. Pregnant women hepatitis B markers investigation and analysis of intrauterine infection. Chinese J Exp Clin Virol. 2009;23(3):235–7.
- 75. Lunel-Fabiani F, Birguel J, Pivert A, Njouom R, Ducancelle A, Gautheret A, et al. Evaluation of the effectiveness of hepatitis B (HB) vaccination of newborns from

HBsAg-positive mothers, followed by the national enlarged vaccination program including HB, in the health district of Tokombere, Cameroon. Hepatology [Internet]. 2018;68 (suppl:1188A-1189A (abstr). Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS= N&AN=624566438

- 76. Ma Y. The importance of standard prenatal screening for pregnant women chronically infected with hepatitis B virus. Front Med. 2014;(18):154–5.
- 77. Michitaka K, Hiraoka A, Imai Y, Utsunomiya H, Tatsukawa H, Shimizu Y, et al. Clinical features and hepatitis B virus (HBV) genotypes in pregnant women chronically infected with HBV. Intern Med [Internet]. 2012;51(24):3317–22. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=IS&PAGE=reference&D=emed13&NEWS

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS =N&AN=366408856

- 78. Peng N, Ling J. Analysis of serum HBV DNA, HBV Pre S1 antigen and alpha fetoprotein in pregnant women chronically infected with hepatitis B. Lab Med Clin. 2012;9(20):2606–8.
- 79. Peng S, Wan Z, Liu T, Zhu H. Incidence and Risk Factors of Intrauterine Transmission among Pregnant Women with Chronic Hepatitis B Virus Infection. J Clin Gastroenterol [Internet]. 2019;53(1):51–7. Available from: http://journals.lww.com/jcge
- 80. Pirillo MF, Bassani L, Germinario EAP, Mancini MG, Vyankandondera J, Okong P, et al. Seroprevalence of hepatitis B and C viruses among HIV-infected pregnant women in Uganda and Rwanda. J Med Virol [Internet]. 2007 Dec;79(12):1797–801. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=IS&PAGE=reference&D=emed10&NEWS

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS =N&AN=350006301

- 81. Pirillo MF, Scarcella P, Andreotti M, Jere H, Buonomo E, Sagno J-B, et al. Hepatitis B virus mother-to-child transmission among HIV-infected women receiving lamivudine-containing antiretroviral regimens during pregnancy and breastfeeding. J Viral Hepat [Internet]. 2015 Mar;22(3):289–96. Available from: http://www.blackwell-science.com/jvh
- 82. Punzalan C. Factors associated with immunoprophylaxis failure against vertical transmission of hepatitis B virus among a cohort of New York City children and mothers. Hepatology [Internet]. 2012;56(SUPPL. 1):638A. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS =N&AN=70942510
- Rouet F, Chaix M-L, Inwoley A, Msellati P, Viho I, Combe P, et al. HBV and HCV prevalence and viraemia in HIV-positive and HIV-negative pregnant women in Abidjan, Cote d'Ivoire: The ANRS 1236 study. J Med Virol [Internet]. 2004 Sep;74(1):34–40. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS

=N&AN=38988857

84. Samadi Kochaksaraei G, Congly SE, Matwiy T, Castillo E, Martin SR, Charlton CL, et al. Cost-effectiveness of quantitative hepatitis B virus surface antigen testing in pregnancy in predicting vertical transmission risk. Liver Int [Internet]. 2016 Nov;36(11):1604–10. Available from:

http://www.wiley.com/bw/journal.asp?ref=1478-3223

- 85. Segeral O, N'Diaye DS, Prak S, Nouhin J, Chhun S, Khamduang W, et al. Usefulness of a serial algorithm of HBsAg and HBeAg rapid diagnosis tests to detect pregnant women at risk of HBV mother-to-child transmission in Cambodia, the ANRS 12328 pilot study. J Clin Virol [Internet]. 2018 Dec;109:29–34. Available from: http://www.elsevier.com/inca/publications/store/5/2/4/0/6/2
- 86. Sellier PO, Maylin S, Bercot B, Chopin D, Lopes A, Simoneau G, et al. Prospective interventional study of tenofovir in pregnancy to prevent vertical transmission of hepatitis B in highly viremic women. Eur J Gastroenterol Hepatol [Internet]. 2017 Mar;29(3):259–63. Available from: http://journals.lww.com/eurojgh/pages/default.aspx
- 87. Seo K II, Bae SH, Sung PS, Park C-H, Lee HL, Kim HY, et al. Effect of antiviral therapy in reducing perinatal transmission of hepatitis B virus and maternal outcomes after discontinuing them. Clin Mol Hepatol [Internet]. 2018 Dec;24(4):374–83. Available from: http://www.e-cmh.org/upload/pdf/cmh-2017-0082.pdf
- 88. Shao Z-J, Zhang L, Xu J-Q, Xu D-Z, Men K, Zhang J-X, et al. Mother-to-infant transmission of hepatitis B virus: A Chinese experience. J Med Virol [Internet]. 2011;83(5):791–5. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS =N&AN=361452842
- 89. Sheng Q-J, Wang S-J, Wu Y-Y, Dou X-G, Ding Y. Hepatitis B virus serosurvey and awareness of mother-To-child transmission among pregnant women in Shenyang, China. Medicine (Baltimore) [Internet]. 2018 Jun;97(22):e10931. Available from: http://journals.lww.com/md-journal
- Shi Y, Luo H, Zhu Q. The association between serum HBV viral load and serological immune markers in pregnant women chronically infected with HBV. J Pract Med. 2012;28(16):2745–7.
- 91. Söderström A, Norkrans G, Lindh M. Hepatitis B virus DNA during pregnancy and post partum: Aspects on vertical transmission. Scand J Infect Dis [Internet]. 2003;35(11–12):814–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS =N&AN=38028916
- 92. Tang A, Lyu J, Chen A, He Q, Wang S. Assessing mother-to-child transmission risk in asian american women with chronic hepatitis B receiving prenatal care at two community health sites in New York City, 2007-2017. Hepatology [Internet]. 2018;68(Supplement 1):1207A. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS= N&AN=624566107
- Tang Y. Quantitative analysis of HBV serological markers and HBV-DNA in 500 pregnant women chronically infected with HBV. J Heze Med Coll. 2013;25(1):53–62.
- 94. Thilakanathan C, Wark G, Maley M, Davison S, Lawler J, Lee A, et al. Mother-tochild transmission of hepatitis B: Examining viral cut-offs, maternal HBsAg serology and infant testing. Liver Int [Internet]. 2018 Jul;38(7):1212–9. Available from: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1478-3231

