

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B VIRUS: Guidelines on antiviral prophylaxis in pregnancy

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Web Annex A. Systematic review of the efficacy and safety of antiviral therapy during pregnancy

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ACRONYMS AND ABBREVIATIONS

0.000	
3TC	lamivudine
ADV	adefovir dipivoxil
ALT	alanine aminotransferase
ANC	antenatal care
APASL	Asian Pacific Association for the Study of the Liver
CI	confidence interval
СК	creatine kinase
ETV	entecavir
FTC	emtricitabine
GHSS	Global Health Sector Strategy (on viral hepatitis)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immunoglobulin
HBV	hepatitis B virus
НСС	hepatocellular carcinoma
HDV	hepatitis D virus
HIV	human immunodeficiency virus
ITT	intention to treat
LdT	telbivudine
МТСТ	mother-to-child transmission
OR	odds ratio
PICO	Population, Intervention, Comparison, Outcome
РМТСТ	prevention of mother-to-child transmission
PPA	per protocol analysis
RCT	randomized controlled trial
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate
ULN	upper limit of normal
WHO	World Health Organization

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 and hepatocellular carcinoma (HCC). The regions with the highest prevalence of chronic HBV infection are the Western Pacific and African regions (*WHO*, 2017a). In 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis, which calls for the elimination of HBV worldwide as a public health threat by 2030, to be accomplished through reducing the incidence of chronic HBV infection by 90%, and its mortality by 65% (*WHO*, 2016).

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 chronic HBV infection (*Edmunds et al., 1993*). Moreover, the risk of developing chronic liver disease, including HCC, may be higher in those with established chronic HBV infection through MTCT compared to those who ended up with chronic HBV infection through horizontal transmission later in life (*Chang 2008; Shimakawa et al., 2013*). To decrease the incidence of chronic HBV infection and eventual chronic liver disease, WHO recommends that all infants be vaccinated against the virus, with the first dose being administered within 24 hours of birth (i.e. timely birth dose vaccination) (*WHO, 2017b*). Since this recommendation made by WHO in 2009, there has been a significant uptake of the HBV birth dose vaccination globally; however, there are many countries, specifically in highly endemic areas in Africa, where coverage of timely administration is very low (*Miyahara et al., 2016; WHO, 2009; WHO, 2017a*).

The birth dose vaccination is meant not only to prevent perinatal MTCT that usually happens at the time of birth, but also to prevent horizontal transmission during early childhood. However, the birth dose vaccination alone may be inadequate to prevent MTCT in infants born to mothers with high replication of HBV. In some countries, therefore, hepatitis B immunoglobulin (HBIG) is additionally administered to babies born to HBV-infected mothers. However, this combined active and passive immunoprophylaxis does not completely prevent all MTCT (*Chen et al., 2012*). The risk of immunoprophylaxis failure is closely correlated with hepatitis B e-antigen

(HBeAg) positivity as well as an elevated viral load in pregnant women (*Keane et al., 2016; Machaira et al., 2015; Wen et al., 2013*). Consequently, MTCT remains a significant contributor to HBV incidence in all regions, and supplementary interventions to further decrease this transmission are urgently needed.

AIM

Rationale

To date, the major international guidelines for the management of chronic HBV infection all recommend the administration of antiviral therapy to pregnant women with high HBV DNA levels to prevent MTCT (*AASLD 2018; EASL 2017; APASL 2016*); all guidelines recommend tenofovir disoproxil fumarate (TDF), and the Asian Pacific Association for the Study of the Liver (APASL) also recommends telbivudine (LdT). The Food and Drug Administration (FDA) of the United States has classified TDF, LdT, and emtricitabine (FTC) as being category B (i.e. no current evidence of a risk to the fetus during pregnancy; however, robust controlled studies are lacking) (*see* Table 1).

	International	guidelines fo	r PMTCT	FDA	Comment
	AASLD ¹	EASL ²	APASL ³	category	Comment
Adefovir dipivoxil (ADV)	ND	ND	ND	С	-
Emtricitabine (FTC)	ND	ND	ND	В	-
Entecavir (ETV)	ND	ND	ND	С	-
Lamivudine (3TC/LAM)	+	+	+	С	-
Telbivudine (LdT)	+	+	+++	В	-
Tenofovir alafenamide fumarate (TAF)	ND	ND	ND	ND	-
Tenofovir disoproxil fumarate (TDF)	+++	+++	+++	В	-
Comment	-	-	-	-	-

Table 1. International recommendations for prevention of mother-to-child transmission(PMTCT) using antiviral therapy

+: Presented in the guidelines; +++: presented as a recommended agent; ND: not described

¹ "The only antivirals studied in pregnant women are lamivudine, telbivudine, and TDF. Of these three options, TDF is preferred to minimize the risk of emergence of viral resistance during treatment. Interim studies show high efficacy of TDF in preventing MTCT." (a quotation from the respective guidelines)

 $^{^{2}}$ "Reproduction studies have been performed in animal and in humans with TDF and LdT and revealed no evidence of harm to the fetus due to these drugs. Among the last two agents, TDF should be preferred, because it has a better resistance profile and more extensive safety data in pregnant HBV-positive women." (a quotation from the respective guidelines)

³ For reduction of the risk of mother-to-infant transmission that occurs during the perinatal period, short-term maternal nucleoside analogues (NAs) starting from 28 to 32 weeks of gestation is recommended using either tenofovir or telbuvidine for those mothers with HBV DNA above 6–7 log10 IU/mL. In pregnant women with chronic HBV infection who need antiviral therapy, tenofovir is the drug of choice for mothers indicated for antiviral treatment during the first through third trimester of pregnancy. It is a pregnancy category B drug with adequate safety data in HIV-positive women and least chance of viral resistance.

Although the WHO HBV treatment guidelines in 2015 contained a systematic review and meta-analysis on the efficacy, safety and cost–effectiveness of antiviral therapy administered during pregnancy for the prevention of MTCT (PMTCT), this review had some limitations, which dissuaded WHO from making a formal recommendation for its use at that time. In addition, only one observational study that examined the efficacy of tenofovir for PMTCT was available for inclusion; tenofovir is considered a key first-line antiviral therapy for chronic HBV infection given its high potency, higher barrier to drug resistance and evidence of safety in pregnancy (*WHO*, *2015*).

An updated systematic review and meta-analysis on this topic is now pertinent for various reasons. First, there have been important new findings with regard to maternal and infant safety of HBV antiviral medications administered during pregnancy; some recent studies have further evaluated the risk of postpartum hepatic flare in the mother after cessation of treatment as well as changes in bone mineral density in the infant (*Pan et al., 2016; Kourtis et al., 2018; Jourdain et al., 2018*). Second, recent epidemiological and modelling studies have demonstrated the likely inadequacy of the birth dose vaccination with or without HBIG administration, alone, to reduce the incidence of HBV enough in order to achieve the 2030 elimination goals (*Nayagam et al., 2016; Hutin et al., 2018*). Third, in countries that have achieved a very high uptake of birth dose vaccination, recommendations are now needed for a further reduction in MTCT.

Objectives

The primary objective is to provide an up-to-date summary estimate of the efficacy, and an overview of the safety of antiviral medicines administered during pregnancy for the reduction of MTCT of HBV; this is meant to inform the WHO's new guidelines on PMTCT of HIV.

Specific objectives included:

exploration of the sources of between-study heterogeneity in the efficacy of antiviral

treatment, done through subgroup analyses in which there is stratification by the following variables:

- maternal HBV viral load threshold at inclusion (e.g. >5 log10 IU/mL, >6 log10 IU/mL, >7 log10 IU/mL)
 - Note: this refers to the minimum threshold imposed by each individual study protocol and does not guarantee that each woman enrolled in the study has a viral load at that level. This measure, rather than the mean or median viral load of women in each study, was preferred, as this would have a direct implication for practice
- maternal hepatitis B e antigen (HBeAg) serostatus
- stage of pregnancy
 - o 1st, 2nd vs 3rd trimester
 - median <28 weeks, median 28 weeks (with maximum range of 26–30 weeks), median >28 weeks
- coinfection with hepatitis D virus (HDV) or human immunodeficiency virus (HIV);
- type of antiviral therapy administered
- type of other preventive measures provided (infant hepatitis B vaccines with or without timely administration of birth dose, HBIG and a combination of these)
- WHO region;
- providing an updated Grading of Recommendations Assessment, Development and Evaluation (GRADE) review for the use of antiviral medication for reduction of HBV MTCT;
- identifying gaps in research.

METHODS

Narrative review question

Are antiviral therapies efficacious and safe at reducing MTCT of HBV if administered during pregnancy in women with chronic HBV infection?

PICO question

Population

Pregnant women with chronic HBV infection

Chronic HBV infection was defined as HBsAg seropositivity on two occasions at least 6 months apart. However, because new HBV infection in adults is 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 [ANC]) in women living in highly prevalent countries was assumed to reflect chronic HBV infection (*Evans et al., 1998*).

Intervention

Maternal treatment with antiviral therapy during pregnancy with or without infant birth dose vaccination and/or HBIG.

- The following antiviral therapies were considered for inclusion:
 - adefovir dipivoxil (ADV)
 - o emtricitabine (FTC)
 - o entecavir (ETV)
 - lamivudine (3TC/LAM)
 - telbivudine (LdT)
 - tenofovir alafenamide fumarate (TAF)
 - o TDF.

Antiviral therapy during pregnancy	Timely administration of birth dose vaccine	Timely administration of HBIG	Completion of three or four doses of infant hepatitis B vaccines
None or placebo	None	None	None
None or placebo	Yes	None	None
None or placebo	None	Yes	None
None or placebo	None	None	Yes
None or placebo	Yes	Yes	None
None or placebo	Yes	None	Yes
None or placebo	None	Yes	Yes
None or placebo	Yes	Yes	Yes

Comparison Table 2. Comparison groups considered in PICO1

Outcomes

The primary outcome of interest will be MTCT of HBV, as indicated by infant HBsAg positivity at 6–12 months of life.

Further infant outcomes of interest, specified in the study protocol, included:

- infant HBV DNA positivity at 6–12 months of life
- any infant adverse event, such as
- neonatal death (within 28 days of life [*WHO*, 2006])
- preterm birth (<37 weeks of gestational age [*WHO*, 2018])
- congenital abnormality
- Apgar score at 1 minute of life
- measurement of bone density of infants.

Maternal outcomes of interest, specified in the study protocol, included:

- any maternal adverse event, including:
 - miscarriage (<28 weeks gestational age, [WHO, https://www.who.int/maternal_child_adolescent/epidemiology/stillbirth/en/])
 stillbirth (>=28 weeks gestational age, [WHO, WHO, age, [WHO, age, [WHO,
 - https://www.who.int/maternal child adolescent/epidemiology/stillbirth/en/.])

- HBV flare after discontinuation of treatment (e.g. elevated HBV DNA and/or elevated ALT)
- postpartum haemorrhage
- antiviral resistance.

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

Randomized controlled trials (RCTs) and non-randomized comparative studies were considered for this analysis. Case series without a comparison group were excluded. Studies published in any language were considered. Non-RCTs with a high risk of bias (i.e. a score on the Newcastle-Ottawa scale of <=5 were excluded from analysis. Studies published till 28 March 2019 were included. Studies reported as conference abstracts only were not considered.

Search strategy

The search terms employed covered hepatitis B infection AND antiviral therapy, AND pregnancy. 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 exact search strategies used are given in **Appendix A**.

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

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 (ALF and KY). Following selection of potentially eligible studies, a 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 persons, a third person (YS) was consulted in order to make the final decision. For 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: CRD42019134614.

Quality appraisal

RCTs were assessed using the Cochrane Collaboration risk of bias tool (*Higgins et al., 2011*) (*see* **Appendix B**). Observational comparative studies that are included were evaluated using the Newcastle–Ottawa Scale (*Wells et al., 2014*) (*see* **Appendix C**). For both RCTs and non-RCTs, each study was independently assessed by two reviewers, with discrepancies being discussed and resolved with the involvement of a third reviewer (YS) when necessary.

Data extraction

The data were extracted from the selected studies by the two independent reviewers using a pre-piloted data extraction form; the information that was extracted can be found in **Appendix D**. 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 (AF) 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 authors explicitly stated in their article that there was overlap, or if the authors responded to the email enquiry confirming overlap, or if the author did not respond, then only the data extracted from the most recently published article were used in data analysis. If authors responded negating any patient overlap between articles then data extracted from all 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.

GRADE review process

For each examined treatment comparison, the quality of the evidence studied was evaluated using the GRADE methodology (*The GRADE Working Group, 2004*). We used this tool to evaluate the risk of bias, inconsistency (high heterogeneity), imprecision (confidence intervals), indirectness (use of surrogate outcomes), reporting and publication bias, and other factors, within each intervention group (i.e. antiviral treatment used as the intervention) from which the evidence was summarized within the review. 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 and 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 the GRADE criteria:

- Limitations this was rated as "not serious" only in the following circumstances: for RCTs, if >50% of the included studies had "low risk of bias" for the majority of criteria according to the Cochrane Collaboration risk of bias assessment tool; for non-RCTs, if >50% of studies had a "low risk of bias" assessment as per the Newcastle–Ottawa risk of bias assessment tool
- *Inconsistency* I²<30%= "not serious", I²>=30% and <60%="serious", I²>60%= "very serious"
- *Indirectness* all studies were considered to have "no serious" issues as this was guaranteed by the PICO question specifications
- Imprecision for odds ratios (ORs), an absolute range in the 95% confidence intervals

of 0.5 was considered as "no serious", a range $\geq=0.5$ and <1.0 was considered as "serious", and a range of $\geq=1$ was considered as "very serious". For risk difference estimates, an absolute range in the 95% confidence intervals of 0.1 was allowed, with the upper range going only as high as 0.05 (indicating a potential harmful effect of treatment in 5% of persons) for a set of studies to be considered as having "no serious" limitations.

- *Publication bias* An Egger's test with p value of <0.05 led to assumption of "possible evidence of publication bias or small study effects" if ORs had been estimated. Where risk difference estimates, only, were estimated, an obviously asymmetrical funnel plot led to the same assumption.
- *Other* a non-RCT study set could be upgraded for "magnitude of effect" if the protective OR was <0.5 and was not considered as imprecise.

Data synthesis

All statistical analyses were done using STATA version 13 (StataCorp LP, CollegeStation, TX). The pooled OR was generated for the efficacy of antiviral therapy. For safety outcomes, the pooled risk difference was generated. If more than three original studies were eligible for the analysis/subanalysis, then pooling was done using Der Simonian and Laird random-effect models. Where possible, data were analysed according to intention to treat (ITT) – meaning that patients would be included in the group they were initially randomized to, regardless of dropout, loss to follow up or regimen changes. Heterogeneity was estimated using the Mantel–Haenszel model. The amount of overall heterogeneity between studies was measured using the I² statistic. Where the number of eligible studies (i.e. at least 10 studies, *Sterne et al., 2011*) and their level of heterogeneity allowed, funnel plots were used to examine the risk of publication bias. When pooled ORs had been estimated, the Egger test was used to assess asymmetry.

RESULTS

Summary of included studies

The search strategy identified 7419 papers across English and Chinese databases. An additional 44 articles were manually included. After excluding 2894 articles that were duplicates, 4569 articles were screened and 595 papers were assessed in full text. Finally, 136 original studies were potentially eligible; however, seven of these were deemed at a very high risk of bias and were excluded from the quantitative analysis in this review (*see* Fig. 1). Although the objectives of this meta-analysis as well as its search strategy included seven different treatments of interest, only studies including TDF 300 mg, LAM 100–150 mg, LdT 100 mg and 600 mg, and ADV 10 mg and 500 mg were found eligible. No studies that investigated any regimens with FTC, ETV, TAF were included (Table 3).

	Excluded from analysis because of high risk of bias	# Original studies included *(unique treatment groups)	Type of analysis presented in this report
Tenofovir disoproxil fumarate (TDF) 300 mg	 1 original study (1 treatment arm) Kochaksaraei GS, 2016 	19 (25)	Qualitative overview (study characteristics), primary analysis, subgroup analysis, safety analysis, GRADE evidence profile
Lamivudine (LAM) 100–150 mg	 2 original studies (each with 1 treatment arm van Zonneveld, 2003 Liu CP, 2015 	40 (44)	Qualitative overview (study characteristics), primary analysis, subgroup analysis, safety analysis, GRADE evidence profile
Telbivudine (LdT) 600 mg	 4 original studies (each with 1 treatment arm) Chen YL, 2014 Liu CP, 2015 Luo DX, 2017 Zhang R, 2016 	83 (97)	Qualitative overview (study characteristics), primary analysis, subgroup analysis, safety analysis, GRADE evidence profile
Telbivudine (LdT) 100 mg	1 original study (1 treatment arm) • Cao YF, 2018	2 (2)	Quantitative and qualitative descriptive summary
Adefovir dipivoxil (ADV) 500 mg	None	1(1)	Quantitative and qualitative descriptive summary
Adefovir dipivoxil (ADV) 10 mg	None	1 (1)	Quantitative and qualitative descriptive summary

Table 3. Excluded and included studies by treatment, with summary of analyses types presented

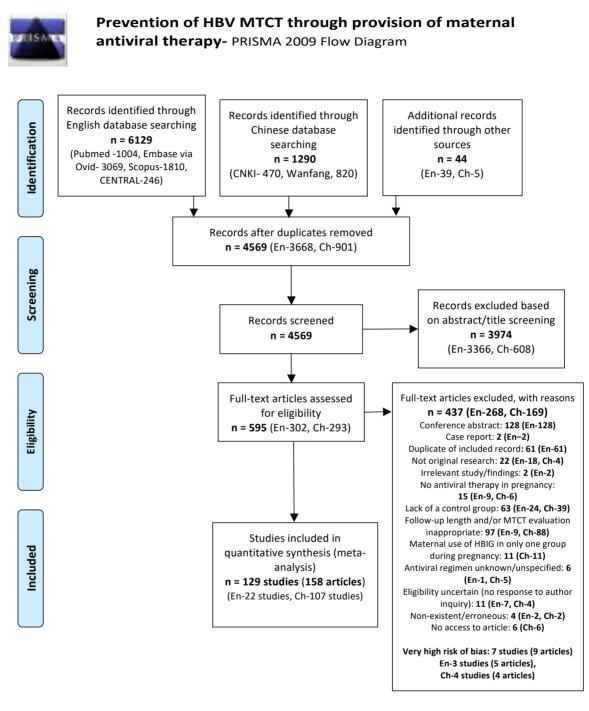
*The total number of original studies is 129. However, this adds up to 146 due to the fact that some studies included multiple types of treatment.

Very few of the RCTs included presented adequate details of loss to follow up (7/33) (*Bai HL*, 2013; *Feng Y*, 2018; *Jourdain G*, 2018; *Lin Y*, 2018; *Pan CQ*, 2016; *Xu WM*, 2009; *Zhang LJ*, 2009), which limited our ability to perform ITT meta-analysis systematically; therefore, per protocol analysis (PPA) was considered throughout (Table 4).

		TDF 300 mg	LAM 100-150 mg	LdT 600 mg
Efficacy	MTCT (defined as infants'	Yes	Yes	Yes
(main	HBsAg)			
analysis)	MTCT (defined as infants'	Yes	Yes	Yes
	HBV DNA)			
Efficacy	By trimester of treatment	Yes	Yes	Yes
(subgroup	start			
analysis)	By median weeks' gestation	Yes	Yes	Yes
	at the time of treatment start			
	By maternal HBV DNA	Yes	Yes	Yes
	level specified in the study			
	inclusion criteria			
	By maternal HBeAg status	Yes (HBeAg-	Yes (HBeAg-	Yes (HBeAg-
		positive only)	positive vs mixed	positive vs mixed
			results)	results)
	By coinfection with HDV	No	No	No
	By coinfection with HIV	No	No	No
	By infant	Yes (birth dose and	Yes (birth dose and	Yes (birth dose and
	immunoprophylaxis regimen	HBIG within 12 h	HBIG within 12 h vs	HBIG within 12 h
		vs 24 h)	24 h)	vs 24 h)
	By the timing of treatment	Yes	Yes	Yes
	discontinuation postpartum			
	(ad hoc)			
	By WHO region	No	No	No
Infant	Neonatal deaths	Yes	Yes	Yes
safety	Prematurity	Yes	Yes	Yes
	Congenital abnormalities	Yes	Yes	Yes
	Bone mineral density	Narrative only	No	No
Maternal	Fetal demise	Yes	Yes	Yes
safety	Postpartum haemorrhage	Yes	Yes	Yes
	Antviral resistance	Narrative only	Narrative only	Narrative only
	HBV flare after treatment	Yes	Yes	Yes
	discontinuation			

Table 4. Summary of quantitative/qualitative results presented by the type of treatment

Fig. 1. PRISMA diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit www.prisma-statement.org.

Tenofovir disoproxil fumarate (TDF) 300 mg versus no treatment or placebo *Summary of included studies*

There were 20 original studies, including 26 unique treatment arms, eligible for this metaanalysis that used TDF 300 mg. Following risk of bias assessment, one study (with one treatment arm) was excluded (*Kochaksaraei et al., 2016*). Therefore, 19 original studies with 25 unique treatment arms were included in the analysis. Of the included studies, five were RCTs and 14 were non-randomized trials/observational studies (six prospective and eight retrospective studies).

Risk of bias assessment

• Randomized controlled trials

Of the five RCTs included that investigated TDF, only one study by Jourdain et al., (2018) achieved a "low risk of bias" rating on the main criteria in the Cochrane Collaboration's Risk of Bias Assessment Tool; only one domain – attrition bias for maternal safety outcomes – was identified as possibly at high risk of bias. Another study, by Pan and colleagues (2016) was deemed at low risk of bias on five of the eight evaluated criteria; however, no allocation concealment was described and blinding was not performed, leading to this study being at a high risk for some selection bias, as well as for performance and detection bias. The other three RCTs were all deemed low risk on the majority of criteria evaluated; the main issues revolved around apparent limited use of blinding and lack of reporting on loss to follow up (*Lin Y et al., 2018; Liu MH et al., 2017; Yu CY et al., 2018*). The detailed risk of bias assessment for the RCTs investigating TDF can be found in **Appendix E**.

• Non-randomized controlled trials

The majority of studies (73.3%) were ranked at a score of 6 (high) to 7 (low) on the Newcastle Risk of Bias scale, and only three studies achieved scores of 8–9 on the scale (signifying very low risk of bias). The main weakness of included studies was in reference to loss to follow up – this information was missing in 11 of 15 articles, and was less than adequate (i.e. <80% follow

up) in two further studies. The detailed risk of bias assessment for the non-RCTs investigating TDF can be found in **Appendix F (Table 5)**.

# stars (risk of bias)	# studies	%
4 (high)	0	0
5 (high)	1 (excluded from analysis)	6.7
6 (high)	5	33.3
7 (low)	6	40.0
8 (low)	2	13.3
9 (low)	1	6.7
Total	15	100

Table 5. Risk of bias scores for non-RCTs (prior to exclusion of very high-risk studies)

Publication bias/small study effects assessment

It was possible to examine publication bias for the following outcomes: MTCT indicated by HBsAg positivity at 6–12 months in non-RCTs, neonatal deaths in non-RCTs, and miscarriages and stillbirths in non-RCTs. Of these, there was possible evidence of publication bias only in the first study set (MTCT indicated by HBsAg positivity at 6–12 months in non-RCTs). Funnel plots for TDF 300 mg study sets, as well as results of the Egger test for asymmetry (if examining OR only) can be found in **Appendix G**.

Characteristics of included studies

Across all included studies (n=19), recruitment took place as early as 2007 and up until 2018. Almost all studies took place in the WHO Western Pacific Region; including China (n=15), Japan (n=1) and Australia (n=1). Additionally, one study took place in the WHO South-East Asia Region (Thailand), and one study in the WHO European Region (Turkey).

HBV genotyping for the entire study population was performed only in three instances. A study from China estimated that the treatment group was 70% genotype B and 30% genotype C, while the control group was 71% B and 29% C (*Chen HL et al., 2015*). One Chinese study estimated the treatment group as 7% B2 and 93% C2, with the control group being 6% B2 and 94% C2 (*Lin Y et al., 2018*). In a small study in Japan (n=8), 50% of participants were genotype C and the other 50% had undetermined genotype (*Wakano Y et al., 2018*).

Most included study arms (i.e. 14/25) started maternal antiviral therapy between 24 and 30 weeks of gestation. The most common HBV DNA level designated for inclusion was >6.0 or >6.3 log10 IU/mL (11 of 25 treatment arms) (table 6).

General stud	ly details and	d design		Treate	d (TDF)	300 mg) pı	egnant wo	omen (tx))		Untrea	ated pregn	ant wom	en (control)		Infant trea	tment (all in	fants)
Author, year	Country	Recruit -ment period	HBV DNA level (as inclusion criterion)	#	Treatr weeks Start du pregnau postpar	uring ncy End	Age, in years	HBe Ag %	Mean or median HBV DNA at baseline	# Infants assessed for MTCT	#	Age, in years	HBe Ag %	Mean or median HBV DNA at baseline	# Infants assessed for MTCT	HBIG at birth, <i>timing</i>	Birth dose vaccine, <i>timing</i>	Infant vaccine, dose 1 /dose 2 in months
Randomized	l controlled t	rials (RCT)															
Jourdain G, 2018	Thailand	2013– 2015	None	168	28	8	25.5 [18.3– 42.2]	100	7.3 log10 IU/mL	149	163	26.7, [18.4– 40.9]	100	7.3 log10 IU/mL	147	Yes, Unclear	Yes, <3 hr	Yes, 1/2/4/6
Lin Y, 2018	China	2013– 2016	> 6.3 log10 IU/mL	60	24	4	28.3 ±3.6	100	7.4 log10 IU/mL	58	60	28.1 ±3.4	100	7.7 log10 IU/mL	52	Yes, "Immed- iate"	Yes, <12 h	Yes, 1/6

Table 6. Characteristics of included studies investigating TDF (n=19)

Liu MH, 2017b	China	2014– 2016	> 5.3 log10 IU/mL	20	28- 30	0	30 [22– 38]	100	6.5 log10 IU/mL	20	20	29 [21– 38]	100	6.5 log10 IU/mL	20	Yes, <24 h	Yes, <24 h	Yes, 1/6
Pan CQ, 2016	China	2012– 2013	> 5.3 log10 IU/mL	100	30- 32	4	27.4 ±3.0	100	8.2 log10 IU/mL	92	100	26.8 ±3.0	100	8.0 log10 IU/mL	88	Yes, <12 h	Yes, <12 h	Yes, 1/6
Yu CY, 2018	China	2017	> 6 log10 IU/mL	30	24	4	26.8 ±4.2	NR	NR	30	30	27.6 ±3.6	NR	NR	30	Yes, <24 h	Yes, <24 h	No
Non-randon	nized contro	lled trials (non-RCTs)															
Celen MK, 2013	Turkey	2010– 2012	≥ 6.3 log10 IU/mL	21	18– 27	4	28.2±4.1	100	8.3 log10 IU/mL	21	24	26.9 ±2.9	100	8.3 log10 IU/mL	23	Yes, <24 h	NR	Yes, 1/2/6
Chen HL, 2015	China	2011– 2013	≥ 7.5 log10 IU/mL	62	30- 32	4	32.4 ±3.1	100	8.3 log10 IU/mL	65	56	32.5 ±3.2	100	8.2 log10 IU/mL	56	Yes, <24 h	Yes, Unclear	Yes, 1/6
Chen WJ, 2017	China	2014– 2015	${}^{\geq 10^6}_{IU/mL}$	30	28	0	28.7 ±5.7	100	7.5 log10 IU/mL	30	44	29.9 ±5.1	100	7.5 log10 IU/mL	44	Yes, "Immed- iate"	Yes, Unclear	Yes, 1/6
Gong Q, 2017	China	2015– 2016	NR	44	1–6	NR	29.1 ±1.0	NR	NR	44	44	29.1 ±1.2	NR	NR	44	Yes, <24 h	Yes, <24 h	Yes, 1/6
Greenup AJ, 2014	Australia	2007– 2013	>7±0.5 log10 IU/mL	62	32	12	30±8.5	94.8	7.9 log10 IU/mL	44	20	28.0±5	100	8 log10 IU/mL	10	Yes, Unclear	Yes, Unclear	Yes, 2/4/6
He LL, 2018	China	2013– 2016	NR	50	28	NR	27.7 ±3.2	NR	3.6 log10 IU/mL	50	35	26.3 ±3.0	NR	3.7 log10 IU/mL	35	Yes, <12 h	Yes, <12 h	Yes, 1/6
				30	Pre- pregn ancy	Various post- pregnan cy	28.4 ±1.4	NR	7.4 log10 IU/mL	29						Yes, Unclear	Yes, Unclear	Yes, 1/6
Hu MF, 2018	China	2016– 2018	>6 log10 IU/mL	30	14	Various post- pregnan cy	23.2 ±3.3	NR	7.5 log10 IU/mL	30	30	26.3 ±2.1	NR	7.5 log10 IU/mL	30	Yes, Unclear	Yes, Unclear	Yes, 1/6
				30	28	Various post- pregnan cy	24.4 ±3.1	NR	7.4 log10 IU/mL	30						Yes, Unclear	Yes, Unclear	Yes, 1/6
Huang Q, 2017	China	2015	>6 log10 IU/mL	20	24– 28	12	27.1 ±2.4	100	NR	20	20	27.0 ±2.3	100	NR	20	Yes, <6 h	Yes, <6 h	Yes, 1/6
Wakano Y, 2018	Japan	2011– 2015	N/A	2	22 or 28	4–8	[28– 37] Entire study group	100	8.3 log10 IU/mL	2	3	[28– 37] For entire study group	100	8.3 log10 IU/mL (Note: only available for n=2)	3	Yes, <12 or <48 h	5/8 infants, <12 h	Yes, 2/3/5 or 1/6

Wan JY, 2017	China	2012– 2015	>5.3 log10 IU/mL	74	28	0	28.5± 4.2	NR	7.7 log10 IU/mL	74	42	27.9 ±4.0	NR	7.6 log10 IU/mL	42	NR	NR	NR
					20	NR	NR	NR	7.0 log10 IU/mL	20						Unclear	Unclear	Unclear
					24	NR	NR	NR	7.1 log10 IU/mL	20						Unclear	Unclear	Unclear
Wang HB, 2018	China	2013– 2016	NR	20	28	NR	NR	NR	7.2 log10 IU/mL	20	20	NR	NR	7.2 log10 IU/mL	20	Unclear	Unclear	Unclear
					32	NR	NR	NR	7.2 log10 IU/mL	20						Unclear	Unclear	Unclear
					36	NR	NR	NR	6.7 log10 IU/mL	20						Unclear	Unclear	Unclear
Xiao XH, 2017	China	2014– 2015	> 6 log10 IU/mL	60	28	0-4	27.6 ±3.2	NR	7.6 log10 IU/mL	60	60	28.5 ±3.6	NR	7.5 log10 IU/mL	61	Unclear	Unclear	Unclear
Zhang BF, 2018	China	2016– 2017	> 6 log10 IU/mL (tx group)	39	24– 28	0	NR	100	4.8 log10 IU/mL	39	75	NR	100	6.0 log10 IU/mL	75	Yes, <6hr	Yes, Unclear	Yes, 1/6
Zhou Y, 2018	China	2015– 2017	>6 log10 IU/mL	60	24– 28	0	28 [21– 38]	100	7.6 log10 IU/mL	60	36	28 [23– 39]	100	7.6 log10 IU/mL	36	Yes, <6 h	Yes, <24 h	Yes, 1/6

NR=not reported in article *Age and HBV DNA at baseline presented as mean ± SD or median with either (interquartile range [IQR]) or [Range]

Primary efficacy analysis, narrative descriptions and forest plots

- PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all HBV DNA levels at inclusion, stratified by study design (RCT and non-RCT).
 - Overall pooled OR=0.16 (95% CI: 0.10–0.26), P<0.001, I²=0%
 - RCTs only: pooled OR=0.10 (95% CI: 0.03–0.35), P<0.001, I²=0%
 - Non-RCTs only: pooled OR=0.17 (95% CI: 0.10-0.29), P<0.001, I²=0%
 - When looking at heterogeneity between RCTs and non-RCTs we arrive at a *P* value of 0.47, indicating no difference between the estimates.

Randomised							DR (95% CI) Treatment	Contro
lourdoin G	contro	olled trials			1				
Jourdain G	2018	Thailand	26-29	8		— o	.14 (0.01, 2	2.70) 0/149	3/147
Lin Y	2018	China	24	4		— o	.09 (0.00, 1	.75) 0/58	4/52
Liu MH	2017	China	28	0		0	.12 (0.01, 1	.14) 1/20	6/20
Pan CQ	2016	China	30-32	4		0	.07 (0.00, 1	.24) 0/92	6/88
Yu CY	2018	China	24	4		— o	.10 (0.00, 1	.88) 0/30	4/30
Subtotal (I-s	quare	d = 0.0%,	p = 0.997)		$\langle \rangle$	0	.10 (0.03, 0).35) 1/349	23/33
Non-randomi	ised c	ontrolled tr	ials						
Celen MK	2013	Turkey	18-27	4	•	O	.20 (0.01, 4	1.42) 0/21	2/23
Chen HL	2015	Taiwan	30-32	4	•	0	.13 (0.02, 1	.12) 1/65	6/56
Chen WJ	2017	China	28	0		0	.06 (0.01, 0).49) 1/30	16/44
Gong Q	2017	China	1-6	NR	•	0	.12 (0.01, 1	.05) 1/44	7/44
Greenup AJ	2014	Australia	32	12	•	0	.06 (0.00, 0).72) 1/69	2/10
He LL	2018	China	28	NR		0	.37 (0.15, 0).93) 13/50	17/35
Hu MF	2018	China	14	NR		0	.10 (0.01, 1	.02) 1/89	3/30
Huang Q	2017	China	24-28	12	•	— o	.12 (0.01, 2	2.53) 0/20	3/20
Wakano Y	2018	Japan	22-28	4-8		o	.12 (0.00, 4	1.61) 0/2	2/3
Wan JY	2017	China	28	0		0	.21 (0.05, 0).87) 3/74	7/42
Wang HB	2018	China	28	NR -		0	.04 (0.00, 0).80) 0/100	2/20
Xiao XH	2017	China	28	0 or 4	•	O	.33 (0.01, 8	3.35) 0/60	1/61
Zhang BF	2018	China	24-28	0		0	.05 (0.00, 0).85) 0/39	15/75
Zhou Y	2018	China	24-28	0 .	•	0	.05 (0.00, 0	0.88) 0/60	5/36
Subtotal (I-s	quare	d = 0.0%,	p = 0.860)		\diamond	0	0.17 (0.10, 0).29) 21/723	88/49
Overall (I-sq	uared	= 0.0%, p	= 0.972)		\diamond	0	0.16 (0.09, 0).25) 22/1072	111/8

TDF 300mg, MTCT=HBsAg+, by study design

- PMTCT, as indicated by detection of HBV DNA at 6–12 months of age, all treatment start times, all HBV DNA levels at inclusion, stratified by study design (RCT and non-RCT).
 - Overall pooled OR=0.08 (95% CI: 0.03–0.19), P<0.001, I²=0%
 - RCTs only: pooled OR=0.11 (95% CI: 0.03-0.43), P=0.001, I^2 =0%
 - Non-RCTs only: pooled OR=0.06 (95% CI: 0.02–0.19), P<0.001, I^2 =0%
 - When looking at heterogeneity between RCTs and non-RCTs we arrive at a *P* value of 0.52, indicating no difference between the estimates.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)			OR (95% CI)	Events, Treatment	Events Contro
							. ,		
Randomise	d contro	olled trials			i.				
Jourdain G	2018	Thailand	26-29	8	 ۲		0.14 (0.01, 2.70)	0/149	3/147
_in Y	2018	China	24	4			0.05 (0.00, 0.93)	0/58	7/52
_iu MH	2017	China	28	0		•	0.21 (0.02, 2.08)	1/20	4/20
Pan CQ	2016	China	30-32	4		_	0.07 (0.00, 1.24)	0/92	6/88
Subtotal (I-	square	d = 0.0%, p	o = 0.868)		$\langle \cdot \rangle$	>	0.11 (0.03, 0.43)	1/319	20/307
Non-randon	nised c	ontrolled tr	ials		1				
Chen WJ	2017	China	28	0			0.05 (0.00, 0.85)	0/30	11/44
Hu MF	2018	China	14	NR			0.04 (0.00, 0.89)	0/88	3/30
Nan JY	2017	China	28	0	 		0.08 (0.00, 1.50)	0/74	3/42
Nang HB	2018	China	28	NR			0.04 (0.00, 0.80)	0/100	2/20
Kiao XH	2017	China	28	0 or 4	 	•	0.20 (0.01, 4.18)	0/60	2/61
Zhang BF	2018	China	24-28	0			0.06 (0.00, 1.01)	0/39	13/75
Zhou Y	2018	China	24-28	0	 		0.06 (0.00, 1.14)	0/60	4/36
Subtotal (I-	square	d = 0.0%, p	o = 0.993)		$\langle \rangle$		0.06 (0.02, 0.19)	0/451	38/308
					-				
Overall (I-s	quared	= 0.0%, p	= 0.997)		\diamond		0.08 (0.03, 0.19)	1/770	58/615
					Ť				

TDF 300mg, MTCT=HBVDNA+, by study design

Subgroup analysis

In the protocol, it was specified that subgroup analysis would be performed by the following variables: type of antiviral therapy administered, stage of pregnancy at time of treatment start, maternal HBV viral load and HBeAg status, coinfections (e.g. HDV, HIV), other preventive measures provided (i.e. infant immunoprophylaxis), and WHO region where the study was conducted. Finally, all analyses have been presented by treatment type (no "all treatment" analysis was performed), and within that, it was possible to do subgroup analysis by stage of pregnancy, maternal HBV viral load and HBeAg status, and types of other preventive measures provided. It was not possible to do a subgroup analysis by coinfection status, as there were eventually no eligible studies that included coinfected populations. Furthermore, it was not possible to do subgroup analysis by WHO region, as almost all studies came from just one region (i.e. Western Pacific). For TDF, one additional subgroup analysis was presented, which is by timing of treatment end postpartum.

 PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all HBV DNA levels at inclusion, all study designs merged (i.e. RCT and non-RCT), stratified by trimester of treatment start

- 1st trimester: not enough studies for meta-analysis (i.e. n<3)
- 2nd trimester: pooled OR=0.14 (95% CI: 0.04-0.48), P=0.002, I²=0.0%
- 3rd trimester: pooled OR=0.21 (95% CI: 0.12-0.36), P<0.001, I²=0.0%
- The *P* value for heterogeneity between 2nd and 3rd trimester was 0.57.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	Events, OR (95% CI) Treatme	Events nt Contro
2nd trimeste	r					
Celen MK	2013	Turkey	18-27	4	0.20 (0.01, 4.42) 0/21	2/23
Hu MF	2018	China	14	NR	0.13 (0.01, 2.61) 0/30	3/30
Lin Y	2018	China	24	4	0.09 (0.00, 1.75) 0/58	4/52
Wang HB	2018	China	20	NR	0.18 (0.01, 4.01) 0/20	2/20
Wang HB	2018	China	24	NR	0.18 (0.01, 4.01) 0/20	2/20
Yu CY	2018	China	24	4	0.10 (0.00, 1.88) 0/30	4/30
Subtotal (I-	squared	d = 0.0%, p	o = 0.999)		0.14 (0.04, 0.48) 0/179	17/175
3rd trimeste	r					
Chen HL	2015	Taiwan	30-32	4	0.13 (0.02, 1.12) 1/65	6/56
Chen WJ	2017	China	28	0	0.06 (0.01, 0.49) 1/30	16/44
Greenup AJ	2014	Australia	32	12	0.06 (0.00, 0.72) 1/69	2/10
HeLL	2018	China	28	NR	0.37 (0.15, 0.93) 13/50	17/35
Hu MF	2018	China	28	NR	0.31 (0.03, 3.17) 1/30	3/30
Liu MH	2017	China	28	0	0.12 (0.01, 1.14) 1/20	6/20
Pan CQ	2016	China	30-32	4	0.07 (0.00, 1.24) 0/92	6/88
Wan JY	2017	China	28	0	0.21 (0.05, 0.87) 3/74	7/42
Wang HB	2018	China	28	NR	0.18 (0.01, 4.01) 0/20	2/20
Wang HB	2018	China	32	NR	0.18 (0.01, 4.01) 0/20	2/20
Wang HB	2018	China	36	NR	0.18 (0.01, 4.01) 0/20	2/20
Xiao XH	2017	China	28	0 or 4	0.33 (0.01, 8.35) 0/60	1/61
Subtotal (I-	squared	d = 0.0%, p	o = 0.923)		0.20 (0.12, 0.36) 21/550	70/446
Overall (I-s	quared	= 0.0%, p	= 0.995)		0.19 (0.12, 0.32) 21/729	87/621

 PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all HBV DNA levels at inclusion, all study designs merged (i.e. RCT and non-RCT),

stratified by median weeks' gestation at the time of treatment start (<28 weeks, 28 weeks, >28 weeks)

- <28 weeks: pooled OR=0.11 (95% CI: 0.05–0.26), P<0.001, I²=0.0%
- 28 weeks: pooled OR=0.24 (95% CI: 0.13–0.44), P<0.001, I²=0.0%
- >28 weeks: pooled OR=0.11(95% CI: 0.03–0.35), P<0.001, I²=0.0%
- When looking at heterogeneity across the three subgroups, the P value was 0.26. If comparing <28 weeks median with 28 weeks median, there was no heterogeneity (P=0.15). If comparing <28 weeks median with >28 weeks median, there was no heterogeneity (P=0.98). If comparing 28 weeks median with >28 weeks median, there was no heterogeneity (P=0.24).

TDF 300mg, MTCT=HBsAg+, by tx start time Tx_start Tx end Events. Events. Year Country (weeks GA) (weeks PP) OR (95% CI) Treatment Control Author Median <28 weeks GA 0.20 (0.01, 4.42) 0/21 Celen MK 2013 Turkey 18-27 4 2/23 NR Gong Q 2017 China 1-6 0.12 (0.01, 1.05) 1/44 7/44 Hu MF 2018 China 14 NR 0.13 (0.01, 2.61) 0/30 3/30 Huang Q 2017 China 24-28 12 0.12 (0.01, 2.53) 0/20 3/20 Lin Y China 0.09 (0.00, 1.75) 0/58 4/52 2018 24 4 22-28 0.12 (0.00, 4.61) 0/2 Wakano Y 2018 Japan 4-8 2/3 Wang HB 2018 China 20 NR 0.18 (0.01, 4.01) 0/20 2/20 Wang HB China NR 0.18 (0.01, 4.01) 0/20 2/20 2018 24 Yu CY 2018 China 24 4 0.10 (0.00, 1.88) 0/30 4/30 0 Zhang BF 2018 China 24-28 0.05 (0.00, 0.85) 0/39 15/75 0 5/36 Zhou Y 2018 China 24-28 0.05 (0.00, 0.88) 0/60 Subtotal (I-squared = 0.0%, p = 1.000) 0.11 (0.05, 0.26) 1/344 49/353 Median 28 weeks GA Chen WJ 2017 China 28 0 0.06 (0.01, 0.49) 1/30 16/44 He LL 2018 China 28 NR 0.37 (0.15, 0.93) 13/50 17/35 Hu MF 2018 China 28 NR 0.31 (0.03, 3.17) 1/30 3/30 Jourdain G 2018 Thailand 26-29 8 0.14 (0.01, 2.70) 0/149 3/147 Liu MH China 0 0.12 (0.01, 1.14) 1/20 6/20 28 2017 Wan JY 2017 China 0 0.21 (0.05, 0.87) 3/74 7/42 28 Wang HB 2018 China NR 0.18 (0.01, 4.01) 0/20 2/20 28 Xiao XH 2017 China 28 0 or 4 0.33 (0.01, 8.35) 0/60 1/61 Subtotal (I-squared = 0.0%, p = 0.853) 55/399 0.24 (0.13, 0.44) 19/433 Median >28 weeks GA Chen HL 2015 Taiwan 30-32 4 0.13 (0.02, 1.12) 1/65 6/56 Greenup AJ 2014 Australia 32 12 0.06 (0.00, 0.72) 1/69 2/10 Pan CQ 2016 China 30-32 4 0.07 (0.00, 1.24) 0/92 6/88 Wang HB 2018 China NR 0.18 (0.01, 4.01) 0/20 2/20 32 NR 0.18 (0.01, 4.01) 0/20 Wang HB 2018 China 36 2/20 18/194 Subtotal (I-squared = 0.0%, p = 0.967) 0.11 (0.03, 0.35) 2/266 Overall (I-squared = 0.0%, p = 0.999) 0.17 (0.11, 0.27) 22/1043 122/946

.17

10

.001

- 3. PMTCT, as indicated by detection of HBsAg at 6-12 months of age, all treatment start times, all study designs merged (i.e. RCT and non-RCT), stratified by the minimum HBV DNA level specified in the study inclusion criteria
 - $>4-4.99 \log 10 \text{ IU/mL}$: not enough studies (i.e. <3)
 - >5-5.99 log10 IU/mL: pooled OR=0.16 (95% CI: 0.05-0.47), P=0.001, • $I^2=0.0\%$
 - >6-6.99 log10 IU/mL: pooled OR=0.11 (95% CI: 0.05-0.26), P<0.001, • $I^2=0.0\%$
 - $>7-7.99 \log 10 \text{ IU/mL}$: not enough studies (i.e. <3) •
 - When looking at heterogeneity between studies with inclusion criteria of >5-• 5.99 log10 IU/mL versus >6-6.99 log10 IU/mL, the *P* value was 0.64.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	OR (95% CI)	Events, Treatment	Events Contro
5-5.99 log1	0 IU/ml						
Liu MH	2017	China	28	0	0.12 (0.01, 1.14)	1/20	6/20
Pan CQ	2016	China	30-32	4	0.07 (0.00, 1.24)	0/92	6/88
Wan JY	2017	China	28	0	0.21 (0.05, 0.87)	3/74	7/42
Subtotal (I	square	d = 0.0%, p) = 0.754)	\diamond	0.16 (0.05, 0.47)	4/186	19/150
•							
6-6.99 l og1	0 IU/ml						
Celen MK	2013	Turkey	18-27	4	0.20 (0.01, 4.42)	0/21	2/23
Chen WJ	2017	China	28	0	0.06 (0.01, 0.49)	1/30	16/44
Hu MF	2018	China	14	NR -	0.13 (0.01, 2.61)	0/30	3/30
Hu MF	2018	China	28	NR -	0.31 (0.03, 3.17)	1/30	3/30
Hu MF	2018	China	Pre-pregnancy	NR	0.13 (0.01, 2.70)	0/29	3/30
Huang Q	2017	China	24-28	12	0.12 (0.01, 2.53)	0/20	3/20
Lin Y	2018	China	24	4	0.09 (0.00, 1.75)	0/58	4/52
Xiao XH	2017	China	28	0 or 4	0.33 (0.01, 8.35)	0/60	1/61
Yu CY	2018	China	24	4	0.10 (0.00, 1.88)	0/30	4/30
Zhang BF	2018	China	24-28	0	0.05 (0.00, 0.85)	0/39	15/75
Zhou Y	2018	China	24-28	0	0.05 (0.00, 0.88)	0/60	5/36
Subtotal (I	square	d = 0.0%, p	e = 0.992)	\diamond	0.11 (0.05, 0.26)	2/407	59/431
Overall (I-	squared	= 0.0%, p	= 0.997)	\diamond	0.13 (0.07, 0.25)	6/593	78/581

 PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all HBV DNA levels specified at inclusion, all study designs merged (i.e. RCT and non-RCT), <u>only including studies where all women were</u> <u>confirmed HBeAg positive</u>

• Pooled OR=0.09 (95% CI: 0.04–0.21), P<0.001, I²=0.0%

			Tx_start	Tx_end				Events,	Events
Author	Year	Country	(weeks GA)	(weeks PP)			OR (95% CI)	Treatment	Contro
Liu MH	2017	China	28	0	 •	_	0.12 (0.01, 1.14)	1/20	6/20
Pan CQ	2016	China	30-32	4		-	0.07 (0.00, 1.24)	0/92	6/88
Celen MK	2013	Turkey	18-27	4			0.20 (0.01, 4.42)	0/21	2/23
Chen WJ	2017	China	28	0	 •		0.06 (0.01, 0.49)	1/30	16/44
Huang Q	2017	China	24-28	12	 •		0.12 (0.01, 2.53)	0/20	3/20
_in Y	2018	China	24	4			0.09 (0.00, 1.75)	0/58	4/52
Zhang BF	2018	China	24-28	0		_	0.05 (0.00, 0.85)	0/39	15/75
Zhou Y	2018	China	24-28	0	 •		0.05 (0.00, 0.88)	0/60	5/36
Chen HL	2015	Taiwan	30-32	4		-	0.13 (0.02, 1.12)	1/65	6/56
Jourdain G	2018	Thailand	26-29	8			0.14 (0.01, 2.70)	0/149	3/147
Wakano Y	2018	Japan	22-28	4-8			0.12 (0.00, 4.61)	0/2	2/3
Overall (I-s	quared	= 0.0%, p =	= 1.000)		\diamond		0.09 (0.04, 0.21)	3/556	68/564

TDF 300mg, MTCT=HBsAg+, all HBeAg+

 PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all HBV DNA levels specified at inclusion, all study designs merged (i.e. RCT and non-RCT), by infant immunoprophylaxis regimen (Table 7).

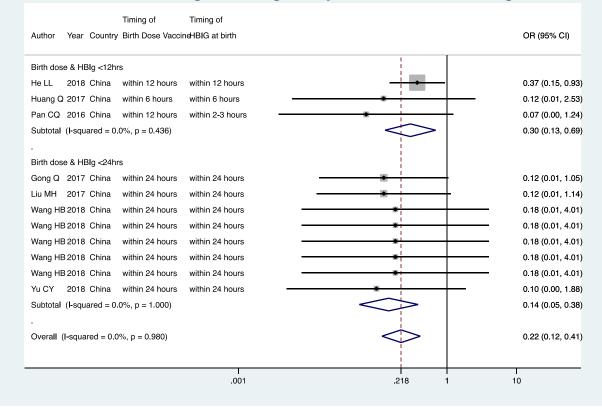
Birth dose vaccine	HBIG at birth	2–4 infant HBV vaccines (not at birth)	# studies (treatment arms)
Yes*	Yes	Yes	15 (21)
Yes	Yes	NR	1 (1) (Yu CY, 2018)
No	Yes	Yes	1 (1) (Celen MK et al., 2013)
NR	Yes	NR	1 (1) (Xiao XH et al., 2017)
NR	NR	NR	1 (1) (Wan JY et al., 2017)

Table 7. Infant immunoprophylaxis regimens seen in studies investigating TDF

*For one study, some infants received birth dose and others did not. NR: not reported

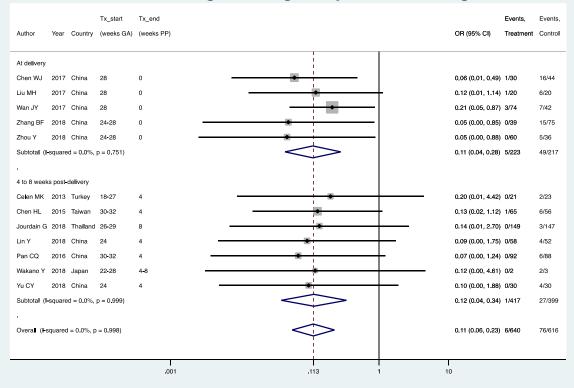
 As most studies provided all of the infant immunoprophylaxis measures (birth dose vaccine, HBIG at birth and subsequent infant vaccinations), stratification by type or combination of infant immunoprophylaxis was not possible in this meta-analysis.

- Therefore, we <u>stratified by whether or not *both* birth dose vaccine and</u> <u>HBIG were given within 12 hours of life, versus within 24 hours of life.</u>
- <12 hours: pooled OR=0.30 (95% CI: 0.13–0.69), P=0.004, I²=0.0%
- <24 hours: pooled OR=0.15 (95% CI: 0.06–0.38), P<0.001, I^2 =0.0%
- When looking at heterogeneity between studies that administered both forms of prophylaxis within 12 hours, versus within 24 hours, the *P* value was 0.28.



TDF 300mg, HBsAg +, by BD & HBIG timing

- PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all study designs merged (i.e. RCT and non-RCT), <u>stratified by the</u> timing that treatment was discontinued postpartum
 - At delivery: pooled OR=0.11 (95% CI: 0.04–0.28), P<0.001, I²=0.0%
 - 4–8 weeks postpartum: pooled OR=0.12 (95% CI: 0.04–0.34), P<0.001, I²=0.0%
 - 12 weeks postpartum: not enough studies for subgroup analysis
 - 24+ weeks postpartum: no studies within this subgroup
 - When looking at heterogeneity across the two subgroups, the *P* value was 0.96.



TDF 300mg, HBsAg +, by tx end timing

Safety analysis, narrative descriptions and selected forest plots

Infant safety outcomes

In the protocol, it was specified that the following safety outcomes for infants would be investigated: neonatal death, prematurity, congenital abnormalities, Apgar score, and bone mineral density. Finally, information on all of these outcomes were collected and results for all of these outcomes, except for the Apgar score, are provided here. The data for Apgar score were not available for the majority of included studies and where it was available the format varied greatly; this led to an inability to combine results in a meaningful way.

1. <u>Neonatal deaths</u> (death within 28 days of life)

Information on this outcome was available for all studies that administered TDF to mothers. Three neonatal deaths were reported across all study populations. Two deaths (non-weighted average 0.2%; one each from two separate studies) occurred across all treatment groups, out of a total of 1079 infants whose mothers were treated with TDF during pregnancy. One death (non-weighted average 0.1%) occurred in one of the control groups in one study, out of total of 858 infants whose mothers were not treated during pregnancy. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.00 (95% CI: -0.01–0.01). The I² statistics for the overall pooled OR, as well for RCTs and non-RCTs separately, were all 0%.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PF		Events, Treatment	Event Contr
Randomise	d contro	olled trials					
Jourdain G	2018	Thailand	26-29	8	-0.01 (-0.02, 0.01) 0	/163	1/160
Lin Y	2018	China	24	4	0.02 (-0.03, 0.06) 1	/59	0/52
Liu MH	2017	China	28	0	0.00 (-0.09, 0.09) 0	/20	0/20
Pan CQ	2016	China	30-32	4	0.01 (-0.02, 0.04) 1	/95	0/88
Yu CY	2018	China	24	4	0.00 (-0.06, 0.06) 0	/30	0/30
Subtotal (I-	square	d = 0.0%,	p = 0.797)		-0.00 (-0.01, 0.01) 2	/367	1/350
Non-randon	ninged o	optrolled to	iolo				
Celen MK		Turkey	18-27	4	0.00 (-0.08, 0.08) 0	/21	0/23
Chen HL	2015	Taiwan	30-32	4	0.00 (-0.03, 0.03) 0	/65	0/56
Chen WJ	2017	China	28	0	0.00 (-0.05, 0.05) 0	/30	0/44
Gong Q	2017	China	1-6	NR	0.00 (-0.04, 0.04) 0	/44	0/44
Greenup AJ	2014	Australia	32	12	0.00 (-0.07, 0.07) 0	/58	0/20
He LL	2018	China	28	NR	0.00 (-0.05, 0.05) 0	/50	0/35
Hu MF	2018	China	14	NR	0.00 (-0.05, 0.05) 0	/89	0/30
Huang Q	2017	China	24-28	12	0.00 (-0.09, 0.09) 0	/20	0/20
Wakano Y	2018	Japan	22-28	4-8	→ 0.00 (-0.53, 0.53) 0	/2	0/3
Wan JY	2017	China	28	0	0.00 (-0.04, 0.04) 0	/74	0/42
Wang HB	2018	China	28	NR		/100	0/20
Xiao XH	2017	China	28	0 or 4	0.00 (-0.03, 0.03) 0	/60	0/60
Zhang BF	2018	China	24-28	0	0.00 (-0.04, 0.04) 0	/39	0/75
Zhou Y	2018	China	24-28	0	0.00 (-0.04, 0.04) 0	/60	0/36
Subtotal (I-	square	d = 0.0%,	p = 1.000)		0 .00 (-0.01, 0.01) 0	/712	0/508
Overall (I-s	quared	= 0.0%, p	= 1.000)		-0.00 (-0.01, 0.01) 2	2/1079	1/858

TDF 300mg, Neonatal deaths risk difference

2. <u>**Prematurity**</u> (typically defined as birth earlier than 37 weeks of gestation)

Information on this outcome was available for nine of the 19 included studies that administered TDF to mothers. Within these studies, 19 of 622 (non-weighted average 3.1%) infants whose mothers were treated with TDF during pregnancy were born prematurely, whereas 22 of 479 (non-weighted average 4.6%) infants whose mothers were not treated during pregnancy were born prematurely. The weighted pooled risk difference for this safety outcome seen following meta-analysis was -0.003 (95% CI: - 0.024-0.019). The I² statistics for the overall pooled OR, as well as for RCTs and non-RCTs separately, were all 0%.

			Tx_start	Tx_end			Events,	Event
Author	Year	Country	(weeks GA)	(weeks PP)		RD (95% CI)	Treatment	Contr
Randomised	controlle	ed trials						
Jourdain G	2018	Thailand	26-29	8		-0.03 (-0.09, 0.02)	8/163	13/16
_in Y	2018	China	24	4		-0.02 (-0.08, 0.04)	1/59	2/52
Liu MH	2017	China	28	0		0.00 (-0.09, 0.09)	0/20	0/20
Pan CQ	2016	China	30-32	4		0.01 (-0.03, 0.05)	2/95	1/88
Subtotal (I-s	quared =	= 0.0%, p =	0.476)		\Diamond	-0.01 (-0.03, 0.02)	11/337	16/32
Non-randomi	sed con	trolled trials						
Chen HL	2015	Taiwan	30-32	4		0.04 (-0.04, 0.12)	5/65	2/56
Greenup AJ	2014	Australia	32	12		0.02 (-0.06, 0.09)	1/58	0/20
Wakano Y	2018	Japan	22-28	4-8	<	→ 0.00 (-0.53, 0.53)	0/2	0/3
Wang HB	2018	China	28	NR		0.00 (-0.07, 0.07)	0/100	0/20
Xiao XH	2017	China	28	0 or 4		-0.03 (-0.11, 0.04)	2/60	4/60
Subtotal (I-s	quared =	= 0.0%, p =	0.769)		\Diamond	0.01 (-0.03, 0.04)	8/285	6/159
Overall (I-sq	uared =	0.0%, p = 0	.832)		♦	-0.00 (-0.02, 0.02)	19/622	22/47
					I I .3 0	l .3		

TDF 300mg, Prematurity risk difference

3. Congenital abnormalities

Information on this outcome was available for 14 of the 19 included studies that administered TDF to mothers. Within these studies, four of 802 (non-weighted average 0.5%) infants whose mothers were treated with TDF during pregnancy were noted to have some sort of congenital abnormality, including: torticollis (n=1), umbilical hernia (n=1), congenital unilateral deafness (n=1), polydactyly (n=1). Five of 687 (non-weighted average 0.7%) infants whose mothers were not treated during pregnancy were noted to have some sort of congenital abnormality, including: hypospadias (n=1), "gross abnormalities" (n=1), no detail provided (n=3). The weighted pooled risk difference for this safety outcome seen

following meta-analysis was -0.002 (95% CI: -0.013–0.009). The I² statistics for the overall pooled OR, as well as for RCTs and non-RCTs separately, were all 0%.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP		Events, Treatment	Event: Contro
Randomised	l contro	lled trials					
Jourdain G	2018	Thailand	26-29	8	← -0.01 (-0.02, 0.01)	0/163	1/160
Lin Y	2018	China	24	4	0.00 (-0.03, 0.03)	0/59	0/52
Liu MH	2017	China	28	0	0.00 (-0.09, 0.09)	0/20	0/20
Pan CQ	2016	China	30-32	4	0.01 (-0.03, 0.05)	2/95	1/88
Yu CY	2018	China	24	4	-0.03 (-0.12, 0.05)	0/30	1/30
Subtotal (I-	quarec	= 0.0%, p	= 0.895)		-0.00 (-0.02, 0.01)	2/367	3/350
Non-random	ised co	ntrolled tria	als				
Celen MK	2013	Turkey	18-27	4	0.00 (-0.08, 0.08)	0/21	0/23
Chen HL	2015	Taiwan	30-32	4	0.02 (-0.03, 0.06)	1/65	0/56
Chen WJ	2017	China	28	0	0.00 (-0.05, 0.05)	0/30	0/44
Greenup AJ	2014	Australia	32	12	0.02 (-0.06, 0.09)	1/58	0/20
Wakano Y	2018	Japan	22-28	4-8	→ 0.00 (-0.53, 0.53)	0/2	0/3
Wang HB	2018	China	28	NR	0.00 (-0.07, 0.07)	0/100	0/20
Xiao XH	2017	China	28	0 or 4	-0.03 (-0.09, 0.02)	0/60	2/60
Zhang BF	2018	China	24-28	0	0.00 (-0.04, 0.04)	0/39	0/75
Zhou Y	2018	China	24-28	0	0.00 (-0.04, 0.04)	0/60	0/36
Subtotal (I-	squarec	= 0.0%, p	= 0.976)		-0.00 (-0.02, 0.02)	2/435	2/337
Overall (I-se	quared	= 0.0%, p =	= 0.997)		-0.00 (-0.01, 0.01)	4/802	5/687

11.00

4. Bone mineral density

This outcome was investigated only for one of the 19 included studies, an RCT, that administered TDF to mothers. In this study, infant lumbar spine bone mineral density was measured in 62 infants from the treatment group, and 53 infants from the control group at 1 year of age (i.e. not the entire original study population of 163 treatment-exposed infants and 161 controls), with a mean score of 0.324 (SD +/- 0.036), and 0.330 (SD +/-0.036), respectively. There was no statistically significant difference detected between the two groups (Jourdain et al., 2018; Salvadori et al., 2019).

Maternal safety outcomes

Information was collected and presented on the following maternal safety outcomes: miscarriage/stillbirth, postpartum haemmorhage, antiviral resistance, HBV flare.

1. <u>Fetal demise</u> (miscarriage [<28 weeks], stillbirth [>=28 weeks])

Information on this outcome was available for all studies that administered TDF to mothers. Four cases of fetal demise were reported across all study populations. Three cases (non-weighted average 0.4%; one each from three separate studies) occurred across all treatment groups, out of a total of 942 mothers/fetuses who were treated with TDF during pregnancy. One case (non-weighted average 0.1%) occurred in one of the control groups in one study, out of a total of 882 mothers/fetuses who were not treated during pregnancy. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.003 (95% CI: -0.006–0.012). The I² statistics for the overall pooled risk difference estimate, and RCTs and non-RCTs separately, were all 0%.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)		RD (95% CI)	Events, Treatment	Events Control
Randomised	controlle	d trials			- F			
Jourdain G	2018	Thailand	26-29	8		0.01 (-0.01, 0.02)	1/163	0/160
Lin Y	2018	China	24	4		0.02 (-0.03, 0.06)	1/61	0/52
Liu MH	2017	China	28	0		0.00 (-0.09, 0.09)	0/20	0/20
Pan CQ	2016	China	30-32	4		0.01 (-0.02, 0.04)	1/98	0/100
Yu CY	2018	China	24	4	•	0.00 (-0.06, 0.06)	0/30	0/30
Subtotal (I-so	uared =	0.0%, p = 0	.991)		\diamond	0.01 (-0.01, 0.02)	3/372	0/362
Non-randomis	sed conti	olled trials			1			
Celen MK	2013	Turkey	18-27	4	• <u>+</u>	-0.04 (-0.15, 0.07)	0/21	1/25
Chen HL	2015	Taiwan	30-32	4		0.00 (-0.03, 0.03)	0/62	0/56
Chen WJ	2017	China	28	0		0.00 (-0.05, 0.05)	0/30	0/44
Gong Q	2017	China	1-6	NR		0.00 (-0.04, 0.04)	0/44	0/44
Greenup AJ	2014	Australia	32	12	<u> </u>	0.00 (-0.07, 0.07)	0/58	0/20
He LL	2018	China	28	NR		0.00 (-0.05, 0.05)	0/50	0/35
Hu MF	2018	China	14	NR		0.00 (-0.06, 0.06)	0/30	0/30
Huang Q	2017	China	24-28	12		0.00 (-0.08, 0.08)	0/20	0/30
Wakano Y	2018	Japan	22-28	4-8	¢	→ 0.00 (-0.53, 0.53)	0/2	0/3
Wan JY	2017	China	28	0		0.00 (-0.04, 0.04)	0/74	0/42
Wang HB	2018	China	28	NR	•	0.00 (-0.09, 0.09)	0/20	0/20
Xiao XH	2017	China	28	0 or 4		0.00 (-0.03, 0.03)	0/60	0/60
Zhang BF	2018	China	24-28	0		0.00 (-0.04, 0.04)	0/39	0/75
Zhou Y	2018	China	24-28	0		0.00 (-0.04, 0.04)	0/60	0/36
Subtotal (I-so	uared =	0.0%, p = 1	.000)		$\mathbf{\Phi}$	-0.00 (-0.01, 0.01)	0/570	1/520
					l l			
Overall (I-squ	uared = 0	0.0%, p = 1.0	000)		•	0.00 (-0.01, 0.01)	3/942	1/882
					Ĩ			

2. Postpartum haemorrhage

Information on this outcome was available for six of the 19 included studies that administered TDF to mothers. Within these studies, nine of 365 (non-weighted average 2.5%) mothers who were treated with TDF during pregnancy experienced postpartum haemorrhage, whereas seven of 256 (2.7%) mothers who were not treated during pregnancy experienced postpartum haemorrhage. The weighted pooled risk difference for this safety outcome seen following meta-analysis was -0.001 (95% CI: -0.024–0.022). The I² statistics for the overall pooled risk difference estimates, as well as for RCTs and non-RCTs separately, were all 0%.

					•			
			Tx_start	Tx_end			Events,	Event
Author	Year	Country	(weeks GA)	(weeks PP	2)	RD (95% CI)	Treatment	Contro
Randomised	d contro	olled trials						
Lin Y	2018	China	24	4		0.00 (-0.03, 0.03)	0/60	0/52
Liu MH	2017	China	28	0		0.00 (-0.09, 0.09)	0/20	0/20
Pan CQ	2016	China	30-32	4		0.00 (-0.05, 0.06	4/97	4/100
Subtotal (I-	square	d = 0.0%,	p = 0.999)		\diamond	0.00 (-0.03, 0.03)	4/177	4/172
Non-random	nised co	ontrolled t	rials					
Chen WJ	2017	China	28	0		0.00 (-0.05, 0.05	0/30	0/44
Greenup AJ	2014	Australia	32	12	· · · ·	-0.06 (-0.24, 0.11) 5/58	3/20
Wang HB	2018	China	28	NR		0.00 (-0.07, 0.07)	0/100	0/20
Subtotal (I-	square	d = 0.0%,	p = 0.587)		\diamond	-0.00 (-0.04, 0.04) 5/188	3/84
Overall (I-se	quared	= 0.0%, p	o = 0.980)		\diamond	-0.00 (-0.02, 0.02) 9/365	7/256
					2 0	1 .2		

TDF 300mg, post-partum haemorrhage risk difference

3. Antiviral resistance

Only one of the 19 studies where mothers were treated with TDF during pregnancy performed antiviral resistance testing for the entire study population. This study, with 120 participants, found no HBV mutations related to antiviral therapy; it was not clearly stated at which time-point this testing was performed (*Lin Y et al., 2018*). Two further studies reported investigations into antiviral resistance for women defaulting from treatment or where infants were found positive for HBV at 6–12 months, both of these studies reported that no resistance mutations were found (*Chen HL et al., 2015; Pan CQ et al., 2016*).

4. HBV flare after treatment discontinuation

Information on this outcome was available for six of the 19 included studies that administered TDF to mothers. Various definitions were used, including: "postpartum flare", "severe flare", "ALT >5 ULN", and others. Within these studies, 34 of 418 (nonweighted average 8.1%) mothers who were treated with TDF during pregnancy experienced a type of HBV flare at the time of treatment discontinuation, whereas 20 of 382 (non-weighted average 5.2%) mothers who were not treated during pregnancy experienced the same type of HBV flare at a matched time-point. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.007 (95% CI: -0.027-0.041). There was no heterogeneity in the RCTs (i.e. I²=0%), however, in non-RCTs and in the overall pooled risk difference estimate, there was an I² of 13.2% and 17.1%, respectively.

				· (),		
			Tx_start	Tx_end	Events,	Events
Author	Year	Country	(weeks GA)	(weeks PP	RD (95% CI) Treatment	Contro
Randomise	d contre	olled trials				
Jourdain G	2018	Thailand	26-29	8	0.03 (-0.02, 0.07) 9/154	5/157
Lin Y	2018	China	24	4	0.03 (-0.02, 0.09) 2/60	0/52
Pan CQ	2016	China	30-32	4	-0.01 (-0.07, 0.06) 5/97	6/100
Subtotal (I-	square	d = 0.0%,	p = 0.575)		0.02 (-0.01, 0.05) 16/311	11/309
•						
Non-randon	nised c	ontrolled t	rials			
Chen HL	2015	Taiwan	30-32	4	-0.07 (-0.15, 0.01) 1/62	5/56
Greenup AJ	2014	Australia	32	12	••••••••••••••••••••••••••••••••••••••	4/14
Wakano Y	2018	Japan	22-28	4-8	→ 0.00 (-0.53, 0.53) 0/2	0/3
Subtotal (I-	square	d = 13.2%	, p = 0.316)		-0.04 (-0.16, 0.07) 18/107	9/73
•						
Overall (I-s	quared	= 17.1%,	p = 0.303)		0.01 (-0.03, 0.04) 34/418	20/382
				-	0 .2	

TDF 300mg, HBV flare risk difference

GRADE summary of findings

Table 8. GRADE evidence profile – TDF 300 mg during pregnancy to prevent HBV mother-to-child transmission (MTCT)

Naarahaa				Quality a	ssessment			Number of	fpatients	Eff	fect	
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	Quality
HBsAg pos	sitivity at 6–12	months									,	
5	Randomized controlled trials (RCTs)	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	1/349 (0.3)	23/337 (6.8)	0.10 (0.03– 0.35)	80 fewer per 1000 (10–140 fewer)	Moderate ^a
14	Non-RCTs	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect	21/723 (2.9)	88/499 (17.6)	0.17 (0.10– 0.29)	140 fewer per 1000 (80–200 fewer)	Low ^b
HBV DNA	positivity at 6-	-12 months										
4	RCTs	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	1/319 (0.3)	20/307 (6.5)	0.11 (0.03– 0.43)	70 fewer per 1000 (0–150 fewer)	Moderate ^c
7	Non-RCTs	No serious	No serious	No serious	No serious	Not able to examine publication bias	Magnitude of the effect	0/451 (0.0)	38/308 (12.3)	0.06 (0.02– 0.19)	110 fewer per 1000 (50–170 fewer)	Moderate ^d
Infant safe	ety: neonatal de	eaths										
5	RCTs	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	2/367 (0.5)	1/350 (0.3)	-	0 (10 fewer – 10 more)	Moderate ^e
14	Non-RCTs	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/712 (0.0)	0/508 (0.0)	-	0 (10 fewer – 10 more)	Low ^f

Infant saf	ety: prematurit	y										
4	RCTs	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	11/337 (3.3)	16/320 (5.0)	-	10 fewer (30 fewer – 20 more)	Moderate ^g
4	Non-RCTs	No serious	No serious	No serious	No serious	Not able to examine publication bias	None	8/285 (2.8)	6/159 (3.8)	-	10 more (30 fewer to 40 more)	Low ^h
Infant saf	ety: congenital	abnormaliti	es	•				•	•	•		
5	RCTs	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	2/367 (0.5)	3/350 (0.9)	-	0 (20 fewer – 10 more)	Moderate ⁱ
9	Non-RCTs	No serious	No serious	No serious	No serious	Not able to examine publication bias	None	2/435 (0.5)	2/337 (0.6)	-	0 (20 fewer – 20 more)	Low ^j
Infant saf	ety: bone miner	al density										
1	RCTs	No serious	N/A	No serious	Serious	Not able to examine publication bias	N/A	N/A	N/A	-	-0.006 g/cm ² (-0.019 to 0.007 g/cm ²); p=0.38)	Low ^k
Maternal	safety: miscarr	iage and stil	lbirth									
5	RCTs	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	3/372 (0.8)	0/362 (0.0)	-	10 more (10 fewer – 20 more)	Moderate ¹
14	Non-RCTs	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/570 (0.0)	1/520 (0.2)	-	0 (10 fewer – 10 more)	Low ^m
Maternal	safety: postpar	tum haemm	orhage									
3	RCTs	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	4/177 (2.3)	5/172 (2.9)	-	0 (30 fewer - 30 more)	Moderate ⁿ
3	Non-RCTs	No serious	No serious	No serious	No serious	Not able to examine	None	5/188 (2.7)	3/84 (3.6)	-	0 (40 fewer	Low ^o

						publication bias					– 40 more)	
Maternal	safety: HBV fla	re after trea	tment discor	ntinuation								
3	RCTs	No serious	No serious	No serious	Serious	Not able to examine publication bias	N/A	16/311 (5.1)	11/309 (3.6)	-	20 more (10 fewer – 50 more)	Moderate ^p
3	Non-RCTs	No serious	No serious	No serious	Serious	Not able to examine publication bias	None	18/107 (16.8)	9/73 (12.3)	-	40 fewer (160 fewer – 70 more)	5

^aDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

^bDowngrading due to possible publication bias/small study effects, upgrading due to magnitude of effect.

^cDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). ^dUpgrading due to magnitude of effect

^eDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). ^fNo upgrading or downgrading

^gDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). ^hNo upgrading or downgrading

ⁱDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). ^jNo upgrading or downgrading

^kDowngrading due to inability to examine certain elements (e.g. inconsistency), and for imprecision due to the fact that there was only one RCT included.

¹Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). ^mNo upgrading or downgrading

ⁿDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

°No upgrading or downgrading

^pDowngrading due to imprecision

^qDowngrading due to imprecision

Lamivudine (LAM) 100–150 mg versus no treatment or placebo

Summary of included studies

There were 42 original studies, including 46 unique treatment arms, eligible for this meta-analysis that used LAM 100–150 mg. Following risk of bias assessment, two studies (each with one treatment arm investigating LAM) were excluded (*van Zonneveld et al., 2003, Liu CP et al., 2015*). Therefore, 40 original studies with 44 unique treatment arms were included in analysis. Of the included studies, eight were RCTs and 32 were non-randomized trials/observational studies (17 prospective and 15 were retrospective studies).

Risk of bias assessment

• Randomized controlled trials

Of the eight RCTs included that investigated LAM, none achieved a "low risk of bias" rating on the majority of the main criteria in the Cochrane Collaboration's Risk of Bias Assessment Tool. One study, by Xu WM et al. (2009), the only study published in English, had a low risk in selection bias (specifically, allocation concealment), as well as in performance bias and detection bias, but had a high or unclear risk in all other domains. The remaining seven of the eight included RCTs only fulfilled one or two criteria as "low risk of bias". In these studies, there was always a low risk of selection bias (specifically random sequence generation) and sometimes a low risk of selective reporting; however, no study described loss to follow up and no study described all important adverse outcomes in mothers and infants. The detailed risk of bias assessment for the RCTs investigating LAM can be found in Appendix E.

Non-randomized controlled trials

Of the original 34 non-RCTs, the majority of studies (67.6%) had low risk of bias scores (i.e. scores of 7, 8, 9) on the Newcastle Risk of Bias scale. The main weakness of included studies was in reference to loss to follow up – this information was missing in 28 of 34 studies, and was less than adequate (i.e. <80% follow up) in three further studies. The

detailed risk of bias assessment for the non-RCTs investigating LAM can be found in Appendix F (Table 9).

# stars (risk of bias)	# studies	%
4 (high)	1 (excluded from analysis)	2.9
5 (high)	1 (excluded from analysis)	2.9
6 (high)	12	35.3
7 (low)	8	23.5
8 (low)	11	32.3
9 (low)	1	2.9
Total	34	100

Table 9. Risk of bias scores for non-RCTs (prior to exclusion of very high-risk studies)

Publication bias/assessment of small study effects

It was possible to examine publication bias for the following outcomes: MTCT indicated by HBsAg positivity at 6–12 months in non-RCTs, MTCT indicated by HBV DNA positivity at 6–12 months in non-RCTs, neonatal deaths in non-RCTs, congenital abnormalities in non-RCTs, and miscarriages and stillbirths in non-RCTs. Of these, there was only possible evidence of publication bias/small study effects in the first study set (MTCT indicated by HBsAg positivity at 6–12 months in non-RCTs. Funnel plots for LAM 100–150 mg study sets, as well as results of the Egger test for asymmetry (if examining OR only) can be found in Appendix G.

Characteristics of included studies

Across all included studies (n=40), recruitment took place as early as 2001 and up to 2016. Almost all studies took place in the WHO Western Pacific Region; including China (n=35), China and the Philippines (n=1), Japan (n=1), and Australia (n=1). Additionally, one study took place in the WHO Eastern Mediterranean Region (i.e. Egypt), and one study took place in the WHO European Region (i.e. Ireland).

HBV genotyping for the entire study population was performed only in three instances. A study from Ireland estimated that the treatment group was 39% genotype B, 33% genotype C, 11% genotype D, 3% genotype E and 14% non-determined (*Jackson et al., 2015*). One Chinese study estimated the treatment group as 37% genotype B, 63% genotype C, whereas in the control group there were 29% genotype B and 71% genotype C (*Shen et al., 2016*). In a small study in Japan, all three mothers treated with LAM were genotype C, and in the control group one mother was genotype C and the two other mothers had indeterminable genotype (*Wakano et al., 2018*).

Most included study arms (i.e. 30/44) started maternal antiviral therapy between 24 and 30 weeks of gestation. The most common HBV DNA level designated for inclusion was >5.3 log10 IU/mL (14 of 44 treatment arms) (Table 10).