- 95. van Zonneveld M, van Nunen AB, Niesters HGM, de Man RA, Schalm SW, Janssen HLA. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. J Viral Hepat [Internet]. 2003 Jul;10(4):294–7. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS =N&AN=36801916
- 96. Wang F, Han G, Li F, Xue Y. Investigation on the association between maternal HBV markers including HBV DNA and neonatal intrauterine infection. Mod Med J. 2009;37(6):435–7.
- 97. Wang J, Liu J, Qi C, Yan T, Cao F, Jin L, et al. Efficacy of tenofovir disoproxil fumarate to prevent vertical transmission in mothers with lamivudine-resistant HBV. Antivir Ther [Internet]. 2015;20(7):681–7. Available from: http://www.intmedpress.com/serveFile.cfm?sUID=06ce1d11-3627-4a99-80cb-e8cc733fb0da
- 98. Wang J, Yin J, Wang H. Survey on hepatitis B infection status among pregnant women in Yangzhou City. Maternal and Child Health Care of China. Matern Child Heal Care China. 2018;33(22):5222–4.
- 99. Wang L, Wiener J, Bulterys M, Wei X, Chen L, Liu W, et al. Hepatitis B virus (HBV) load response to 2 antiviral regimens, tenofovir/lamivudine and lamivudine, in HIV/HBV-coinfected pregnant women in Guangxi, China: The tenofovir in pregnancy (TiP) study. J Infect Dis [Internet]. 2016 Dec;214(11):1695–9. Available from: http://jid.oxfordjournals.org/content/current
- 100. Wang M, Cai Q, Wan J. The expression of Toll-like receptor 4 and 7 in placental tissues of pregnant women infected with hepatitis B virus. Matern Child Heal Care China. 2018;33(22):5254–7.
- Wang X, Li C, Liu M, Yi W, Wang S, Liu X. Impact of different feeding patterns on mother-to-child transmission of hepatitis B virus. Chin J Perinat Med. 2015;18(8):616–20.
- 102. Wang X, Xu Y, Wei Y, Deng B, Huang H. Clinical significance of detection of Pre S1 antigen and alpha fetoprotein in patients with gestational diabetic mellitus complicated with HBV infections. Chin J Nosocomiol. 2015;25(4):5672–4.
- 103. Wang Z, Ji C, Gao S, Tang L, Xia J. HBV infection status of pregnant women in outpatient department of Guangdong women and children hospital. Chinese J Woman Child Heal Res. 2018;29(11):1491–3.
- 104. Wei K, Lu Y, Yan L, Liu J, Zhai X, Chang Z. Prenatal serological and virological characteristics of pregnant women with chronic HBV infection in community population. Chinese J Pract Intern Med. 2017;37(12):1074–8.
- 105. Wiseman E, Fraser MA, Holden S, Glass A, Kidson BL, Heron LG, et al. Perinatal transmission of hepatitis B virus: An Australian experience. Med J Aust [Internet]. 2009 May;190(9):489–92. Available from: http://www.mja.com.au/public/issues/190_09_040509/wis11122_fm.pdf
- 106. Xu C, Liu J, Liu L, Bi Y, Xu B, Chen J, et al. Comparison of hepatitis B viral loads and viral antigen levels in child-bearing age women with and without pregnancy. BMC Pregnancy Childbirth [Internet]. 2018 Jul;18(1):292. Available from: http://www.biomedcentral.com/bmcpregnancychildbirth/
- 107. Xu H, Shi D, Zhao X. Analysis on serum HBV DNA levels, HBV serological

markers patterns and ALT, AST in pregnant women chronically infected with HBV. Chin J Hemorh. 2008;18(4):599–600.

- 108. Yin Y, Wu L, Zhang J, Zhou J, Zhang P. Identification of risk factors associated with immunoprophylaxis failure to prevent the vertical transmission of hepatitis B virus. J Infect [Internet]. 2013;66(5):447–52. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS =N&AN=52388409
- 109. Zhang L, Tang X, Liu C, Zhao S, Su F, Wang Y. Study on hepatitis B virus markers and HBV-DNA levels among pregnant women in Guizhou Province. Mod Prev Med. 2017;44(4):637–41.
- 110. Gong Q-M, Kong X-F, Yang Z-T, Xu J, Wang L, Li X-H, et al. Association study of IFNAR2 and IL10RB genes with the susceptibility and interferon response in HBV infection. J Viral Hepat [Internet]. 2009 Sep;16(9):674–80. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS =N&AN=355131278
- 111. Zheng H, Ren X. Quantitative analysis of serum HBV DNA in pregnant women positive for HBsAg and its influence on pregnancy outcome. Guangzhou Med. 2010;41(6):33–4.
- 112. Zhu B, Li S, Tian H, Xu J, Li N, Chen Y. Influence of serum HBV DNA level in pregnant women with HBV infection on the effect of blocking mother-to-infant transmission by passive-active immunoprophylaxis. Matern Child Heal Care China. 2013;28(24):3903–5.
- 113. Cheung KW, Seto MTY, Kan ASY, Wong D, Kou KO, So PL, et al. Immunoprophylaxis Failure of Infants Born to Hepatitis B Carrier Mothers Following Routine Vaccination. Clin Gastroenterol Hepatol [Internet]. 2018;16(1):144–5. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85040764264&doi=10.1016%2Fj.cgh.2017.07.013&partnerID=40&md5=ddcdd20 c82aa27036a0fb32ed29ace44
- 114. Yi W, Pan CQ, Hao J, Hu Y, Liu M, Li L, et al. Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers. J Hepatol [Internet]. 2014 Mar;60(3):523–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed15&NEWS =N&AN=52905112
- 115. Zhang L, Gui X-E, Wang B, Fan J-Y, Cao Q, Mullane K, et al. Serological positive markers of hepatitis B virus in femoral venous blood or umbilical cord blood should not be evidence of in-utero infection among neonates. BMC Infect Dis [Internet]. 2016 Aug;16(1):408. Available from: http://www.biomedcentral.com/bmcinfectdis/
- 116. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat. 2012 Feb;19(2):e18-25.
- 117. Zhang Z, Li A, Xiao X. Risk factors for intrauterine infection with hepatitis B virus. Int J Gynecol Obstet [Internet]. 2014 May;125(2):158–61. Available from: http://www.elsevier.com/locate/ijgo
- 118. Lu Y, Zhu F-C, Liu J-X, Zhai X-J, Chang Z-J, Yan L, et al. The maternal viral

threshold for antiviral prophylaxis of perinatal hepatitis B virus transmission in settings with limited resources: A large prospective cohort study in China. Vaccine [Internet]. 2017 Dec;35(48):6627–33. Available from: http://www.elsevier.com/locate/vaccine