Genera	ll study detai	ls and desi	gn		Treated	d (TDF 3	00 mg) preg	nant wo	men (tx)			Untreated p	regnant	women (con	trol)	Infant ti	eatment (all	infants)
Author, year	Country	Recruit -ment period	HBV DNA level (inclusion)	#	Treatment Start du pregnancy postpart	ring End	Age, in years	HBe Ag %	HBV DNA at baseline	# Infants assessed for MTCT	#	Age, in years	HBe Ag %	HBV DNA at baseline	# Infants assessed for MTCT	HBIG at birth, <i>timing</i>	Birth dose vaccine, <i>timing</i>	Non- birthdos e vaccine, dose 1 /dose 2 in months
Randomized co	ntrolled tria	ls (RCTs)																
Bai XW, 2011	China	2006– 2010	NR	30	28	4	NR	NR	NR	30	25	NR	NR	NR	25	Yes <24 h	Yes <24 h	Yes, 1/6

Table 10. Characteristics of included studies investigating LAM 100-150 mg

		r		1	1		r	1		1	r				r		1	
Chen SM, 2017	China	2013– 2014	4.3 log10 IU/mL	30	28	NR	27.9±3.6	100	7.5 log10 IU/mL	30	30	27.5±3.9	100	8.0 log10 IU/mL	30	Yes, unclear	Yes, unclear	Yes, N/A
Guo YZ, 2008	China	2003– 2006	NR	70	28	0	NR	100	NR	70	40	NR	100	NR	40	Yes <6 h	Yes, at birth	Yes, 1/6
Ji YY, 2015	China	2010– 2013	5.3 log10 IU/mL	65	28	4	26.2±3.1	100	7.6 log10 IU/mL	65	65	27.5±4.1	100	7.7 log10 IU/mL	65	Yes <24 h	Yes <24 h	Yes, 1/6
Li ZG, 2015	China	2013– 2014	4.3 log10 IU/mL	25	28	6	NR	100	NR	25	25	NR	100	NR	25	Yes <24 h	Yes <24 h	Yes, 1/6
Tian XQ, 2015	China	2010– 2014	5.3 log10 IU/mL	110	28	0	29±3	100	7.9 log10 IU/mL	110	110	28±4	100	8.1 log10 IU/mL	110	Yes <24 h	Yes <24 h	Yes, 1/6
Xu WM, 2009	China, Philippin es	NR	NR	93	30–34	4	26 (19– 32)	99	8.6 log10 IU/mL	49	62	25 (20– 36)	100	8.7 log10 IU/mL	41	Yes <24 h	Yes <24 h	Yes, 1/6
Yang HW, 2014	China	2010– 2013	5.3 log10 IU/mL	53	28	4	29±4	100	7.3 log10 IU/mL	53	53	28±4	100	7.3 log10 IU/mL	53	Yes <24 h	Yes, at birth	Yes, 1/6
Non-randomize	ed controlled	trials (nor	n-RCTs)															
Chen QR, 2018	China	2014– 2016	NR	33	28	4	25.0±3.9	100	7.6 log10 IU/mL	33	28	24.1±4.7	100	7.7 log10 IU/mL	28	Yes, <24 h	Yes, <24 h	Yes, 1/6
Cheng YC, 2011	China	2007– 2009	6.3 log 10 IU/mL	30	32	4	27±4	100	8.2 log 10 IU/mL	30	26	25±5	100	7.5 log10 IU/mL	26	Yes, <24 h	Yes, <24 h	Yes, 1/6
Feng HF, 2007	China	2004– 2006	5.3 log10 IU/mL	48	28	4	NR	100	7.6 log10 IU/mL	48	42	NR	100	7.5 log10 IU/mL	42	Yes, <24 h	Yes, <24 h	Yes, 1/6
Foaud HM, 2019	Egypt	2012– 2015	NR	34	Anytime	NR	27.0±2.9 (tx in last trimester) 27.7±4.0 (tx throughout pregnancy)	44	NR	29	39	$\begin{array}{c} 27.4 \pm 4.6 \\ (\text{low HBV} \\ \text{DNA} \\ \text{group}) 25.7 \\ \pm 4.3 \\ (\text{diagnosed} \\ \text{too late for} \\ \text{tx}) \end{array}$	13	NR	30	Yes, at birth	Yes, at birth	No
Ge YL, 2015	China	NR	5.3 log10 IU/mL	16	28–30	12	27.9±3.6	100	7.2 log10 IU/mL	16	22	26.5±4.2	100	6.9 log10 IU/mL	22	Yes, <24 h	Yes, at birth	Yes, 1/6
Greenup AJ, 2014	Australia	2007– 2013	7 log10 IU/mL	48	32	12	28±5	96	NR	43	20	28±5	100	NR	10	Yes, unknown	Yes, at birth	Yes, 2/4/6
Han YP, 2014	China	2010– 2012	4.3 log10 IU/mL	30	28	6	26±4	100	7.6 log10 IU/mL	30	30	26±4	100	7.7 log10 IU/mL	30	Yes, <24 h	Yes, <24 h	Yes, 1/6
Han ZH, 2005	China	2001– 2003	4.9 log 10 IU/mL	43	28	0	NR	100	6.4 log10 IU/mL	43	35	NR	100	NR	35	Yes, <6 h	NR	Yes, 2/3

He T,	CI.	2008-	NR	27	1st	ND	20.212.0	74	6.3	20	25	20.012.0	0.0	6.25	34	Yes,	Yes,	Yes,
2018	China	2016		27	trimester	NR	29.2±2.9	/4	log10 IU/mL	29	35	29.0±3.6	80	log10 IU/mL	34	<6 h	<12 h	1/6
Jackson V, 2015	Ireland	2007– 2012	7.2 log10 IU/mL	36	32	0	26 (16– 40)	100	8.1 log10 IU/mL	21	9	NR	100	NR	6	Yes, <2–3 h	Yes, <2–3 h	Yes, 2/4/6
Jiang HX, 2012	China	2007– 2010	5.3 log10 IU/mL	164	20–34	0	27.3±4.4	100	7.1 log10 IU/mL	164	92	26.4±3.2	100	7.2 log10 IU/mL	92	Yes, <24 h	Yes, at birth	Yes, 1/6
Li G, 2006	China	2005– 2006	NR	40	28	0	24±3	100	NR	35	37	24±5	100	NR	32	Yes, <24 h	NR	Yes, 1/2/7
Li JH, 2017	China	2012– 2016	NR	33	28	4	28.2±6.3	NR	8.0 log10 IU/mL	33	27	29.4±5.7	NR	7.7 log10 IU/mL	27	Yes, <6 h	Yes, at birth	Yes, 1/6
Li WF, 2006	China	2001– 2003	4.3 log10 IU/mL	36	34	0	NR	100	6.1 log10 IU/mL	36	44	NR	100	NR	44	Yes, <6 h	NR	Yes, 2/3/7
Ma J, 2006	China	NR	NR	18	pre- pregnancy	NR	NR	10	NR	18	22	NR	100	NR	16	Yes, unknown /unclear	Yes, unknown /unclear	Yes, NR
Pan CQ,	China	2008-	5.3 log10	66	13–26	NR	27.5±3.8	100	6.5 log10 IU/mL	66	- 89	27.1±4.2	100	6.6 log10	89	Yes,	Yes,	Yes,
2017	China	2015	IU/mL	94	28–30	NR	27.5±3.8	100	6.5 log10 IU/mL	94	07	27.144.2	100	IU/mL	07	<6 h	<12 h	1/6
Ren CJ, 2016	China	2010– 2012	5.3 log10 IU/mL	67	28	0	25.8±4.7	100	6.1 log10 IU/mL	67	72	25.4±5.1	100	6.1 log10 IU/mL	72	Yes, <6 h	Yes, at birth	Yes, 1/6
Ren YJ, 2011	China	2008– 2009	NR	30	28	0	NR	100	NR	30	155	NR	100	NR	155	Yes, <24 h	Yes, at birth	Yes, 1/6
Shen ML, 2016	China	2010– 2014	4.3 log10 IU/mL	60	26	4	NR	NR	6.1 log10 IU/mL	60	28	NR	NR	6.0 log10 IU/mL	28	Yes, <24 h	Yes, unknown	Yes, NR
Su TB, 2009	China	2004– 2007	NR	128	32	0	NR	NR	NR	128	120	NR	NR	NR	120	Yes, <2–3 h	Yes, at birth	Yes, 1/6
Tang X, 2009	China	2007– 2008	5.3 log10 IU/mL	17	33	4	NR	100	6.6 log10 IU/mL	17	24	NR	100	6.7 log10 IU/mL	24	Yes <24 h	Yes, <24 h	Yes, 1/6
Wakano Y, 2018	Japan	2011– 2015	NR	3	28–32	4–8	All groups ranged from 28– 37	100	8.3 log10 IU/mL	3	3	All groups ranged from 28– 37	100	8.3 log10 IU/mL	3	Yes, at birth	Mixed, <12 h	Yes, varied
Wang DM, 2016	China	2011– 2014	5.3 log10 IU/mL	42	28-30	12	31.4±7.3	100	7.1 log10 IU/mL	42	20	31.7±7.0	100	7.1 log10 IU/mL	20	NR	Yes, <24 h	Yes, 1/6

Wang EJ, 2012	China	2008– 2010	6.3 log10 IU/mL	32	28	4	25.0±3.8	100	7.6 log10 IU/mL	32	27	24.0±4.7	100	7.7 log10 IU/mL	27	Yes, <24 hr	Yes, at birth	Yes, 1/6
Wang TM, 2005	China	2001– 2003	5.7 log10 IU/mL	32	pre- pregnancy	0	NR	100	NR	32	32	NR	100	NR	32	NR	Yes, <12 h	Yes, 1/6
Wang W, 2014	China	2011– 2012	NR	35	28	4	28.4±3.8	NR	7.4 log10 IU/mL	35	28	27.2±4.2	NR	7.2 log10 IU/mL	28	Yes, <24 h	Yes, at birth	Yes, 1/6
Yuan QF, 2012	China	2010– 2011	NR	30	27	4	All groups 26.5±4.5	100	NR	32	30	All groups 26.5±4.5	100	NR	32	Yes, <24 h	Yes, <24 h	Yes, 6/13
				30	28	0	NR	100	6.6 log10 IU/mL	30								
Zeng YM, 2013	China	2008– 2010	4.3 log10 IU/mL	30	28	4	NR	100	6.6 log10 IU/mL	30	30	NR	100	6.5 log10 IU/mL	30	Yes, at birth	Yes, at birth	Yes, 1/6
				30	28	6	NR	100	6.5 log10 IU/mL	30								
Zhang H, 2014	China	2009– 2011	6.3 log 10 IU/mL	55	28 - 30	4	28.4±7.1	100	6.9 log10 IU/mL	52	374	29.0±4.6	100	6.8 log10 IU/mL	352	Yes, <6 h	Yes, <6 h	Yes, 1/6
Zhang YF, 2010	China	2006– 2007	5.3 log10 IU/mL	50	28	4	NR	100	6.1 log10 IU/mL	50	50	NR	100	6.1 log10 IU/mL	50	Yes, <24 h	Yes, at birth	Yes, 1/6
Zhou DS,	China	2009-	5.3	49	20	NR	27.4±6.7	NR	6.8 log10 IU/mL	49	- 95	29.2±6.1	NR	6.9	95	Yes,	Yes,	Yes,
2013	China	2012	log10 IU/mL	64	28	NR	28.1±5.3	NR	6.7 log10 IU/mL	64	95	29.2±0.1		log10 IU/mL	95	<12 h	at birth	1/6
Zhu M, 2014	China	2012– 2013	NR	24	26	0	NR	100	NR	24	25	NR	100	NR	24	Yes, <6 h	Yes, <6 h	Yes, 1/6

NR=not reported in article *Age and HBV DNA at baseline presented as mean ± SD or median with either (IQR) or [range]

Primary efficacy analysis, narrative descriptions and forest plots

- 1. PMTCT, as indicated by detection of HBsAg at 6-12 months of age, all treatment start times, all HBV DNA levels at inclusion, stratified by study design (RCT and non-RCT)
 - Overall pooled OR=0.17 (95% CI: 0.13–0.22), P<0.001, I²=0%
 - RCTs only: pooled OR=0.16 (95% CI: 0.10–0.26), P<0.001, I²=0% 0
 - Non-RCTs only: pooled OR=0.17 (95% CI: 0.12–0.24), P<0.001, I²=0% 0
 - When looking at heterogeneity between RCTs and non-RCTs, we arrive at a 0 *P* value of 0.80, indicating no difference between the estimates.

LAM 100mg, MTCT=HBsAg+, by study design Tx_start (weeks GA) Tx_end (weeks PP) Events. Events Author Year Country OR (95% CI) Treatment Contro Randomised controlled trials 0.24 (0.05, 1.02) 3/30 0.07 (0.01, 0.58) 1/30 8/25 10/30 Bai XW 28 2011 China 4 NR Chen SM 2017 China 28 Guo YZ Ji YY 2008 2015 China 28 0 0.09 (0.02, 0.35) 3/70 13/40 28 0.14 (0.03, 0.65) 2/65 12/65 China 4 Li ZG 2015 China 28 0.22 (0.02, 2.11) 1/25 6 4/25 49/110 Tian XQ 2015 China 28 0 0.14 (0.07, 0.29) 11/110 Xu WM 2009 China, Philippines 30-34 0.47 (0.11, 2.10) 3/49 5/41 Yang HW 2014 China 28 4 0 24 (0 03 2 18) 1/53 4/53 105/389 Subtotal (I-squared = 0.0%, p = 0.794) 0.16 (0.10, 0.26) 25/432 Non-randor mised controlled trials Chen QR 2018 2011 China 28 4 0.14 (0.02, 1.31) 1/33 1.21 (0.36, 4.10) 8/30 5/28 Cheng YC 32 4 6/26 China 4 NR 0.28 (0.10, 0.77) 7/48 0.33 (0.01, 8.52) 0/29 Feng HF 2007 China 28 16/42 Foaud HM 2019 1/30 Anytime Egypt Ge YL 2015 China 28-30 12 12 0.17 (0.01, 3.51) 0/16 3/22 2/10 Greenup AJ 2014 Australia 32 0.04 (0.00, 0.89) 0/43 Han YP 2014 China 28 6 0.22 (0.02, 2.14) 1/30 4/30 0 0.06 (0.00, 1.20) 0/43 5/35 Han ZH 2005 China 28 NR 0.11 (0.01, 2.23) 0/29 4/34 He T 2018 China 1st Trin Jackson V 2015 reland 32 0 0.09 (0.00, 2.39) 0/21 1/6 Jiang HX 2012 China 20-34 0 0.03 (0.00, 0.53) 0/164 8/92 LiG 2006 China 28 0 0.11 (0.01, 0.91) 1/35 7/32 Li JH 0.07 (0.01, 0.64) 2017 China 28 1/33 8/27 0 NR Li WF 2006 China 24 0.15 (0.02, 1.29) 1/36 7/44 Ma J 2006 Pre-pregna 0.02 (0.00, 0.41) 0/18 China 9/16 0.05 (0.00, 0.88) 0/160 0.19 (0.04, 0.91) 2/67 Pan CQ 2017 China 13-26 NR 5/89 0 2016 10/72 Ren CJ China 28 2011 2016 0.38 (0.05, 2.99) 1/30 0.01 (0.00, 0.22) 0/60 Ren YJ China 28 26 0 4 13/155 Shen ML China 11/28 Su TB 2009 China 32 33 0 4 0.33 (0.12, 0.97) 5/128 13/120 0.13 (0.01, 2.59) 0/17 2009 4/24 Tang X China Wakano Y 2018 28-32 4-8 0.09 (0.00, 3.10) 0/3 Japan 2/3 2016 12 Wang DM China 28-30 0.07 (0.01, 0.68) 1/42 5/20 Wang EJ 2012 China 28 4 0.14 (0.02, 1.30) 1/32 5/27 Wang TM 2005 China Pre-prec 0 0.04 (0.00, 0.81) 0/32 8/32 0.15 (0.01, 3.24) Wang W 2014 China 28 0/35 2/28 Yuan QF 2012 China 27 4 0.31 (0.03, 3.17) 1/32 3/32 Zeng YM 2013 China 28 0.04 (0.00, 0.87) 0/90 3/30 Zhang H Zhang YF 2014 China 28-30 4 0.31 (0.02, 5.38) 0/52 10/352 2010a China 28 0.14 (0.04, 0.50) 3/50 16/50 Zhou DS 2013 China 28 NR 0.11 (0.04, 0.30) 5/113 28/95 Zhu M 0.15 (0.03, 0.80) 2/24 9/24 2014 China 26 0 Subtotal (I-squared = 0.0%, p = 0.686) 0.17 (0.12, 0.24) 41/1575 233/1655 Overall (I-squared = 0.0%, p = 0.830) Φ 0.17 (0.13, 0.22) 66/2007 338/2044

.001

Т

.167

10

- PMTCT, as indicated by detection of HBV DNA at 6–12 months of age, all treatment start times, all HBV DNA levels at inclusion, stratified by study design (RCT and non-RCT).
 - Overall pooled OR=0.16 (95% CI: 0.11–0.23), P<0.001, I²=0.0%
 - RCTs only: pooled OR=0.22 (95% CI: 0.10–0.47), P < 0.001, $I^2 = 39.8\%$
 - Non-RCTs only: pooled OR=0.14 (95% CI: 0.09–0.23), P<0.001, I²=0%
 - When looking at heterogeneity between RCTs and non-RCTs, we arrive at a *P* value of 0.47.

LAM 100mg, MTCT=HBVDNA+, by study design

Author	Year	Country	Tx_start (weeks GA)	Tx_end weeks PP)		OR (95% CI)	Events, Treatment	Events, Control
Randomis	ed cont	rolled trials						
Bai XW	2011	China	28	4	•	1.28 (0.20, 8.32)	3/30	2/25
Guo YZ	2008	China	28)		0.10 (0.03, 0.33)	4/70	15/40
Tian XQ	2015	China	28			0.13 (0.06, 0.29)	9/110	44/110
Xu WM	2009	China, Philippine	s30-34	4	4	0.32 (0.09, 1.12)	4/49	9/41
Yang HW	2014	China	28	4	<u> </u>	0.32 (0.03, 3.18)	1/53	3/53
Subtotal (I-square	ed = 39.8%, p = 0.1	156)	\diamond		0.22 (0.10, 0.47)	21/312	73/269
Non-rando	omised o	controlled trials						
Cheng YC	2011	China	32	4	-	0.25 (0.07, 0.92)	4/30	10/26
Feng HF	2007	China	28	4		0.28 (0.10, 0.77)	7/48	16/42
Foaud HN	I 2019	Egypt	Anytime	NR	<u> </u>	0.33 (0.01, 8.52)	0/29	1/30
Ge YL	2015	China	28-30	12		0.17 (0.01, 3.51)	0/16	3/22
Не Т	2018	China	1st Trimester	NR	<u> </u>	0.11 (0.01, 2.23)	0/29	4/34
Jiang HX	2012	China	20-34			0.03 (0.00, 0.53)	0/164	8/92
LiG	2006	China	28		+	0.13 (0.01, 1.12)	1/35	6/32
Li JH	2017	China	28	4		0.06 (0.01, 0.53)	1/33	9/27
Pan CQ	2017	China	13-26	NR	-	0.05 (0.00, 0.88)	0/160	5/89
Wang DM	2016	China	28-30	12 •		0.07 (0.01, 0.68)	1/42	5/20
Wang TM	2005	China	Pre-pregnancy)	+	0.08 (0.00, 1.45)	0/32	5/32
Wang W	2014	China	28	1	+-	0.08 (0.00, 1.49)	0/35	4/28
Yuan QF	2012	China	27	4	_	0.47 (0.08, 2.75)	2/32	4/32
Zeng YM	2013	China	28	4	-	0.04 (0.00, 0.87)	0/90	3/30
Zhang H	2014	China	28-30	4	<u> </u>	0.31 (0.02, 5.38)	0/52	10/352
Zhang YF	2010a	China	28	4		0.10 (0.02, 0.45)	2/50	15/50
Zhou DS	2013	China	28			0.10 (0.03, 0.33)	3/113	21/95
Zhu M	2014	China	26)		0.09 (0.01, 0.77)	1/24	8/24
Subtotal (I-square	ed = 0.0%, p = 0.93	35)	\diamond		0.14 (0.09, 0.23)	22/1014	137/10
Overall (I	square	d = 0.0%, p = 0.80	1)	\$		0.16 (0.11, 0.23)	43/1326	210/13

Subgroup analysis

Of the potential sources of heterogeneity prespecified in the protocol, it was not possible to do a subgroup analysis by coinfection status, as there were eventually no eligible populations who were coinfected. Furthermore, it was not possible to do subgroup analysis by WHO region, as almost all studies came from just one region (i.e. Western Pacific). For LAM, one ad hoc subgroup analysis is presented; timing of treatment being end postpartum. PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all HBV DNA levels at inclusion, all study designs merged (i.e. RCT and non-RCT), <u>stratified by</u>

trimester of treatment start.

- 1st trimester: not enough studies for meta-analysis (i.e. n < 3)
- 2nd trimester: pooled OR=0.09 (95% CI: 0.02–0.37), P=0.001, I²=0.0%
- 3rd trimester: pooled OR=0.19 (95% CI: 0.14–0.25), P<0.001, I²=0.0%
- When looking at heterogeneity between studies where treatment was started in the 2nd versus the 3rd trimester, we arrive at a *P* value of 0.29, indicating no difference between the estimates.

LAM 100mg, MTCT=HBsAg+, by trimester

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)		OR (95% CI)	Events, Treatment	Events, Control
2nd trimeste	r							
Li WF	2006	China	24	0		0.15 (0.02, 1.29)	1/36	7/44
Pan CQ	2017	China	13-26	NR		0.12 (0.01, 2.13)	0/66	5/89
Zhou DS	2013	China	20	NR -		0.02 (0.00, 0.40)	0/49	28/95
Subtotal (I-s	squared	= 0.0%, p = 0.538)				0.09 (0.02, 0.37)	1/151	40/228
3rd trimester	·				i			
Bai XW	2011	China	28	4		0.24 (0.05, 1.02)	3/30	8/25
Chen QR	2018	China	28	4		0.14 (0.02, 1.31)		5/28
Chen SM	2017	China	28	NB		0.07 (0.01, 0.58)		10/30
Chena YC	2011	China	32	4		 1.21 (0.36, 4.10) 		6/26
Feng HF	2007	China	28	4		0.28 (0.10, 0.77)		16/42
Ge YL	2015	China	28-30	12		0.17 (0.01, 3.51)		3/22
Greenup AJ		Australia	32	12 -		0.04 (0.00, 0.89)		2/10
Guo YZ	2008	China	28	0		0.09 (0.02, 0.35)		13/40
Han YP	2014	China	28	6		0.22 (0.02, 2.14)		4/30
Han ZH	2005	China	28	0		0.06 (0.00, 1.20)		5/35
Jackson V	2015	Ireland	32	0		0.09 (0.00, 2.39)		1/6
Ji YY	2015	China	28	4		0.14 (0.03, 0.65)		12/65
LiG	2006	China	28	0		0.11 (0.01, 0.91)		7/32
Li JH	2000	China	28	4		0.07 (0.01, 0.64)		8/27
Li ZG	2017	China	28	4		0.22 (0.02, 2.11)		4/25
Pan CQ	2013	China	28-30	NR		0.08 (0.00, 1.49)		5/89
Ren CJ	2017	China	28-30	0		0.19 (0.04, 0.91)		10/72
Ren YJ	2010	China	28	0		0.38 (0.05, 2.99)		13/155
Su TB	2011	China	20 32	0		0.38 (0.05, 2.99)		13/120
	2009	China	33	4				4/24
Tang X			28	4		0.13 (0.01, 2.59)		
Tian XQ Wakano Y	2015	China		0 4-8		0.14 (0.07, 0.29)		49/110 2/3
	2018	Japan	28-32	4-0 12		0.09 (0.00, 3.10)		
Wang DM	2016	China	28-30			0.07 (0.01, 0.68)		5/20
Wang EJ	2012	China	28	4		0.14 (0.02, 1.30)		5/27
Wang W	2014	China	28	4		0.15 (0.01, 3.24)		2/28
Xu WM	2009	China, Philippines		4		0.47 (0.11, 2.10)		5/41
Yang HW	2014	China	28	4		0.24 (0.03, 2.18)		4/53
Yuan QF	2012	China	27	4		0.31 (0.03, 3.17)		3/32
Zeng YM	2013	China	28	0		0.13 (0.01, 2.61)		3/30
Zeng YM	2013	China	28	4		0.13 (0.01, 2.61)		3/30
Zeng YM	2013	China	28	6		0.13 (0.01, 2.61)		3/30
Zhang H	2014	China	28-30	4	•	- 0.31 (0.02, 5.38)		10/352
Zhang YF	2010a		28	4		0.14 (0.04, 0.50)		16/50
Zhou DS	2013	China	28	NR		0.20 (0.07, 0.56)		28/95
Subtotal (I-s	squared	= 0.0%, p = 0.959)				0.19 (0.14, 0.26)	63/1500	287/18
Overall (I-so	quared =	= 0.0%, p = 0.958)			\$	0.19 (0.14, 0.25)	64/1651	327/203

- PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all HBV DNA levels at inclusion, all study designs merged (i.e. RCT and non-RCT), <u>stratified by</u> median weeks of gestation at the time of start of treatment (<28 weeks, 28 weeks, >28 weeks).
 - <28 weeks: pooled OR=0.10 (95% CI: 0.04–0.26), P<0.001, I²=0.0%
 - 28 weeks: pooled OR=0.16 (95% CI: 0.11–0.23), P<0.001, I²=0.0%
 - >28 weeks: pooled OR=0.31(95% CI: 0.16–0.57), P<0.001, I²=7.7%
 - When looking at heterogeneity across the three subgroups, the P value was 0.06. If comparing <28 weeks median with 28 weeks median, there was no heterogeneity (P=0.38). If comparing <28 weeks median with >28 weeks median, or if comparing 28 weeks median with >28 weeks median, there was evidence of heterogeneity (both with P=0.04); however, because of the mild heterogeneity within the subgroup starting at >28 weeks median, this test may not be valid.

LAM 100mg, MTCT=HBsAg+, by tx start time

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	OR (95% CI)	Events, Treatment	Events, Control
Median <28	weeks G	A		I			
He T	2018	China	1st Trimester	NR	0.11 (0.01, 2.23)	0/29	4/34
Li WF	2006	China	24	0	0.15 (0.02, 1.29)	1/36	7/44
Pan CQ	2017	China	13-26	NR	0.12 (0.01, 2.13)		5/89
Shen ML	2016	China	26	4	0.01 (0.00, 0.22)		11/28
Yuan QF	2012	China	27	4	0.31 (0.03, 3.17)		3/32
Zhou DS	2012	China	20		0.02 (0.00, 0.40)		28/95
Zhu M	2014	China	26	0	0.15 (0.03, 0.80)		9/24
Subtotal (I-s	quared :	= 0.0%, p = 0.583)		\sim	0.10 (0.04, 0.26)	4/296	67/346
Median 28 w	eeks GA	۱.					
Bai XW	2011	China	28	4	0.24 (0.05, 1.02)	3/30	8/25
Chen QR	2018	China	28	4	0.14 (0.02, 1.31)		5/28
Chen SM	2017	China	28	NB	0.07 (0.01, 0.58)		10/30
Feng HF	2007	China	28	4	0.28 (0.10, 0.77)		16/42
Guo YZ	2008	China	28		0.09 (0.02, 0.35)		13/40
Han YP	2008	China	28	6	0.09 (0.02, 0.35)		4/30
Han ZH	2005	China	28	0	0.06 (0.00, 1.20)		5/35
Ji YY	2015	China	28	4	0.14 (0.03, 0.65)		12/65
Li G	2006	China	28	0	0.11 (0.01, 0.91)		7/32
Li JH	2017	China	28	4	0.07 (0.01, 0.64)	1/33	8/27
Li ZG	2015	China	28	6	0.22 (0.02, 2.11)	1/25	4/25
Ren CJ	2016	China	28	0	0.19 (0.04, 0.91)	2/67	10/72
Ren YJ	2011	China	28	0	0.38 (0.05, 2.99)	1/30	13/155
Tian XQ	2015	China	28	0	0.14 (0.07, 0.29)	11/110	49/110
Wang EJ	2012	China	28	4	0.14 (0.02, 1.30)		5/27
Wang W	2014	China	28	4	0.15 (0.01, 3.24)		2/28
Yang HW	2014	China	28	4	0.24 (0.03, 2.18)		4/53
	2014	China	28	0			4/53 3/30
Zeng YM					0.13 (0.01, 2.61)		
Zeng YM	2013	China	28	4	0.13 (0.01, 2.61)		3/30
Zeng YM	2013	China	28	6	0.13 (0.01, 2.61)		3/30
Zhang YF		China	28	4	0.14 (0.04, 0.50)		16/50
Zhou DS	2013	China	28	NR	0.20 (0.07, 0.56)		28/95
Subtotal (I-s	quared :	= 0.0%, p = 1.000)		\$	0.16 (0.11, 0.22)	45/973	228/105
Median >28	weeks G	A					
Cheng YC	2011	China	32	4 –	1.21 (0.36, 4.10)	8/30	6/26
Ge YL	2015	China	28-30	12	0.17 (0.01, 3.51)		3/22
Greenup AJ		Australia	32	12	0.04 (0.00, 0.89)		2/10
Jackson V	2015	Ireland	32	0	0.09 (0.00, 2.39)		1/6
Pan CQ	2017	China	28-30	NR	0.08 (0.00, 1.49)		5/89
Su TB	2009	China	32		0.33 (0.12, 0.97)		13/120
Tang X	2009	China	33	4	0.13 (0.01, 2.59)		4/24
Wakano Y	2018	Japan	28-32	4-8	0.09 (0.00, 3.10)		2/3
Wang DM	2016	China	28-30	12	0.07 (0.01, 0.68)		5/20
Xu WM	2009	China, Philippines		4	0.47 (0.11, 2.10)	3/49	5/41
Zhang H	2014	China	28-30	4	0.31 (0.02, 5.38)	0/52	10/352
Subtotal (I-s	quared :	= 7.7%, p = 0.371)		\diamond	0.31 (0.16, 0.57)	17/495	56/713
Overa∎ (I-sq	juared =	0.0%, p = 0.939)		\$	0.18 (0.14, 0.24)	66/1764	351/211
				001 181	1 10		

- PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all study designs merged (i.e. RCT and non-RCT), <u>stratified by the</u> minimum HBV DNA level specified in the inclusion criteria of the study.
 - >4–4.99 log10 IU/mL: pooled OR=0.11 (95% CI: 0.05–0.25), P<0.001, I²=0.0%
 - >5–5.99 log10 IU/mL: pooled OR=0.15 (95% CI: 0.10–0.22), P<0.001, I²=0.0%
 - >6–6.99 log10 IU/mL: pooled OR=0.51 (95% CI: 0.12–2.12), P=0.357, I²=36.4%
 - $>7-7.99 \log 10 \text{ IU/mL}$: not enough studies (i.e. <3)
 - When looking at heterogeneity between studies with inclusion criteria of 4–4.99 log10 IU/mL versus 5–5.99 log10 IU/mL, the *P* value was 0.48. No comparison was done with 6–6.99 log10 IU/mL, as this OR was both heterogeneous and non-significant.

LAM 100mg, MTCT=HBsAg+, HBVDNA level

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)		OR (95% CI)	Events, Treatment	Events, Control
4-4.99 log	10 IU/ml							
Chen SM	2017	China	28	NR –	•	0.07 (0.01, 0.58)	1/30	10/30
Han YP	2014	China	28	6		0.22 (0.02, 2.14)	1/30	4/30
Han ZH	2005	China	28	0		0.06 (0.00, 1.20)	0/43	5/35
Li WF	2006	China	24	0		0.15 (0.02, 1.29)	1/36	7/44
Li ZG	2015	China	28	6		0.22 (0.02, 2.11)		4/25
Shen ML	2016	China	26	4 ←	<u> </u>	0.01 (0.00, 0.22)		11/28
Zeng YM	2013	China	28	0 -		0.13 (0.01, 2.61)		3/30
Zeng YM	2013	China	28	4		0.13 (0.01, 2.61)		3/30
Zeng YM		China	28	6		0.13 (0.01, 2.61)		3/30
			p = 0.904)	-	\diamond	0.11 (0.05, 0.25)		50/282
5-5.99 log ⁻	10 IU/ml							
Feng HF	2007	China	28	4		0.28 (0.10, 0.77)	7/48	16/42
Ge YL	2015	China	28-30	12 -	•	0.17 (0.01, 3.51)		3/22
Ji YY	2015	China	28	4		0.14 (0.03, 0.65)		12/65
Jiang HX	2012	China	20-34	0		0.03 (0.00, 0.53)		8/92
Pan CQ	2017	China	13-26	NR —		0.12 (0.01, 2.13)		5/89
Pan CQ	2017	China	28-30	NR		0.08 (0.00, 1.49)		5/89
Ren CJ	2016	China	28	0		0.19 (0.04, 0.91)		10/72
Tang X	2009	China	33	4 -		0.13 (0.01, 2.59)		4/24
Tian XQ	2015	China	28	0		0.14 (0.07, 0.29)		49/110
Wang DM		China	28-30	12 -		0.07 (0.01, 0.68)		5/20
Wang TM		China	Pre-pregnancy			0.04 (0.00, 0.81)		8/32
Yang HW		China	28	4	-	0.24 (0.03, 2.18)		4/53
Zhang YF			28	4		0.14 (0.04, 0.50)		16/50
Zhou DS	2010a	China	20	NR		0.02 (0.00, 0.40)		28/95
Zhou DS	2013	China	28	NR		0.20 (0.07, 0.56)		28/95
			p = 0.952)		4	0.15 (0.10, 0.22)		201/95
6-6.99 log [.]	10 IU/ml							
Cheng YC		China	32	4	·	1.21 (0.36, 4.10)	8/30	6/26
Wang EJ		China	28	4		0.14 (0.02, 1.30)		5/27
Zhang H	2012	China	28-30	4		0.31 (0.02, 5.38)		10/352
0			b, p = 0.207)	-	$\langle \rangle$	0.51 (0.12, 2.12)		21/405
Overall (I-	squared	= 0.0%, p	o = 0.700)		\	0.17 (0.12, 0.24)	45/1365	272/16
					<u> </u>			
				.001	169 1	10		

- PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all HBV DNA levels specified at inclusion, all study designs merged (i.e. RCT and non-RCT), <u>stratified by whether or not all women were HBeAg-positive.</u>
 - All HBeAg-positive: pooled OR=0.17 (95% CI: 0.12–0.23), P<0.001, I²=0.0%
 - Mixed HBeAg positivity: pooled OR=0.26 (95% CI: 0.08–0.82), P=0.022, I²=0.0%
 - When looking at heterogeneity between studies where all women versus only some women were HBeAg positive, we arrive at a *P* value of 0.46, indicating no difference between the estimates.

LAM 100mg, MTCT=HBsAg+, by HBeAg positivity

Han YP 2 Han ZH 2 Li WF 2 Li ZG 2 Zeng YM 2 Zeng YM 2 Zeng YM 2	itive 2017 2014 2005 2006 2015 2013 2013 2013 2013 2007	China China China China China China	28 28 28 24 28 28	NR 6 0 0		-	0.07 (0.01, 0.58) 0.22 (0.02, 2.14)	1/30 1/30	10/30 4/30
Chen SM 2 Han YP 2 Han ZH 2 Li WF 2 Li ZG 2 Zeng YM 2 Zeng YM 2 Zeng YM 2	2017 2014 2005 2006 2015 2013 2013 2013	China China China China China	28 28 24 28	6 0 0		-	0.22 (0.02, 2.14)		
Han YP 2 Han ZH 2 Li WF 2 Li ZG 2 Zeng YM 2 Zeng YM 2 Zeng YM 2 Zeng YM 2	2014 2005 2006 2015 2013 2013 2013	China China China China China	28 28 24 28	6 0 0			0.22 (0.02, 2.14)		
Han ZH 2 Li WF 2 Li ZG 2 Zeng YM 2 Zeng YM 2 Zeng YM 2	2005 2006 2015 2013 2013 2013	China China China China	28 24 28	0 0					
Li WF 2 Li ZG 2 Zeng YM 2 Zeng YM 2 Zeng YM 2	2006 2015 2013 2013 2013	China China China	24 28	0			0.06 (0.00, 1.20)	0/43	5/35
Li ZG Zeng YM	2015 2013 2013 2013	China China	28	-			0.15 (0.02, 1.29)	1/36	7/44
Zeng YM 2 Zeng YM 2 Zeng YM 2	2013 2013 2013	China		6			0.22 (0.02, 2.11)	1/25	4/25
Zeng YM Zeng Y	2013 2013			0			0.13 (0.01, 2.61)	0/30	3/30
Zeng YM 2	2013		28	4			0.13 (0.01, 2.61)	0/30	3/30
		China	28	6			0.13 (0.01, 2.61)	0/30	3/30
reng n		China	28	4			0.28 (0.10, 0.77)	7/48	3/30 16/42
Ge YL 2	2015	China	28-30	12			0.17 (0.01, 3.51)	0/16	3/22
	2015	China	28-30 28	4		_	0.14 (0.03, 0.65)	2/65	3/22
	2015	China	28 20-34	4 0 —		_		2/65 0/164	8/92
0							0.03 (0.00, 0.53)		
	2017	China	13-26	NR			0.12 (0.01, 2.13)	0/66	5/89
	2017	China	28-30	NR			0.08 (0.00, 1.49)	0/94	5/89
	2016	China	28	0			0.19 (0.04, 0.91)	2/67	10/72
	2009	China	33	4			0.13 (0.01, 2.59)	0/17	4/24
	2015	China	28	0			0.14 (0.07, 0.29)	11/110	49/110
0	2016	China	28-30	12			0.07 (0.01, 0.68)	1/42	5/20
0	2005	China	Pre-pregnancy	0 -			0.04 (0.00, 0.81)	0/32	8/32
0	2014	China	28	4			0.24 (0.03, 2.18)	1/53	4/53
	2010a	China	28	4	•		0.14 (0.04, 0.50)	3/50	16/50
0	2011	China	32	4		•	1.21 (0.36, 4.10)	8/30	6/26
0	2012	China	28	4	-		0.14 (0.02, 1.30)	1/32	5/27
	2014	China	28-30	4			0.31 (0.02, 5.38)	0/52	10/352
	2015	Ireland	32	0	•		0.09 (0.00, 2.39)	0/21	1/6
	2018	China	28	4			0.14 (0.02, 1.31)	1/33	5/28
	2008	China	28	0			0.09 (0.02, 0.35)	3/70	13/40
	2006	China	28	0			0.11 (0.01, 0.91)	1/35	7/32
	2006	China	Pre-pregnancy	NR			0.02 (0.00, 0.41)	0/18	9/16
	2011	China	28	0			0.38 (0.05, 2.99)	1/30	13/155
	2018	Japan	28-32	4-8			0.09 (0.00, 3.10)	0/3	2/3
Yuan QF 🛛 🏻 🏻	2012	China	27	4		_	0.31 (0.03, 3.17)	1/32	3/32
Zhu M 🛛 🏾	2014	China	26	0		-	0.15 (0.03, 0.80)	2/24	9/24
Subtotal (I-squ	uared =	0.0%, p = 0.947)			\mathbf{Q}		0.17 (0.12, 0.23)	49/1458	267/1755
Mixed HBeAg p	positivity	,							
Greenup AJ	2014	Australia	32	12			0.04 (0.00, 0.89)	0/43	2/10
Foaud HM 2	2019	Egypt	Anytime	NR		_	0.33 (0.01, 8.52)	0/29	1/30
He T 🛛	2018	China	1st Trimester	NR		-	0.11 (0.01, 2.23)	0/29	4/34
Xu WM 🛛	2009	China, Philippines	30-34	4			0.47 (0.11, 2.10)	3/49	5/41
Subtotal (I-squ	uared =	0.0%, p = 0.504)			\sim	>	0.26 (0.08, 0.82)	3/150	12/115
Overall (I-squa	ared = 0	.0%, p = 0.952)			•		0.17 (0.13, 0.23)	52/1608	279/1870
				Ι					
				.001	.171	1 10)		

 PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all HBV DNA levels specified at inclusion, all study designs merged (i.e. RCT and non-RCT), by infant immunoprophylaxis regimen (Table 11).

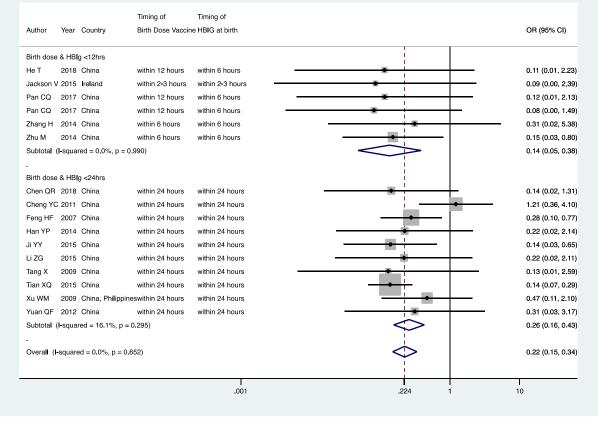
Table 11. Infant immunoprophylaxis regimens seen in studies investigating LAM

Birth dose vaccine	HBIG at birth	2–4 infant HBV vaccines (not at birth)	# studies (treatment arms)
Yes*	Yes	Yes	34 (38)
Yes	Yes	NR	1 (1) (Foaud HM et al., 2019)

No	Yes	Yes	3 (3) (Han ZH et al., 2005; Li G et
			al., 2006; Li WF et al., 2006)
Yes	NR	Yes	2 (2) (Wang DM et al., 2016;
			Wang TM et al., 2005)

*For one study, some infants received birth dose and others did not. NR: not reported

- As most studies provided all of birth dose vaccine, HBIG at birth, and subsequent infant vaccinations, stratification by type or combination of infant immunoprophylaxis was not done in this meta-analysis.
- Therefore, we stratified by whether or not both birth dose vaccine and HBIG were given within 12 hours of life, versus within 24 hours of life.
 - \circ <12 hours: pooled OR=0.14 (95% CI: 0.05–0.39), P<0.001, I²=0.0%
 - \circ <24 hours: pooled OR=0.26 (95% CI: 0.16-0.43), P<0.001, I²=16.1%
 - The P value for heterogeneity between the two subgroups was 0.31.



LAM 100mg, HBsAg +, by BD & HBIG timing

6. PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all study designs merged (i.e. RCT and non-RCT), <u>stratified by the</u>

timing that treatment was discontinued postpartum.

- At delivery: pooled OR=0.15 (95% CI: 0.10–0.23), P<0.001, I²=0.0%
- 4–8 weeks postpartum: pooled OR=0.23 (95% CI: 0.15–0.36), P<0.001, I²=0.0%
- 12 weeks postpartum: pooled OR=0.08 (95% CI: 0.02–0.37), P=0.001, I²=0.0%
- 24+ weeks postpartum: no studies within this subgroup
- When looking at heterogeneity across the four subgroups, the *P* value was 0.20.

Author	Year	Country	Birth Dose Vaccin	BIG at birth	OR (95% CI)
At delivery					
Guo YZ	2008	China	'at birth'	rithin 6 hours	0.09 (0.02, 0
-lan ZH	2005	China	N/A	ithin 6 hours	0.06 (0.00, 1.
lackson V	2015	Ireland	within 2-3 hours	ithin 2-3 hours	0.09 (0.00, 2
liang HX	2012	China	'at birth'	ithin 24 hours	0.03 (0.00, 0
iG	2006	China	N/A	ithin 24 hours	0.11 (0.01, 0.
i WF	2006	China	N/A	ithin 6 hours	0.15 (0.02, 1,
len CJ	2016	China	'at birth'	ithin 6 hours	0.19 (0.04, 0.
en YJ	2011	China	'at birth'	ithin 24 hours	0.38 (0.05, 2
u TB	2009	China	'at birth'	ithin 2-3 hours	0.33 (0.12, 0.
ian XQ	2015	China	within 24 hours	ithin 24 hours	0.14 (0.07, 0
ang TM	2005	China	within 12 hours	/A •	0.04 (0.00, 0
eng YM	2013	China	'at birth'	t birth'	• 0.13 (0.01, 2
hu M		China	within 6 hours	ithin 6 hours	0.15 (0.03, 0.
ubiotar (F	-square	d = 0.0%, p =	0.913)		0.15 (0.10, 0.
to 8 week					
ai XW	2011	China	within 24 hours	ithin 24 hours	0.24 (0.05, 1
hen QR	2018	China	within 24 hours	ithin 24 hours	0.14 (0.02, 1.
heng YC	2011	China	within 24 hours	ithin 24 hours	1.21 (0.36, 4
eng HF	2007	China	within 24 hours	ithin 24 hours	0.28 (0.10, 0.
an YP	2014	China	within 24 hours	ithin 24 hours	0.22 (0.02, 2
YY	2015	China	within 24 hours	ithin 24 hours	0.14 (0.03, 0.
JH	2017	China	'at birth'	ithin 6 hours	0.07 (0.01, 0
ZG	2015	China	within 24 hours	ithin 24 hours	0.22 (0.02, 2
hen ML	2016	China	unknown/unclear	ithin 24 hour	0.01 (0.00, 0
ang X	2009	China	within 24 hours	ithin 24 hours	0.13 (0.01, 2
/akano Y	2018	Japan	within 12 hours	t birth'	0.09 (0.00, 3
/ang EJ	2012	China	'at birth'	ithin 24 hours	0.14 (0.02, 1
/ang W	2014	China	'at birth'	ithin 24 hours	0.15 (0.01, 3.
u WM	2009		pineswithin 24 hours	ithin 24 hours	0.47 (0.11, 2.
ang HW	2014	China	'at birth'	ithin 24 hours	0.24 (0.03, 2
uan QF	2012	China	within 24 hours	ithin 24 hours	0.31 (0.03, 3)
eng YM	2012	China	'at birth'	t birth'	0.13 (0.01, 2
eng YM	2013	China	'at birth'	t birth'	0.13 (0.01, 2
hang H		China	within 6 hours	ithin 6 hours	0.13 (0.01, 2)
	2014 2010a		'at birth'	ithin 24 hours	
		d = 0.0%, p =		Innin 24 hours	0.14 (0.04, 0.
ubtotal (I-	-square	a = 0.0%, p =	0.680)		0.23 (0.15, 0.
2 weeks p	ost-del	ivery			
ie YL	2015	China	'at birth'	ithin 24 hours	0.17 (0.01, 3
ireenup A.	J2014	Australia	'at birth'	nknown/unclear	0.04 (0.00, 0
/ang DM	2016	China	within 24 hours	/A	0.07 (0.01, 0
ubtotal (I	square	d = 0.0%, p =	0.799)		0.08 (0.02, 0.
verall (I-s	quarec	l = 0.0%, p = 0).885)		0.18 (0.14, 0.
				.001	.183 1 10
				.001	.100 1 10

LAM 100mg, HBsAg +, by tx end timing

Safety analysis, narrative descriptions and selected forest plots

Infant safety outcomes

Of the infant safety outcomes prespecified in the protocol, the data for Apgar score were not available for the majority of included studies and where it was available the format varied greatly; this led to an inability to combine results in a meaningful way. None of the included studies for LAM investigated bone mineral density in infants.

1. <u>Neonatal deaths</u> (death within 28 days of life)

Information on this outcome was available for all except one study that administered LAM to mothers. One death in 2010 infants (non-weighted average 0.05%) was reported across the treatment groups and one death in 2093 infants (non-weighted average 0.05%) was reported across the control groups. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.000 (95% CI: -0.006–0.006). The I² statistics for the overall pooled risk difference, as well as for RCTs and non-RCTs separately, were all 0.0%.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)		RD (95% CI)	Events, Treatment	Events Contro
Randomised	d control	ed trials						
Bai XW	2011	China	28	4		0.00 (-0.07, 0.07)	0/30	0/25
Chen SM	2017	China	28	NB		0.00 (-0.06, 0.06)		0/30
Guo YZ	2008	China	28	0	_	0.00 (-0.04, 0.04)		0/40
Ji YY	2015	China	28	4	_	0.00 (-0.03, 0.03)		0/65
_i ZG	2015	China	28	6		0.00 (-0.07, 0.07)		0/25
Fian XQ	2015	China	28	0	-	0.00 (-0.02, 0.02)		0/110
Ku WM	2009	China, Philippines	30-34	4		0.00 (-0.05, 0.05)		1/59
Yang HW	2014	China	28	4	_	0.00 (-0.04, 0.04)		0/53
		= 0.0%, p = 1.000)			Ŷ	0.00 (-0.01, 0.01)		1/407
Non-random	nised cor	trolled trials						
Chen QR	2018	China	28	4		0.00 (-0.06, 0.06)	0/33	0/28
Chena YC	2011	China	32	4		0.00 (-0.07, 0.07)		0/26
Feng HF	2007	China	28	4		0.00 (-0.04, 0.04)		0/42
Foaud HM	2019	Egypt	Anytime	NR		0.00 (-0.05, 0.05)		0/39
Ge YL	2015	China	28-30	12		0.00 (-0.10, 0.10)		0/22
Greenup AJ		Australia	32	12	————	0.00 (-0.07, 0.07)		0/20
Han YP	2014	China	28	6		0.00 (-0.06, 0.06)		0/30
Han ZH	2005	China	28	0		0.00 (-0.05, 0.05)		0/35
He T	2018	China	1st Trimester	NR		0.00 (-0.06, 0.06)		0/34
Jiang HX	2012	China	20-34	0	÷	0.00 (-0.02, 0.02)		0/92
_i G	2006	China	28	0		0.00 (-0.06, 0.06)		0/32
_i JH	2017	China	28	4		0.00 (-0.06, 0.06)		0/27
i WF	2006	China	24	0		0.00 (-0.05, 0.05)		0/44
Ma J	2006	China	Pre-pregnancy	NR		0.00 (-0.11, 0.11)		0/16
Pan CQ	2017	China	28-30	NR	.	0.00 (-0.02, 0.02)		0/89
Ren CJ	2016	China	28	0		0.00 (-0.03, 0.03)		0/72
Ren YJ	2011	China	28	0		0.00 (-0.05, 0.05)		0/155
Shen ML	2016	China	26	4	—	0.00 (-0.05, 0.05)		0/28
Su TB	2009	China	32	0	÷	0.00 (-0.02, 0.02)		0/120
Tang X	2009	China	33	4		0.00 (-0.09, 0.09)		0/24
Nakano Y	2018	Japan	28-32	4-8		→ 0.00 (-0.46, 0.46)		0/3
Nang DM	2016	China	28-30	12	_	0.00 (-0.07, 0.07)		0/20
Wang EJ	2012	China	28	4	—	0.00 (-0.06, 0.06)		0/27
Wang TM	2005	China	Pre-pregnancy	0		0.00 (-0.06, 0.06)		0/32
Nang W	2014	China	28	4		0.00 (-0.06, 0.06)		0/28
Yuan QF	2012	China	27	4	_ _	0.00 (-0.06, 0.06)		0/32
Zeng YM	2012	China	28	4		0.00 (-0.05, 0.05)		0/30
Zhang H	2014	China	28-30	4	-	0.00 (-0.03, 0.03)		0/370
Zhang YF	2014 2010a		28	4		0.00 (-0.04, 0.04)		0/50
Zhou DS	2013	China	28	NR	.	0.00 (-0.02, 0.02)		0/95
Zhu M	2014	China	26	0		0.00 (-0.08, 0.08)		0/24
		= 0.0%, p = 1.000)		•	, i i i i i i i i i i i i i i i i i i i	0.00 (-0.01, 0.01)		0/168
Overa li (i- so	quared =	0.0%, p = 1.000)			•	0.00 (-0.01, 0.01)	1/2010	1/209

LAM 100mg, Neonatal deaths risk difference

Prematurity (typically defined as birth earlier than 37 weeks of gestation) Information on this outcome was available for 10 of the 40 included studies that administered LAM to mothers. Within these studies, 14 of 609 (non-weighted average 2.3%) infants whose mothers were treated with LAM during pregnancy were born prematurely, whereas 11 of 399 (non-weighted average 2.8%) infants whose mothers were not treated during pregnancy were born prematurely. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.000 (95% CI: -0.025–0.025). The I² statistics for the overall pooled risk difference estimated was 43.0%. The I² statistics for non-RCTs was 55.6%. There were too few RCTs (i.e. <3) to consider the pooled risk difference separately in this subgroup.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)		RD (95% CI)	Events, Treatment	Events Contro
Randomised								
Guo YZ		China	28	0		0.00 (-0.04, 0.04)	0/70	0/40
Yang HW	2014	China	28	4		0.00 (-0.04, 0.04)	0/53	0/53
Subtotal (I-s	quared :	= 0.0%, p =	1.000)		$\mathbf{\Phi}$	0.00 (-0.03, 0.03)	0/123	0/93
Non-randomi Greenup AJ		trolled trials Australia		12		0.06 (-0.04, 0.15)	3/53	0/20
•						,		
He T	2018		1st Trimester	NR		→ 0.21 (0.05, 0.38)	7/29	1/34
Jiang HX	2012	China	20-34	0		-0.03 (-0.07, 0.02)	3/164	4/92
Ma J	2006	China	Pre-pregnancy	NR		-0.31 (-0.55, -0.08)	0/18	5/16
Pan CQ	2017	China	28-30	NR	-	-0.00 (-0.03, 0.02)	1/160	1/89
Wakano Y	2018	Japan	28-32	4-8	<	→ 0.00 (-0.46, 0.46)	0/3	0/3
Wang W	2014	China	28	4		0.00 (-0.06, 0.06)	0/35	0/28
Zhu M	2014	China	26	0		0.00 (-0.08, 0.08)	0/24	0/24
Subtotal (I-s	quared :	= 55.6%, p	= 0.027)		$\overline{\Phi}$	0.00 (-0.04, 0.04)	14/486	11/306
Overall (I-sq	uared =	43.0%, p =	0.071)		\$	-0.00 (-0.03, 0.02)	14/609	11/399

LAM 100mg, Prematurity risk difference

3. Congenital abnormalities

Information on this outcome was available for 16 of the 40 included studies that administered LAM to mothers. Within these studies, eight of 845 (non-weighted average 0.9%) infants whose mothers were treated with LAM during pregnancy were noted to have some sort of congenital abnormality, including: atrial septal defect with Ebstein anomaly and pneumothorax (n=1), cleft palate (n=1), polydactyly (n=3), auricular defect (n=1), left ear pinna turn malformation (n=1), and absent ear (n=1). Five of 953 (nonweighted average 0.5%) infants whose mothers were not treated during pregnancy were noted to have some sort of congenital abnormality, including: polydactyly (n=1), talipes equinovarus (n=1), ear accessory (n=1), pulmonary stenosis (n=1), hydrocephalus (n=1). The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.003 (95% CI: -0.007–0.014). The I² statistics for the overall pooled risk, as well as for RCTs and non-RCTs separately, were all 0%.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	RD (95% CI)	Events, Treatment	Event Contro
Randomised	contro	led trials					
Tian XQ	2015	China	28	0 🔶	0.00 (-0.02, 0.02)	0/110	0/110
Xu WM	2009	China, Philippines	30-34	4	0.02 (-0.03, 0.07	1/56	0/59
Yang HW	2014	China	28	4	0.00 (-0.04, 0.04	0/53	0/53
Subtotal (I-s	quared	= 0.0%, p = 0.730)		Ŷ	0.00 (-0.01, 0.02	1/219	0/222
Non-random	ised co	ntrolled trials					
Foaud HM	2019	Egypt	Anytime	NR	0.00 (-0.05, 0.05)	0/34	0/39
Ge YL	2015	China	28-30	12	0.00 (-0.10, 0.10)	0/16	0/22
Greenup AJ	2014	Australia	32	12	0.04 (-0.05, 0.12)	2/53	0/20
Не Т	2018	China	1st Trimester	NR	-0.09 (-0.20, 0.02) 0/29	3/34
Ma J	2006	China	Pre-pregnancy	NR -	0.00 (-0.11, 0.11)	0/18	0/16
Pan CQ	2017	China	28-30	NR -	0.03 (-0.00, 0.06)	5/160	0/89
Shen ML	2016	China	26	4	0.00 (-0.05, 0.05)	0/60	0/28
Wakano Y	2018	Japan	28-32	4-8	→ 0.00 (-0.46, 0.46)	0/3	0/3
Wang DM	2016	China	28 - 30	12	- 0.00 (-0.07, 0.07)	0/42	0/20
Wang W	2014	China	28	4	0.00 (-0.06, 0.06)	0/35	0/28
Yuan QF	2012	China	27	4	0.00 (-0.06, 0.06)	0/32	0/32
Zeng YM	2013	China	28	4	0.00 (-0.05, 0.05)	0/90	0/30
Zhang H	2014	China	28 - 30	4	-0.01 (-0.03, 0.02) 0/54	2/370
Subtotal (I-s	quared	= 0.0%, p = 0.872)		Ŷ	0.00 (-0.01, 0.02)	7/626	5/731
Overall (I-sq	uared :	= 0.0%, p = 0.950)		•	0.00 (-0.01, 0.01)	8/845	5/953
				3 0	.3		

LAM 100mg, Congenital abnormalities risk difference

Maternal safety outcomes

1. <u>Fetal demise</u> (miscarriage [<28 weeks], stillbirth [>=28 weeks])

Information on this outcome was available for 39 of the 40 studies that administered LAM to mothers. Ten cases of fetal demise were reported across all study populations. One case (non-weighted average 0.05%) occurred across 2003 mothers/fetuses who were treated with LAM during pregnancy. Nine cases (non-weighted average 0.4%) occurred across 2087 mothers/fetuses who were not treated during pregnancy. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.000 (95% CI: -0.006–0.005). The I² statistics for the overall pooled risk difference estimate as well as for RCTs and non-RCTs separately, were all 0%.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	RD (95% CI)	Events, Treatment	Event Contr
Randomised	control	led trials					
Bai XW	2011	China	28	4	0.00 (-0.07, 0.07)	0/30	0/25
Chen SM	2017	China	28	NR	0.00 (-0.06, 0.06)	0/30	0/30
Guo YZ	2008	China	28	0	0.00 (-0.04, 0.04)	0/70	0/40
Ji YY	2015	China	28	4	0.00 (-0.03, 0.03)	0/65	0/65
Li ZG	2015	China	28	6	0.00 (-0.07, 0.07)	0/25	0/25
Tian XQ	2015	China	28	0	0.00 (-0.02, 0.02)	0/110	0/110
Xu WM	2009	China, Philippines		4	0.01 (-0.02, 0.05)	1/89	0/61
Yang HW	2014	China	28	4	0.00 (-0.04, 0.04)	0/53	0/53
5		= 0.0%, p = 1.000)	20	Î Î	0.00 (-0.01, 0.01)	1/472	0/409
Non rondom	iood oor	ntrolled trials					
Chen QR	2018	China	28	4	0.00 (-0.06, 0.06)	0/33	0/28
	2018	China	28 32	4		0/33	0/28
Cheng YC					0.00 (-0.07, 0.07)		
Feng HF	2007	China	28	4	0.00 (-0.04, 0.04)	0/48	0/42
Ge YL	2015	China	28-30	12	- 0.00 (-0.10, 0.10)	0/16	0/22
Greenup AJ	2014	Australia	32	12	0.00 (-0.07, 0.07)	0/52	0/20
Han YP	2014	China	28	6	0.00 (-0.06, 0.06)	0/30	0/30
Han ZH	2005	China	28	0	0.00 (-0.05, 0.05)	0/43	0/35
He T	2018	China	1st Trimester	NR	-0.06 (-0.15, 0.04)	0/27	2/35
Jiang HX	2012	China	20-34	0	0.00 (-0.02, 0.02)	0/164	0/92
Li G	2006	China	28	0	0.00 (-0.06, 0.06)	0/35	0/32
Li JH	2017	China	28	4	0.00 (-0.06, 0.06)	0/33	0/27
Li WF	2006	China	24	0	0.00 (-0.05, 0.05)	0/36	0/44
Ma J	2006	China	Pre-pregnancy	NR 🔶	-0.27 (-0.47, -0.08	0/18	6/22
Pan CQ	2017	China	28-30	NR 🔶	0.00 (-0.02, 0.02)	0/160	0/89
Ren CJ	2016	China	28	0	0.00 (-0.03, 0.03)	0/67	0/72
Ren YJ	2011	China	28	0	0.00 (-0.05, 0.05)	0/30	0/15
Shen ML	2016	China	26	4	0.00 (-0.03, 0.03)	0/60	0/60
Su TB	2009	China	32	•	0.00 (-0.02, 0.02)	0/128	0/120
Tang X	2009	China	33	4	0.00 (-0.09, 0.09)	0/17	0/24
Wakano Y	2018	Japan	28-32	4-8	0.00 (-0.46, 0.46)	0/3	0/3
Wang DM	2016	China	28-30	12	0.00 (-0.07, 0.07)	0/42	0/20
Wang EJ	2012	China	28	4	0.00 (-0.06, 0.06)	0/32	0/27
Wang TM	2005	China	Pre-pregnancy		0.00 (-0.06, 0.06)	0/32	0/32
Wang W Wang W	2003	China	28	4	0.00 (-0.06, 0.06)	0/35	0/28
Yuang W Yuan QF	2014	China	28 27	4	0.00 (-0.06, 0.06)	0/35	0/28
	2012	China	28	4	0.00 (-0.05, 0.05)	0/30	0/30
Zeng YM	2013		28 28-30	4			
Zhang H		China			0.00 (-0.03, 0.03)	0/53	0/36
Zhang YF	2010a		28	4	0.00 (-0.04, 0.04)	0/50	0/50
Zhou DS	2013	China	28	NR 🔶	0.00 (-0.02, 0.02)	0/113	0/95
Zhu M	2014	China	26	0	-0.04 (-0.15, 0.07)		1/25
Subtotal (I-s	quared	= 0.0%, p = 0.998)			-0.00 (-0.01, 0.01)	0/1531	9/16
Overall (I-so	uared =	0.0%, p = 1.000)		•	-0.00 (-0.01, 0.01)	1/2003	9/208

LAM 100mg, fetal demise risk difference

2. Postpartum haemorrhage

Information on this outcome was available for eight of the 40 included studies that administered LAM to mothers. Within these studies, 98 of 611 (non-weighted average 16.0%) mothers who were treated with LAM during pregnancy experienced postpartum haemorrhage, whereas 61 of 752 (8.1%) mothers who were not treated during pregnancy experienced postpartum haemorrhage. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.008 (95% CI: -0.012–0.028). The I² statistics for the overall pooled OR, as well as for non-RCTs separately were 0%. Not enough RCTs evaluated this safety outcome to consider this subgroup separately.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)		Events, Treatment	Events Contro
Randomised	control	ed trials			<u>i</u>		
Yang HW	2014	China	28	4	0.00 (-0.04, 0.04)	0/53	0/53
Subtotal (I-se	quared	= .%, p = .)			0.00 (-0.04, 0.04)	0/53	0/53
•							
Non-randomi	sed cor	trolled trial	5				
Greenup AJ	2014	Australia	32	12	-0.05 (-0.23, 0.12)	5/52	3/20
He T	2018	China	1st Trimester	NR	0.08 (-0.05, 0.21)	3/27	1/35
Jiang HX	2012	China	20-34	0	0.04 (-0.08, 0.16)	69/164	35/92
Pan CQ	2017	China	28-30	NR	0.02 (-0.02, 0.07)	7/160	2/89
Ren CJ	2016	China	28	0	-0.01 (-0.15, 0.12)	13/67	15/72
Wang W	2014	China	28	4	0.00 (-0.06, 0.06)	0/35	0/28
Zhang H	2014	China	28-30	4	0.01 (-0.03, 0.04)	1/53	5/363
Subtotal (I-se	quared	= 0.0%, p =	0.862)		0.01 (-0.01, 0.04)	98/558	61/699
Overall (I-sq	uared =	0.0%, p =	0.877)		0.01 (-0.01, 0.03)	98/611	61/752
					0 .2		

LAM 100mg, post-partum haemorrhage risk difference

3. Antiviral resistance

Four studies that treated mothers with LAM during pregnancy reported on some results of antiviral resistance testing. One study from Australia reported the selection of primary resistant variants to LAM in 21 treated women (*Greenup AJ et al., 2014*). One study from China reported no cases of antiviral resistance in both treated and control groups, with no other details provided (*Shen ML et al., 2016*). Another Chinese study performed resistance testing in five women with viral breakthrough and found no resistance mutants (*Zhang H et al., 2014*). Finally, a study from Ireland carried out antiviral resistance testing on 28 of the 36 women treated with LAM during pregnancy and reported identification of wild-type strains in all women (*Jackson V et al., 2015*).

4. HBV flare after treatment discontinuation

Information on this outcome was available for six of the 40 included studies that administered LAM to mothers. Various definitions were used, including: "postpartum ALT elevations", "postpartum flare", "grade 3/4 elevation", as well as no definition in some cases. Within these studies, 53 of 370 (non-weighted average 14.3%) mothers who were treated with LAM during pregnancy experienced a type of HBV flare at the time of treatment discontinuation, whereas 46 of 550 (non-weighted average 8.4%) mothers who were not treated during pregnancy experienced the same type of HBV flare at a matched time-point. The weighted pooled risk difference for this safety outcome seen following meta-analysis was -0.059 (95% CI: -0.207–0.089). Overall, the pooled risk difference had a high level of heterogeneity (I² of 88.3%), as well as within the non-RCTs only, the I² was 87.8%. It was not possible to examine the RCTs alone as a subgroup as there was only one study.

			Tx_start	Tx_end			Events,	Ever
Author	Year	Country	(weeks GA)	(weeks PP)		RD (95% CI)	Treatment	Cont
Randomised	control	led trials						
Xu WM	2009	China, Philippines	30-34	4		-0.13 (-0.29, 0.03)	16/83	15/4
Subtotal (I-s	quared	= .%, p = .)				-0.13 (-0.29, 0.03)	16/83	15/4
•								
Non-randomi	sed co	ntrolled trials						
Greenup AJ	2014	Australia	32	12		• 0.21 (-0.06, 0.49)	22/44	4/14
He T	2018	China	1st Trimester	NR		-0.17 (-0.31, -0.04)	0/27	6/35
Pan CQ	2017	China	28-30	NR		-0.14 (-0.24, -0.04)	15/160	21/8
Wakano Y	2018	Japan	28-32	4-8		0.00 (-0.46, 0.46)	0/3	0/3
Zhang H	2014	China	28-30	4	+	0.00 (-0.03, 0.03)	0/53	0/36
Subtotal (I-s	quared	= 87.8%, p = 0.000)			-0.04 (-0.20, 0.11)	37/287	31/5
Overall (I-sq	uared =	= 88.3%, p = 0.000)				-0.06 (-0.21, 0.09)	53/370	46/5
				5		I .5		

LAM 100mg, HBV flare risk difference

GRADE summary of findings

Table 12. GRADE evidence profile: LAM 100–150 mg during pregnancy to prevent HBV mother-to-child transmission (MTCT)

		Q	uality assessm	nent				Number of	patients	E	ffect	
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	Quality
HBsAg pos	sitivity at 6–12	months										
8	Randomized controlled trials (RCTs)	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	25/432 (5.8)	105/389 (27.0)	0.16 (0.10– 0.26)	190 fewer per 1000 (90–280 fewer)	Moderate ^a
32	Non-RCTs	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect.	41/1575 (2.6)	233/1655 (14.1)	0.17 (0.12– 0.24)	140 fewer per 1000 (110–180 fewer)	Low ^b
HBV DNA	positivity at 6-	-12 months										
5	RCTs	Serious	Serious I ² =39.8%	No serious	No serious	Not possible to examine publication bias	N/A	21/312 (6.7)	73/269 (27.1)	0.22 (0.10– 0.47)	160 fewer per 1000 (320 fewer to 4 more)	Low ^c
18	Non-RCTs	No serious	No serious	No serious	No serious	No evidence of publication bias	Magnitude of the effect.	22/1014 (2.2)	137/1057 (13.0)	0.14 (0.09– 0.23)	140 fewer per 1000 (90–190 fewer)	Moderate ^d
Infant safe	ty: neonatal de	aths										
8	RCTs	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/439 (0.2)	1/407 (0.2)	-	0 (10 fewer – 10 more)	Moderate ^e
31	Non-RCTs	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/1571 (0.0)	0/1686 (0.0)	-	0 (10 fewer – 10 more)	Low ^f

	Γ	1				Г Г		Ι				
Infant safe	ty: prematurity	v										
2	RCTs	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	0/123 (0.0)	0/93 (0.0)	-	0 (30 fewer – 30 more)	Moderate ^g
8	Non-RCTs	Serious	Serious I ² =55.6%	No serious	No serious	Not possible to examine publication bias	None	14/486 (2.9)	11/306 (3.6)	-	0 (40 fewer – 40 more)	Very low ^h
Infant safe	ty: congenital a	abnormalitie	es									
3	RCTs	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/219 (0.5)	0/222 (0.0)	-	0 (10 fewer – 20 more)	Moderate ⁱ
13	Non-RCTs	No serious	No serious	No serious	No serious	No evidence of publication bias	None	7/626 (1.1)	5/953 (0.5)	-	0 (10 fewer – 20 more)	Low ^j
Maternal s	afety: miscarri	age and still	birth			, ,					I	
8	RCTs	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/472 (0.2)	0/409 (0.0)	-	0 more (10 fewer – 10 more)	Moderate ^k
31	Non-RCTs	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/1531 (0.0)	9/1678 (0.5)	-	0 (10 fewer – 10 more)	Low ¹
Maternal s	safety: postpart	um haemmo	orhage			· · · · · ·						
1	RCTs	Serious	Not applicable	No serious	No serious	Not possible to examine publication bias	N/A	0/53 (0.0)	0/53 (0.0)	-	0 (40 fewer – 40 more)	Low ^m
7	Non-RCTs	No serious	No serious	No serious	No serious	Not possible to examine publication bias	None	98/558 (17.6)	61/699 (8.7)	-	10 more (10 less – 40 more)	Low ⁿ
Maternal s	safety: HBV fla	re after trea	tment discon	tinuation								

1	RCTs	Serious	Not applicable	No serious	Very serious	Not possible to examine publication bias	N/A	16/83 (19.3)	15/46 (32.6)	-	130 less (290 fewer – 30 more)	Very low ^o
5	Non-RCTs	Serious	Very serious I ² =87.8%	No serious	Very serious	Not possible to examine publication bias	None	37/287 (12.9)	31/504 (6.2)	-	40 fewer (200 fewer - 110 more)	Very low ^p

^aDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

^bDowngrading due to evidence of possible publication bias, however, upgrading due to magnitude of effect.

^cDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inconsistency >30%.

^dUpgrading due to magnitude of effect

^eDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

^fNo upgrading or downgrading

^gDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

^hDowngrading due to "serious" study design limitations (the majority of non-RCTs had a score of 6 on the Newcastle–Ottawa scale), downgrading due to inconsistency >30%. ⁱDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

^jNo upgrading or downgrading

^kDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

¹No upgrading or downgrading

^mDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inability to examine certain elements (e.g. inconsistency) due to the fact that there was only one RCT included

ⁿNo upgrading or downgrading

^oDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inability to examine certain elements (e.g. inconsistency) due to the fact that there was only one RCT included, downgrading due to serious imprecision.

^pDowngrading due to "serious" study design limitations (the majority of non-RCTs had a score of 6 on the Newcastle–Ottawa scale), downgrading due to severe inconsistency >30%, downgrading due to imprecision.

Telbivudine (LdT) 600 mg versus no treatment or placebo

Summary of included studies

There were 87 original studies, including 101 unique treatment arms, eligible for this meta-analysis that used LdT 600 mg. Following risk of bias assessment, four studies (all non-RCTs and each with one treatment arm investigating LdT) were excluded (*Chen YL et al., 2014; Liu CP, 2015; Luo DX et al., 2017; Zhang R et al., 2016*). Therefore, 83 original studies with 97 unique treatment arms were included in the analysis. Of the included studies, 21 were RCTs and 62 were non-randomized trials/observational studies (39 prospective and 23 retrospective studies).

Risk of bias assessment

Randomized controlled trials

Of the 21 RCTs included that investigated LdT, none achieved a "low risk of bias" rating on the majority of the main criteria in the Cochrane Collaboration's Risk of Bias Assessment Tool. All studies had only one or two criteria deemed as "low risk of bias"; in almost all studies there was a low risk of selection bias (specifically random sequence generation) and sometimes a low risk of selective reporting. The remaining criteria for all studies had a high or unclear risk, usually due to a lack of detailed reporting. The detailed risk of bias assessment for the RCTs investigating LdT 600 mg can be found in Appendix E.

• Non-randomized controlled trials

Of the original 66 non-RCTs, the majority of studies (70.0%) had low risk of bias scores (i.e. scores of 7, 8, 9) on the Newcastle Risk of Bias scale. The main weakness of included studies was in reference to loss to follow up – this information was missing in 58 of 66 studies, and was less than adequate (i.e. <80% follow up) in one further study. The detailed risk of bias assessment for the non-RCTs investigating LdT 600 mg can be found in Appendix F (Table 13).

# stars (risk of bias)	# studies	%
4 (high)	2 (excluded from analysis)	3.0
5 (high)	2 (excluded from analysis)	3.0
6 (high)	16	24,2
7 (low)	23	34.9
8 (low)	20	30.3
9 (low)	3	4.6
Total	66	100

Table 13. Risk of bias scores for non-RCTs (prior to exclusion of very high-risk studies)

Publication bias/assessment of small study effects

It was possible to examine publication bias for most of the outcomes examined. Of these, there was possible evidence of publication bias/small study effects in the three study sets: MTCT indicated by HBsAg positivity at 6–12 months in non-RCTs, MTCT indicated by HBV DNA positivity at 6–12 months in non-RCTs, postpartum haemorrhage in non-RCTs. Funnel plots for LdT 600 mg study sets, as well as results of the Egger test for asymmetry (if examining OR only) can be found in Appendix G.

Characteristics of included studies

Across all included studies, recruitment took place as early as 2000 and up until 2017. All studies took place in the WHO Western Pacific Region, specifically, all studies took place in China (n=83).

HBV genotyping for the entire study population was performed in four instances. One estimated that the treatment group was 44% genotype B, 56% genotype C, whereas the control group was 37% genotype B, 63% genotype C (*Hu Y et al., 2018*). One study estimated the treatment group as 72% genotype B, 28% genotype C, and the control group was similar with 74% genotype B and 26% genotype C (*Liu Y et al., 2016*). Another study estimated 40% genotype B, 60% genotype C in the treatment group, compared to 29% genotype B and 71% genotype C in the control group (*Shen ML et al., 2016*). Finally, one study found 73% genotype B, 26% genotype C, and 1% mixed genotype B/C in the treatment group, compared to 75% genotype B and 25% genotype C in the control group (*Wu Q et al., 2015*)

Most included study arms (i.e. 59/97) started maternal antiviral therapy between 24 and 30 weeks of gestation. The most common HBV DNA levels designated for inclusion were >5.3 log10 IU/mL (25 of 97 treatment arms) or >6.3 log10 IU/mL (24/97 treatment arms).

General stud	ly details :	and design		Treated	l (TDF 300 mg) pregna	nt womei	n (tx)			Untre	ated preg	gnant worr	ien (control)		Infant trea	atment (all in	fants)
Author, year	Coun try	Recruit- ment period	HBV DNA level (inclusio n)	#	Treatment weeks Start during pregnancy End postpartum	Age, in years	HBcAg %	Mean or median HBV DNA at baseline	# Infants assessed for MTCT	#	Age, in years	HBeAg %	Mean or median HBV DNA at baseline	# Infant s assesse d for MTC T	HBIG at birth, <i>timing</i>	Birth dose vaccine, <i>timing</i>	Non- birth dose vaccine, dose 1 /dose 2 in months
Randomized	controlle	d trials (RC	CTs)														

Table 14. Characteristics of included studies investigating LdT 600 mg

Bai HL, 2013	China	2009– 2011	6.3 log10 IU/mL	30	28–32	4	NR	NR	6.5 log10 IU/mL	27	30	NR	NR	6.6 log10 IU/mL	30	Yes, <6 h	Yes, At birth	Yes, 1/6
Chen SM, 2017	China	2013– 2014	4.3 log10 IU/mL	30	28	NR	27.4 ±3.5	100	7.8 log10 IU/mL	30	30	27.5± 3.9	100	8.0 log10 IU/mL	30	Yes, NR	Yes, NR	Yes, NR
Fu PX, 2016	China	2014– 2015	NR	100	24–28	4	31.5 ± 1.5	NR	NR	100	100	31.7 ± 1.6	NR	NR	100	Yes, NR	Yes, NR	Yes, NR
Guan ZF, 2017	China	2005– 2015	6.3 log10 IU/mL	12	24	12	26.5± 9.5	100	7.1 log10 IU/mL	123	120	27.2± 9.4	100	7.1 log10 IU/mL	122	Yes, <6 h	Yes, At birth	Yes, 1/6
Guo HJ, 2011	China	2008– 2010	6.3 log10 IU/mL	25	28	4	$\frac{28}{3} \pm$	100	7.0 log10 IU/mL	28	25	27± 4	100	7.2 log10 IU/mL	26	Yes, <6 h	Yes, At birth	Yes, 1/6
				30	20	0	28.2 ± 3.5	100	7.3 log10 IU/mL	30								
Huang HY, 2016	China	2012– 2013	5.3 log10 IU/mL	30	24	0	28.6 ± 3.4	100	7.3 log10 IU/mL	30	30	28.9 ± 3.5	100	7.2 log10 IU/mL	30	No, NR	No, NR	No
				30	28	0	28.4 ± 3.2	100	7.3 log10 IU/mL	30								
Ji YY, 2015	China	2010– 2013	5.3 log10 IU/mL	65	28	4	27.2 ± 3.6	100	7.7 log10 IU/mL	65	65	27.5 ± 4.1	100	7.7 log10 IU/mL	65	Yes, <24 h	Yes, <24 h	Yes, 1/6
Li SF, 2015	China	2012– 2014	6.3 log10 IU/mL	60	28	24	NR	NR	6.9 log10 IU/mL	60	60	NR	NR	6.7 log10 IU/mL	60	Yes, At birth	No, NR	Yes, 1/6
Lu QY, 2016	China	2013– 2014	NR	152	28	0	Range: 29-36	47	NR	152	132	Range : 29- 36	41	NR	132	Yes, <12 h	Yes, <12 h	Yes, 1/6
Peng ML, 2014	China	2011– 2012	NR	30	28	NR	25.9 ± 4.2	100	6.1 log10 IU/mL	30	30	26.4 ± 4.4	100	6.1 log10 IU/mL	30	Yes, <24 h	Yes, <24 h	Yes, 1/6
Shi QW, 2017	China	NR	5.3 log10 IU/mL	100	24	0	Range: 23–40	NR	7.1 log10 IU/mL	100	100	Range : 23- 40	NR	6.9 log10 IU/mL	100	Yes, <2–3 h	Yes, <2–3 h	Yes, 1/6
Wang HY, 2018	China	2015– 2017	5.3 log10 IU/mL	40	12–14	24	NR	100	6.8 log10 IU/mL	40	40	NR	100	6.9 log10 IU/mL	40	Yes, <6 h	Yes, <6 h	Yes, 1/6
Xie PY, 2016	China	2015– 2015	NR	60	28	4	26.6 ± 12.5	NR	NR	60	60	26.1 ± 11.6	NR	NR	60	Yes, At birth	Yes, At birth	Yes, NR
Xing Y, 2018	China	2013– 2015	NR	30	28	4	29.0 ± 6.0	NR	6.5 log10 IU/mL	30	30	29.5 ± 5.3	NR	6.5 log10 IU/mL	30	Yes, <6 h	Yes, <6 h	Yes, 1
Yang HW, 2015	China	2012– 2014	5.3 log10 IU/mL	50	28	4	NR	100	6.1 log10 IU/mL	50	50	NR	100	6.1 log10 IU/mL	50	Yes, <24 h	Yes, <24 h	Yes, 1/6

Zhang LJ, 2009	China	2007– 2008	6.3 log10 IU/mL	31	28–32	4	NR	NR	6.6 log10 IU/mL	30	30	NR	NR	6.7 log10 IU/mL	30	Yes, <6 h	Yes, At birth	Yes, 1/6
Zhang Y, 2018	China	2015– 2017	6.3 log10 IU/mL	34	Pre- pregnant	NR	28.4 ± 3.1	NR	6.6 log10 IU/mL	34	34	28.0 ± 3.1	NR	6.9 log10 IU/mL	34	Yes, NR	Yes, NR	Yes, NR
Zhao DB, 2010	China	2006– 2008	NR	30	28	4	NR	100	NR	30	30	NR	100	NR	30	Yes, <6 h	Yes, At birth	Yes, 1/6
Zhao Y, 2017	China	2013– 2016	6.3 log10 IU/mL	40	12	12	28.1 ± 4.1	100	7.3 log10 IU/mL	40	40	27.9 ± 3.9	100	7.2 log10 IU/mL	40	Yes, At birth	Yes, At birth	Yes, 1/6
Zhu J, 2017	China	2012– 2015	NR	60	28	0	NR	NR	7.4 log10 IU/mL	60	60	NR	NR	6.9 log10 IU/mL	54	Yes, <24 h	Yes, At birth	Yes, 1/6
Zhu, LP, 2014	China	2011– 2012	NR	30	28	4	NR	NR	6.7 log10 IU/mL	30	30	NR	NR	6.6 log10 IU/mL	30	Yes, <6 h	Yes, At birth	Yes, 1/6
Non-random	nized cont	rolled trials	s (non-RCT	`s)														
Chen CY,2015	China	2008– 2011	6.3 log10 IU/mL	43	1st trimester	NR	29.7 ± 8.9	100	7.1 log10 IU/mL	42	41	27.5 ± 6.6	100	7.0 log10 IU/mL	40	Yes, NR	Yes, NR	Yes, NR
Chen F, 2016	China	2008– 2014	6.3 log10 IU/mL	31	Pre- pregnant	NR	26.5 ± 4.0	100	6.9 log10 IU/mL	31	33	26.0 ± 4.4	100	6.7 log10 IU/mL	32	Yes, NR	Yes, NR	Yes, NR
Chen QR, 2018	China	2014– 2016	NR	29	28	4	26.9 ± 4.3	100	7.8 log10 IU/mL	29	28	24.1 ± 4.7	100	7.7 log10 IU/mL	28	Yes, <24 h	Yes, <24 h	Yes, 1/6
Chen WJ, 2017	China	2014– 2015	6 log10 IU/mL	79	28	0	31.1 ± 6.3	100	8.3 log10 IU/mL	79	44	29.9 ± 5.1	100	7.5 log10 IU/mL	44	Yes, <24 h	Yes, At birth	Yes, 1/6
Chen ZX, 2017	China	2001– 2015	5.3 log10 IU/mL	43	13-32	NR	28.1 ± 6.7	70	6.5 log10 IU/mL	41	89	26.2 ± 4.5	83	6.5 log10 IU/mL	89	Yes, <6 h	Yes, <6 h	Yes, 1/6
Cui ZL, 2015	China	2013– 2014	5.3 log10 IU/mL	50	28	4	28.0 ± 1.8	100	7.1 log10 IU/mL	50	50	27.6 ± 2.1	100	6.9 log10 IU/mL	46	Yes, <24 h	Yes, <24 h	Yes, 1/6
Deng Y, 2015	China	2011– 2014	6 log10 IU/mL	82	24–36	4	25.4 ±3.7	NR	7.0 log10 IU/mL	82	75	25.7 ± 3.6	NR	7.0 log10 IU/mL	75	Yes, At birth	Yes, At birth	Yes, 1/6
Ding XP, 2018	China	2013– 2017	6.3 log10 IU/mL	38	28	4	NR	100	7.3 log10 IU/mL	38	38	NR	100	7.2 log10 IU/mL	38	Yes, <24 h	Yes, <24 h	Yes, 1/6
Fan LY, 2013	China	2010– 2011	5.3 log10 IU/mL	58	28	24	27.8 ± 3.0	100	6.9 log10 IU/mL	58	60	29.0 ± 2.9	100	6.7 log10 IU/mL	60	Yes, <24 h	Yes, <24 h	Yes, 1/6
Feng XM, 2017	China	2014– 2016	6.3 log10 IU/mL	36	28	4	29.6 ± 6.3	100	6.9 log10 IU/mL	36	36	28.4 ± 5.1	100	6.7 log10 IU/mL	36	Yes, <6 h	Yes, At birth	Yes, 1/6