- 119. Pan CQ, Zou H-B, Chen Y, Zhang X, Zhang H, Li J, et al. Cesarean section reduces perinatal transmission of hepatitis B virus infection from hepatitis b surface antigen-positive women to their infants. Clin Gastroenterol Hepatol [Internet]. 2013 Oct;11(10):1349–55. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS =N&AN=52726220
- 120. Ott JJ, Stevens GA, Wiersma ST. The risk of perinatal hepatitis B virus transmission: hepatitis B e antigen (HBeAg) prevalence estimates for all world regions. BMC Infect Dis [Internet]. 2012 Dec 9 [cited 2019 Sep 7];12(1):131. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22682147
- 121. Lin H-H, Kao J-H, Chang T-C, Hsu H-Y, Chen D-S. Secular trend of age-specific prevalence of hepatitis B surface and e antigenemia in pregnant women in Taiwan. J Med Virol [Internet]. 2003 Apr [cited 2019 Sep 7];69(4):466–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12601752
- 122. Shimakawa Y, Lemoine M, Njai HF, Bottomley C, Ndow G, Goldin RD, et al. Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia. Gut [Internet]. 2016 Dec [cited 2019 Sep 7];65(12):2007–16. Available from: http://gut.bmj.com/lookup/doi/10.1136/gutjnl-2015-309892
- 123. Thompson AJ V, Nguyen T, Iser D, Ayres A, Jackson K, Littlejohn M, et al. Serum hepatitis B surface antigen and hepatitis B e antigen titers: disease phase influences correlation with viral load and intrahepatic hepatitis B virus markers. Hepatology [Internet]. 2010 Jun [cited 2019 Sep 7];51(6):1933–44. Available from: http://doi.wiley.com/10.1002/hep.23571
- 124. Shimakawa Y, Ndow G, Njie R, Njai HF, Takahashi K, Akbar SMF, et al. Hepatitis B Core-related Antigen: An Alternative to Hepatitis B Virus DNA to Assess Treatment Eligibility in Africa. Clin Infect Dis [Internet]. 2019 May 17 [cited 2019 Nov 29]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/31102406

8. APPENDICES

8.1. Appendix A: Search strategies

Database: PubMed Date searched: From 1 January 2000 to 3 April 2019 Search strategy:

Item	Search words	# Records
1	"hepatitis b"[MeSH] OR "hepatitis b virus"[MeSH]	36043
2	hepatitis b[Text] OR type b hepatitis[Text] OR hepatitis type b[Text] OR hbv[Text] OR vhb[Text] OR hep b[Text] OR hbsag[Text] OR hbs ag[Text] OR hbs antigen*[Text]	58981
3	1 OR 2	58981
4	"viral load"[MeSH] OR "viremia"[MeSH] OR "DNA, viral"[MeSH] OR "nucleic acid amplification techniques"[MeSH]	404088
5	viral load*[Text] OR viremi*[Text] OR viraemi*[Text] OR DNA[Text] OR nucleic acid test*[Text] OR nucleic acid amplification*[Text] OR NAT[Text] OR polymerase chain reaction*[Text] OR PCR[Text]	1469530
6	4 OR 5	1470454
7	"pregnancy"[MeSH] OR "pregnant women"[MeSH] OR "maternal-fetal relations"[MeSH] OR "infectious disease transmission, vertical"[MeSH] OR "pregnancy complications, infectious"[MeSH] OR "prenatal diagnosis"[MeSH]	374590
8	pregnan*[Text] OR trimest*[Text] OR gestation*[Text] OR antepartum[Text] OR ante-partum[Text] OR prepartum[Text] OR intrapartum[Text] OR intrapartum[Text] OR intra-partum[Text] OR peripartum[Text] OR peri-partum[Text] OR antenatal*[Text] OR peri- natal*[Text] OR prenatal*[Text] OR pre-natal*[Text] OR perinatal*[Text] OR peri-natal*[Text] OR intrauterine[Text] OR intra-uterine[Text] OR inutero[Text] OR in utero[Text] OR transplacental*[Text] OR placenta*[Text] OR matern*[Text] OR fetomaternal*[Text] OR foetomaternal*[Text] OR fetal*[Text] OR foetal*[Text] OR foetomaternal*[Text] OR fetal*[Text] OR foetal*[Text] OR fetus[Text] OR foetus[Text] OR offspring[Text] OR MTCT[Text] OR TME[Text]	920702
9	7 OR 8	924605
10	3 AND 6 AND 9	1131

Database: Embase via Ovid Date searched: from 1 January ^t 2000 to 3 April 2019 Search Strategy:

Item	Search words	# Records
1	exp hepatitis B/ OR exp Hepatitis B virus/	88165
2	(hepatitis b OR type b hepatitis OR hepatitis type b OR hbv OR vhb OR	114021
	hep b OR hbsag OR hbs ag OR hbs antigen*).mp.	
3	1 OR 2	114021
4	exp virus load/ OR exp viremia/ OR exp virus DNA/ OR exp nucleic acid amplification/	124590
5	(viral load* OR viremi* OR viraemi* OR DNA OR nucleic acid test* OR nucleic acid amplification* OR NAT OR polymerase chain reaction* OR PCR).mp.	2014356
6	4 OR 5	2031867
7	exp pregnancy/ OR exp pregnant women/ OR exp mother fetus relationship/ OR exp vertical transmission/ OR exp pregnancy complication/ OR exp prenatal diagnosis/	462746
8	(pregnan* OR trimest* OR gestation* OR antepartum OR ante-partum OR prepartum OR pre-partum OR intrapartum OR intra-partum OR peripartum OR peri-partum OR antenatal* OR ante-natal* OR prenatal* OR pre-natal* OR perinatal* OR peri-natal* OR intrauterine OR intra- uterine OR inutero OR in utero OR transplacental* OR placenta* OR vertical* OR congenital* OR mother* OR matern* OR fetomaternal* OR foetomaternal* OR fetal* OR foetal* OR fetus OR foetus OR offspring OR MTCT OR TME).mp.	1348015
9	7 OR 8	1351584
10	3 AND 6 AND 9	2696

Database: Scopus Date searched: From 1 January 2000 to 3 April 2019 Search Strategy:

Item	Search words	# Records
1	TITLE-ABS-KEY ("hepatitis b" OR "type b hepatitis" OR "hepatitis type	88699
	b" OR "hbv" OR "vhb" OR "hep b" OR "hbsag" OR "hbs ag" OR "hbs	
	antigen*")	
2	TITLE-ABS-KEY ("viral load*" OR "viremi*" OR "viraemi*" OR	2077123
	"DNA" OR "nucleic acid test*" OR "nucleic acid amplification*" OR	
	"NAT" OR "polymerase chain reaction*" OR "PCR")	
3	TITLE-ABS-KEY ("pregnan*" OR "trimest*" OR "gestation*" OR	1632184
	"antepartum" OR "ante-partum" OR "prepartum" OR "pre-partum" OR	
	"intrapartum" OR "intra-partum" OR "peripartum" OR "peri-partum" OR	
	"antenatal*" OR "ante-natal*" OR "prenatal*" OR "pre-natal*" OR	
	"perinatal*" OR "peri-natal*" OR "intrauterine" OR "intra-uterine" OR	
	"inutero" OR "in utero" OR "transplacental*" OR "placenta*" OR	
	"vertical*" OR "congenital*" OR "mother*" OR "matern*" OR	
	"fetomaternal*" OR "foetomaternal*" OR "fetal*" OR "foetal*" OR	
	"fetus" OR "foetus" OR "offspring" OR "MTCT" OR "TME")	
4	#1 AND #2 AND #3	1851

Database: CENTRAL Database (The Cochrane Library) Date searched: From 1 January 2000 to 3 April 2019 Search strategy:

Item	Search words	# Trials
1	hepatitis b [MeSH, exp] OR hepatitis b virus [MeSH, exp]	1744
2	"hepatitis b" OR "type b hepatitis" OR "hepatitis type b" OR hbv OR vhb	6913
3	1 OP 2	6013
4	"viral load"[MeSH, exp] OR "viremia"[MeSH, exp] OR "DNA, viral"[MeSH, exp] OR "nucleic acid amplification techniques"[MeSH, exp]	4212
5	"viral load*" OR viremi* OR viraemi* OR DNA OR "nucleic acid test*" OR "nucleic acid amplification*" OR NAT OR "polymerase chain reaction*" OR PCR	29632
6	4 OR 5	29637
7	pregnancy [MeSH, exp] OR pregnant women [MeSH, exp] OR maternal- fetal relations [MeSH, exp] OR infectious disease transmission, vertical [MeSH, exp] OR pregnancy complications, infectious [MeSH, exp] OR prenatal diagnosis [MeSH, exp]	5294
8	pregnan* OR trimest* OR gestation* OR antepartum OR ante-partum OR prepartum OR pre-partum OR intrapartum OR intra-partum OR peripartum OR peri-partum OR antenatal* OR ante-natal* OR prenatal* OR pre-natal* OR perinatal* OR peri-natal* OR intrauterine OR intra- uterine OR inutero OR "in utero" OR transplacental* OR placenta* OR vertical* OR congenital* OR mother* OR matern* OR fetomaternal* OR foetomaternal* OR fetal* OR foetal* OR fetus OR foetus OR offspring* OR MTCT OR TME	76201
9	7 OR 8	76271
10	3 AND 6 AND 9	218

Database: Wanfang

主题:("乙型肝炎"+"乙肝"+"乙型病毒性肝炎"+"乙型肝炎病毒"+"乙肝病毒 "+"HBV"+"乙型肝炎表面抗原"+"乙肝表面抗原"+"乙型肝炎病毒表面抗原"+"乙肝病 毒表面抗原"+"HBsAg") and 主题:("病毒载量"+"病毒血症"+"病毒 DNA"+"DNA"+" 核酸扩增技术"+"核酸检测"+"核酸扩增"+"NAT"+"多聚酶链反应"+"多聚酶链式反应 "+"聚合酶链反应"+"PCR") and 主题:("妊娠"+"孕妇"+"孕期"+"母胎"+"母亲"+"胎儿 "+"新生儿"+"婴儿"+"子代"+"子女"+"母婴传播"+"垂直传播"+"妊娠并发症"+"产前 筛查"+"产前诊断"+"出生前诊断"+"先天"+"产前"+"产时"+"围产"+"出生前"+"围生 "+"宫内"+"跨胎盘"+"胎盘") Database: CNKI

SU='乙型肝炎'+'乙肝'+'乙型病毒性肝炎'+'乙型肝炎病毒'+'乙肝病毒'+'HBV'+'乙型肝 炎表面抗原'+'乙肝表面抗原'+'乙型肝炎病毒表面抗原'+'乙肝病毒表面抗原'+'HBsAg' AND SU='病毒载量'+'病毒血症'+'病毒 DNA'+'DNA'+'核酸扩增技术'+'核酸检测'+'核 酸扩增'+'NAT'+'多聚酶链反应'+'多聚酶链式反应'+'聚合酶链反应'+'PCR' AND SU=' 妊娠'+'孕妇'+'孕期'+'母胎'+'母亲'+'胎儿'+'新生儿'+'婴儿'+'子代'+'子女'+'母婴传播'+' 垂直传播'+'妊娠并发症'+'产前筛查'+'产前诊断'+'出生前诊断'+'先天'+'产前'+'产时'+' 围产'+'出生前'+'围生'+'宫内'+'跨胎盘'+'胎盘'

8.2. Appendix B: QUADAS2 protocol

Domain 1: Patient Selection (PICO2A, 2B and 2C)

- Risk of Bias: Could the selection of patients have introduced bias?

• Signaling question 1: Was a consecutive or random sample of patients or specimens enrolled?

Answer "yes" if the study enrolled a consecutive or random sample of eligible patients or specimens; "no" if the study selected patients or specimens by convenience; and "unclear" if the study did not report the sample selection methods.

• Signaling question 2: Was a case-control design avoided?

Answer "no" for a case-control study (i.e., study in which the chance of being included differs between cases (with high viral load for PICO2A and with MTCT for PICO2B & 2C) and controls (with low viral load for PICO2B and with no MTCT for PICO2B & 2C)); and "yes" for a retrospective/prospective cohort or a cross-sectional study.

• Signaling question 3: Did the study avoid inappropriate exclusions?

Answer "no" if the study excluded HBsAg-positive pregnant women with a criterion other than concomitant anti-HBV therapy (e.g., HCV/HDV co-infection, sever liver disease, having HBsAg-positive spouse, etc...); and "unclear" if unable to tell.

Risk of bias is rated as "low" if selection was done in a random or consecutive manner and the study was not a case-control design and did not exclude HBsAg-positive pregnant women with a criterion other than concomitant anti-HBV therapy (i.e., all answers to signaling questions rated "yes"); "high" if any signaling question was answered "no"; and "unclear" if insufficient data were reported to permit a judgment (i.e., at least one signaling question rated "unclear" and no question rated "no").