Gao P, 2016	China	2012– 2014	NR	51	1st trimester	0	28.4 ± 3.8	NR	7.1 log10 IU/mL	51	51	27.2 ± 3.6	NR	7.0 log10 IU/mL	51	Yes, At birth	Yes, At birth	Yes, NR
Ge YL, 2015	China	NR	5.3 log10 IU/mL	20	28–30	12	28.6 ±3.5	100	7.1 log10 IU/mL	20	22	26.5 ± 4.2	100	6.9 log10 IU/mL	22	Yes, <24 h	Yes, At birth	Yes, 1/6
Han GR,	China	2008-	5.3 log10	257	20–27	NR	27 (20– 35)	100	7.9 log10 IU/mL	256	92	26 (20-	100	7.9 log10	86	Yes,	Yes,	Yes,
2015	Cillia	2010	IU/mL	105	28-32	NR	28 (20– 38)	100	7.8 log10 IU/mL	102	92	35)	100	IU/mL	80	<2–3 h	<12 h	1/6
Han YP, 2014	China	2010– 2012	4.3 log10 IU/mL	30	28	6	26 ± 4	100	7.7 log10 IU/mL	30	30	26±4	100	7.7 log10 IU/mL	30	Yes, <24 h	Yes, <24 h	Yes, 1/6
He T, 2018	China	2008– 2016	NR	32	1st trimester	NR	29.2 ±2.9	84	6.6 log10 IU/mL	32	35	29.0 ±3.6	80	6.2 log10 IU/mL	34	Yes, <6 h	Yes, <12 h	Yes, 1/6
Hu WH, 2016	China	2013– 2015	NR	46	28	28	28.9 ±3.3	NR	6.7 log10 IU/mL	46	40	29.2 ± 3.4	NR	6.6 log10 IU/mL	40	Yes, <24 h	Yes, <24 h	Yes, 1/6
Hu Y, 2018	China	2012– 2014	NR	149	28–32	3-4	25.9 ± 3.7	100	7.4 log10 IU/mL	105	179	26.4 ± 3.4	100	7.3 log10 IU/mL	122	Yes, <24 h	Yes, <24 h	Yes, 1/6
Huang Q, 2017	China	2015– 2015	6 log10 IU/mL	20	24–28	12	26.8 ±2.5	100	NR	20	20	27.0 ±2.3	100	NR	20	Yes, <6 h	Yes, <6 h	Yes, 1/6
Jiang S, 2017	China	2015– 2016	NR	44	28	NR	28.3 ± 3.4	NR	6.1 log10 IU/mL	44	44	NR	NR	6.1 log10 IU/mL	44	Yes, At birth	Yes, At birth	Yes, 1/6
Jiang XN, 2013	China	2010– 2011	4.3 log10 IU/mL	65	26–30	NR	NR	100	6.0 log10 IU/mL	65	51	NR	100	5.9 log10 IU/mL	51	Yes, At birth	Yes, At birth	Yes, 1/6
Li CM, 2017	China	2013– 2015	2.3 log10 IU/mL	30	28	4	43.2 ± 1.3	NR	6.1 log10 IU/mL	30	30	43.2 ± 1.3	NR	6.1 log10 IU/mL	30	Yes, <24 h	Yes, <24h	Yes, 1/6
Li N,	China	2012-	4.3	30	28	NR	NR	NR	5.1 log10 IU/mL	30	25	NR	NR	5.0 log10	25	Yes,	Yes,	Yes,
2016	Cillia	2015	log10 IU/mL	35	Pre- pregnant	NR	NR	NR	5.1 log10 IU/mL	35	23	INK	INK	IU/mL	23	<6 h	<6 h	1/6
Li YH, 2017	China	2015– 2017	6.3 log10 IU/mL	30	28	~36	29.5 ± 2.7	100	3.2 log10 IU/mL	30	31	28.8 ± 3.5	100	3.2 log10 IU/mL	32	Yes, <24 h	Yes, NR	Yes, NR
Li ZY, 2018	China	2015– 2016	5.3 log10 IU/mL	41	28	NR	26.2 ± 4.4	100	6.1 log10 IU/mL	41	41	26.3 ±4.2	100	6.1 log10 IU/mL	41	Yes, <24 h	No, NR	Yes, 1/6

Liu CY, 2014	China	2011– 2011	5.3 log10 IU/mL	34	28	4	27.2 ± 3.6	100	7.1 log10 IU/mL	34	34	26.9 ± 4.1	100	7.4 log10 IU/mL	34	Yes, <6 h	Yes, At birth	Yes, 1/6
Liu J, 2017	China	2013– 2015	6 log10 IU/mL	102	30	NR	27.8 ± 4.1	100	8.1 log10 IU/mL	97	28	26.7 ± 3.9	100	8.1 log10 IU/mL	28	No, NR	Yes, <12 h	Yes, 1/6
Liu XB, 2016	China	2014– 2015	6 log10 IU/mL	20	28–36	4	25.4 ± 3.7	100	7.0 log10 IU/mL	20	20	25.4 ± 3.6	100	7.0 log10 IU/mL	20	Yes, At birth	Yes, At birth	Yes, 1/6
Liu Y,	China	2010-	6 log10	32	28–32	4	27.9 ± 3.7	97	7.4 log10 IU/mL	32	- 78	27.5	97	7.5 log10	78	Yes,	Yes,	Yes, 1/6
2016	Cillia	2012	IU/mL	50	4–27	4	28.3 ±3.8	94	7.6 log10 IU/mL	50	78	±3.5	91	IU/mL	78	NR	At birth	Yes, 1/6
Lou JJ, 2015	China	2012– 2013	4.6 log10 IU/mL	127	28	4	30 ± 6	100	6.8 log10 IU/mL	125	58	31± 6	100	6.7 log10 IU/mL	58	Yes, <6 h	Yes, At birth	Yes, 1/6
Pan YC, 2017	China	2012– 2015	6.3 log10 IU/mL	81	32	0	28.8 ± 3.3	100	8.3 log10 IU/mL	81	453	27.6 ± 3.8	100	8.1 log10 IU/mL	370	Yes, <2–3 h	Yes, <2–3 h	Yes, 1/6
Peng BA, 2012	China	2008– 2009	5.3 log10 IU/mL	40	28	0	NR	100	6.0 log10 IU/mL	40	40	NR	100	6.1 log10 IU/mL	40	Yes, At birth	Yes, At birth	Yes, 1/6
Qiu B,	China	2009–	5.3 log10	60	Pre- pregnant	0	NR	NR	6.9 log10 IU/mL	60	60	NR	NR	6.8 log10	60	Yes,	Yes,	Yes,
2016	China	2014	IU/mL	60	24	0	NR	NR	6.9 log10 IU/mL	60	00	INK	NK	IU/mL	00	<12 h	<12 h	1/6
Ren N, 2015	China	2011– 2014	5.3 log10 IU/mL	46	28	24	NR	100	7.2 log10 IU/mL	46	46	NR	100	7.5 log10 IU/mL	46	Yes, <24 h	Yes, <24 h	Yes, 1/6
Shen ML, 2016	China	2010– 2014	4.3 log10 IU/mL	60	26	4	NR	NR	5.9 log10 IU/mL	61	28	NR	NR	6.0 log10 IU/mL	28	Yes, <24 h	Yes, NR	Yes, NR
Sheng Q, 2018a	China	2013– 2015	5 log10 IU/mL	91	24–32	4	27.8 ± 4.2	100	8.1 log10 IU/mL	79	21	26.8 ± 3.7	100	8.0 log10 IU/mL	21	Yes, <12h	Yes, <12 h	Yes, 1/6
Sheng Q, 2018b	China	2016– 2016	6.3 log10 IU/mL	66	24–28	0	31.3 ± 4.4	89	8.1 log10 IU/mL	66	46	30.4 ± 4.2	89	7.9 log10 IU/mL	46	Yes, <12 h	Yes, <12 h	Yes, 1/6
Sun W,	China	2013-	6.3 log10	61	20–28	12	28.9 ± 11.8	100	7.1 log10 IU/mL	62	- 65	27.5 ±	100	7.0 log10	65	Yes,	Yes,	Yes, 1/6
2017	Ciniid	2015	IU/mL	62	12	12	29.7 ± 9.8	100	7.1 log10 IU/mL	61	05	± 12.9	100	IU/mL	05	<6 h	<12 h	1/0

Sun WH, 2015	China	2009– 2013	6.3 log10 IU/mL	42	12	12	28.9 ± 11.8 29.7	100	7.1 log10 IU/mL 7.2	43	45	27.5 ± 12.9	100	7.1 log10 IU/mL	46	Yes, <6 h	Yes, <6 h	Yes, 1/6
				41	20–28	12	±9.8	100	log10 IU/mL	41				7.5				
Tan J, 2019	China	2013– 2015	NR	41	28	0	NR	NR	7.6 log10 IU/mL	41	59	NR	NR	/.5 log10 IU/mL	59	Yes, <24 h	Yes, At birth	Yes, 1/6
Tan Z,	nhina	2012-	6 log10 IU/mL	145	14–28	NR	29 (23- 39)	90	7.6 log10 IU/mL	137	- 334	28 (20-	85	7.6 log10	320	Yes,	Yes,	Yes,
2016	nnina	2015	NR	37	<14	NR	29 (20- 38)	65	2 log10 IU/mL	34	334	(20-41)	85	IU/mL	320	<6 h	At birth	1/6
Tian JH, 2018	China	2000– 2017	4.6 log10 IU/mL	135	Anytime	NR	NR	100	NR	135	203	NR	100	NR	203	Yes, <6 h	Yes, <12 h	Yes, 1/6
Tian RH, 2016	China	2013– 2013	6 log10 IU/mL	318	28	4	27.2 ± 3.2	100	6.5 log10 IU/mL	318	374	27.3 ± 3.2	100	6.6 log10 IU/mL	374	Yes, At birth	Yes, At birth	Yes, 1/6
Wang B, 2016	China	2011– 2012	6 log10 IU/mL	110	28	4	24 ± 5	100	7.9 log10 IU/mL	110	187	24± 4	100	7.9 log10 IU/mL	187	Yes, At birth	Yes, At birth	Yes, 1/6
Wang DM, 2016	China	2011– 2014	5.3 log10 IU/mL	36	28–30	12	31.4 ± 7.3	100	7.1 log10 IU/mL	36	20	31.7 ± 7.0	100	7.1 log10 IU/mL	20	No, NR	Yes, <24 h	Yes, 1/6
Wang EJ, 2012	China	2008– 2010	6.3 log10 IU/mL	28	28	4	27.0 ± 3.4	100	7.9 log10 IU/mL	28	27	24.0 ± 4.7	100	7.7 log10 IU/mL	27	Yes, <24 h	Yes, At birth	Yes, 1/6
				20	20	NR	NR	NR	6.9 log10 IU/mL	20								
				20	24	NR	NR	NR	7.2 log10 IU/mL	20								
Wang HB, 2016	China	2013– 2016	NR	20	28	NR	NR	NR	7.1 log10 IU/mL	20	20	NR	NR	7.2 log10 IU/mL	20	Yes, <24 h	Yes, <24 h	Yes, 1/6
				20	32	NR	NR	NR	7.2 log10 IU/mL	20								
				20	36	NR	NR	NR	6.7 log10 IU/mL	20								
Wang J, 2017	China	2010– 2015	6 log10 IU/mL	329	24–28	NR	27.8 ± 3.7	NR	7.8 log10 IU/mL	329	65	27.6 ± 3.5	NR	7.8 log10 IU/mL	65	Yes, <12 h	Yes, <12 h	Yes, 1/6

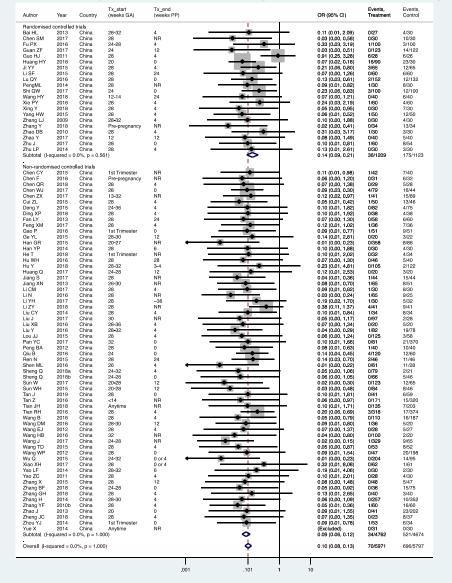
Wang TD, 2015	China	2012– 2013	6.3 log10 IU/mL	53	28	4	26.3 ± 3.1	100	7.3 log10 IU/mL	53	52	25.8 ± 3.9	100	7.5 log10 IU/mL	52	Yes, <24 h	Yes, <24 h	Yes, 1/6
Wang WP,	China	2010-	4.3 log10	25	28	0	NR	100	6.7 log10 IU/mL	25	198	NR	100	6.3 log10	198	Yes,	Yes,	Yes,
2012	Ciiiia	2011	IU/mL	22	<27	0	NR	100	6.8 log10 IU/mL	22	190	INK	100	IU/mL	198	<6 h	<6 h	1/6
Wu Q, 2015	China	2008– 2014	6 log10 IU/mL	279	24–32	0 or 4	27 (17– 38)	100	7.2 log10 IU/mL	204	171	28 (18– 40)	100	7.4 log10 IU/mL	95	Yes, At birth	Yes, At birth	Yes, 1/6
Xiao XH, 2017	China	2014– 2015	6 log10 IU/mL	60	28	0 or 4	28.6 ± 3.2	NR	7.5 log10 IU/mL	62	60	28.5 ± 3.6	NR	7.5 log10 IU/mL	61	Yes, NR	No, NR	Yes, NR
Yao LF, 2014	China	2012– 2013	6 log10 IU/mL	30	28–32	6	NR	100	7.3 log10 IU/mL	30	30	NR	100	8.2 log10 IU/mL	30	Yes, NR	No, NR	Yes, NR
Yao ZC, 2011	China	2008– 2010	5.3 log10 IU/mL	28	28	4	NR	NR	6.8 log10 IU/mL	28	30	NR	NR	6.8 log10 IU/mL	30	Yes, <6 h	Yes, At birth	Yes, 1/6
Yue X, 2014	China	2007– 2012	5.3 log10 IU/mL	31	Anytime	NR	29.7 ±5.1	0	5.5 log10 IU/mL	31	31	27.6 ±2.9	0	5.6 log10 IU/mL	30	Yes, <24 h	Yes, At birth	Yes, 1/6
Zhang BF, 2018	China	2016– 2017	6 log10 IU/mL	36	24–28	0	NR	100	5.0 log10 IU/mL	36	75	NR	100	NR	75	Yes, <6 h	Yes, At birth	Yes, 1/6
Zhang GH, 2018	China	2012– 2014	6.3 log10 IU/mL	40	28	4	NR	100	NR	40	40	NR	100	NR	40	Yes, <24 h	Yes, At birth	Yes, 1/6
Zhang H, 2014	China	2009– 2011	5.3 log10 IU/mL	263	28–30	4	29.8 ±6.3	100	6.9 log10 IU/mL	257	374	29.0 ±4.6	100	6.8 log10 IU/mL	352	Yes, <6 h	Yes, <6 h	Yes, 1/6
Zhang X, 2015	China	2012– 2013	6.3 log10 IU/mL	48	28	12	NR	100	7.0 log10 IU/mL	48	47	NR	100	6.8 log10 IU/mL	47	Yes, <24 h	Yes, At birth	Yes, 1/6
Zhang YF, 2010b	China	2008– 2009	5.3 log10 IU/mL	60	28	4	NR	100	6.1 log10 IU/mL	60	60	NR	100	6.1 log10 IU/mL	60	Yes, <24 h	Yes, <24 h	Yes, 1/6
Zhao J, 2013	China	2010– 2011	6.3 log10 IU/mL	41	20	0	NR	100	NR	41	202	NR	100	NR	202	Yes, <6 h	Yes, <6 h	Yes, 1/6
Zheng JC, 2018	China	2012– 2015	5.3 log10 IU/mL	23	28	4	NR	100	NR	23	37	NR	100	NR	37	Yes, <6 h	Yes, <24 h	Yes, 1/6
Zhou YJ, 2014	China	2007– 2013	6.3 log10 IU/mL	70	1st trimester	0	NR	NR	NR	53	39	NR	NR	NR	34	Yes, NR	Yes, <24 h	Yes, 1/6

NR=not reported in article *Age presented as mean ± SD or median with either (IQR) or [range]

Primary efficacy analysis, narrative descriptions and forest plots

- PMTCT, as indicated by detection of HBsAg at 6-12 months of age, all treatment start times, all HBV DNA levels at inclusion, stratified by study design (RCT and non-RCT).
 - Overall pooled OR=0.10 (95% CI: 0.08-0.13), P < 0.001, $I^2 = 0\%$
 - RCTs only: pooled OR=0.14 (95% CI: 0.10–0.26), P < 0.001, $I^2 = 0\%$
 - Non-RCTs only: pooled OR=0.09 (95% CI: 0.07-0.12), P<0.001, I²=0%
 - \circ The *P* value for heterogeneity between RCTs and non-RCTs was 0.08.

LdT 600mg, MTCT=HBsAg+, by study design



- PMTCT, as indicated by detection of HBV DNA at 6-12 months of age, all treatment start times, all HBV DNA levels at inclusion, stratified by study design (RCT and non-RCT).
 - Overall pooled OR=0.08 (95% CI: 0.06-0.11), P<0.001, I²=0.0%
 - RCTs only: pooled OR=0.12 (95% CI: 0.05–0.26), P<0.001, I²=0%
 - Non-RCTs only: pooled OR=0.07 (95% CI: 0.05-0.10), P<0.001, I²=0%
 - \circ The *P* value for heterogeneity between RCTs and non-RCTs was 0.29.

Tx_end (weeks PP) Tx_start (weeks GA) Events, Events. OR (95% CI) Author Year Country Treatment Contro Bandomised controlled trials Fu PX Guo HJ 24**-**28 3/100 2016 China 0.33 (0.03, 3.19) 1/100 4 4 24 4 0.26 (0.05, 0.13) 0.26 (0.05, 1.41) 0.07 (0.00, 1.21) 0.06 (0.01, 0.46) 2011 China 28 2/28 6/26 Wang HY 2018 12-14 0/40 6/40 13/50 China Yang HW 2015 China 28 1/50 Zhang Y Zhao DB 2018 2010 Pre-pregnancy 0.04 (0.00, 0.70) 0.09 (0.01, 0.82) China NR 0/34 9/34 1/30 8/30 China 28 4 Zhao Y 2017 China 12 12 0.10 (0.01, 1.92) 0.08 (0.01, 0.69) 0/40 4/40 2017 China 28 0 1/60 9/54 Zhu J 58/374 Subtota quared : 0.0%, p 0.888)0.11 (0.05, 0.26) 6/382 Non-randomised controlled trials Chen CY Chen F 2015 China China 1st Trimester NR NR 0.05 (0.00, 0.95) 0.06 (0.00, 1.20) 0/42 0/31 7/40 6/32 2016 Pre-pregnancy Chen WJ Chen ZX 2017 2017 China 28 0 NR 0.04 (0.00, 0.31) 0.11 (0.01, 0.83) 1/79 11/44 1/41 13-32 17/89 China 0.06 (0.01, 0.47) 0.10 (0.01, 1.82) Cui ZL 2015 China 28 4 4 1/50 12/46 Deng Y Fan LY 2015 China 24-36 0/82 4/75 2013 China 28 24 0.07 (0.00, 1.30) 0.09 (0.01, 0.72) 0/58 6/60 1/36 0/51 Feng XM 2017 China 28 4 0 9/36 1st Trimester 0.04 (0.00, 0.77) 9/51 Gao P 2016 China 12 NR NR Ge YL Han GR 2015 2015 China 28-30 0.14 (0.01, 2.81) 0.01 (0.00, 0.23) 0/20 0/358 3/22 8/86 China 20-27 He T 2018 China China 1st Trimester 0.10 (0.01, 2.02) 0.07 (0.00, 1.30) 0/32 4/34 Hu WH 2016 28 0/46 5/40 28 Hu Y 2018 China 28-32 3-4 NR 0.23 (0.01, 4.81) 0/105 2/122 Jiang S Li CM 28 28 1/44 1/30 2017 China 0.05 (0.01, 0.40) 14/44 4 NR NR 2017 China 0.11 (0.01, 0.99) 7/30 Li N Li ZY 2016 China 28 28 0.03 (0.00, 0.24) 0.24 (0.06, 0.97) 1/65 3/41 9/25 10/41 2018 China 2014 2017 4 NR 0.12 (0.01, 1.01) 0.05 (0.00, 1.17) 1/34 0/97 7/34 2/28 Liu CY China 28 30 Liu J China 0/20 0/82 1/40 Liu XB 2016 China China 28-36 4 0 24 4 0 12 NR NR 0.09 (0.00, 1.78) 0.03 (0.00, 0.50) 4/20 Liu Y 2016 28-32 13/78 Peng BA Qiu B 2012 China 28 24 0.23 (0.02, 2.16) 4/40 2016 China 0.08 (0.02, 0.35) 2/120 11/60 Ren N 2015 China 28 0.08 (0.01, 0.65) 1/46 10/462018a 2018b 0/79 0/66 2/21 5/46 Sheng Q China 24-32 0.05 (0.00, 1.06) Sheng Q 24-28 0.06 (0.00, 1.05) China Sun W Tan Z 2017 2016 China 20-28 0.02 (0.00, 0.30) 0.06 (0.00, 0.97) 0/123 0/171 12/65 China 15/320 <14 0.11 (0.01, 2.01) 0.05 (0.00, 0.79) Tian JH 2018 China Anytime 0/135 6/203 4 12 NR NR Wang B 2016 China 0/110 16/187 28 Wang DM Wang HB 28-30 2016 China 0.09 (0.01, 0.80) 1/36 5/20 0.04 (0.00, 0.80) 0.02 (0.00, 0.15) 2016 China 32 0/100 2/20 24-28 1/329 Wang J 2017 China 9/65 Wang WP Wu Q 2012 China 28 24-32 0 0.09 (0.01, 1.54) 0.01 (0.00, 0.23) 0/47 20/198 14/95 0/204 2015 China 0 or 4 Xiao XH Zhang BF 2017 2018 China China 28 24-28 0 or 4 0 0.19 (0.01, 4.05) 0.06 (0.00, 1.10) 0/62 0/36 2/61 13/75 Zhang GH Zhang H 2018 China 28 4 4 12 0.13 (0.01, 2.65) 0.06 (0.00, 1.09) 0/40 3/40 2014 28-30 0/257 10/352 China Zhang X Zhang YF 0/48 2015 China 28 0.08 (0.00, 1.48) 5/47 15/60 23/202 2010b China 28 20 4 0 0.05 (0.01, 0.40) 1/60 Zhao J 2013 China 0.09 (0.01, 1.55) 0/41 2018 2014 4 NR 6/37 0/30 Zheng JC China 28 0.10 (0.01, 1.92) 0/23 Anytime Yue X China (Excluded) 0/31 Subtotal (I-squared 0.0%, r 1.000) 0.07 (0.05, 0.10) 18/3648 377/3367 φ 0.08 (0.06, 0.11) Overall (I-squared = 0.0%, p = 1.000) 24/4030 435/3741 t 10 .001 .078 1

LdT 600mg, MTCT=HBVDNA+

Subgroup analysis

Of the potential sources of heterogeneity predefined in the protocol, it was not possible to do a subgroup analysis by coinfection status, as there were eventually no eligible populations that included those coinfected. Furthermore, it was not possible to do subgroup analysis by WHO region, as almost all studies came from just one region (i.e. Western Pacific). For LdT, one ad hoc subgroup analysis is presented; timing of treatment end postpartum.

 PMTCT, as indicated by detection of HBsAg at 6-12 months of age, all HBV DNA levels at inclusion, all study designs merged (i.e. RCT and non-RCT), <u>stratified by</u> trimestor of treatment start

trimester of treatment start.

- 1st trimester: pooled OR=0.09 (95% CI: 0.04-0.22), P=0.001, I²=0.0%
- 2nd trimester: pooled OR=0.09 (95% CI: 0.05-0.20), P=0.001, I²=24.3%
- 3rd trimester: pooled OR=0.13 (95% CI: 0.10-0.17), P<0.001, I²=0.0%
- There was no detected heterogeneity between any of the subgroups (i.e. 1st versus 2nd, 2nd versus 3rd, 1st versus 3rd), with *P* values between 0.49 and 0.80. However, because of the mild heterogeneity seen in the 2nd trimester treatment start subgroup, heterogeneity comparisons with this subgroup may not be valid.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)		OR (95% CI)	Events, Treatment	Events, Control
1st trimester Chen CY Gao P He T Sun W Sun WH Tan Z	2015 2016 2018 2017 2015 2016	China China China China China China	1st Trimester 1st Trimester 1st Trimester 12 22 <14	NR 0 NR 12 12 NR		0.11 (0.01, 0.98) 0.09 (0.01, 0.77) 0.10 (0.01, 2.02) 0.03 (0.00, 0.59) 0.05 (0.00, 0.93) 0.29 (0.02, 4.88)	1/42 1/51 0/32 0/62 0/43 0/34	7/40 9/51 4/34 12/65 8/46 15/320
Zhao Y Zhou YJ Subtotal (I-s	2017 2014	China China	12 1st Trimester	12 0		0.08 (0.00, 1.49) 0.09 (0.01, 0.78) 0.09 (0.04, 0.22)	0/40 1/53 3/357	5/40 6/34 66/630
2nd trimester Guan ZF Han GR	2017 2015	China China	24 20-27	12 NR		0.03 (0.00, 0.51) 0.02 (0.00, 0.32)	0/123 0/256	14/122 8/86
Huang HY Huang HY Qiu B	2016 2016 2016 2017	China China China	20 24 24	0 -		0.01 (0.00, 0.09) 0.06 (0.02, 0.22) 0.29 (0.09, 0.94) 0.23 (0.06, 0.83)	1/30 5/30 4/60	23/30 23/30 12/60
Shi QW Tan Z	2016	China China	24 14-28	0 NR		0.07 (0.00, 1.21)	3/100 0/137	12/100 15/320
Wang HB Wang HB	2016 2016	China China	20 24	NR NR		0.18 (0.01, 4.01) 0.18 (0.01, 4.01)	0/20 0/20	2/20 2/20
Zhao J Subtotal (I-s	2013	China	20	0		0.09 (0.01, 1.55) 0.09 (0.04, 0.19)	0/41 13/817	23/202 134/990
3rd trimester Bai HL Chen QR	2013 2018	China China	28-32 28	4		0.11 (0.01, 2.09) 0.07 (0.00, 1.38)	0/27 0/29	4/30 5/28
Chen SM Chen WJ	2017	China China	28 28	NR 0		0.03 (0.00, 0.58) 0.09 (0.03, 0.30)	0/30 4/79	10/30 16/44
Cui ZL Ding XP	2015 2018	China China	28 28	4		0.05 (0.03, 0.30) 0.05 (0.01, 0.42) 0.10 (0.01, 1.92)	1/50 0/38	13/46 4/38
FanIY	2013	China	28	24		0.07 (0.00, 1.30)	0/58	6/60
Feng XM Ge YL	2017 2015	China China	28 28-30	4 12		0.12 (0.01, 1.02) 0.14 (0.01, 2.81)	1/36 0/20	7/36 3/22
Guo HJ Han GR	2011 2015	China China	28 28-32	4 NB		0.91 (0.25, 3.28) 0.05 (0.00, 0.79)	6/28 0/102	6/26 8/86
Han YP Hu WH	2014 2016	China China	28 28	6 28		0.10 (0.00, 1.88) 0.07 (0.00, 1.30)	0/30 0/46	4/30 5/40
Hu Y	2018	China	28-32	3-4		0.23 (0.01, 4.81)	0/105	2/122
Huang HY Ji YY	2016 2015	China China	28 28	0 4		0.15 (0.05, 0.47) 0.21 (0.06, 0.80)	10/30 3/65	23/30 12/65
Jiang S Li CM	2017 2017	China China	28 28	NR 4		0.04 (0.01, 0.36) 0.09 (0.01, 0.82)	1/44 1/30	15/44 8/30
Li N Li SF	2016 2015	China China	28 28	NR 24		0.06 (0.01, 0.53) 0.07 (0.00, 1.26)	1/30 0/60	9/25 6/60
Li YH	2017	China	28 28 28	24 ~36 NB		0.19 (0.02, 1.70)	0/60 1/30 4/41	5/32 9/41
Li ZY Liu CY	2018 2014	China China	28	4		0.38 (0.11, 1.37) 0.10 (0.01, 0.84)	1/34	8/34
Liu J Liu XB	2017 2016	China China	30 28-36	NR 4		0.05 (0.00, 1.17) 0.07 (0.00, 1.34)	0/97 0/20	2/28 5/20
Liu Y Lou JJ	2016 2015	China China	28-32 28	4 4		0.10 (0.01, 0.78) 0.06 (0.00, 1.24)	1/32 0/125	19/78 3/58
Lu QY	2016	China	28	0		0.13 (0.03, 0.61)	2/152	12/132
Pan YC Peng BA	2017 2012	China China	32 28	0 0		0.10 (0.01, 1.66) 0.08 (0.01, 0.63)	0/81 1/40	21/370 10/40
PengML Ben N	2014	China China	28 28	NR 24		0.09 (0.01, 0.82) 0.14 (0.03, 0.70)	1/30 2/46	8/30 11/46
Tan J	2019	China	28 28	0		0.10 (0.01, 1.81)	0/41 3/318	6/59
Tian RH Wang B	2016 2016	China China	28	4 4		0.20 (0.06, 0.69) 0.05 (0.00, 0.79)	0/110	16/187
Wang DM Wang EJ	2016 2012	China China	28-30 28	12 4		0.09 (0.01, 0.80) 0.07 (0.00, 1.37)	1/36 0/28	5/20 5/27
Wang HB Wang HB	2016 2016	China China	28 32	NR NR		0.18 (0.01, 4.01) 0.18 (0.01, 4.01)	0/20 0/20	2/20 2/20
Wang HB	2016	China	36	NR		0.18 (0.01, 4.01)	0/20	2/20
Wang TD Wang WP	2015 2012	China China	28 28	4 0	• • •	0.05 (0.00, 0.87) 0.17 (0.01, 2.91)	0/53 0/25	8/52 20/198
Xiao XH Xie PY	2017	China China	28 28	0 or 4 4		0.32 (0.01, 8.08) 0.24 (0.03, 2.19)	0/62	1/61 4/60
Xing Y	2018	China	28 28 28	4		0.05 (0.00, 0.95)	0/30	7/30
Yang HW Yao LF	2015 2014	China China	28-32	4 6		0.06 (0.01, 0.52) 0.19 (0.01, 4.06)	0/30	12/50 2/30
Yao ZC Zhang GH	2011 2018	China China	28 28	4 4		0.10 (0.01, 2.01) 0.13 (0.01, 2.65)	0/28 0/40	4/30 3/40
Zhang H Zhang LJ	2014 2009	China China	28-30 28-32	4		0.06 (0.00, 1.09) 0.10 (0.00, 1.88)	0/257 0/30	10/352 4/30
Zhang X	2015	China	28	12		0.08 (0.00, 1.48)	0/48	5/47
Zhang YF Zhao DB	2010b 2010	China China	28 28	4 4		0.05 (0.01, 0.36) 0.31 (0.03, 3.17)	1/60 1/30	16/60 3/30
Zheng JC Zhu J	2018 2017	China China	28 28	4 0		0.07 (0.00, 1.35) 0.10 (0.01, 0.81)	0/23 1/60	8/37 8/54
Zhu LP Subtotal (I-s	2014	China	28	4	8	0.13 (0.01, 2.61) 0.13 (0.10, 0.17)	0/30 50/3174	3/30 452/3719
Overall (I-sq	uared = (0.0%, p = 1.0	000)		\$	0.12 (0.09, 0.15)	66/4348	652/5339

LdT 600mg, MTCT=HBsAg+, by trimester

- 2. PMTCT, as indicated by detection of HBsAg at 6-12 months of age, all HBV DNA levels at inclusion, all study designs merged (i.e. RCT and non-RCT), stratified by median weeks of gestation at the time of treatment start (<28 weeks, 28 weeks, >28 weeks).
 - <28 weeks: pooled OR=0.09 (95% CI: 0.06-0.13), P<0.001, I²=0.0%
 - 28 weeks: pooled OR=0.13 (95% CI: 0.10-0.18), P<0.001, I²=0.0%
 - >28 weeks: pooled OR=0.10 (95% CI: 0.05-0.21), P<0.001, I²=0.0%

• When looking at heterogeneity across the three subgroups, the *P* value was 0.28. If comparing <28 weeks median with 28 weeks median, there was no heterogeneity (p=0.12). If comparing <28 weeks median with >28 weeks median for treatment start, there was no evidence of heterogeneity (*P*=0.72). If comparing 28 weeks median with >28 weeks median, there was no evidence of heterogeneity (*P*=0.52).

LdT 600mg, MTCT=HBsAg+, by tx start time

Median <28 we Chen CY Fu PX Gao P Guan ZF	eks GA 2015 2016	China	1st Trimester					
Fu PX Gao P				NR		0.11 (0.01, 0.98)	1/42	7/40
Gao P		China	24-28	4		0.33 (0.03, 3.19)	1/100	3/100
Juan 7E	2016	China	1st Trimester	0		0.09 (0.01, 0.77)	1/51	9/51
00121	2017	China	24	12	•	0.03 (0.00, 0.51)	0/123	14/122
an GR	2015	China	20-27	NR		0.02 (0.00, 0.32)	0/256	8/86
θT	2018	China	1st Trimester	NR		0.10 (0.01, 2.02)	0/32	4/34
uang HY	2016	China	20	0		0.01 (0.00, 0.09)	1/30	23/30
uang HY	2016	China	24	0		0.06 (0.02, 0.22)	5/30	23/30
uang Q	2017	China	24-28	12		0.12 (0.01, 2.53)	0/20	3/20
ιY	2016	China	4-27	4		0.03 (0.00, 0.51)	0/50	19/78
u B	2016	China	24	0		0.29 (0.09, 0.94)	4/60	12/60
ien ML	2016	China	26	4		0.01 (0.00, 0.22)	0/61	11/28
eng Q	2018b	China	24-28	0		0.06 (0.00, 1.05)	0/66	5/46
ni QW In W	2017 2017	China China	24	0		0.23 (0.06, 0.83) 0.03 (0.00, 0.59)	3/100	12/100
			12	12		0.03 (0.00, 0.60)	0/62	12/65
in W in WH	2017 2015	China China	20-28 12	12 12			0/61 0/43	12/65 8/46
n WH	2015	China	20-28	12		0.05 (0.00, 0.93) 0.05 (0.00, 0.98)	0/41	8/46
n Z	2015	China	14-28	NR		0.07 (0.00, 1.21)	0/137	15/320
nZ	2016	China	<14	NR		0.29 (0.02, 4.88)	0/34	15/320
ang HB	2016	China	20	NR		0.18 (0.01, 4.01)	0/20	2/20
ang HB	2016	China	20	NR		0.18 (0.01, 4.01)	0/20	2/20
ang HY	2018	China	24 12-14	24		0.07 (0.00, 1.21)	0/20	6/40
ang J	2018	China	24-28	NR NR		0.07 (0.00, 1.21)	1/329	9/65
ang WP	2017	China	<27	0		0.19 (0.01, 3.31)	0/22	20/198
ang BF	2012	China	24-28	0		0.05 (0.00, 0.92)	0/36	15/75
iang bi iao J	2013	China	20	0		0.09 (0.01, 1.55)	0/41	23/202
ao Y	2017	China	12	12		0.08 (0.00, 1.49)	0/40	5/40
iou YJ	2014	China	1st Trimester	0		0.09 (0.01, 0.78)	1/53	6/34
ibtotal (I-squa				-	õ	0.09 (0.06, 0.13)	18/2000	311/2381
(• oqu		, p 3.000)			-	(5.66, 61.6)		22001
edian 28 weel								
nen QR	2018	China	28	4		0.07 (0.00, 1.38)	0/29	5/28
nen SM	2017	China	28	NR	•	0.03 (0.00, 0.58)	0/30	10/30
en WJ	2017	China	28	0		0.09 (0.03, 0.30)	4/79	16/44
ii ZL	2015	China	28	4		0.05 (0.01, 0.42)	1/50	13/46
ng XP	2018	China	28	4		0.10 (0.01, 1.92)	0/38	4/38
in LY	2013	China	28	24		0.07 (0.00, 1.30)	0/58	6/60
ng XM	2017	China	28	4		0.12 (0.01, 1.02)	1/36	7/36
io HJ	2011	China	28	4		0.91 (0.25, 3.28)	6/28	6/26
in YP	2014	China	28	6		0.10 (0.00, 1.88)	0/30	4/30
WH	2016	China	28	28		0.07 (0.00, 1.30)	0/46	5/40
iang HY	2016	China	28	0		0.15 (0.05, 0.47)	10/30	23/30
YY	2015	China	28	4		0.21 (0.06, 0.80)	3/65	12/65
ang S	2017	China	28	NR		0.04 (0.01, 0.36)	1/44	15/44
ang XN	2013	China	26-30	NR		0.08 (0.01, 0.70)	1/65	8/51
СМ	2017	China	28	4		0.09 (0.01, 0.82)	1/30	8/30
N	2016	China	28	NR		0.06 (0.01, 0.53)	1/30	9/25
SF	2015	China	28	24		0.07 (0.00, 1.26)	0/60	6/60
YH	2017	China	28	~36		0.19 (0.02, 1.70)	1/30	5/32
ZY	2018	China	28	NR		0.38 (0.11, 1.37)	4/41	9/41
1 CY	2014	China	28	4		0.10 (0.01, 0.84)	1/34	8/34
u JJ	2015	China	28	4	•	0.06 (0.00, 1.24)	0/125	3/58
QY	2016	China	28	0		0.13 (0.03, 0.61)	2/152	12/132
ing BA	2012	China	28	0		0.08 (0.01, 0.63)	1/40	10/40
engML	2014	China	28	NR		0.09 (0.01, 0.82)	1/30	8/30
en N	2015	China	28	24		0.14 (0.03, 0.70)	2/46	11/46
nJ	2019	China	28	0		0.10 (0.01, 1.81)	0/41	6/59
an RH	2016	China	28	4		0.20 (0.06, 0.69)	3/318	17/374
ang B	2016	China	28	4		0.05 (0.00, 0.79)	0/110	16/187
ang EJ	2012	China	28	4		0.07 (0.00, 1.37)	0/28	5/27
ang HB	2016	China	28	NR		0.18 (0.01, 4.01)	0/20	2/20
ang TD	2015	China	28	4		0.05 (0.00, 0.87)	0/53	8/52
ang WP	2012	China	28	0		0.17 (0.01, 2.91)	0/25	20/198
ao XH	2017	China	28	0 or 4		0.32 (0.01, 8.08)	0/62	1/61
9 PY	2016	China	28	4		0.24 (0.03, 2.19)	1/60	4/60
ng Y	2018	China	28	4		0.05 (0.00, 0.95)	0/30	7/30
ng HW	2015	China	28	4		0.06 (0.01, 0.52)	1/50	12/50
o ZC	2011	China	28	4		0.10 (0.01, 2.01)	0/28	4/30
ang GH	2018	China	28	4		0.13 (0.01, 2.65)	0/40	3/40
ang X	2015	China	28	12		0.08 (0.00, 1.48)	0/48	5/47
ang YF	2010b	China	28	4		0.05 (0.01, 0.36)	1/60	16/60
ao DB	2010	China	28	4		0.31 (0.03, 3.17)	1/30	3/30
ieng JC	2018	China	28	4		0.07 (0.00, 1.35)	0/23	8/37
u J	2017	China	28	0		0.10 (0.01, 0.81)	1/60	8/54
u LP	2014	China	28	4		0.13 (0.01, 2.61)	0/30	3/30
btotal (I-squa	ared = 0.0°	%, p = 0 . 995)			P	0.13 (0.10, 0.18)	49/2362	371/2542
edian >28 we	eks GA				i l			
ai HL	2013	China	28-32	4		0.11 (0.01, 2.09)	0/27	4/30
e YL	2015	China	28-30	12		0.14 (0.01, 2.81)	0/20	3/22
an GR	2015	China	28-32	NR		0.05 (0.00, 0.79)	0/102	8/86
Y	2018	China	28-32	3-4		0.23 (0.01, 4.81)	0/105	2/122
J	2017	China	30	NR		0.05 (0.00, 1.17)	0/97	2/28
XB	2016	China	28-36	4		0.07 (0.00, 1.34)	0/20	5/20
iΥ	2016	China	28-32	4		0.10 (0.01, 0.78)	1/32	19/78
n YC	2017	China	32	0		0.10 (0.01, 1.66)	0/81	21/370
ang DM	2016	China	28-30	12		0.09 (0.01, 0.80)	1/36	5/20
ang HB	2016	China	32	NR		0.18 (0.01, 4.01)	0/20	2/20
ang HB	2016	China	36	NR		0.18 (0.01, 4.01)	0/20	2/20
ang HB o LF	2016	China	28-32	NH 6		0.18 (0.01, 4.01)	0/20	2/20
				6 4		0.19 (0.01, 4.06) 0.06 (0.00, 1.09)	0/30	2/30 10/352
ang H ang L	2014	China	28-30					
ang LJ htotal (l-cour	2009 ared = 0.0%	China % p = 1.000)	28-32	4		0.10 (0.00, 1.88) 0.10 (0.05, 0.21)	0/30 2/877	4/30
ibtotal (I-squa	areu = 0.0°	/o, p = 1.000)				0.10 (0.05, 0.21)	2/877	89/1228
eral (I-squa	red = 0.0%	, p = 1.000)			\$	0.11 (0.09, 0.14)	69/5239	771/6151
					I			

- PMTCT, as indicated by detection of HBsAg at 6-12 months of age, all treatment start times, all study designs merged (i.e. RCT and non-RCT), <u>stratified by the</u> <u>minimum HBV DNA level specified in the study inclusion criteria.</u>
 - >4-4.99 log10 IU/mL: pooled OR=0.07 (95% CI: 0.03-0.15), P<0.001, I²=0.0%
 - >5-5.99 log10 IU/mL: pooled OR=0.12 (95% CI: 0.08-0.17), P<0.001, I²=0.0%
 - >6-6.99 log10 IU/mL: pooled OR=0.10 (95% CI: 0.07-0.15), P<0.001, I²=0.0%
 - >7-7.99 log10 IU/mL: no studies included
 - When looking at heterogeneity across the three HBV DNA level subgroups, the *P* value was 0.46. If comparing >4-4.99 log10 IU/mL with >5-5.99 log10 IU/mL, there was no heterogeneity (*P*=0.22). If comparing >5-5.99 log10 IU/mL with >6-6.99 log10 IU/mL, there was no evidence of heterogeneity (*P*=0.58). If comparing >4-4.99 log10 IU/mL with >6-6.99 log10 IU/mL, there was no evidence of heterogeneity (*P*=0.36).

LdT 600mg, MTCT=HBsAg+, HBVDNA level

4-4.99 log10 IU/ml Chen SM 2017 China 28 NR Han YP 2014 China 28 6 Jiang XN 2013 China 28 6 Jiang XN 2013 China 28 6 Li N 2016 China 28 NR Li N 2016 China 28 NR Li N 2016 China 28 4 Shen ML 2016 China 26 4 Wang WP 2012 China 28 0 Wang WP 2012 China 28 0 Wang WP 2012 China 427 0 Subtotal (I-squared = 0.0%, p = 0.958) 5-5.99 log10 IU/ml Chinz 28 4 Solution 10 - 10 - 10 - 10 - 10 - 10 - 10 - 10	$\begin{array}{c} 0.03 & (0.00, \ 0.58) \\ 0.10 & (0.00, \ 1.88) \\ 0.08 & (0.01, \ 0.73) \\ 0.06 & (0.01, \ 0.53) \\ 0.06 & (0.01, \ 0.53) \\ 0.06 & (0.00, \ 1.24) \\ 0.01 & (0.00, \ 0.22) \\ 0.10 & (0.01, \ 1.71) \\ 0.17 & (0.01, \ 2.91) \\ 0.19 & (0.01, \ 3.31) \\ 0.06 & (0.03, \ 0.15) \end{array}$	0/30 0/30 1/65 1/30 0/35 0/125 0/61 0/135 0/25 0/22 2/558	10/30 4/30 8/51 9/25 9/25 3/58 11/28 7/203 20/198
Chen ZX 2017 China 13-32 NR Cui ZL 2015 China 28 4		2/000	20/198 101/846
Ge YL 2015 China 28-30 12 Han GR 2015 China 20-27 NR Huang HY 2016 China 28-32 NR Huang HY 2016 China 24 0 Huang HY 2016 China 28 0 Ji YY 2016 China 28 4 Li ZY 2018 China 28 4 Li ZY 2018 China 28 4 Peng BA 2012 China 28 4 Qiu B 2016 China 28 4 Qiu B 2016 China 28 4 Sheng Q 2018a China 24-32 4 Sheng Q 2018a China 24-32 4 Shi QW 2017 China 28 24 Shi QW 2017 China 28 4 Sheng Q 2018a China 12-14 24 Yang HW 2015 China 28 4 Zhang HY 2018 China 28 4 Zhang YF 2010b China 28 4 Zhang YF 2010	$\begin{array}{c} 0.12 \ (0.02, 0.97) \\ 0.07 \ (0.00, 1.30) \\ 0.07 \ (0.00, 0.130) \\ 0.07 \ (0.00, 0.32) \\ 0.07 \ (0.00, 0.32) \\ 0.05 \ (0.00, 0.032) \\ 0.01 \ (0.00, 0.032) \\ 0.01 \ (0.00, 0.032) \\ 0.01 \ (0.00, 0.032) \\ 0.01 \ (0.00, 0.030) \\ 0.01 \ (0.00, 0.030) \\ 0.01 \ (0.00, 0.030) \\ 0.01 \ (0.00, 0.030) \\ 0.01 \ (0.00, 0.030) \\ 0.01 \ (0.00, 0.030) \\ 0.01 \ (0.00, 0.030) \\ 0.01 \ (0.00, 0.030) \\ 0.01 \ (0.00, 0.030) \\ 0.01 \ (0.01, 0.030$	1/41 1/50 0/28 0/20 0/256 0/102 1/30 5/30 3/65 4/41 1/34 1/34 1/34 1/34 1/34 1/34 1/30 2/46 0/60 2/46 0/79 3/100 1/36 0/40 1/50 0/28 0/257 1/60 0/21 39/1667	15/89 13/46 6/60 3/22 8/86 23/30 23/30 23/30 23/30 12/65 9/41 12/60 11/46 2/21 12/100 5/20 6/40 12/50 4//30 10/35/ 10/30 271/1565
6-6-99 log10 IU/mI Bai HL 2013 China 28-32 4 Chen CY 2015 China 1st Trimester NR Chen F 2016 China 28 0 Deng Y 2015 China 24-36 4 Feng XM 2017 China 28 4 Fug XM 2017 China 28 4 Huang Q 2017 China 28 4 Huang Q 2017 China 28 24 Li YF 2015 China 28 24 Li YF 2015 China 28 24 Li YF 2015 China 28 24 Li YF 2016 China 28 24 Li YF 2016 China 28 23 Sheng Q 2018b China 24-28 0 Sheng Q 2018b China 24-28 0 Sheng Q 2018b China 24-28 0 Sheng Q 2018b China 20-28 12 Sun W 2017 China 12 12 Sun WH 2015 China 14-27 4 Wang B 2016 China 14-28 NR Tan Z 2016 China 14-28 NR Wang B 2016 China 28 4 Wang B 2016 China 28 4 Zhang X 2017 China 24-28 NR Wang D 2017 China 24-28 NR Wang D 2017 China 28 4 Wang B 2016 China 28 4 Wang B 2016 China 28 4 Zhang X 2017 China 28 4 Zhang X 2017 China 28 4 Zhang Y 2018 China 28 4 Zhang Y 2019 China 18 Trimester 0 Subtotal (I-squared = 0.0%, p = 0.989)	$\begin{array}{c} 0.11 \ (0.01, 2.09)\\ 0.11 \ (0.01, 0.98)\\ 0.06 \ (0.00, 1.20)\\ 0.09 \ (0.03, 0.30)\\ 0.10 \ (0.01, 1.82)\\ 0.10 \ (0.01, 1.82)\\ 0.10 \ (0.01, 1.92)\\ 0.12 \ (0.01, 1.92)\\ 0.12 \ (0.01, 1.92)\\ 0.12 \ (0.01, 1.25)\\ 0.07 \ (0.00, 1.26)\\ 0.17 \ (0.00, 1.26)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.17)\\ 0.05 \ (0.00, 1.37)\\ 0.03 \ (0.00, 0.59)\\ 0.03 \ (0.00, 0.59)\\ 0.03 \ (0.00, 0.59)\\ 0.03 \ (0.00, 0.59)\\ 0.03 \ (0.00, 0.59)\\ 0.03 \ (0.00, 0.59)\\ 0.05 \ (0.00, 0.98)\\ 0.07 \ (0.00, 1.87)\\ 0.02 \ (0.00, 0.137)\\ 0.02 \ (0.00, 0.137)\\ 0.02 \ (0.00, 0.137)\\ 0.02 \ (0.00, 0.137)\\ 0.05 \ (0.00, 0.98)\\ 0.15 \ (0.00, 0.148)\\ 0.05 \ (0.00, 0.48)\\ 0.05 \ (0.00, 0.48)\\ 0.05 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.02 \ (0.00, 0.148)\\ 0.08 \ (0.00, 1.48)\\ 0.09 \ (0.01, 0.78)\\ 0.09 \ (0.01, 0.78)\\ 0.10 \ (0.07, 0.15)\\ 0.10 \ (0.08, 0.13)\\ 0.10 \$	0/27 1/42 0/31 4/79 0/82 0/38 1/36 0/123 6/28 0/20 0/20 0/97 0/20 0/97 0/20 0/97 0/20 0/97 0/20 0/97 0/20 0/97 0/20 0/97 0/20 0/97 0/20 0/97 0/20 0/97 0/20 0/97 0/20 0/41 0/41 0/41 0/41 0/41 0/43 0/28 1/329 0/25 0/20 0/26 0/26 0/26 0/20 0/26 0/20 0/41 0/41 0/41 0/41 0/41 0/41 0/41 0/41 0/41 0/41 0/41 0/41 0/41 0/41 0/28 0/20 0/20 0/20 0/20 0/20 0/20 0/20 0/20 0/20 0/20 0/20 0/20 0/20 0/20 0/20 0/22 0/20 0/41 0/28 0/28 0/28 0/28 0/20 0/20 0/41 0/28 0/30 0/36 0/24 0/30 0/36 0/36 0/36 0/34 0/41 0/40 0/28 0/34 0/40 0/24 0/34 0/44 0/44 0/45 1/27 0/27 0/27 0/27 0/27 0/204 0/34 0/44 0/44 0/45 1/27 0/2 0/27 0/2 0/2 0/27 0/2 0/27 0/2 0/27 0/2 0/27 0/2 0/27 0/2 0/2 0/2 0/2 0/2 0/27 0/2 0/2 0/2 0/2 0/27 0/2 0/27	4/30 7/40 6/32 16/44 4/73 7/36 2/26 6/26 3/20 5/22 2/28 5/20 5/22 2/28 5/20 5/27 12/65 12/73 1/61 12/73 1/61 12/73 1/61 12/73 13/40 12/73 13/40 12/73 13/40

- PMTCT, as indicated by detection of HBsAg at 6-12 months of age, all treatment start times, all HBV DNA levels specified at inclusion, all study designs merged (i.e. RCT and non-RCT), <u>stratified by whether or not all women were HBeAgpositive.</u>
 - All HBeAg-positive: pooled OR=0.11 (95% CI: 0.08-0.14), P<0.001, I²=0.0%
 - Mixed HBeAg-positive: pooled OR=0.10 (95% CI: 0.05-0.23), P<0.001, I²=0.0%
 - There was no heterogeneity (*P*=0.94) between the two subgroups.

LdT 600mg, MTCT=HBsAg+, by HBeAg+

All HBeAg p							
Chen CY	2015	China	1st Trimester	NR	0.11 (0.01, 0.98)	1/42	7/40
Chen F	2016	China	Pre-pregnancy	NR	0.06 (0.00, 1.20)	0/31	6/32
Chen QR	2018	China	28	4	0.07 (0.00, 1.38)	0/29	5/28
Chen SM	2017	China	28	NR	0.03 (0.00, 0.58)	0/30	10/30
Chen WJ	2017	China	28	0	0.09 (0.03, 0.30)	4/79	16/44
Cui ZL	2015	China	28	4	0.05 (0.01, 0.42)	1/50	13/46
Ding XP Fan LY	2018 2013	China China	28 28	4	0.10 (0.01, 1.92) 0.07 (0.00, 1.30)	0/38 0/58	4/38 6/60
Feng XM	2013	China	28	4	0.12 (0.01, 1.02)	1/36	7/36
Ge YL	2017	China	28-30	12	- 0.12 (0.01, 1.02) 0.14 (0.01, 2.81)	0/20	3/22
Guan ZF	2015	China	24	12	0.03 (0.00, 0.51)	0/123	14/122
Guo HJ	2017	China	28	4	- 0.91 (0.25, 3.28)	6/28	6/26
Han GR	2015	China	20-27	NR	0.02 (0.00, 0.32)	0/256	8/86
Han GR	2015	China	28-32	NR	0.05 (0.00, 0.79)	0/102	8/86
lan YP	2014	China	28	6	0.10 (0.00, 1.88)	0/30	4/30
łu Y	2018	China	28-32	3-4	0.23 (0.01, 4.81)	0/105	2/122
luang HY	2016	China	20	0	0.01 (0.00, 0.09)	1/30	23/30
luang HY	2016	China	24		0.06 (0.02, 0.22)	5/30	23/30
luang HY	2016	China	28	0	0.15 (0.05, 0.47)	10/30	23/30
luang Q	2017	China	24-28	12	0.12 (0.01, 2.53)	0/20	3/20
i YY	2015	China	28	4	0.21 (0.06, 0.80)	3/65	12/65
iang XN	2013	China	26-30	NR	0.08 (0.01, 0.70)	1/65	8/51
.i YH	2017	China	28	~36	0.19 (0.02, 1.70)	1/30	5/32
.i ZY	2018	China	28	NR .	0.38 (0.11, 1.37)	4/41	9/41
iu CY	2014	China	28	4	0.10 (0.01, 0.84)	1/34	8/34
iu J	2017	China	30		0.05 (0.00, 1.17)	0/97	2/28
iu XB	2016 2015	China China	28-36 28	4	0.07 (0.00, 1.34) 0.06 (0.00, 1.24)	0/20 0/125	5/20 3/58
ou JJ Pan YC	2015	China	32	4	0.10 (0.00, 1.24)	0/125	21/370
eng BA	2012	China	28	ů	0.08 (0.01, 0.63)	1/40	10/40
PengML	2012	China	28	NB	0.09 (0.01, 0.82)	1/30	8/30
Ren N	2015	China	28	24	0.14 (0.03, 0.70)	2/46	11/46
Sheng Q	2018a	China	24-32	4	0.05 (0.00, 1.06)	0/79	2/21
Sun W	2017	China	12	12	0.03 (0.00, 0.59)	0/62	12/65
Sun W	2017	China	20-28	12	0.03 (0.00, 0.60)	0/61	12/65
Sun WH	2015	China	12	12	0.05 (0.00, 0.93)	0/43	8/46
Sun WH	2015	China	20-28	12	0.05 (0.00, 0.98)	0/41	8/46
"ian JH	2018	China	Anytime	NR	0.10 (0.01, 1.71)	0/135	7/203
ïan RH	2016	China	28	4	0.20 (0.06, 0.69)	3/318	17/374
Vang B	2016	China	28	4	0.05 (0.00, 0.79)	0/110	16/187
Vang DM	2016	China	28-30	12	0.09 (0.01, 0.80)	1/36	5/20
Vang EJ	2012 2018	China China	28 12-14	4 24	0.07 (0.00, 1.37)	0/28 0/40	5/27 6/40
Vang HY Vang TD	2018	China	28	4	0.07 (0.00, 1.21) 0.05 (0.00, 0.87)	0/40 0/53	6/40 8/52
Vang VD Vang WP	2015	China	28	4	- 0.17 (0.01, 2.91)	0/55	6/52 20/198
Vang WP	2012	China	<27	0	- 0.19 (0.01, 2.91)	0/25	20/198
Vu Q	2012	China	24-32	0 or 4	0.01 (0.00, 0.23)	0/204	14/95
ang HW	2015	China	28	4	0.06 (0.01, 0.52)	1/50	12/50
ao LF	2014	China	28-32	6	0.19 (0.01, 4.06)	0/30	2/30
hang BF	2018	China	24-28	ŏ	0.05 (0.00, 0.92)	0/36	15/75
hang GH	2018	China	28	4	0.13 (0.01, 2.65)	0/40	3/40
hang H	2014	China	28-30	4	0.06 (0.00, 1.09)	0/257	10/352
hang X	2015	China	28	12	0.08 (0.00, 1.48)	0/48	5/47
hang YF	2010b	China	28	4	0.05 (0.01, 0.36)	1/60	16/60
hao DB	2010	China	28	4	- 0.31 (0.03, 3.17)	1/30	3/30
'hao J	2013	China	20	0	0.09 (0.01, 1.55)	0/41	23/202
hao Y	2017	China	12	12	0.08 (0.00, 1.49)	0/40	5/40
heng JC	2018	China	28	4	0.07 (0.00, 1.35)	0/23	8/37
		= 0.0%, p =	0.988)	Y	0.11 (0.08, 0.14)	50/3753	555/437
lixed HBeA			10.00	ND L	0.40 (0.00, 0.07)	4 / 4 4	15/00
Chen ZX le T	2017 2018	China China	13-32 1st Trimester	NR NR	0.12 (0.02, 0.97) 0.10 (0.01, 2.02)	1/41 0/32	15/89 4/34
iu Y	2018	China	28-32	4	0.10 (0.01, 2.02)	1/32	4/34 19/78
.iu Y	2016	China	4-27	4	0.03 (0.00, 0.51)	0/50	19/78
u QY	2016	China	28	ō —	0.13 (0.03, 0.61)	2/152	12/132
Sheng Q	2018b	China	24-28	ů	0.06 (0.00, 1.05)	0/66	5/46
an Z	2016	China	14-28	NR	0.07 (0.00, 1.21)	0/137	15/320
an Z	2016	China	<14	NR	0.29 (0.02, 4.88)	0/34	15/320
Subtotal (I-s	squared =	= 0.0%, p =	0.978)	\diamond	0.10 (0.05, 0.23)	4/544	104/109
overa li (i- so	quared =	0.0%, p = 0	.998)	\$	0.11 (0.08, 0.14)	54/4297	659/547

 PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all HBV DNA levels specified at inclusion, all study designs merged (i.e. RCT and non-RCT), by infant immunoprophylaxis regimen (Table 15).

Birth dose vaccine	HBIG at birth	2-4 infant vaccines (not at birth)	# studies (treatment arms)
Yes	Yes	Yes	76 (88)
Yes	NR	NR	2 (2) (Liu J et al., 2017; Wang DM et al. 2016),
No	Yes	Yes	2 (2) (Li SF et al., 2015; Li ZY et al., 2018)
NR	Yes	NR	2 (2) (Xiao XH et al., 2017; Yao LF et al., 2014)
NR	NR	NR	1 (3) (Huang HY et al., 2016)

Table 15. Infant immunoprophylaxis regimens seen in studies investigating LdT

NR: not reported

• As most studies provided all of birth dose vaccines, HBIG at birth, and subsequent infant vaccinations, stratification by type or combination of infant immunoprophylaxis was not done in this meta-analysis.

• Therefore, we <u>stratified by whether or not *both* birth dose vaccine and</u> <u>HBIG were given within 12 hours of life, versus within 24 hours of life.</u>

- \circ <12 hours: pooled OR=0.09 (95% CI: 0.06-0.15), P<0.001, I²=0.0%
- <24 hours: pooled OR=0.11 (95% CI: 0.06-0.19), P<0.001, I²=0.0%
- \circ The *P* value for heterogeneity between the two subgroups was 0.67.

LdT 600mg, HBsAg +, by BD & HBIG timing

Author Ye	'ear C	ountry	Timing of Birth Dose Vaccine	īming of IBIG at birth	OR (95% Cl)
Birth dose &	HBlg <	12hrs		I	
Chen ZX 20	017 C	hina	within 6 hours	vithin 6 hours	0.12 (0.02, 0.
Han GR 20	015 C	hina	within 12 hours	vithin 2-3 hou rs	0.02 (0.00, 0.
Han GR 20	015 C	hina	within 12 hours	vithin 2-3 hours	0.05 (0.00, 0.
		hina	within 12 hours	vithin 6 hours	0.10 (0.01, 2.
luang Q 20		hina	within 6 hours	vithin 6 hours	0.12 (0.01, 2.
		hina	within 6 hours	vithin 6 hours	0.06 (0.01, 0.
		hina	within 6 hours	vithin 6 hours	0.02 (0.00, 0.
		hina	within 12 hours	vithin 12 hours	0.13 (0.03, 0.
		hina	within 2-3 hours	vithin 2-3 hours	0.13 (0.03, 0.
		hina	within 12 hours	vithin 12 hours	• 0.10 (0.01, 1 0.29 (0.09, 0
		hina	within 12 hours	vithin 12 hours	
					0.03 (0.00, 0.
Sheng Q 20			within 12 hours	vithin 12 hours	0.05 (0.00, 1.
Sheng Q 20			within 12 hours	vithin 12 hours	0.06 (0.00, 1.
		hina	within 2-3 hours	vithin 2-3 hours	0.23 (0.06, 0.
		hina	within 12 hours	vithin 6 hours	0.03 (0.00, 0.
		hina	within 12 hours	vithin 6 hours	0.03 (0.00, 0.
		hina	within 6 hours	vithin 6 hours	0.05 (0.00, 0.
		hina	within 6 hours	vithin 6 hours	0.05 (0.00, 0.
		hina	within 12 hours	vithin 6 hours	0.10 (0.01, 1.
Nang HY 20		hina	within 6 hours	vithin 6 hours	0.07 (0.00, 1.
Nang J 20	017 C	hina	within 12 hours	vithin 12 hours	0.02 (0.00, 0.
Nang WP 20	012 C	hina	within 6 hours	vithin 6 hours	0.17 (0.01, 2.
Nang WP 20	012 C	hina	within 6 hours	vithin 6 hours	0.19 (0.01, 3.
King Y 20	018 C	hina	within 6 hours	vithin 6 hours	0.05 (0.00, 0.
Zhang H 20	014 C	hina	within 6 hours	vithin 6 hours	0.06 (0.00, 1.
	013 C		within 6 hours	vithin 6 hours	0.09 (0.01, 1.
			o, p = 0.974)	\bigcirc	0.09 (0.06, 0.
Birth dose &	HBla <	24hrs			
Chen QR 20			within 24 hours	vithin 24 hours	0.07 (0.00, 1.
		hina	within 24 hours	vithin 24 hours	0.05 (0.01, 0.
		hina	within 24 hours	vithin 24 hours	0.10 (0.01, 1.
		hina	within 24 hours	vithin 24 hours	0.07 (0.00, 1
		hina	within 24 hours	vithin 24 hours	0.07 (0.00, 1
		hina	within 24 hours	vithin 24 hours	0.10 (0.00, 1
		hina			
			within 24 hours	vithin 24 hours	0.23 (0.01, 4.
		hina	within 24 hours	vithin 24 hours	0.21 (0.06, 0.
		hina	within 24 hours	vithin 24 hours	0.09 (0.01, 0.
		hina	within 24 hours	vithin 24 hours	0.09 (0.01, 0.
		hina	within 24 hours	vithin 24 hours	0.14 (0.03, 0.
Wang HB 20		hina	within 24 hours	vithin 24 hours	0.18 (0.01, 4.
Nang HB 20		hina	within 24 hours	vithin 24 hours	0.18 (0.01, 4
Nang HB 20		hina	within 24 hours	vithin 24 hours	0.18 (0.01, 4.
Nang HB 20		hina	within 24 hours	vithin 24 hours	0.18 (0.01, 4.
Nang HB 20		hina	within 24 hours	vithin 24 hours	0.18 (0.01, 4.
Wang TD 20	015 C	hina	within 24 hours	vithin 24 hours	0.05 (0.00, 0.
Yang HW 20		hina	within 24 hours	vithin 24 hours	0.06 (0.01, 0.
Zhang YF 20	010b C	hina	within 24 hours	vithin 24 hours	0.05 (0.01, 0.
			o, p = 1.000)		0.11 (0.06, 0.
Overall (I-so	quared :	= 0.0%,	p = 1.000)	\$	0.10 (0.07, 0.
				•	•
				.001 .1	1 10

- PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all study designs merged (i.e. RCT and non-RCT), <u>stratified by the</u> <u>timing that treatment was discontinued postpartum.</u>
 - At delivery: pooled OR=0.11 (95% CI: 0.07-0.17), P<0.001, I²=0.0%
 - 4-8 weeks postpartum: pooled OR=0.13 (95% CI: 0.09-0.19), P<0.001, I²=0.0%
 - 12 weeks postpartum: pooled OR=0.06 (95% CI: 0.3-0.15), P<0.001, I²=0.0%
 - 24+ weeks postpartum: pooled OR=0.11 (95% CI: 0.04-0.29), P<0.001, I²=0.0%
 - When looking at heterogeneity across the four subgroups, the *P* value was 0.55.

LdT 600mg, HBsAg +, by tx end timing

Author	Year	Country	Timing of Birth Dose Vaccine	Timing of HBIG at birth	OR (95% C
At delivery					
Chen WJ	2017	China	'at birth'	within 24 hours	0.09 (0.03,
Gao P	2016	China	'at birth'	'at birth'	0.09 (0.01,
Huang HY	2016	China	N/A	N/A	0.01 (0.00,
Huang HY	2016	China	N/A	N/A	0.06 (0.02,
Huang HY	2016	China	N/A	N/A	0.15 (0.05,
Lu QÝ	2016	China	within 12 hours	within 12 hours	0.13 (0.03,
Pan YC	2017	China	within 2-3 hours	within 2-3 hours	0.10 (0.01,
Peng BA	2012	China	'at birth'	'at birth'	0.08 (0.01,
Qiu B	2016	China	within 12 hours	within 12 hours	0.29 (0.09,
Qiu B	2016	China	within 12 hours	within 12 hours	0.03 (0.00.
Sheng Q	2018b	China	within 12 hours	within 12 hours	0.06 (0.00,
Shi QW	2017	China	within 2-3 hours	within 2-3 hours	0.23 (0.06,
Tan J	2019	China	'at birth'	within 24 hours	0.10 (0.01,
Wang WP	2012	China	within 6 hours	within 6 hours	0.17 (0.01,
Wang WP	2012	China	within 6 hours	within 6 hours	0.19 (0.01,
Zhang BF	2018	China	'at birth'	within 6 hours	0.05 (0.00,
Zhao J	2013	China	within 6 hours	within 6 hours	0.09 (0.01,
Zhou YJ	2013	China	within 24 hours	unknown/unclear	0.09 (0.01,
Zhu J	2017	China	'at birth'	within 24 hours	0.10 (0.01,
Subtotal (I-s	quared = 0	0.0%, p = 0.	887)	A 1	0.11 (0.07,
4 to 8 weeks	post-delive	ery			
Bai HL	2013	China	'at birth'	within 6 hours	0.11 (0.01,
Chen QR	2018	China	within 24 hours	within 24 hours	0.07 (0.00,
Cui ZL	2015	China	within 24 hours	within 24 hours	0.05 (0.01,
Deng Y	2015	China	'at birth'	at birth'	0.10 (0.01,
Ding XP	2018	China	within 24 hours	within 24 hours	0.10 (0.01,
Feng XM	2010	China	'at birth'	within 6 hours	0.12 (0.01,
Fu PX	2016	China	unknown/unclear	unknown/unclear	0.33 (0.03,
Guo HJ	2010	China	'at birth'	within 6 hours	0.91 (0.25,
Han YP	2014	China	within 24 hours	within 24 hours	0.10 (0.00,
Hu Y	2014	China	within 24 hours	within 24 hours	0.23 (0.01,
Ji YY	2015	China	within 24 hours	within 24 hours	0.21 (0.06,
LiCM	2015	China	within 24 hours	within 24 hours	0.09 (0.01,
Liu CY	2017	China	at birth'	within 24 hours	0.10 (0.01,
Liu C f	2014	China	'at birth'	'at birth'	0.07 (0.00,
Liu XD	2016	China	'at birth'	unknown/unclear	0.10 (0.01,
Liu Y	2016	China	'at birth'	unknown/unclear	0.03 (0.00,
Lou JJ	2015	China	'at birth'	within 6 hours	0.06 (0.00,
Shen ML	2015	China	unknown/unclear	within 8 hours	0.01 (0.00,
SherriviL					0.01 (0.00,
Sheng Q	2018a	China China	within 12 hours 'at birth'	vithin 12 hours	0.05 (0.00,
Tian RH	2016				0.20 (0.06,
Wang B	2016	China	'at birth'	'at birth'	0.05 (0.00,
Wang EJ	2012	China	'at birth'	within 24 hours	0.07 (0.00,
Wang TD	2015	China	within 24 hours	within 24 hours	0.05 (0.00,
Xie PY	2016	China	'at birth'	'at birth'	0.24 (0.03,
Xing Y	2018	China	within 6 hours	within 6 hours	0.05 (0.00,
Yang HW	2015	China	within 24 hours	within 24 hours	0.06 (0.01,
Yao LF	2014	China	N/A	unknown/unclear	0.19 (0.01,
Yao ZC	2011	China	'at birth'	within 6 hours	0.10 (0.01,
Zhang GH	2018	China	'at birth'	within 24 hours	0.13 (0.01,
Zhang H	2014	China	within 6 hours	within 6 hours	0.06 (0.00,
Zhang LJ	2009	China	'at birth'	within 6 hours	0.10 (0.00,
Zhang YF	2010b	China	within 24 hours	within 24 hours	0.05 (0.01,
Zhao DB	2010	China	'at birth'	within 6 hours	0.31 (0.03,
Zheng JC	2018	China	within 24 hours	within 6 hours	0.07 (0.00,
Zhu LP	2014	China	'at birth'	within 6 hours	0.13 (0.01,
Subtotal (I -s	quared = 0	0.0%, p = 0.	959)	\diamond	0.13 (0.09,
12 weeks po					
Ge YL	2015	China	'at birth'	within 24 hours	0.14 (0.01,
Guan ZF	2017	China	'at birth'	within 6 hours	0.03 (0.00,
Huang Q	2017	China	within 6 hours	within 6 hours	0.12 (0.01,
Sun W	2017	China	within 12 hours	within 6 hours	0.03 (0.00,
Sun W	2017	China	within 12 hours	within 6 hours	0.03 (0.00,
Sun WH	2015	China	within 6 hours	within 6 hours	0.05 (0.00,
Sun WH	2015	China	within 6 hours	within 6 hours	0.05 (0.00,
Wang DM	2016	China	within 24 hours	N/A	0.09 (0.01,
Zhang X	2015	China	'at birth'	within 24 hours	0.08 (0.00,
Zhao Y	2017	China	'at birth'	'at birth'	0.08 (0.00,
Subtotal (I-s	quared = 0	0.0%, p = 0.	999)		0.06 (0.03,
24+ weeks p		у			
Fan LY	2013	China	within 24 hours	within 24 hours	0.07 (0.00,
Hu WH	2016	China	within 24 hours	within 24 hours	0.07 (0.00,
Li SF	2015	China	N/A	'at birth'	0.07 (0.00,
Li YH	2017	China	unknown/unclear	within 24 hours	0.19 (0.02,
Ren N	2015	China	within 24 hours	within 24 hours	0.14 (0.03,
Wang HY	2018	China	within 6 hours	within 6 hours	0.07 (0.00,
Subtotal (I-s	iquared = 0	.∪%, p = 0.	390)		0.11 (0.04,
Overall (I-sq	uared = 0.	0%, p = 1.0	00)	\$	0.11 (0.09,
				I I I .001 .109 1	10

Safety analysis, narrative descriptions and selected forest plots

Infant safety outcomes

Of the infant safety outcomes predefined in the protocol, the data for Apgar score were not available for the majority of included studies and where it was available the format varied greatly; this led to an inability to combine results in a meaningful way. None of the included studies for LdT investigated bone mineral density in infants.

1. <u>Neonatal deaths</u> (death within 28 days of life)

Information on this outcome was available for all except one study that administered LdT to mothers. Two deaths of 5752 infants (non-weighted average 0.03%) were reported across the treatment groups and no deaths in the 5863 infants (0.0%) were reported across the control groups. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.000 (95% CI: -0.002–0.003). The I² statistics for the overall pooled risk difference, as well as for RCTs and non-RCTs separately, were all 0.0%.

LdT 600mg, Neonatal deaths risk difference

	/ear	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	RD (95% CI)	Events, Treatment	Events, Control
Chen SM 2 Cuan ZF 2 Guan ZF 2 Huang HY 2 Ji YY 2 Shi QW 2 Shi QW 2 Xang HY 2 Zhang Y 2 Zhang DB 2 Zhao DB 2 Zhao Y 2	2013 2017 2016 2017 2011 2015 2015 2015 2016 2015 2016 2018 2018 2018 2018 2018 2018 2018 2019 2018 2019 2018 2019 2018 2017 2016 2017 2016 2017 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2015 2016 2015 2016 2015 2016 2015 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2017 2016 2015 2016 2017 2016 2015 2016 2017 2016 2015 2016 2017 2016 2017 2016 2015 2016 2017 2016 2017 2016 2017 2016 2017 2017 2016 2017 2017 2017 2017 2017 2017 2017 2017	China China	28-32 28 24-28 24 28 20 28 28 28 24 12-14 28 28 28 28 28 28 28 32 28 28 32 8 32	4 NR 4 12 4 0 4 24 0 24 4 4 4 4 4 4 4 4 4 4 4 4	$\begin{array}{c} 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.04, \ 0.04) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06,$	0/30 0/30 0/123 0/28 0/90 0/65 0/60 0/152 0/30 0/40 0/60 0/30 0/50 0/31 0/34 0/30 0/34 0/30 0/34 0/30 0/40 0/30 0/3	0/30 0/30 0/102 0/122 0/26 0/30 0/30 0/132 0/30 0/100 0/40 0/40 0/30 0/30 0/34 0/30 0/34 0/30 0/34 0/30 0/40 0/4
Chen F 2 Chen OR 2 Chen WJ 2 Chen WJ 2 Chen ZX 2 Chan ZX 2 Chen ZX 2 Coli ZL 2 Deng YP 2 Fan LY 2 Gao P 2 Gao P 2 Hu YP 2 Hu YH 2 Hu WH 2 Jiang XN 2 Li CM 2 Li IN 2 Shen Q 2 Wang BA 2 Wang BH 2	0015 0018 0017 0015 0017 0015 0017 0015 0018 0018 0018 0018 0018 0018 0018	China China	,	NR 4 4 4 4 4 4 4 4 4 4 4 4 4 0 12 6 NR 28 34 4 12 6 NR 4 8 34 4 12 6 NR 4 8 34 4 12 6 NR 4 8 34 4 12 6 NR 4 8 34 4 12 6 NR 4 8 34 4 12 6 NR 4 8 34 4 12 6 NR 4 8 34 4 12 6 NR 4 8 8 8 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	$\begin{array}{c} 0.00 & (-0.5, 0.05) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.07, 0.07) \\ 0.00 & (-0.04, 0.04) \\ 0.00 & (-0.04, 0.04) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.03, 0.03) \\ 0.00 & (-0.05, 0.05) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.02, 0.02) \\ 0.00 & (-0.03, 0.03) \\ 0.00 & (-0.04, 0.04) \\ 0.00 & (-0.04, 0.04) \\ 0.00 & (-0.07, 0.07) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.05, 0.05) \\ 0.00 & (-0.06, 0.06) \\ 0.00 & (-0.06, 0$	0/42 0/31 0/29 0/79 0/41 0/52 0/38 0/36 0/51 0/20 0/30 0/32 0/46 0/32 0/44 0/30 0/44 0/30 0/44 0/20 0/32 0/46 0/30 0/41 0/30 0/41 0/30 0/41 0/20 0/46 0/149 0/20 0/30 0/46 0/30 0/46 0/149 0/20 0/46 0/149 0/20 0/46 0/149 0/20 0/46 0/149 0/20 0/46 0/149 0/20 0/46 0/149 0/20 0/46 0/127 0/46 0/141 0/20 0/46 0/127 0/46 0/127 0/46 0/127 0/46 0/127 0/46 0/127 0/46 0/127 0/46 0/127 0/46 0/127 0/46 0/127 0/46 0/13 0/82 0/13 0/51 0/30 0/84 0/100 0/328 0/100 0/328 0/100 0/33 0/57 2/280 0/30 0/36 0/31 0/36 0/31 0/36 0/31 0/36 0/149 0/20 0/46 0/149 0/27 0/46 0/27 0/46 0/27 0/46 0/27 0/46 0/28 0/103 0/57 2/280 0/30 0/30 0/31 0/36 0/30 0/32 0/36 0/31 0/36 0/37 0/36 0/37 0/36 0/30 0/32 0/36 0/30 0/32 0/36 0/30 0/32 0/36 0/30 0/36 0/30 0/36 0/36 0/30 0/36 0/30 0/36 0/37 0/36 0/36 0/36 0/36 0/36 0/36 0/37 0/36 0/41 0/28 0/40 0/28 0/36 0/36 0/41 0/28 0/40 0/28 0/36 0/41 0/28 0/41 0/28 0/41 0/23 0/23 0/23 0/23 0/23 0/26 0/23 0/26 0/23 0/26 0/23 0/26 0/23 0/26 0/23 0/23 0/26 0/41 0/23 0/25 0/25 0/25 0/25 0/25 0/25 0/25 0/25 0/25 0/	0/40 0/32 0/32 0/44 0/89 0/44 0/89 0/40 0/75 0/30 0/51 0/22 0/34 0/40 0/32 0/41 0/32 0/41 0/32 0/41 0/32 0/42 0/28 0/27 0/34 0/28 0/27 0/37 0/40 0/37 0/40 0/58 0/27 0/20 0/37 0/20 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/40 0/32 0/37 0/20 0/37 0/40 0/27 0/20 0/32 0/37 0/20 0/37 0/40 0/27 0/20 0/37 0/20 0/37 0/30 0/37 0/40 0/27 0/20 0/37 0/20 0/37 0/40 0/27 0/20 0/37 0/20 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/30 0/37 0/40 0/27 0/20 0/37 0/20 0/37 0/20 0/37 0/40 0/27 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/27 0/20 0/37 0/20 0/27 0/20 0/37 0/20 0/27 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/20 0/37 0/27 0/20 0/37 0/27 0/20 0/30 0/30 0/30 0/30 0/30 0/30 0/30 0/37 0/40 0/30 0/30 0/30 0/30 0/37 0/40 0/30 0/30 0/30 0/30 0/37 0/40 0/27 0/20 0/37 0/40 0/30 0/30 0/30 0/37 0/40 0/27 0/20 0/37 0/40 0/30 0/30 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/40 0/37 0/47 0/40 0/37 0/47 0/47 0/47 0/47 0/47 0/47 0/47 0/40 0/37 0/47 0/47 0/27 0/27 0/37 0/47 0/20 0/37 0/37 0/47 0/20 0/37 0/47 0/20 0/37 0/47
Overall (I-squa	ared = (0.0%, p = 1.	000)	•	0.00 (-0.00, 0.00)	2/5752	0/5863

2. <u>**Prematurity**</u> (typically defined as birth earlier than 37 weeks gestation)

Information on this outcome was available for 24 of the 83 included studies that administered LdT to mothers. Within these studies, 105 of 2427 (non-weighted average 4.3%) infants whose mothers were treated with LdT during pregnancy were born prematurely, whereas 120 of 2191 (non-weighted average 5.5%) infants whose mothers were not treated during pregnancy were born prematurely. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.001 (95% CI: - 0.010–0.008). The I² statistics for the overall pooled risk difference estimated was 0.0%. The I² statistics for non-RCTs was 0.0%. There were too few RCTs (i.e. <3) to consider the pooled risk difference separately in this subgroup.