- Applicability: Are there concerns that the included patients and setting do not match the review question?

Our primary objective is to assess the performance of HBeAg as an alternative to HBV DNA to assess eligibility for antiviral therapy initiation in pregnant women who are identified to carry HBsAg. Therefore, if a study included only selected pregnant women on

the basis of HBV DNA levels or HBeAg sero-status, it may not be relevant to the study question. We will rate concerns about applicability as "low" if patients were selected irrespective of HBV DNA levels, "high" if study participants were only those with high (or low) HBV DNA levels, and "unclear" if the eligibility for inclusion in the study was not well described. Of note, if a study was designed to only include HBeAg-positive women or HBeAg-negative women, the study should be excluded from our systematic review.

Domain 2: Index Test

PICO2A and PICO2B:

- *Risk of Bias: Could the conduct or interpretation of the index test have introduced bias?*

• Signaling question 1: Were the index test results interpreted without knowledge of the results of the reference standard?

Consider "yes" if the examiner of the index text was blinded to the results of the reference standard, "no" if reference standard results were not blinded, and "unclear" if no mention of blinding, or if it is not known when the test was done.

• Signaling question 2: If a threshold was used, was it pre-specified?

Consider "yes" unless the study explicitly mentioned the use of a specific HBeAg threshold (PEIU/mL or cut-off index (COI)) which differs from its limit of detection.

Risk of bias is rated as "low" if both signaling questions were answered "yes"; "high" if at least one signaling question was answered "no"; and "unclear" if at least one question was rated as "unclear" and no question rated "no".

- Applicability: Are there concerns that the index test, its conduct, or its interpretation differ from the review question?

Rate concerns about applicability as "high" if the test was done outside pregnancy or if the type of assay used was not one of these: lateral flow immunochromatographic rapid diagnostic test (RDT), Enzyme immunoassay (EIA, ELISA), chemiluminescence immunoassay (CLIA), Radioimmunoassay (RIA), Counting immunoassay (CIA), Fluoroimmunoassay (FIA); "unclear" if some information was missing on the test (not know what type of assay was used or when it was done); "low" otherwise.

PICO2C:

- *Risk of Bias: Could the conduct or interpretation of the index test have introduced bias?*

• Signaling question 1: Were the index test results interpreted without knowledge of the results of the reference standard?

Consider "yes" if the examiner of the index text was blinded to the results of the reference standard, "no" if reference standard results were not blinded, and "unclear" if no mention of blinding, or if it is not known when the test was done.

• Signaling question 2: If a threshold was used, was it pre-specified?

Consider "yes" as mentioning HBV DNA threshold is part of inclusion criteria for this review.

- Applicability: Are there concerns that the index test, its conduct, or its interpretation differ from the review question?

Rate concerns about applicability as "low", or "unclear" if the type of test used is not reported.

Domain 3: Reference Standard

PICO2A:

- *Risk of Bias: Could the reference standard, its conduct, or its interpretation have introduced bias?*

• Signaling question 1: Is the reference standard likely to correctly classify the target condition?

Answer "no" if the reference test is a non-validated "in-house" method (without citing a previous study validating the method). Answer "unclear" if the reference test used is not described. For the other studies, answer "yes" because although there are several different methods of NAT, the test results are reliable particularly for the high HBV DNA thresholds that the current review targets.

• Signaling question 2: Were the reference standard results interpreted without knowledge of the results of the index test?

Answer "yes" if the examiner of the reference standard was blinded to the results of the index test; "no" if index test results were not blinded. Answer "unclear" if it is not known when the test was done or no notion of blinding was reported.

Risk of bias is rated as "low" if both signaling questions were answered "yes"; "high" if at least one signaling question was answered "no"; and "unclear" if at least one question was rated as "unclear" and no question rated "no".

- Applicability: Are there concerns that the target condition as defined by the reference standard does not match the question?

Since our target condition is high HBV DNA levels defined by the NAT, all studies will be rated as "low concern".

PICO2B and PICO2C:

- Risk of Bias: Could the reference standard, its conduct, or its interpretation have introduced bias?

• Signaling question 1: Is the reference standard likely to correctly classify the target condition?

Answer "yes" if the reference test is performed in infants aged 6-12 months, extended to 24 months in infants who received three doses of HBV vaccine. Answer "unclear" if no mention of timing of testing.

• Signaling question 2: Were the reference standard results interpreted without knowledge of the results of the index test?

Answer "yes" if the examiner of the reference standard was blinded to the results of the index test; "no" if index test results were not blinded. Answer "unclear" if no notion of blinding was reported.

Risk of bias is rated as "low" if both signaling questions were answered "yes"; "high" if at least one signaling question was answered "no"; and "unclear" if at least one question was rated as "unclear" and no question rated "no".

- Applicability: Are there concerns that the target condition as defined by the reference standard does not match the question?

Since our target condition is clinical mother-to-child transmission of HBV defined by the HBsAg or HBV DNA positivity in infants, all studies will be rated as "low concern".

Domain 4: Flow and Timing

PICO2A:

- Risk of Bias: Could the patient flow have introduced bias?

• Signaling question 1: Was there an appropriate interval between the index test and reference standard?

Answer "yes" if both HBeAg and HBV DNA tests were done using the same sample. Answer "no" if the sample used for HBeAg test and the sample used for HBV DNA test were not collected on the same day. Answer "unclear" if information on when HBeAg or HBV DNA testing was performed is missing.

• Signaling question 2: Did all patients in the study receive the same reference standard? Answer "no" if different NAT methods were used for different patients; and "unclear" if NAT method was not defined.

• Signaling question 3: Were all patients included in the analysis?

Answer "yes" if the number of patients enrolled was the same as the number of individual patient data obtained; "no" if the number of individual patient data obtained was smaller than the number of patients enrolled; and "unclear" if the number of patients enrolled was not presented in the original study.

Risk of bias is rated as "low" all signaling questions are answered "yes"; "high" if at least one question is answered "no"; and "unclear" if at least one question was answered "unclear" and no question rated "no".

PICO2B:

- Risk of Bias: Could the patient flow have introduced bias?

• Signaling question 1: Was there an appropriate interval between the index test and reference standard?

Answer "yes" if maternal HBeAg was measured during pregnancy and MCTC was measured between 6 and 12 months. Answer "no" if different from this. Answer "unclear" if timing of HBeAg testing in mothers or MTCT timing of testing is unknown.

• Signaling question 2: Did all patients in the study receive the same reference standard? Answer "yes" if the markers used to assess MTCT and timing of its assessment were the same for all infants.

• Signaling question 3: Were all patients included in the analysis?

Answer "yes" if the number of patients enrolled was the same as the number of individual patient data obtained; "no" if the number of individual patient data obtained was smaller than the number of patients enrolled; and "unclear" if the number of patients enrolled was not presented in the original study.

Risk of bias is rated as "low" all signaling questions are answered "yes"; "high" if at least one question is answered "no"; and "unclear" if at least one question was answered "unclear" and no question rated "no".

PICO2C:

- Risk of Bias: Could the patient flow have introduced bias?

• Signaling question 1: Was there an appropriate interval between the index test and reference standard?

Answer "yes" if maternal HBV DNA was measured during pregnancy and MCTC was measured between 6 and 12 months. Answer "no" if different from this. Answer "unclear" if timing of HBV DNA testing in mothers or MTCT timing of testing is unknown.

• Signaling question 2: Did all patients in the study receive the same reference standard? Answer "yes" if the markers used to assess MTCT and timing of its assessment were the same for all infants.

• Signaling question 3: Were all patients included in the analysis?

Answer "yes" if the number of patients enrolled was the same as the number of individual patient data obtained; "no" if the number of individual patient data obtained was smaller than the number of patients enrolled; and "unclear" if the number of patients enrolled was not presented in the original study.

Risk of bias is rated as "low" all signaling questions are answered "yes"; "high" if at least one question is answered "no"; and "unclear" if at least one question was answered "unclear" and no question rated "no".

8.3. Appendix C: Data extraction sheet protocol

• Publication details

- ID screening
- First author
- Year
- Journal
- Language

• Methods

- Country
- Study main objective
- Study design
- Recruitment period
- Recruitment setting (center or regional details, number of study sites)
- Inclusion criteria
- Exclusion criteria
- Maternal HBV DNA: Type of sample
- Maternal HBV DNA: When sample was taken
- Maternal HBV DNA: Type of assay, commercial name
- Maternal HBV DNA: Qualitative or quantitative
- Maternal HBeAg: Type of sample
- Maternal HBeAg: When sample was taken
- Maternal HBeAg: Type of assay, commercial name
- Maternal HBeAg: Qualitative or quantitative
- Maternal HBeAg : Limit of detection of the assay used
- Clinical endpoint for MTCT is reported (Yes/No)

- Infant HBsAg: Type of sample
- Infant HBsAg: When sample was taken
- Infant HBsAg: Type of assay, commercial name
- Infant HBV DNA: Type of sample
- Infant HBV DNA: When sample was taken
- Infant HBV DNA: Type of assay, commercial name
- Infant HBV DNA: Qualitative or quantitative
- Infant HBV DNA: Limit of detection of the assay used

• Preventive measures

- Maternal antiviral therapy during pregnancy (type of drug, duration of treatment)
- First dose of HBV vaccine: timely (≤24h) or delayed (>24h)
- HBIG at birth
- 3 doses of hepatitis B vaccine completed
- Other

• No. of participants at enrolment

- No. of women eligible for HBsAg screening
- No. of women screened for HBsAg
- No. of women tested positive for HBsAg
- No. of women who had both HBV DNA & HBeAg tested
- No. of women tested for HBV DNA
- Maternal HBV DNA threshold used
- No. of women with high viral load
- No. of women with low viral load
- No. of women screened for HBeAg
- No. of women tested positive for HBeAg
- No. of women tested negative for HBeAg
- Women's characteristics

- Define the population for the following characteristics (ideally this should be women who had both HBV DNA & HBeAg tested, but this may be often those who tested positive for HBsAg, irrespective of subsequent HBeAg/HBV DNA tests)
- Mean (SD) or median (IQR) maternal age
- Numerator/denominator by HBV viral genotypes
- Numerator/denominator by HIV status
- Numerator/denominator by HCV status
- Numerator/denominator by HDV status
- Outcomes 1: sensitivity and specificity of HBeAg to diagnose high viremia
- Maternal HBV DNA: i) For quantitative test: HBV DNA threshold to dichotomize into high or low viral load; ii) For qualitative test: Limit of detection
- No. with TP1 (high VL & HBeAg-pos)
- No. with FN1 (high VL & HBeAg-neg)
- No. with TN1 (low VL & HBeAg-neg)
- No. with FP1 (low VL & HBeAg-pos)
- Sensitivity of HBeAg to identify mothers with a high HBV viral load (TP / (TP+FN))
- No. of women with indeterminate result for HBeAg (if any)
- Infants' characteristics
 - No. of infants tested for HBsAg at the age of 6-12 months
 - No. of infants tested for HBV DNA at the age of 6-12 months
 - Outcomes 2-1: sensitivity and specificity of maternal HBeAg during pregnancy to predict MTCT (only those reporting MTCT endpoint)
 - Definition of MTCT: infant HBsAg or HBV DNA, & in which period for the following data
 - No. with TP2-1 (MTCT & maternal HBeAg-pos)

- No. with FN2-1 (MTCT & maternal HBeAg-neg)
- No. with TN2-1 (No MTCT & maternal HBeAg-neg)
- No. with FP2-1 (No MTCT & maternal HBeAg-pos)
- Sensitivity of maternal HBeAg to predict MTCT (TP/ (TP+FN))
- Specificity of maternal HBeAg to predict MTCT (TN / (TN+FP))
- Outcomes 2-2: sensitivity and specificity of maternal high HBV DNA levels during pregnancy to predict MTCT (only those reporting MTCT endpoint)
- Definition of MTCT: infant HBsAg or HBV DNA, & in which period for the following data
- Maternal HBV DNA: i) For quantitative test: HBV DNA threshold to dichotomize into high or low viral load; ii) For qualitative test: Limit of detection
- No. with TP2-2 (MTCT & maternal high VL)
- No. with FN2-2 (MTCT & maternal low VL)
- No. with TN2-2 (No MTCT & maternal low VL)
- No. with FP2-2 (No MTCT & maternal high VL)
- Sensitivity of maternal high VL to predict MTCT (TP / (TP+FN))
- Specificity of maternal high VL to predict MTCT (TN / (TN+FP))

• Other

- Funding by industry
- Comments
- Need to contact an author for individual data
- Need to contact an author for aggregated data
- Only when there is a need to contact the author
- Name of the author contacted
- Title of the author contacted (e.g. PhD)
- Affiliation of the author contacted
- Email address of the author contacted