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	Events, Eve RD (95% CI) Treatment Con	
Randomise	ed contro	led trials				
Lu QY	2016	China	28	0 🔶	0.01 (-0.01, 0.03) 1/152 0/13	32
Shi QW	2017	China	24	0 🔶	0.00 (-0.02, 0.02) 0/100 0/10	ю
Subtotal (-squared	d = 0.0%, p	o = 0.629)	\diamond	0.00 (-0.01, 0.02) 1/252 0/23	32
Non-rando	mised co	ontrolled tri	als			
Chen ZX	2017	China	13-32	NR	-0.01 (-0.09, 0.07) 2/41 5/89)
Fan LY	2013	China	28	24	0.00 (-0.06, 0.07) 2/58 2/60)
Han GR	2015	China	20 - 27	NR	0.02 (-0.03, 0.07) 22/365 4/92	2
He T	2018	China	1st Trimester	NR —	0.00 (-0.08, 0.08) 1/32 1/34	ł
Hu Y	2018	China	28-32	3-4	-0.01 (-0.06, 0.04) 8/149 11/1	79
Jiang S	2017	China	28	NR	0.05 (-0.09, 0.18) 6/44 4/44	ł
Jiang XN	2013	China	26-30	NR	-0.15 (-0.26, -0.03) 2/65 9/51	
Li ZY	2018	China	28	NR	-0.10 (-0.21, 0.01) 1/41 5/41	
Lou JJ	2015	China	28	4	0.00 (-0.07, 0.07) 7/127 3/58	3
Pan YC	2017	China	32	0	-0.00 (-0.05, 0.04) 3/81 15/3	370
Peng BA	2012	China	28	0	0.05 (-0.08, 0.18) 5/40 3/40)
Sheng Q	2018b	China	24-28	0	0.00 (-0.04, 0.04) 0/66 0/46	3
Tan J	2019	China	28	0	- 0.00 (-0.13, 0.13) 5/41 7/59)
Tan Z	2016	China	<14	NR	-0.01 (-0.06, 0.05) 14/171 28/3	320
Wang J	2017	China	24-28	NR	0.02 (-0.02, 0.05) 10/329 1/65	;
Wu Q	2015	China	24-32	0 or 4	-0.04 (-0.09, 0.01) 12/280 14/1	73
Xiao XH	2017	China	28	0 or 4	-0.03 (-0.11, 0.04) 2/60 4/60)
Yao LF	2014	China	28-32	6	0.00 (-0.06, 0.06) 0/30 0/30)
Yue X	2014	China	Anytime	NR	-0.07 (-0.22, 0.08) 2/31 4/30)
Zhang X	2015	China	28	12	0.00 (-0.04, 0.04) 0/48 0/47	,
Zheng JC	2018	China	28	4	0.00 (-0.07, 0.07) 0/23 0/37	,
Zhou YJ	2014	China	1st Trimester	0	0.00 (-0.05, 0.05) 0/53 0/34	ł
Subtotal (-squared	d = 0.0%, p	o = 0.734)	•	-0.00 (-0.02, 0.01) 104/2175 120	/195
Overall (I-	squared	= 0.0%, p	= 0.660)	•	- 0.00 (-0.01, 0.01) 105/2427 120	/219 ⁻

LdT 600mg, Prematurity risk difference

3. Congenital abnormalities

Information on this outcome was available for 40 of the 83 included studies that administered LdT to mothers. Within these studies, 11 of 3585 (non-weighted average 0.3%) infants whose mothers were treated with LdT during pregnancy were noted to have some sort of congenital abnormality, including: anotia (n=1), cerebral palsy (n=1), cinesipathy (n=1), cleft lip and/or palate (n=2), auricular defect (n=1), ear accessory (n=1), no detail provided (n=4). Nine of 2983 (non-weighted average 0.3%) infants whose mothers were not treated during pregnancy were noted to have some sort of congenital abnormality, including: polydactyly (n=1), talipes equinovarus (n=1), ear accessory (n=1), pulmonary stenosis (n=1), hydrocephalus (n=1), congenital ventricular septal defect (n=1), no detail provided (n=3). The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.000 (95% CI: -0.004–0.004). The I² statistics for the overall pooled risk, as well as for RCTs and non-RCTs separately, were all 0%.

Randomised Lu QY Shi QW Wang HY Zhang Y Subtotal (I-so	controlle 2016 2017	d tria l s China					
∟u QY Shi QW Wang HY Zhang Y	2016						
Shi QW Wang HY Zhang Y			28	0	0.00 (-0.01, 0.01)	0/152	0/132
Wang HY Zhang Y		China	24	0	➡ 0.00 (-0.02, 0.02		0/100
Zhang Y	2018	China	12-14	24	0.00 (-0.05, 0.05		0/40
	2018	China	Pre-pregnancy	NR			0/34
					0.00 (-0.01, 0.01		0/306
Non-randomi:	sed cont	rolled trials					
Chen CY	2015	China	1st Trimester	NR	0.00 (-0.05, 0.05	0/42	0/40
Chen F	2016	China	Pre-pregnancy	NR	0.00 (-0.06, 0.06		0/32
Chen WJ	2017	China	28	0	0.00 (-0.04, 0.04		0/44
Chen ZX	2017	China	13-32	NR	0.00 (-0.04, 0.04		0/89
Deng Y	2015	China	24-36	4			0/75
Ding XP	2013	China	28	4	0.00 (-0.02, 0.02		0/38
an LY	2013	China	28	24			0/60
Ge YL	2013	China	28-30	12	0.00 (-0.09, 0.09		0/22
Han GR	2015	China	20-27	NR	➡ 0.00 (-0.02, 0.02		0/92
He T	2015	China	1st Trimester	NR	-0.03 (-0.15, 0.10		3/34
⊣eı ⊣uY	2018	China	28-32	NH 3-4	-0.03 (-0.15, 0.1		3/34 0/179
	2018	China	26-32	NR			0/1/9
Jiang XN	2013	China	28-30	~36	0.00 (-0.03, 0.03		0/32
Li YH Li ZY	2017		28	~36 NR	0.00 (-0.06, 0.06		0/32
_i _ ĭ _iu XB	2018	China		NR 4	0.00 (-0.05, 0.05		
		China	28-36	4	0.00 (-0.09, 0.09		0/20
Liu Y	2016	China	28-32		• 0.00 (-0.02, 0.02		0/78
_ou JJ	2015	China	28	4	-0.00 (-0.04, 0.04		1/58
Peng BA	2012	China	28	0	0.00 (-0.05, 0.05		0/40
Ren N	2015	China	28	24	0.00 (-0.04, 0.04		0/46
Shen ML	2016	China	26	4			0/28
Sheng Q	2018a	China	24-32	4	0.00 (-0.06, 0.06		0/21
Sun W	2017	China	20-28	12			0/65
lan Z	2016	China	<14	NR	• 0.00 (-0.01, 0.01		0/320
Fian JH	2018	China	Anytime	NR	• 0.00 (-0.01, 0.01		0/203
Nang DM	2016	China	28-30	12	0.00 (-0.08, 0.08		0/20
Nang HB	2016	China	32	NR	0.00 (-0.07, 0.07		0/20
Nang J	2017	China	24-28	NR	0.00 (-0.02, 0.03		0/65
Nang TD	2015	China	28	4	0.00 (-0.04, 0.04		0/52
Nu Q	2015	China	24-32	0 or 4	 -0.00 (-0.02, 0.0 	,	1/173
Kiao XH	2017	China	28	0 or 4	-0.02 (-0.07, 0.04		2/60
Yao LF	2014	China	28-32	6	0.00 (-0.06, 0.06		0/30
Yue X	2014	China	Anytime	NR	0.00 (-0.06, 0.06		0/30
Zhang BF	2018	China	24-28	0	0.00 (-0.04, 0.04		0/75
Zhang GH	2018	China	28	4	0.00 (-0.05, 0.05		0/40
Zhang H	2014	China	28-30	4	• -0.00 (-0.01, 0.0		2/370
Zhou YJ	2014	China	1st Trimester	0	0.00 (-0.05, 0.05	0/53	0/34
Subtotal (I-so	quared =	0.0%, p =	1.000)		0.00 (-0.00, 0.00	11/3259	9/267
Overall (I-squ	uared = (0.0%, p = 1	.000)		0.00 (-0.00, 0.00	11/3585	9/298

LdT 600mg, Congenital abnormalities

Maternal safety outcomes

1. <u>Fetal demise</u> (miscarriage [<28 weeks], stillbirth [>=28 weeks])

Information on this outcome was available for 81 of the 83 studies that administered LdT to mothers. Twenty-three cases of fetal demise were reported across all study populations. Three cases (non-weighted average 0.05%) occurred across 5645 mothers/fetuses who were treated with LdT during pregnancy. Twenty cases (non-weighted average 0.3%) occurred across 5823 mothers/fetuses who were not treated during pregnancy. The weighted pooled risk difference for this safety outcome seen following meta-analysis was –0.001 (95% CI: -0.003–0.002). The I² statistics for the overall pooled risk difference estimate, as well as for RCTs and non-RCTs separately, were all 0%.

LdT 600mg, fetal demise risk difference

Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)		RD (95% CI)	Events, Treatment	Events, Control
Randomised c			28-32	4		0.00/0.00 0.00	0/30	0/30
lai HL Chen SM	2013 2017	China China	28-32	4 NR		0.00 (-0.06, 0.06) 0.00 (-0.06, 0.06)	0/30	0/30
u PX iuan ZF	2016 2017	China China	24-28 24	4 12		0.00 (-0.02, 0.02) 0.00 (-0.02, 0.02)	0/100 0/120	0/100 0/120
iuo HJ	2011	China	28	4		0.00 (-0.07, 0.07)	0/25	0/25
luang HY	2016	China	20	0		0.00 (-0.05, 0.05)	0/90	0/30
ΥY	2015	China	28	4		0.00 (-0.03, 0.03)	0/65	0/65
i SF	2015	China	28	24		0.00 (-0.03, 0.03)	0/60	0/60
u QY	2016	China	28	0		0.00 (-0.01, 0.01)	0/152	0/132
engML	2014	China	28	NR		0.00 (-0.06, 0.06)	0/30	0/30
Vang HY	2018	China	12-14	24		0.00 (-0.05, 0.05)	0/40	0/40
ie PY	2016	China	28	4		0.00 (-0.03, 0.03)	0/60	0/60
ing Y	2018	China	28	4		0.00 (-0.06, 0.06)	0/30	0/30
ang HW	2015	China	28	4		0.00 (-0.04, 0.04)	0/50	0/50
hang LJ	2009	China	28-32	4		0.00 (-0.06, 0.06)	0/31	0/30
hang Y	2018	China	Pre-pregnancy	NR		0.00 (-0.06, 0.06)	0/34	0/34
hao DB	2010	China	28	4		0.00 (-0.06, 0.06)	0/30	0/30
hao Y	2017	China	12	12		0.00 (-0.05, 0.05)	0/40	0/40
hu J	2017	China	28	0 -	Ĩ	-0.10 (-0.18, -0.02)	0/60	6/60
hu LP	2014	China	28	4	·	0.00 (-0.06, 0.06)	0/30	0/30
ubtotal (I -squ					•	-0.00 (-0.01, 0.01)	0/1107	6/1026
lon-randomise	ed controlle	d trials						
Chen CY	2015	China	1st Trimester	NR	_	0.00 (-0.05, 0.05)	0/42	0/40
Chen F	2016	China	Pre-pregnancy	NB		0.00 (-0.06, 0.06)	0/31	0/32
hen QR	2018	China	28	4	_	0.00 (-0.07, 0.07)	0/29	0/28
hen WJ	2017	China	28	0	—	0.00 (-0.04, 0.04)	0/79	0/44
hen ZX	2017	China	13-32	NR		0.05 (-0.02, 0.12)	2/43	0/89
ui ZL	2015	China	28	4	·	-0.08 (-0.16, 0.00)	0/50	4/50
eng Y	2015	China	24-36	4	· · · · · · · · · · · · · · · · · · ·	0.00 (-0.02, 0.02)	0/82	0/75
ing XP	2018	China	28	4		0.00 (-0.05, 0.05)	0/38	0/38
an LY	2018	China	28	24		0.00 (-0.03, 0.03)	0/58	0/60
eng XM	2013	China	28	4		0.00 (-0.05, 0.05)	0/36	0/36
iao P	2017	China	1st Trimester	0		0.00 (-0.04, 0.04)	0/51	0/58
				12			0/20	0/51
e YL	2015 2014	China	28-30 28	6		0.00 (-0.09, 0.09)	0/20	0/22
an YP		China				0.00 (-0.06, 0.06)		
e T	2018	China	1st Trimester	NR		-0.06 (-0.15, 0.04)	0/32	2/35
u WH	2016	China	28	28		0.00 (-0.04, 0.04)	0/46	0/40
uΥ	2018	China	28-32	3-4		0.00 (-0.01, 0.01)	0/149	0/179
uang Q	2017	China	24-28	12		0.00 (-0.09, 0.09)	0/20	0/20
ang S	2017	China	28	NR		0.00 (-0.04, 0.04)	0/44	0/44
ang XN	2013	China	26-30	NR		0.00 (-0.03, 0.03)	0/65	0/51
CM	2017	China	28	4		0.00 (-0.06, 0.06)	0/30	0/30
i N	2016	China	28	NR		0.00 (-0.06, 0.06)	0/65	0/25
YH	2017	China	28	~36	_	0.00 (-0.06, 0.06)	0/30	0/31
ΖY	2018	China	28	NR	_ 	0.00 (-0.04, 0.04)	0/36	0/75
iu CY	2014	China	28	4	+	0.00 (-0.06, 0.06)	0/34	0/34
iu J	2017	China	30	NR		0.00 (-0.05, 0.05)	0/102	0/28
iu XB	2016	China	28-36	4		0.00 (-0.09, 0.09)	0/20	0/20
iu Y	2016	China	28-32	4		0.00 (-0.02, 0.02)	0/82	0/78
bu JJ	2015	China	28	4		0.00 (-0.03, 0.03)	0/127	0/58
an YC	2017	China	32	0	-	0.00 (-0.02, 0.02)	0/81	0/366
eng BA	2012	China	28	0		0.00 (-0.05, 0.05)	0/40	0/40
iu B	2016	China	24	0		0.00 (-0.03, 0.03)	0/120	0/60
en N	2015	China	28	24		0.00 (-0.04, 0.04)	0/46	0/46
hen ML heng Q	2016 2018a	China China	26 24-32	4		0.00 (-0.03, 0.03) 0.00 (-0.06, 0.06)	0/60 0/91	0/60 0/21
heng Q heng Q	2018a 2018b	China	24-32 24-28	4		0.00 (-0.06, 0.06)	0/91	0/21
un W	2017	China	20-28	12		0.00 (-0.02, 0.02)	0/103	0/65
un WH	2015	China	20-28	12		0.00 (-0.03, 0.03)	0/84	0/45
an J	2019	China	28	0		0.00 (-0.04, 0.04)	0/41	0/59
an Z	2016	China	<14	NR		0.00 (-0.01, 0.01)	0/169	0/316
an JH	2018	China	Anytime	NR	-	0.00 (-0.01, 0.01)	0/135	0/203
an RH	2016	China	28	4	•	0.00 (-0.01, 0.01)	0/318	0/374
/ang B	2016	China	28	4		0.00 (-0.01, 0.01)	0/110	0/187
/ang DM	2016	China	28-30	12		0.00 (-0.08, 0.08)	0/36	0/20
/ang EJ	2012	China	28	4		0.00 (-0.07, 0.07)	0/28	0/27
/ang HB	2016	China	32	NR	_	0.00 (-0.07, 0.07)	0/100	0/20
/ang J	2017	China	24-28	NR		0.00 (-0.02, 0.02)	0/329	0/65
/ang TD	2015	China	28	4		0.00 (-0.04, 0.04)	0/53	0/52
/ang WP	2012	China	28	0		0.00 (-0.02, 0.02)	0/57	0/198
/u Q	2015	China	24-32	0 or 4		-0.01 (-0.03, 0.01)	0/276	2/170
iao XH	2017	China	28	0 or 4		0.00 (-0.03, 0.03)	0/60	0/60
ao LF	2014	China	28-32	6		0.00 (-0.06, 0.06)	0/30	0/30
ao ZC	2011	China	28	4	i	0.00 (-0.06, 0.06)	0/28	0/30
ue X	2014	China	Anytime	NR	_	-0.03 (-0.12, 0.05)	0/31	1/31
hang BF	2018	China	24-28	0		0.00 (-0.04, 0.04)	0/36	0/75
hang GH	2018	China	24-20	4		0.00 (-0.05, 0.05)	0/40	0/40
hang H	2018	China	28-30	4		0.00 (-0.01, 0.01)	0/257	0/363
hang X	2014	China	28	4		0.00 (-0.04, 0.04)	0/48	0/363
	2015 2010b	China		4			0/48	0/47
hang YF			28			0.00 (-0.03, 0.03)		
hao J	2013	China	20	0		0.00 (-0.03, 0.03)	0/41	0/202
heng JC	2018	China	28	4		0.00 (-0.07, 0.07)	0/23	0/37
hou YJ ubtotal (I -squ	2014 uared = 0.09	China 6 n = 1 000)	1st Trimester	0 🔶		-0.11 (-0.22, -0.01) -0.00 (-0.00, 0.00)	1/70 3/4538	5/39 14/479
more (r-squ	aaroo = 0.01				I			
verall (I-squa	ared = 0.0%	, p = 1.000)			•	-0.00 (-0.00, 0.00)	3/5645	20/582

2. Postpartum haemorrhage

Information on this outcome was available for 19 of the 83 included studies that administered LdT to mothers. Within these studies, 284 of 1729 (non-weighted average 16.4%) mothers who were treated with LdT during pregnancy experienced postpartum haemorrhage, whereas 116 of 2020 (5.7%) mothers who were not treated during pregnancy experienced postpartum haemorrhage. The weighted pooled risk difference for this safety outcome seen following meta-analysis was 0.041 (95% CI: -0.089–0.171). The I² statistics for the overall pooled risk difference was 99.4%; that for non-RCTs was 99.5%. Not enough RCTs evaluated this safety outcome to consider this subgroup separately.

				371	1			0	
Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)			RD (95% CI)	Events, Treatment	Events, Control
Randomise	ed cont	trolled tria	ls						
Guan ZF	2017	China	24	12			0.03 (-0.09, 0.14)	38/120	35/120
Zhu J	2017	China	28	0			-0.03 (-0.10, 0.03)	1/60	3/60
Subtotal (I	l-squar	ed = 34.5	%, p = 0.216)				-0.01 (-0.09, 0.06)	39/180	38/180
Non-rando	mised	controlled	trials						
Chen WJ	2017	China	28	0			0.00 (-0.04, 0.04)	0/79	0/44
Cui ZL	2015	China	28	4	-		-0.02 (-0.09, 0.05)	1/50	2/50
Не Т	2018	China	1st Trimester	NR			0.03 (-0.07, 0.13)	2/32	1/35
Hu Y	2018	China	28-32	3-4			-0.00 (-0.04, 0.03)	4/149	5/179
Jiang XN	2013	China	26-30	NR	-		-0.08 (-0.16, 0.00)	0/65	4/51
Liu Y	2016	China	28-32	4			0.00 (-0.02, 0.02)	0/82	0/78
Lou JJ	2015	China	28	4			0.00 (-0.05, 0.06)	5/127	2/58
Pan YC	2017	China	32	0	+		0.00 (-0.02, 0.02)	0/81	0/366
Peng BA	2012	China	28	0	 +		0.00 (-0.05, 0.05)	0/40	0/40
Sun W	2017	China	20-28	12			-0.02 (-0.14, 0.09)	20/123	12/65
Sun WH	2015	China	20-28	12 —			-0.03 (-0.20, 0.14)	25/83	15/45
Tan J	2019	China	28	0			-0.00 (-0.09, 0.08)	2/41	3/59
Tan Z	2016	China	<14	NR		>	0.94 (0.91, 0.97)	164/169	9/316
Wang HB	2016	China	32	NR			0.00 (-0.07, 0.07)	0/100	0/20
Yue X	2014	China	Anytime	NR			-0.10 (-0.30, 0.10)	5/31	8/31
Zhang GH	2018	China	28	4 -			0.03 (-0.18, 0.23)	13/40	12/40
Zhang H	2014	China	28-30	4	*		0.00 (-0.02, 0.02)	4/257	5/363
Subtotal (l-squar	ed = 99.5	%, p = 0.000)				0.05 (-0.09, 0.19)	245/1549	78/1840
Overall (l-	square	d = 99.4%	b, p = 0.000)				0.04 (-0.09, 0.17)	284/1729	116/202
				l 3	0	l .3			

LdT 600mg, post-partum haemorrhage

3. Antiviral resistance

Seven studies that treated mothers with LdT during pregnancy reported on some results of testing for antiviral resistance. One study reported that in 11 of 257 women in the treated group with previous antiviral therapy (LdT or other) no resistance mutations were detected, and that in the entire study, no participant discontinued due to resistance (*Han et al., 2015*). One study reported that of 78 treatment women, one participant developed an M204I drug-resistance mutation after receiving LdT for 40 weeks (*Liu et al., 2016*). Another study evaluated drug resistance in all 103 treated participants (timing not clear) and found no evidence of resistance mutations (*Sun et al., 2017*). Three studies reported antiviral resistance as a quantitative outcome (few details provided), giving case numbers of two in 31 treated women (*Chen et al., 2016*), one in 35 treated women (*Li et al., 2016*), and none in 60 treated women (*Shen et al., 2016*), respectively. Finally, one study evaluated antiviral resistance in seven women (of 105) whose HBV DNA levels did not reduce during treatment, and found no resistance mutations (*Hu et al., 2018*).

4. HBV flare

Information on this outcome was available for five of the 83 included studies that administered LdT to mothers. Various definitions were used, including: "ALT >40 U/L", "ALT >2 times baseline", "ALT >= 8 times ULN", "ALT >8 ULN or 5 times baseline". Within these studies, 38 of 517 (non-weighted average 7.4%) mothers who were treated with LdT during pregnancy experienced a type of HBV flare at the time of treatment discontinuation, whereas 47 of 689 (non-weighted average 6.8%) mothers who were not treated during pregnancy experienced the same type of HBV flare at a matched timepoint. The weighted pooled risk difference for this safety outcome seen following metaanalysis was 0.001 (95% CI: -0.061–0.064). Overall, the pooled risk difference (non-RCTs only were included) had a high level of heterogeneity ($I^2 = 73.9\%$).

			Tx_start	Tx_end			Events,	Events
Author	Year	Country	(weeks GA)	(weeks PP)		RD (95% CI)	Treatment	Contro
Non-rando	omised	controlled	trials					
Chen ZX	2017	China	13-32	NR		0.09 (-0.06, 0.24)	11/43	15/89
Не Т	2018	China	1st Trimester	NR	- *	-0.17 (-0.30, -0.04)	0/32	6/35
Hu Y	2018	China	28-32	3-4		0.01 (-0.09, 0.12)	22/103	25/12
Liu Y	2016	China	28-32	4		0.05 (-0.01, 0.11)	5/82	1/78
Zhang H	2014	China	28-30	4	•	0.00 (-0.01, 0.01)	0/257	0/363
Subtotal	(I-squai	red = 73.9°	%, p = 0.004)		\Diamond	0.00 (-0.06, 0.06)	38/517	47/68
Overall (I	-square	ed = 73.9%	o, p = 0.004)		\diamond	0.00 (-0.06, 0.06)	38/517	47/689
				4	0	I .4		

LdT 600mg, HBV flare risk difference

GRADE summary of findings

Table 16. GRADE evidence profile: LdT 600 mg during pregnancy to prevent HBV mother-to-child transmission (MTCT)

Nach		Q	uality assessm	lent				Number of	of patients	Ef	fect	
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	Quality
HBsAg pos	sitivity at 6–12	months										
21	Randomized controlled trials (RCTs)	Serious	No serious	No serious	No serious	No evidence of publication bias	N/A	36/1209 (3.0)	175/1123 (15.6)	0.14 (0.09– 0.21)	150 fewer per 1000 (100–200 fewer)	Moderate ^a
62	Non-RCTs	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect	34/4762 (0.7)	521/4674 (11.1)	0.09 (0.06– 0.12)	130 fewer per 1000 (110–150 fewer)	Low ^b
HBV DNA	positivity at 6-	-12 months										
8	RCTs	Serious	No serious	No serious	No serious	Not possible to examine publication bias.	N/A	6/382 (1.6)	58/374(15. 5)	0.12 (0.05– 0.26)	160 fewer per 1000 (60–250 fewer)	Moderate ^c
45	Non-RCTs	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect	18/3648 (0.5)	377/3367 (11.2)	0.07 (0.05– 0.10)	130 fewer per 1000 (100–150 fewer)	Low ^d
Infant safe	ety: neonatal de	eaths										
21	RCTs	Serious	No serious	No serious	No serious	No evidence of publication bias	N/A	0/1213 (0.0)	0/1123 (0.0)	-	0 per 1000 (10 fewer– 10 more)	Moderate ^e
61	Non-RCTs	No serious	No serious	No serious	No serious		None	2/4539 (0.0)	0/4740 (0.0)	-	0 per 1000 (2 fewer–3 more)	Low ^f

						No evidence of publication bias						
Infant safe	ty: prematurity	y						•		•	•	
2	RCTs	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/252 (0.4)	0/232 (0.0)	-	0 per 1000 (10 fewer- 20 more)	Moderate ^g
22	Non-RCTs	No serious	No serious	No serious	No serious	No evidence of publication bias	None	104/2175 (4.8)	120/1959 (6.1)	-	0 per 1000 (20 fewer– 10 more)	Low ^h
Infant safe	ty: congenital a	abnormaliti	es									
4	RCTs	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	0/326 (0.0)	0/306 (0.0)	-	0 per 1000 (10 fewer- 10 more)	Moderate ⁱ
36	Non-RCTs	No serious	No serious	No serious	No serious	No evidence of publication bias	None	11/3529 (0.3)	9/2677 (0.3)	-	0 per 1000 (4 fewer–4 more)	Low ^j
Maternal s	afety: miscarri	iage and stil	lbirth									
20	RCTs	Serious	No serious	No serious	No serious	No evidence of publication bias	N/A	0/1107 (0.0)	6/1026 (0.6)	-	1 fewer per 1000 (8 fewer-6 more)	Moderate ^k
61	Non-RCTs	No serious	No serious	No serious	No serious	No evidence of publication bias	None	3/4538 (0.1)	14/4797 (0.3)	-	0 per 1000 (3 fewer–2 more)	Low ¹
Maternal s	afety: postpart	tum haemor	rhage							r		
2	RCTs	Serious	Serious I ² =34.5%	No serious	Serious	Not possible to examine publication bias	N/A	39/180 (21.7)	38/180 (21.1)	-	10 fewer (90 fewer- 60 more)	Very low ^m
17	Non-RCTs	No serious	Very serious I ² =99.5%)	No serious	Serious	Evidence of possible publication bias/small study efects	None	245/1549 (15.8)	78/1840 (4.2)	-	50 more (90 fewer– 190 more)	Very low ⁿ

Maternal safety: HBV flare after treatment discontinuation													
5	Non-RCTs	No serious	Very serious I ² =73.9%	No serious	Serious	Not possible to examine publication bias	N/A	38/517 (7.4)	47/689 (6.8)	-	1 more (61 fewer– 64 more)	Very low ^o	

^aDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

^bDowngrading due to possible evidence of publication bias/small study effects, upgrading due to magnitude of effect.

^cDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high. ^dDowngrading due to possible evidence of publication bias/small study effects, upgrading due to magnitude of effect.

^eDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). ^fNo upgrading or downgrading

^gDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). ^hNo upgrading or downgrading

¹Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). ¹No upgrading or downgrading

^kDowngrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

¹No upgrading or downgrading

^mDowngrading due to "serious" study design limitations (all RCTs had ≤ 4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to "serious" inconsistency ($1^2>30\%$), downgrading due to imprecision.

ⁿDowngrading due to "very serious" inconsistency (I^2 >60%), downgrading due to imprecision, downgrading due to evidence of possible publication bias/small study effects. ^oDowngrading due to "very serious" inconsistency (I^2 >60%), downgrading due to imprecision.

Other antiviral therapies

Telbivudine (LdT) 100 mg

Three studies were eligible for this meta-analysis that used LdT 100 mg (*Ge JQ et al., 2015; Li ZG et al., 2015; Mu YSJ et al., 2018*). Of these, one was an RCT and two were non-RCTs. Of the non-RCTs, the risk of bias scores, according to the Newcastle–Ottawa scale, were 5 (high) and 6 (high), respectively (*Mu YSJ et al., 2018; Ge JQ et al., 2015*); as per protocol, studies with a high risk of bias with scores of 5 or lower were excluded from analysis. Therefore, we describe only the basic details of two studies (one RCT and one non-RCT) here.

One RCT was performed that examined use of LdT 100 mg during pregnancy for the PMTCT of HBV (*Li ZG et al., 2015*). This study took place in China from 2013 to 2014. Treatment was started at 28 weeks of pregnancy, and stopped after 6 weeks postpartum. Birth dose vaccination and HBIG were given to all infants on the first day of life, and two further vaccinations were given at 1 and 6 months of life. Of 25 infants whose mothers were treated during pregnancy, none were positive for HBsAg at 1 year of life, compared to four of 25 control infants at the same time-point (OR=0.09, 95% CI: 0.01– 1.84). Infant and maternal adverse events were not well described in the article.

One non-RCT, specifically a retrospective cohort study, was performed that examined use of LdT 100 mg during pregnancy for the PMTCT of HBV (*Ge JQ et al., 2015*). This study took place in China from 2012 to 2013. Treatment was started between 28 and 32 weeks of pregnancy, and stopped after 6 weeks postpartum. Birth dose vaccination and HBIG were given to all infants within 12 hours of life, and two further vaccinations were given at 1 and 6 months of life. Of 40 infants whose mothers were treated during pregnancy, one was positive for HBsAg at 12 months of life, compared to 11 of 40 control infants at the same time-point (OR=0.07, 95% CI: 0.01–0.55). Most infant and maternal adverse events were not addressed in the article; however, authors did confirm that there were no congenital abnormalities in either the treated or control group at the time of birth.

Adefovir dipivoxil (ADV) 500 mg

One RCT was performed that examined use of ADV 500 mg during pregnancy for the PMTCT of HBV (*Feng Y et al., 2018*). This study took place in China in 2017. Treatment was started at 28 weeks of pregnancy, and stopped at the time of delivery. HBIG was given within 24 hours of birth, a vaccination was given at "0 months", and two further vaccinations were given at 1 and 6 months of life. Of 254 infants whose mothers were treated during pregnancy, six were positive for HBsAg at 1 year of life, compared to 24 of 251 control infants at the same timepoint (OR=0.23, 95% CI: 0.09–0.57). Infant adverse events were not well described in the article. Of maternal adverse events, the authors did report that 5.4% (95% CI: 3.0–8.9) of women in the treated arm had postpartum haemorrhage, whereas this was 10.1% (95% CI: 6.7–14.4) in the control group.

Adefovir dipivoxil (ADV) 10 mg

One non-RCT, specifically a prospective cohort study, was performed that examined uthe se of ADV 10 mg during pregnancy for the PMTCT of HBV (*Fang HS et al., 2011*). This study took place in China from 2006 to 2008. Treatment with ADV was started prior to pregnancy in all women (end time not reported), and additionally, HBIG was given to women in both the treatment and control groups at 28, 32 and 36 weeks of gestation. Birth dose vaccination was done (timing unclear), and two further vaccinations were given at 1 and 6 months of life. There was no mention of administration of HBIG to infants in the article. Of 42 infants whose mothers were treated during pregnancy, none were positive for HBsAg at 12 months of life, compared to five of 52 control infants at the same time-point (OR=0.10, 95% CI: 0.01–1.89). Most infant and maternal adverse events were not addressed in the article; however, authors did confirm that there were no congenital abnormalities or cases of prematurity in either the treated or control group at the time of birth.

CONCLUSION

This meta-analysis shows that certain antiviral therapies may be efficacious if used during pregnancy for the PMTCT of HBV, as indicated by the proportion of infants with HBsAg detected at 6–12 months of life. Specifically, meta-analysis of RCTs investigating TDF 300 mg had a protective, pooled OR of 0.10 (95% CI: 0.03–0.35), those investigating LAM 100–150 mg had a protective pooled OR of 0.16 (95% CI: 0.10–0.26), and those investigating LdT 600 mg had a protective pooled OR of 0.14 (95% CI: 0.09–0.21). The GRADE evidence quality for each of these three treatment regimens was "moderate" for RCTs, and "low" for non-RCTs; however, the results for RCTs and non-RCTs were concordant (see Table 17).

	All (by HBsAg positivity)			RCT			Non-RCT					
	# Studies	Odds ratio	Lower 95% CI	Upper 95% CI	# studies	Odds ratio	Lower 95% CI	Upper 95% CI	# Studies	Odds ratio	Lower 95% CI	Upper 95% CI
TDF 300 mg	19	0.16	0.10	0.26	5	0.10	0.03	0.35	14	0.17	0.10	0.29
LAM 100 mg	40	0.17	0.13	0.22	8	0.16	0.10	0.26	32	0.17	0.12	0.24

Table 17. Meta-analysis odds ratios (OR) for all studies using infant HBsAg as outcome, by study design, by treatment type

LdT 600	83	0.10	0.08	0.13	21	0.14	0.10	0.26	62	0.09	0.07	0.12
mg												

There were almost no differences seen (heterogeneity across pooled OR estimates) for any subgroup analyses for any treatment type included. Only in one subgroup analysis for LAM 100 mg, which examined the difference between treatment starting at a median <28 weeks, 28 weeks or >28 weeks, was heterogeneity observed. In this case, it appeared that starting treatment at median 28 weeks or <28 weeks was significantly more protective than starting treatment at a median >28 weeks.

There was moderate- to low-grade evidence that taking antiviral therapies for PMTCT did not increase the risk of certain infant and maternal safety outcomes, such as neonatal death, congenital abnormalities, fetal demise (miscarriage or stillbirth). However, it is important to note that for some of these outcomes, notably neonatal death and fetal demise, there are important concerns regarding data quality in this review (*see* Limitations section below). There was always very low evidence with regards to maternal antiviral therapy and the occurrence of HBV flare; few studies presented this information and where it was presented, definitions and time-points varied considerably, limiting our ability to combine these findings in a meaningful way. Across all treatment types, there was very little or no information on antiviral resistance in mothers, and bone mineral density changes in infants; other study designs and evidence should be considered by policy-makers for a better understanding of these risks.

Strengths

This is a thorough and up-to-date review and meta-analysis of the literature on the PMTCT through provision of maternal antiviral therapy. The main strength of this review is its extensive scoping of the Chinese literature; this has not been as exhaustively performed in other recent systematic reviews (*Zhou YH, 2016*). This led to a large number of studies included for each treatment type when compared to other reviews; for example, two recent meta-analyses with similar objectives as the study we have presented here included 59 and 41 studies, respectively (*Song et al., 2019; Tavakolpour et al., 2018*). Furthermore, extensive efforts were employed to examine crossover between patient

groups from different articles; the inclusion of overlapping patient populations has been criticized in other recent systematic reviews (*Zhou YH*, 2016).

Limitations

The major limitation of this review is the high risk of bias that defined many of the studies included; only two of 33 (6%) included RCTs could be considered to have a low risk of bias, only seven of 33 (21%) RCTs reported loss to follow up adequately. This limited our ability to perform ITT analysis, which has important implications in terms of attrition bias, and should be considered when interpreting the results for the primary outcomes, as well as for some safety outcomes (e.g. difference in the risk of neonatal death, fetal demise). Furthermore, although non-RCTs with a very high risk of bias were excluded from analysis, 31% of the remaining non-RCTs had a score of 6 (high) on the Newcastle–Ottawa scale (i.e. one point below being "low risk of bias").

It was not possible to fully examine all important safety outcomes, such as HBV flare, as standardized information was lacking in most papers. Another limitation of this review is that very few studies outside of the Western Pacific Region were included – this limits the ability to generalize our findings to other important regions in terms of prevalence of HBV, such as the African Region.

Implications for research

Due to limited information found in the included studies in this review, some subgroup and safety analyses were not possible. Further research is needed on this PMTCT topic in the following areas:

- differences in populations coinfected with HIV, HCV, HDV
- differences according to more specific timing/well-defined time periods for starting antiviral therapy (e.g. start of 2nd trimester versus start of 3rd trimester)

 differences according to very timely birth dose vaccination – possibly, with prompt delivery of HBIG and birth dose vaccine, the beneficial effect of antiviral therapy during pregnancy diminishes.

Very importantly, no study was included in this meta-analysis that took place in the African Region. There are many differences between Africa and other regions with regard to this topic such as in HBV epidemiology (e.g. high prevalence of genotypes A, D, E in Africa versus higher prevalence of genotypes B and C in Asia) and the natural history of chronic HBV infection. Additionally, the current standard of care varies considerably when comparing Africa and Asia; there is a relatively high coverage of timely birth dose vaccine in Asia as well as some availability of HBIG; however, there is a low coverage of timely birth dose vaccine in Africa as well as a lack of access to HBIG. Along these lines, it is notable that no study included in this review investigated the efficacy of maternal antiviral therapy in the absence of HBIG given to infants at birth even though in resource-limited countries access to HBIG is severely limited.

Finally, no study examined the efficacy of antiviral therapy for PMTCT in HBeAgnegative mothers with a high viral load. There is potentially an important population of women with a high viral load but negative for HBeAg; in the review for the PICO2 question, it was found that 16.4% of women with viraemia \geq 5 log10 IU/mL and 2.2% of women with viraemia \geq 7 log10 IU/mL are negative for HBeAg.