- Question to ask to the author contacted
- Was the author contacted?
- Reply from the author contacted

• Decision

- Eligibility for the review
- Reason for non-eligibility
Appendix D: Detailed QUADAS2 results for studies included in 8.4. PICO2A

Cow Risk	😕 High Risl	с ?	Unclear Risk				
Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Bai H, 2010	$\overline{\mathbf{S}}$?	?	\odot	\odot	\odot	\odot
Bissinger, A, 2013	?	?	?	8	\odot	\odot	
Cai J, 2005		?	?	\odot	\odot	\odot	©
Cai S, 2009		?	?	$\overline{\mbox{\scriptsize (s)}}$	\odot	\odot	
Carey I, 2017	$\overline{\mbox{\scriptsize (S)}}$?	?	\odot	$\overline{\otimes}$	\odot	
Carey I, 2018	$\overline{\mathfrak{S}}$?	?	\odot	\odot	\odot	\odot
Chang C , 2017	$\overline{\mathfrak{S}}$?	?	?	$\overline{\otimes}$?	\odot
Chen T, 2018	$\overline{\mathfrak{S}}$?	?	$\overline{\otimes}$	\odot	\odot	\odot
Chen T, 2018	$\overline{\mathfrak{S}}$?	?	?	8	\odot	
Chen ZX, 2017	$\overline{\mathfrak{S}}$?	?	$\overline{\otimes}$	$\overline{\otimes}$	\odot	\odot
Cheng S, 2006	$\overline{\mathfrak{S}}$?	?	?	\odot	\odot	\odot
Cheung K, 2019		?	?	$\overline{\otimes}$	\odot	?	\odot
Chotun N, 2017	$\overline{\mathfrak{S}}$?	?	\odot	\odot	\odot	\odot
Dervisevic S, 2007		?	?	\odot	\odot	?	
Ding Y, 2013		?	?	?	\odot	\odot	\odot
Dolman G, 2018	$\overline{\mathfrak{S}}$?	?	?	\odot	?	\odot
Dopico E, 2013	$\overline{\otimes}$?	?	?	\odot	\odot	\odot
Dyson J, 2014		?	?	$\overline{\mathfrak{S}}$	\odot	?	
Eilard A, 2019	$\overline{\otimes}$?	?	?	\odot	\odot	\odot
Elefsiniotis I, 2007	$\overline{\otimes}$?	?	$\overline{\mathbf{S}}$	\odot	?	\odot
Foaud H, 2019	$\overline{\otimes}$?	?	$\overline{\mbox{\scriptsize (c)}}$	\odot	\odot	\odot
Fujiko M, 2015	8	?	?	?	\odot	<u></u>	\odot
Godbole G, 2013	\odot	?	?	$\overline{\odot}$	\odot	\odot	\odot
Guo F, 2007	\odot	?	?	\odot	\odot	\odot	\odot
Han Y, 2007	?	?	?	\odot	\odot	\odot	\odot
Hao X, 2015	?	?	?	\odot	\odot	\odot	\odot
Hu Q, 2007	\odot	?	?	?	\odot	<u></u>	\odot
Huang L, 2014	$\overline{\mathfrak{S}}$?	?	\odot	\odot	\odot	
Jackson V, 2015	$\overline{\mathfrak{S}}$?	?	$\overline{\otimes}$	8	?	
Jin C, 2007	?	?	?	\odot		?	\odot
Johannessen A, 2017	?	?	?	$\overline{\odot}$	\odot	\odot	\odot
Köse, S, 2011	$\overline{\otimes}$?	?	?	$\overline{\mbox{\scriptsize (c)}}$?	\odot
Kubo, A, 2014		?	?	$\overline{\odot}$	\odot	$\overline{\mbox{\scriptsize (s)}}$	
Lao, T , 2012	$\overline{\mbox{\scriptsize (S)}}$?	?	?	\odot	?	\odot
Latthaphasavang, V, 2019	8	?	?	$\overline{\otimes}$		\odot	
Lee, L, 2015	\odot	?	?	$\overline{\mathbf{S}}$	\odot		
Li Xue-Li, 2018	$\overline{\mathbf{O}}$?	?	\odot	\odot		
Li Yan, 2013	$\overline{\mathbf{O}}$?	?	\odot	\odot	\odot	\odot

Liang Pei-Song, 2017	\odot	?	?	$\overline{\mbox{\scriptsize (S)}}$	\odot	\odot	\odot
Lin Jian, 2002	?	?	?	\odot	\odot	\odot	\odot
Liu CP, 2015	8	?	?	?		\odot	
Liu Hui-Yuan, 2013	8	?	?	?	\odot	\odot	\odot
Liu, Yingxia, 2016	8	?	?	$\overline{\otimes}$	8	\odot	\odot
Lu Hui-Fen, 2009		?	?	\odot	\odot	\odot	\odot
Lunel-Fabiani, F, 2018	\odot	?	?	$\overline{\otimes}$	\odot	\odot	\odot
Ma Yan-Hua, 2014	8	?	?	?	\odot	\odot	\odot
Michitaka, Kojiro, 2012	\odot	?	?	\odot	\odot	\odot	\odot
Peng Ning, 2012	?	?	?	\odot	\odot	\odot	\odot
Peng, Songxu, 2019	$\overline{\otimes}$?	?	$\overline{\otimes}$	\odot	\odot	\odot
Pirillo, M, 2007	$\overline{\otimes}$?	?	$\overline{\otimes}$	\odot	\odot	\odot
Pirillo, MF, 2015	$\overline{\otimes}$?	?	$\overline{\otimes}$	©	\odot	\odot
Punzalan, C M, 2012	$\overline{\otimes}$?	?	?	\odot	?	\odot
Rouet, F, 2004	$\overline{\otimes}$?	?	$\overline{\otimes}$	\odot	\odot	\odot
Samadi Kochaksaraei, G, 2016	8	?	?	8		\odot	©
Ségéral, O, 2018	?	?	?	\odot	\odot	\odot	\odot
Sellier, PO, 2017	$\overline{\mathbf{S}}$?	?	$\overline{\mbox{\scriptsize (c)}}$	8	\odot	\odot
Seo, Kwang Il, 2018	$\overline{\mbox{\scriptsize (S)}}$?	?	$\overline{\mbox{\scriptsize (s)}}$	8		\odot
Shao, Z, 2011	8	?	?	\odot	\odot	\odot	\odot
Sheng, Q, 2018	\odot	?	?	?	\odot	\odot	\odot
Shi Yan-Yan, 2012	\odot	?	?	\odot	\odot	\odot	\odot
Söderström, A, 2003	$\overline{\otimes}$?	?	?	\odot	\odot	\odot
Tang Yong-Chun, 2013	$\overline{\otimes}$?	?	$\overline{\otimes}$	8	$\overline{\otimes}$	
Tang, A, 2018	\odot	?	?	?	\odot	\odot	
Thilakanathan, C, 2018	\odot	?	?	$\overline{\otimes}$	\odot	\odot	\odot
van Zonneveld, M, 2003	8	?	?	$\overline{\mbox{\scriptsize (s)}}$	8	?	\odot
Wang Feng, 2009	$\overline{\mathbf{i}}$?	?	\odot	\odot	\odot	\odot
Wang Jing, 2018	8	?	?	$\overline{\mathbf{i}}$	8	\odot	\odot
Wang Miao, 2018	\odot	?	?	?		?	\odot
Wang Xing-Xing, 2015	8	?	?	$\overline{\mathbf{i}}$	\odot	\odot	\odot
Wang Xue-Ling, 2015	$\overline{\otimes}$?	?	\odot	\odot	\odot	\odot
Wang Zhi-Qiang, 2018	8	?	?	\odot	\odot	\odot	\odot
Wang, Jing, 2015	$\overline{\otimes}$?	?	\odot	\odot	\odot	\odot
Wang, L, 2016		?	?	$\overline{\otimes}$?	
Wei Kai-Ping, 2017	$\overline{\otimes}$?	?	\odot	\odot	\odot	\odot
Wiseman, E, 2009	$\overline{\mathfrak{S}}$?	?	$\overline{\otimes}$	8	\odot	
Xu Hui-Li, 2008	$\overline{\otimes}$	\odot	\odot	\odot	©	\odot	\odot
Xu, Chenyu, 2018	\odot	?	?	\odot	\odot	\odot	
Yin, Yu-zhu, 2013	$\overline{\otimes}$?	?	$\overline{\otimes}$	\odot	\odot	\odot
Zhang Li, 2017	$\overline{\otimes}$?	?	\odot	\odot	\odot	\odot
Zhang Qing, 2009	$\overline{\otimes}$?	?	?	\odot	\odot	\odot
Zheng Hong, 2010	$\overline{\otimes}$?	?	$\overline{\otimes}$	\odot	\odot	\odot
Zhu Bao-Shen, 2013	$\overline{\otimes}$?	?	\odot	\odot	\odot	\odot

8.5. Appendix E: Detailed QUADAS2 results for studies included in PICO2B

🙂 Low Risk 🛛 😕 High Risk		? Unclear Risk						
Study	RISK OF BIAS				APPLICABILITY CONCERNS			
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	
Chen Z, 2017	\odot	?	?	<u>(;)</u>	\odot	\odot	<u>(</u>	
Chotun N, 2017	$\overline{\mathfrak{S}}$?	?	$\overline{\mbox{\scriptsize (s)}}$	\odot	?	\odot	
Ding Y, 2013	\odot	?	?	\odot	\odot	\odot	\odot	
Foaud H, 2019	$\overline{\mbox{\scriptsize (c)}}$?	?	$\overline{\mbox{\scriptsize (c)}}$		<u></u>	<u></u>	
Latthaphasavang, V, 2019	8	?	?	$\overline{\ensuremath{\mathfrak{S}}}$	8			
Lee, L, 2015	8	?	?	$\overline{\ensuremath{\mathfrak{S}}}$	\odot	$\overline{\odot}$	\odot	
Liu CP, 2015	8	?	?	\odot	\odot	\odot	\odot	
Liu, Yingxia, 2016	8	?	?	$\overline{\otimes}$		\odot	\odot	
Lunel-Fabiani, F, 2018		?	?	$\overline{\otimes}$	8			
Peng, Songxu, 2019	8	?	?	$\overline{\otimes}$	8	?		
Shao, Z, 2011	8	?	?	$\overline{\ensuremath{\mathfrak{S}}}$	8	\odot	\odot	
Thilakanathan, C, 2018		?	?	$\overline{\ensuremath{\mathfrak{S}}}$	8			
Wang, Jing, 2015	8	?	?	$\overline{\ensuremath{\mathfrak{S}}}$	\odot	\odot	\odot	
Wiseman, E, 2009	8	?	?	$\overline{\mbox{\scriptsize (c)}}$	\odot	\odot	\odot	
Yin, Yu-zhu, 2013	8	?	?	\odot	\odot	\odot	\odot	
Zhu Bao-Shen, 2013	8	?	?	\odot				

8.6. Appendix F: Detailed QUADAS2 results for studies included in PICO2C

Cow Risk OHigh Risk		? Unclear Ris	k				
Study	RISK OF BIAS	5			APPLICABILITY CONCERNS		
	PATIENT SELECTIO N	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMIN G	PATIENT SELECTIO N	INDE X TEST	REFERENC E STANDARD
Chen Z, 2017	8	?	?	$\overline{\mathbf{i}}$	\odot	\odot	<u>(</u>)
Chotun N, 2017	$\overline{\otimes}$?	?	8	\odot	\odot	\odot
Ding Y, 2013	\odot	?	?	\odot	\odot	\odot	\odot
Latthaphasavang, V, 2019	8	?	?		\odot		
Lee, L, 2015	8	?	?	$\overline{\mathbf{i}}$	8	\odot	\odot
Lui CP, 2015	8	?	?	\odot	\odot	?	\odot
Lunel-Fabiani, F, 2018		?	?	$\overline{\otimes}$			
Peng, Songxu, 2019	$\overline{\otimes}$?	?	$\overline{\otimes}$	\odot	\odot	\odot
Shao, Z, 2011	8	?	?	$\overline{\mathbf{S}}$	\odot	\odot	\odot
Thilakanathan, C, 2018		?	?	$\overline{\otimes}$		\odot	
Wiseman, E, 2009	8	?	?	\odot	\odot	\odot	\odot
Yin, Yu-zhu, 2013	8	?	?	\odot	\odot	\odot	\odot
Zhu Bao-Shen, 2013	8	?	?	\odot	\odot	\odot	\odot

😇Low Risk 😕 High Risk ? Unclear Risk

8.7. Appendix G: Funnel plots for publication bias

Appendix G.1. Funnel plot for all studies included in the bivariate meta-analysis of the performance of HBeAg to identify maternal HBV DNA $\geq 5 \log 10 \text{ IU/mL}$















Appendix G.5. Funnel plot for all studies included in the bivariate meta-analysis of the performance of maternal HBV DNA \geq 5 log10 IU/mL during pregnancy to predict MTCT of HBV