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APPENDICES

APPENDIX A: Search strategies

Database: PubMed

Date searched: 28 March 2019

ltem	Search words	# Records
1	"hepatitis b"[MeSH] OR "hepatitis b virus"[MeSH]	63 464
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]	98 948
3	1 OR 2	98 948
4	"antiviral agents" [MeSH]OR "nucleosides" [MeSH] OR "nucleotides" [MeSH] OR "adefovir" [Supplementary Concept] OR "emtricitabine" [MeSH] OR "entecavir" [Supplementary Concept] OR "lamivudine" [MeSH] OR "telbivudine" [MeSH] OR "tenofovir" [MeSH]	822 520
5	antiviral*[Text] OR nucleoside*[Text] OR nucleotide*[Text] OR (nucleos*[Text] AND analog*[Text]) OR (nucleot*[Text] AND analog*[Text]) OR NA[Text] OR adefovir[Text] OR hepsera[Text] OR preveon[Text] OR bis-POM PMEA[Text] OR GS 840[Text] OR ADV[Text] OR emtricitabine[Text] OR emtriva[Text] OR FTC[Text] OR entecavir[Text] OR baraclude[Text] OR ETV[Text] OR lamivudine[Text] OR epivir[Text] OR 3TC[Text] OR telbivudine[Text] OR sebivo[Text] OR tyzeka[Text] OR LdT[Text] OR tenofovir[Text] OR viread[Text] OR TDF[Text] OR vemLidy[Text] OR TAF[Text]	755 458
6	4 OR 5	1 335 890

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]	870 293
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 ante- 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 wertical*[Text] OR congenital*[Text] OR mother*[Text] OR matern*[Text] OR fetomaternal*[Text] OR foetomaternal*[Text] OR fetal*[Text] OR foetal*[Text] OR fetus[Text] OR	1 793 242
9	7 OR 8	1 803 794
10	3 AND 6 AND 9	1004

Database: Embase Classic + Embase via OvidSP (1947–2019 March 26th)

Date searched: 28 March 2019

ltem	Search words	# Records		
1	exp hepatitis B/ OR exp Hepatitis B virus/	120 132		
2	(hepatitis b OR type b hepatitis OR hepatitis type b OR hbv OR vhb OR hep b OR hbsag OR hbs ag OR hbs antigen*).mp.	158 928		
3	1 OR 2	158 928		
4	exp antiviral therapy/ OR exp antivirus agent/ OR exp nucleoside/ OR exp nucleotide/ OR exp adefovir/ OR exp adefovir dipivoxil/ OR exp emtricitabine/ OR exp entecavir/ OR exp lamivudine/ OR exp telbivudine/ OR exp tenofovir/ OR exp tenofovir disoproxil/ OR exp tenofovir alafenamide/	1 657 284		
5	(antiviral* OR nucleoside* OR nucleotide* OR (nucleos* AND analog*) OR (nucleot* AND analog*) OR NA OR adefovir OR hepsera OR preveon OR bis-POM PMEA OR GS 840 OR ADV OR emtricitabine OR emtriva OR FTC OR entecavir OR baraclude OR ETV OR lamivudine OR epivir OR 3TC OR telbivudine OR sebivo OR tyzeka OR LdT OR tenofovir OR viread OR TDF OR vemlidy OR TAF).mp.	1 421 448		
6	4 OR 5	2 708 549		
7	exp pregnancy/ OR exp pregnant women/ OR exp mother fetus relationship/ OR exp vertical transmission/ OR exp pregnancy complication/ OR exp prenatal diagnosis/	807 598		
8	(pregnan* OR trimest* OR gestation* OR antepartum OR ante-partum OR prepartum OR pre-partum OR intrapartum OR intra-partum OR	2 268 793		

10	3 AND 6 AND 9	3069		
9	7 OR 8	2 274 006		
	OR MTCT OR TME).mp.			
	foetomaternal* OR fetal* OR foetal* OR fetus OR foetus OR offspring			
	vertical* OR congenital* OR mother* OR matern* OR fetomaternal* OR			
	uterine OR inutero OR in utero OR transplacental* OR placenta* OR			
	OR pre-natal* OR perinatal* OR peri-natal* OR intrauterine OR intra-			
	peripartum OR peri-partum OR antenatal* OR ante-natal* OR prenatal*			

Database: Scopus

Date searched: 28 March 2019

Item	Search words	# Records
1	TITLE-ABS-KEY ("hepatitis b" OR "type b hepatitis" OR "hepatitis type b" OR "hbv" OR "vhb" OR "hep b" OR "hbsag" OR "hbs ag" OR "hbs antigen*")	138 899
2	TITLE-ABS-KEY ("antiviral*" OR "nucleoside*" OR "nucleotide*" OR ("nucleos*" AND "analog*") OR ("nucleot*" AND "analog*") OR "NA" OR "adefovir" OR "hepsera" OR "preveon" OR "bis-POM PMEA" OR "GS 840" OR "ADV" OR "emtricitabine" OR "emtriva" OR "FTC" OR "entecavir" OR "baraclude" OR "ETV" OR "lamivudine" OR "epivir" OR "3TC" OR "telbivudine" OR "sebivo" OR "tyzeka" OR "LdT" OR "tenofovir" OR "viread" OR "TDF" OR "vemlidy" OR "TAF")	1 781 759
3	TITLE-ABS-KEY ("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 "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")	2 892 112
4	#1 AND #2 AND #3	1810

Database: CENTRAL Database (The Cochrane Library)

Date searched: 28 March 2019

ltem	Search words	# Trials and reviews
1	hepatitis b [MeSH, exp] OR hepatitis b virus [MeSH, exp]	2462
2	"hepatitis b" OR "type b hepatitis" OR "hepatitis type b" OR hbv OR vhb OR "hep b" OR hbsag OR "hbs ag" OR "hbs antigen" OR "hbs antigens"	7692
3	1 OR 2	7692
4	antiviral agents [MeSH, exp] OR nucleosides [MeSH, exp] OR nucleotides [MeSH, exp] OR emtricitabine [MeSH, exp] OR lamivudine [MeSH, exp] OR telbivudine [MeSH, exp] OR tenofovir [MeSH, exp]	17 552
5	antiviral* OR nucleoside* OR nucleotide* OR (nucleos* AND analog*) OR (nucleot* AND analog*) OR NA OR adefovir OR hepsera OR preveon OR "bis-POM PMEA" OR "GS 840" OR ADV OR emtricitabine OR emtriva OR FTC OR entecavir OR baraclude OR ETV OR lamivudine OR epivir OR 3TC OR telbivudine OR sebivo OR tyzeka OR LdT OR tenofovir OR viread OR TDF OR vemlidy OR TAF	34 424
6	4 OR 5	44 913
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]	8 802

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*	74 080
	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	
9	7 OR 8	74 912
10	3 AND 6 AND 9	246

Database: CNKI

Date searched: 28 March 2019

Search strategy:

SU='乙型肝炎'+'乙肝'+'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' AND SU='抗病毒'+'抗病毒药物'+'核苷'+'核苷酸'+'核苷类似物'+'核苷酸 类似物'+'NAs'+'阿德福韦酯'+'hepsera'+'preveon'+'bis-POM PMEA'+'GS 840'+'ADV'+'恩曲他滨'+'emtriva'+'FTC'+'恩替卡韦'+'baraclude'+'ETV'+'拉米夫定 '+'epivir'+'3TC'+'LAM'+'替比夫定'+'sebivo'+'tyzeka'+'LdT'+'替诺福韦酯 '+'viread'+'TDF'+'替诺福韦艾拉酚胺'+'vemLidy'+'TAF' AND SU='妊娠'+'怀孕'+'孕 妇'+'孕期'+'母胎'+'母亲'+'胎儿'+'子代'+'子女'+'垂直传播'+'产前'+'产时'+'产间'+'围产

'+'妊娠并发症'+'产前诊断'+'先天'

Date searched: 28 March 2019 Search strategy: 主题: ("乙型肝炎"+"乙肝"+"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") and 主题: ("抗病毒"+"抗病毒药物"+"核苷"+"核苷酸"+"核苷类 似物"+"核苷酸类似物"+"NAs"+"阿德福韦酯"+"hepsera"+"preveon"+"bis-POM PMEA"+"GS 840"+"ADV"+"恩曲他滨"+"emtriva"+"FTC"+"恩替卡韦 "+"baraclude"+"ETV"+"拉米夫定"+"epivir"+"3TC"+"LAM"+"替比夫定 "+"sebivo"+"tyzeka"+"LdT"+"替诺福韦酯"+"viread"+"TDF"+"替诺福韦艾拉酚胺 "+"vemlidy"+"TAF") and 主题: ("妊娠"+"怀孕"+"孕妇"+"孕期"+"母胎"+"母亲"+"胎儿 "+"子代"+"子女"+"垂直传播"+"产前"+"产时"+"产间"+"围产"+"出生前"+"围生"+"宫内 "+"跨胎盘"+"胎盘"+"母婴传播"+"预防母婴传播"+"阻断母婴传播"+"妊娠并发症"+" 产前诊断"+"先天")

Database: Wanfang

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APPENDIX B: Guidance – Cochrane Collaboration's risk of bias assessment tool

	in ecuy myyms jr	1 ct uii, 2011 j	
	Source of bias	Description	Review author's judgement
Bias domain			Assess as low, unclear or high
			risk of bias
	Sequence	Describe the method used to generate	Selection bias (biased allocation to
Selection bias	generation	the allocation sequence in sufficient	interventions) due to inadequate
		detail to allow an assessment of	generation of a randomized
		whether it should produce comparable	sequence
		groups.	
	Allocation	Describe the method used to conceal	Selection bias (biased allocation to
	concealment	the allocation sequence in sufficient	interventions) due to inadequate
		detail to determine whether	concealment of allocations before
		intervention allocations could have	assignment
		been foreseen before or during	-
		enrolment.	

(table taken directly Higgins JPT et al., 2011)

		D 1 11 1 1 0	
D C	Blinding of	Describe all measures used, if any, to	Performance bias due to
Performance	participants,	blind trial participants and researchers	knowledge of the allocated
bias	personnel and	from knowledge of which intervention	interventions by participants and
	outcome assessors.	a participant received. Provide any	personnel during the study
	Assessments should	information relating to whether the	
	be made for each	intended blinding was effective.	
	main outcome (or	C	
	class of outcomes).		
		Describe all measures used, if any, to	Detection bias due to knowledge
Detection bias	Blinding of outcome	blind outcome assessment from	of the allocated interventions by
	assessment.	knowledge of which intervention a	outcome assessment
	Assessments should	participant received. Provide any	
	be made for each	information relating to whether the	
	main outcome (or	intended blinding was effective.	
	class of outcomes).	intended binding was effective.	
	Incomplete outcome	Describe the completeness of outcome	Attrition bias due to amount,
Attrition bias	data. Assessments	data for each main outcome, including	nature, or handling of incomplete
	should be made for	attrition and exclusions from the	outcome data
	each main outcome	analysis. State whether attrition and	
	(or class of	exclusions were reported, the numbers	
	outcomes).	in each intervention group (compared	
	outcomes).	with total randomized participants),	
		reasons for attrition or exclusions	
		where reported, and any reinclusions in	
	C.L	analyses for the review.	Dementione lies des te selection
Reporting bias	Selective outcome	State how the possibility of selective	Reporting bias due to selective
Reporting plas	reporting	outcome reporting was examined by	outcome reporting
		the review authors, and what was	
		found.	
Others his a	Other sources of	State any important concerns about	Bias due to problems not covered
Other bias	bias	bias not addressed in the other domains	elsewhere
		in the tool. If particular	
		questions/entries were prespecified in	
		the review's protocol, responses should	
		be provided for each question/entry.	

Notes for filling out the table (adapted/made specific for this systematic review and meta-analysis from the *Cochrane handbook 2008* and from *Higgins JPT et al., 2011*):

- Within the table, summary descriptions should be provided in order to give an independent reader enough information to see why the specific judgement has been made. For example, if no information on sequence generation can be found in the article or correspondence with the author, you could enter "Comment: no information provided". If it states that patients were randomly allocated in the article, then you could copy out the phrase directly from the article, e.g. "Quote: "patients were randomly allocated". In any case, if you have doubts regarding whether or not the study actually did certain things that are mentioned in the article, please include an extra comment describing concern/contradiction in the article.

- When providing your judgement as a review author, indicate "low risk" of bias, and "high risk" of bias. If insufficient information is provided, then the judgement should be "unclear" risk of bias.
 - See table 8.5c on pages 198–202 in the 2008 Cochrane handbook for systematic reviews of intervention (pages 223–227 of the pdf) for specific guidance on how to make your judgement.

APPENDIX C: Guidance for the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies (Adapted to PICO1)

<u>Note</u>: The below has been adapted for this specific meta-analysis from the guidance found on the Newcastle–Ottawa quality assessment group website (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

SELECTION

1) <u>Representativeness of the exposed cohort (0 or 1 star)</u>

a) Truly representative of the average HBV-infected pregnant women in the community *

- Women identified to carry HBsAg at a general antenatal care clinic or general practitioner with or without subsequent referral to the specialist obstetric care centre or hepatologist or infectious disease specialist
- Not part of a special group (e.g. all with recent treatment for hepatocellular carcinoma), then we might assume they reflect/are representative of HBV-infected pregnant women in that community.

b) Somewhat representative of the average HBV-infected pregnant women in the community **★**

- e.g. women known to be chronically infected with HBV and have been followed by hepatologist or infectious disease specialist
- c) Selected group of users
 - e.g. Women with severe liver disease (cirrhosis or hepatocellular carcinoma) only, part of a special group (HIV-infected women, intravenous drug users [IVDU]), women working in study centres/hospitals, etc.
 - Please provide a comment if you believe that the exposed group does not match well the general community.

d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort (0 or 1 star)

- a) Drawn from the same community as the exposed cohort *
 - Women presenting at the hospital, pregnant and with HBV (not, most of our studies should fall here in this review)
- b) Drawn from a different source
 - e.g. controls drawn from a historical sample
 - Please make a comment if you believe that the controls have been drawn from a different source.
- c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure (exposure = treatment) (0 or 1 star)

a) Valid method was used to ascertain adherence to the antiviral therapy*

- Ideally with some mention of methods to ascertain maternal adherence to treatment (e.g. evaluation of pill count, immunoassay to detect serum/urine metabolite of antiviral agents, or decrease in viral load levels subsequent to the treatment)
- b) Based on a secure record about adherence *
 - Study staff have recorded good adherence to treatment based on self-report
 - Description on the treatment duration supports the confirmation of adherence by study staff
- c) Data collection through registry
 - Care must be taken for a study based on registry data; having started antivirals during pregnancy does not necessarily guarantee that the women adhered to the treatment throughout the intended period.
- d) No description

4) <u>Demonstration that outcome of interest was not present at start of study (0 or 1 star)</u>

- a) Yes \star
 - This will always be yes in our case... for this study topic as the outcome of interest is HBV status in infants and infants are born during the course of the study.
- b) No

COMPARABILITY

1) Comparability of cohorts on the basis of the design or analysis (0 or 1 or 2 star(s))

a) Study controls/is comparable for both HBV DNA level (within 1 log IU/mL) and HBeAg serostatus (within 10 % points)*

- The same threshold for HBV DNA level AND same HbeAg serostatus should be used for inclusion of treated and controls and/or the reported mean/median HBV DNA level and HBeAg seroprevalence at baseline should be reported and should be similar.
- If not reported threshold or not reported mean/median and/or not similar then no star. If only one is reported/similar and the other not, then no star.

b) Study controls for child immunoprophylaxis at birth (birth dose vaccination, HBIG at birth) ★

• All have or all don't have or similar proportions across exposed and unexposed group with a similar timeliness. If not reported at all or very different proportions then no star.

OUTCOME

1) Assessment of outcome (0 or 1 star)

a) Independent blind assessment *

• Examiner of infant outcome (e.g. laboratory staff) was blinded to the maternal exposure status.

b) Medical records related to outcome were seen and verified by study personnel, or there was record linkage *

- In the case where testing is done as part of the study, and it is indicated that the same laboratory assays were used to test all infants, then it will be assumed that there was direct verification of test results by study personnel using these medical records.
- c) No description
 - If there is no description of laboratory methods (specifically, specifying which assay was used or indicating that all testing was done by study personnel or records were sent to study personnel) then no star will be given.

2) Was follow up long enough for outcomes to occur (0 or 1 star)

- a) Yes (at 6–12 months) *
 - Because we have defined our inclusion criteria for the review as testing needing to be done between 6 and 12 months, all of our studies should fall here.
- b) No
 - This should not be the case for any of our studies. Please provide a detailed comment if you think it is the case.

3) Adequacy of follow up of cohorts (0 or 1 star)

a) Complete follow up – all subjects accounted for and lost to follow up reported clearly as 0 *

b) Subjects lost to follow up unlikely to introduce bias – small number lost – >80% (or description provided of those lost) *

c) Follow up rate <80% (select an adequate %) and no description of those lost

- d) No statement about LFU
 - If not reporting any LFU, and also not mentioning clearly that "There were no cases of LFU" then we should assume that LFU was not well reported, and this should not be given a star.

APPENDIX D: List of variables present on the data extraction tool

1. Publication details

- First author
- Year
- Journal
- Language

2. Methods

- Country
- Study design
- Recruitment period
- Recruitment setting (regional details, number of sites)
- Inclusion criteria
- Exclusion criteria
- Intervention arm treatment including birth dose vaccination and/or HBIG administration if relevant
- Intervention treatment schedule (including birth dose vaccination and/or HBIG administration if relevant) and timing (including hours since birth for birth dose/HBIG)
- Control arm treatment
- Control arm treatment schedule and timing
- Infant treatment 1. Birth dose vaccination (dose, manufacturer)
- Infant treatment 1. Birth dose vaccination (detail the number of hours since birth)
- Infant treatment 2. HBIG (dose, manufacturer)
- Infant treatment 2. HBIG (detail the number of hours since birth)
- Infant treatment 3. Any other treatment (e.g. antiviral therapy in infants)
- Follow-up schedule (mothers)
- Follow-up schedule (infants)

3. Number (no.) of participants at enrolment

- No. of women assessed for eligibility
- No. of women who underwent randomization (or included if non-randomized)

4. Women's characteristics in the treatment arm

- Treatment arm: No. of women assigned to treatment (or included if non-randomized)
- Treatment arm: Mean treatment duration
- Treatment arm: Mean or median age
- Treatment arm: No. by ethnicity
- Treatment arm: No. positive for HBeAg
- Treatment arm: HBV DNA threshold used (IU/mL or copies/mL)
- Treatment arm: No. with HBV DNA >threshold
- Treatment arm: No. HDV-positive

- Treatment arm: No. HCV-positive
- Treatment arm: No. HIV-positive
- Treatment arm: No. loss to F/U or regimen change

5. Women's characteristics in control arm

- Control arm: No. of women assigned to control (or included if non-randomized)
- Control arm: Mean treatment duration
- Control arm: Mean or median age
- Control arm: No. by ethnicity
- Control arm: No. positive for HBeAg
- Control arm: HBV DNA threshold used (IU/mL or copies/mL)
- Control arm: No. with HBV DNA >threshold
- Control arm: No. HDV-positive
- Control arm: No. HCV-positive
- Control arm: No. HIV-positive
- Control arm: No. loss to F/U or regimen change

6. Infant outcomes at birth in the treatment arm

- No. of infants in treatment arm at birth
- Treatment arm: No. of twins
- Treatment arm: No. of triplets
- Treatment arm: mean gestational age at birth (weeks)
- Treatment arm: mean birthweight (kg)
- Treatment arm: No. male
- Treatment arm: No. by each type of delivery (vaginal or caesarean section)

7. Infant outcomes at birth in the control arm

- No. of infants in control arm at birth
- Control arm: No. of twins
- Control arm: No. of triplets
- Control arm: mean gestational age at birth (weeks)
- Control arm: mean birthweight (kg)
- Control arm: No. of male
- Control arm: No. by each type of delivery (vaginal or caesarean section)

8. MTCT definition

- MTCT definition used
- HBsAg assay method used to define MTCT
- HBV DNA assay method used to define MTCT
- Exact timing of 6–12 months assessment to define MTCT

9. MTCT (intention-to-treat) in the treatment arm

- Denominator for intention-to-treat analysis: mothers assigned to intervention + twin/triplet
- No. of infants completed MTCT evaluation at 6–12 months time-point
- No. of infants with HBsAg at 6–12 months (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)

- No. of infants with HBV DNA at 6–12 months (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- Intention-to-treat MTCT risk (defined by HBsAg)
- Intention-to-treat MTCT risk (defined by HBV DNA)

10. MTCT (per protocol) in the treatment arm

- Denominator for per-protocol analysis: mother-infant pairs completed the intervention treatment and completed MTCT evaluation at 6–12 months time-point
- No. of infants with HBsAg at 6–12 months in mother–infant pairs completed the intervention treatment and completed MTCT evaluation at 6–12 months time-point (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- No. of infants with HBV DNA at 6–12 months in mother–infant pairs completed the intervention treatment and completed MTCT evaluation at 6–12 months time-point (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- Per-protocol MTCT risk (defined by HBsAg)
- Per-protocol MTCT risk (defined by HBV DNA)

11. MTCT (intention-to-treat) in the control arm

- Denominator for intention-to-treat analysis: mothers assigned to control + twins/triplets
- No. of infants completed MTCT evaluation at 6–12 months time-point
- No. of infants with HBsAg at 6–12 months (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- No. of infants with HBV DNA at 6–12 months (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- Intention-to-treat MTCT risk (defined by HBsAg)
- Intention-to-treat MTCT risk (defined by HBV DNA)

12. MTCT (per protocol) in the control arm

- Denominator for per-protocol analysis: mother–infant pairs completed the control treatment and completed MTCT evaluation at 6–12 months time-point
- No. of infants with HBsAg at 6–12 months in mother–infant pairs completed the control treatment and completed MTCT evaluation at 6–12 months time-point (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- No. of infants with HBV DNA at 6–12 months in mother–infant pairs completed the control treatment and completed MTCT evaluation at 6–12 months time-point (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- Per-protocol MTCT risk (defined by HBsAg)
- Per-protocol MTCT risk (defined by HBV DNA)
- **13.** No. of infant adverse events in the treatment arm (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
 - Treatment arm: Fetal death
 - Treatment arm: Neonatal death (within 28 days)
 - Treatment arm: Prematurity (give definition used)
 - Treatment arm: Congenital abnormalities #

- Treatment arm: Congenital abnormalities: describe
- Treatment arm: Apgar score at 1 minute is <10
- Treatment arm: Suboptimal bone density (give definition and the age at evaluation)
- Treatment arm: Any other event
- 14. No. of infant adverse events in the control arm (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
 - Control arm: Fetal death
 - Control arm: Neonatal death (within 28 days)
 - Control arm: Prematurity (give definition used)
 - Control arm: Congenital abnormalities #
 - Control arm: Congenital abnormalities: describe
 - Control arm: Apgar score at 1 minute is <10
 - Control arm: Suboptimal bone density (give definition and the age at evaluation)
 - Control arm: Any other event
- 15. HBV flare
 - Definition of HBV flare used
- 16. No. of maternal adverse events in the treatment arm (list by maternal HBeAg, HBV DNA, HDV, HIV status where possible)
 - Treatment arm: HBV flare after treatment discontinuation
 - Treatment arm: Postpartum haemmorhage
 - Treatment arm: Antiviral resistance
 - Treatment arm: Any other event
- 17. No. of maternal adverse events in the control arm (list by maternal HBeAg, HBV DNA, HDV, HIV status where possible)
 - Control arm: HBV flare after treatment discontinuation
 - Control arm: Postpartum haemorrhage
 - Control arm: Antiviral resistance
 - Control arm: Any other event
- 18. Other
 - Summary of study conclusions
 - Funding by industry

Appendix E: Cochrane Collaboration's Risk of Bias Assessment Tool for Randomized Controlled Trials

TDF 300 mg

A. English language studies

Study	Selecti	on bias	Performance bias	Detection bias		Attrition bias		Reporting bias
	Random		Blinding of	Blinding of	Incomplet	e outcome data ad	dressed	
(year)	sequence generation	Allocation concealment	participants, personnel	outcome assessment	МТСТ	Infant safety	Mother safety	Selective reporting
Pan CQ	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
(2016)	Quotes: "Enrollment at each center was performed with the use of blocks and randomized for sample balance. Using a randomization table, we randomly assigned 200 mothers, in a 1:1 ratio"	Comment:no concealment described	Quotes: "open- label"	<i>Quotes:</i> "open-label"	<i>Comment:</i> Loss to follow up detailed carefully in Figure 1. Minimal loss to follow up (95% in treated group, 88% in control group), and <10 % points different between control and treated groups.	<i>Comment:</i> Reports on all infant adverse events of interest for 88% and 97.8% of control and treated group, respectively. This excludes bone density measurements.	<i>Comment:</i> Reports on all maternal adverse events of interest for >95% of both treated and control groups, including antiviral resistance testing.	<i>Comment:</i> the protocol is available in a separate publication as well as online at NEJM.org. The current outcomes of interest that this meta- analysis is recording were pre- specified.
Jourdain	Low risk	Low/Unclear	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
G (2018)	<i>Quotes:</i> "participants were randomly assigned in a 1:1	risk <i>Quotes:</i> "The participants, the trial staff on site	<i>Quotes:</i> "The participants, the trial staff on site and at the coordination	<i>Quotes:</i> "The participants, the trial staff on site and at the coordination center,	<i>Comment:</i> 88 and 90% with full follow up in treated and	<i>Comment:</i> 95 and 98% of infants included in this analysis from	<i>Comment:</i> although >90% women considered	<i>Comment:</i> the protocol is available in a separate

	ratio" "Randomization was performed with the use of permuted blocks and stratified according to trial site"	and at the coordination center, the investigators, and the laboratory personnel were unaware of the trial-group assignments" <i>Comment:</i> no detail provided about sealed envelopes	center, the investigators, and the laboratory personnel were unaware of the trial- group assignments." "matching placebo (similar to active tablets minus the active pharmaceutical ingredient)"	the investigators, and the laboratory personnel were unaware of the trial- group assignments."	control group, respectively. Numbers of mothers/infants withdrawn or LFU detailed in Fig. 1. Similar withdrawal/LFU proportions in each group and 1 fetal/ infant death in each group.	treated and control, respectively. All relevant adverse events addressed, including bone mineral density (although for this variable, many lost to follow up, would have to say "high risk")	until discontinuatio n of the trial regimen, some key adverse events not addressed (e.g. antiviral resistance, postpartum haemorrhage)	publication as well as online at NEJM.org. The current outcomes of interest that this meta- analysis is recording were pre- specified.
Lin Y (2018)	Low risk Quotes: "A random number table was used to group the pregnancies into each group (60 individuals per group) based on their enrollment time. Simple randomization was performed"	Low risk Quotes: "sealed envelopes were used for concealment of the random allocation."	High risk Quotes: "The control individuals did not receive anti- viral treatment." "The participants, care providers did not know whether the patients had accepted the intervention." Comment: Information is contradictory as it says that participants did not receive treatment (and no mention of placebo) but also that it is double blinded. Unclear if participants were actually blinded	Low/Unclear Risk Quotes: " persons who examined the viral DNA loads and evaluated the outcomes of the patients did not know whether the patients had accepted the intervention." Comment: It mentions blinding but if participants were not properly blinded then other staff etc can easily understand which treatment they are on.	High risk Comment: 100% follow up in treated group but 87% in control. This indicates that blinding was probably not done well, and could also introduce bias with dissimilar proportions. No breakdown of LFU cases given.	High risk Comment: same numbers used and therefore comment as for MTCT outcome.	High risk Comment: same numbers used and therefore comment as for MTCT outcome.	Low risk Comment: the protocol is available online where the article can be accessed on Scientific Reports website. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol.

Study		Performance bias	Detection bias		Attrition bias		Reporting bias	
(year)	Random	Allocation	Blinding of	Blinding of	Incomplet	e outcome data ad	dressed	
(No.)	sequence generation	concealment	participants, personnel	outcome assessment	МТСТ	Infant safety	Mother safety	Selective reporting
Yu CY (2018)	Low risk/Unclear Quotes: "60 cases of pregnant women with asymptomatic hepatitis B virus were selected and randomly divided into liver protection group and tenofovir group, with 30 cases in each group" Comment: the study did not describe the exact random component in the sequence generation process	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received liver protecting treatment" "The observation group received antiviral treatment with tenofovir" <i>Comment</i> : the study did not address this outcome and no use of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	High risk Comment: same numbers used as for MTCT outcome. Only congenital abnormality reported. Other key adverse events not addressed.	High risk Comment: same numbers used as for MTCT outcome. Women considered until late pregnancy. Only elevated bile acid level and amniotic fluid turbidity reported. Other key adverse events of interest in this review not addressed (e.g. HBV flare after treatment discontinuatio n, antiviral resistance)	Low risk Comment: the protocol is available in the method section of the article. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol.
Liu MH (2017b)	Low risk/Unclear Quotes :"participants	Unclear Comment: the method of concealment not	High risk Quotes: "The control group received no antiviral treatment"	Unclear Comment: the study did not address this	Low risk Comment:100% follow up in both treated and	High risk Comment: same numbers used as for MTCT	High risk Comment: same numbers used as for	Low risk Comment: the protocol is available in

B. Chinese language studies

were randomLy	described	"The observation group	outcome	control group	outcome. Only	MTCT	the method
assigned in a 1:1		received antiviral			Apgar score,	outcome.	section of the
ratio"		treatment with TDF"			premature labour,	Women	article. The
Comment: the		Comment: the study did			congenital	considered	current
study did not		not address this			abnormality and	until delivery.	outcomes of
describe the exact		outcome and no			retarded	Only	interest that
random		mention of placebo			development	postpartum	this meta-
component in the		_			reported. Other	haemorrhage	analysis is
sequence					key adverse	reported.	recording
generation					events not	Other key	were pre-
process					addressed.	adverse events	specified in
_						not addressed.	that protocol.

LAM 100–150 mg

A. English language studies

Study	Selecti	on bias	Performance bias	Detection bias		Attrition bias		Reporting bias
-	Random	Allocation	Blinding of	Blinding of	Incomplet	e outcome data ad	dressed	
(year)	sequence generation	concealment	participants, personnel	outcome assessment	МТСТ	Infant safety	Mother safety	Selective reporting
Xu WM (2009)	High risk Comment: Mentions that women were randomly assigned but does not give any indication of method for randomization.	Low/unclear risk Quotes: "After written informed consent was obtained, participants were randomly assigned in a 1:1 ratio ~" Comment: No method for allocation concealment is mentioned except calling the trial 'blinded' and 'double-blind'. However, from the above quote it	Low risk Quotes: "To preserve study blinding, the investigators were instructed not to determine serum HBV DNA levels locally while the mother was receiving blinded treatment"; "matching placebo orally once daily" Comment: Calls the trial blinded and mentions some extra efforts put in	Low risk Quotes: "To preserve study blinding, the investigators were instructed not to determine serum HBV DNA levels locally while the mother was receiving blinded treatment" <i>Comment:</i> Calls the trial blinded and mentions some extra efforts put in to preserve blinding with study personnel (specifically lab personnel)	Unclear risk Comment: All lost to follow up, withdrawals, etc. detailed carefully in text and a figure within the report. Appropriate analysis methods used to consider loss to follow up (e.g. mITT analysis). However, only 78% and 66% retention in treated and control groups,	High risk Comment: Though all the infants were included in this analysis from three arms, respectively, some key adverse events including prematurity, Apgar and bone density were not reported.	High risk Comment: Though >90% women were included in this analysis, some key adverse events, were not addressed (e.g. antiviral resistance, postpartum haemorrhage)	Unclear risk Comment: Both reviewers were unable to find the trial protocol online.
		seems that randomization occurred after informed consent.	to preserve blinding with study personnel.		respectively (these proportions also differ by >10 % points)			

B. Chinese language studies

Study	Selecti	on bias	Performance bias	Detection bias		Attrition bias		Reporting bias
(year)	Random	Allocation	Blinding of	Blinding of	Incomplet	e outcome data ad	dressed	
(No.)	sequence	concealment	participants,	outcome	МТСТ	Infant safety	Mother	Selective
	generation		personnel	assessment			safety	reporting
Chen SM	Low risk/Unclear	Unclear Comment: the	High risk Quotes: "The control	Unclear Comment: the	Unclear Comment: no	Unclear Comment: the	Unclear Comment: the	Low risk Comment: the
(2017)	<i>Quotes:</i> "90 cases of pregnant women chronically infected with HBV were selected and randomly divided into lamivudine group, telbivudine group, telbivudine group, telbivudine group, with 30 cases in each group" <i>Comment:</i> the study did not describe the exact random component in the sequence generation process	method of concealment not described	group received no antiviral treatment" "The observation groups received antiviral treatment with lamivudine or telbivudine" <i>Comment</i> : the study did not address this outcome and no mention of placebo	study did not address this outcome	statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	study did not address this outcome	study did not address this outcome	protocol is available in the method section of the article. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol.
Ji YY	Low risk Quotes:	Unclear Comment: the	High risk Quotes: "The control	Unclear Comment: the	Unclear Comment: no	Unclear Comment: the	Unclear Comment: the	High risk Comment: the
(2015)	"Referring to random number table, the patients were divided into telbivudine group, lamivudine group	comment: the method of concealment not described	<i>Quotes:</i> The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine or	comment: the study did not address this outcome	<i>Comment:</i> no statement about LFU (not reporting any LFU, and also not mentioning clearly that there	comment: the study did not address this outcome	study did not address this outcome	<i>Comment:</i> the protocol is available in the method section of the article. But not all of the

	and control group, with 65 cases in each group"		lamivudine" <i>Comment:</i> the study did not address this outcome and no mention of placebo.		were no cases LFU)			study's pre- specified primary outcomes have been reported (e.g. maternal liver function after antiviral treatment).
Li 2 (2015)	ZG Low risk/Unclear Quotes: "The patients were randomly divided into lamivudine group,telbivudine group and control group, with 25 cases in each group" Comment: the study did not describe the exact random component in the sequence generation process.	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group received antiviral treatment with lamivudine or telbivudine" Comment: the study did not address this outcome and no mention of placebo.	Unclear Comment: the study did not address this outcome.	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear Comment: the study did not address this outcome.	Unclear Comment: the study did not address this outcome.	Low risk Comment: the protocol is available in the method section of the article. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol.
Tian	Low risk Quotes:	Unclear Comment: the	High risk Quotes: "The control	Unclear Comment: the	Unclear Comment: no	High risk	High risk	High risk Comment: the
XQ	"Referring to random number	method of concealment not	group received HBIG" "The observation group	study did not address this	statement about LFU (not	<i>Comment:</i> though all the infants were included in	<i>Comment:</i> though all women were	protocol is available in
(2015)	table, the patients were divided into the observation group and the control group, with 110 cases in	described	received lamivudine on the basis of HBIG for the control group" <i>Comment:</i> the study did not address this outcome and no	outcome	reporting any LFU, and also not mentioning clearly that there were no cases LFU)	were included in this analysis, some key adverse events including Apgar and bone density were not	women were included in this analysis, the adverse events observed were	the method section of the article. But one or more reported primary

	each group"		mention of placebo			reported.	not addressed.	outcomes were not pre- specified (mainly maternal and infantile adverse reactions).
Yang HW	Low risk/Unclear	Unclear Comment: the	High risk Quotes: "The	Unclear Comment: the	Unclear Comment: no	High risk	High risk	High risk Comment: the
(2014)	<i>Quotes:</i> "152 cases of pregnant women with chronic hepatitis B were randomly divided into experimental I group, experimental II group and control group, 53, 53 and 46 cases in the above three groups, respectively" <i>Comment:</i> the study did not describe the exact random component in the sequence generation process; and importantly, there's a disparity between the number of cases in the experimental group and that of the control group	method of concealment not described	experimental II group received HBIG" "The experimental I group received lamivudine on the basis of HBIG" <i>Comment</i> : the study did not address this outcome and no mention of placebo	study did not address this outcome	statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	<i>Comment:</i> though all the infants were included in this analysis, some key adverse events including Apgar and bone density were not reported.	<i>Comment:</i> though all women were included in this analysis, some key adverse events, were not addressed (e.g. antiviral resistance)	protocol is available in the method section of the article. But one or more reported primary outcomes were not pre- specified (mainly maternal and infantile adverse reactions)

Bai XW (2011)	Low risk/Unclear Quotes: "The patients were randomly divided into observation group 1, observation group 2 and control group, with 30, 30 and 25 cases, respectively" Comment: the study did not describe the exact random component in the sequence generation process. Importantly, disparity exists between the number of cases in observation groups and control groups.	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group 1 received HBIG and the observation group 2 antiviral treatment with lamivudine" <i>Comment</i> : the study did not address this outcome and no mention of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear Comment: the study did not address this outcome	Unclear Comment: the study did not address this outcome	Low risk Comment: the protocol is available in the method section of the article. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol.
Guo YZ (2008)	Low risk/Unclear Quotes: "The patients were randomly divided into the observation group and the control group, with 70 cases in the observation group and 40 cases in the control group"	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group received antiviral treatment with lamivudine" Comment: the study did not address this outcome and no mention of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear Comment: the study did not address this outcome	Unclear Comment: the study did not address this outcome	Low risk Comment: the protocol is available in the method section of the article. The current outcomes of interest that this meta- analysis is recording

<i>Comment:</i> the study did not describe the exact				were pre- specified in that protocol.
random				•
component in the				
sequence				
generation				
process;				
importantly, there				
was a huge				
disparity between				
the numbers of				
cases in				
observation and				
control groups				

LDT 600 mg

A. Chinese language studies

Study	Selecti	on bias	Performance bias	Detection bias		Attrition bias		Reporting bias
(year)	Random	Allocation	Blinding of	Blinding of	Incomplet	e outcome data ad	ldressed	
(No.)	sequence generation	concealment	participants, personnel	outcome assessment	МТСТ	Infant safety	Mother safety	Selective reporting
Wang HY (2018)	Low risk/Unclear Quotes: "80 cases of pregnant women with chronic hepatitis B were randomly divided into experimental group and control group, 40 cases in each group" Comment: the study did not describe the exact random component in the sequence generation process	Unclear Comment: the method of concealment not described	High risk Quotes: "The experimental group received LdT" "The control individuals did not receive antiviral treatment and were given supportive treatment or observation" <i>Comment</i> : the study did not address this outcome and no mention of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	High risk Comment: same numbers used as for MTCT outcome. Some key adverse events not addressed (e.g. prematurity, neonatal death, suboptimal bone density)	Unclear Comment: the study did not address this outcome	High risk Comment: the protocol is available in the method section of the article. But not all of the study's pre- specified primary outcomes have been reported (i.e. maternal ALT). One or more reported primary outcomes were not pre- specified (body length, birth weight, gestational age and congenital abnormality)

Xing Y (2018) Zhang Y	Low risk Quotes: "Referring to random number table, the patients were divided into the observation group and the control group, with 30 cases in each group"	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received regular liver protecting treatment with compound glycyrrhizin" "The observation group received LdT on the basis of regular liver protecting treatment for the control group" <i>Comment</i> : the study did not address this outcome and no mention of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	High risk Comment: same numbers used as for MTCT outcome. Only Apgar score reported. Some key adverse events not addressed (e.g. neonatal death, prematurity, congenital abnormality, suboptimal bone density) High risk Comment: same	Unclear Comment: the study did not address this outcome High risk Comment:	Low risk Comment: the protocol is available in the method section of the article. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol. High risk Comment: the
(2018)	<i>Quotes:</i> "Referring to random number table, the patients were divided into the observation group and the control group, with 34 cases in each group"	<i>Comment:</i> the method of concealment not described	<i>Quotes:</i> "The control group received regular internal treatment" "The observation group received antiviral treatment with telbivudine on the basis of regular internal treatment for the control group" <i>Comment:</i> the study did not address this outcome and no mention of placebo	<i>Comment:</i> the study did not address this outcome	<i>Comment:</i> no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	<i>Comment:</i> same numbers used as for MTCT outcome. Only congenital abnormality and Apgar score reported. Other key adverse events not addressed.	<i>Comment:</i> same numbers used as for MTCT outcome. Only creatine kinase (CK) reported. Key adverse events not addressed	<i>Comment</i> : the protocol is available in the method section of the article. But not all of the study's pre- specified primary outcomes have been reported (e.g. maternal adverse events, HBV serological markers).
Chen SM (2017)	Low risk/Unclear Quotes: "90 cases of pregnant women chronically	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation groups received	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not	Unclear Comment: the study did not address this outcome	Unclear Comment: the study did not address this outcome	Low risk Comment: the protocol is available in the method section of the

	infected with HBV were selected and randomly divided into lamivudine group, telbivudine group and control group, with 30 cases in each group" <i>Comment:</i> the study did not describe the exact random component in the sequence generation process		antiviral treatment with lamivudine or telbivudine" <i>Comment</i> : the study did not address this outcome and no mention of placebo		mentioning clearly that there were no cases LFU)			article. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol.
Guan ZF (2017)	Low risk Quotes: "Referring to random number table, the patients were divided into the observation group and the control group, with 120 cases in each group"	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received liver protecting treatment with compound glycyrrhizin" "The observation group received antiviral treatment with telbivudine" Comment: the study did not address this outcome and no use of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	High risk Comment: same numbers used as for MTCT outcome. Only Apgar score reported. Other key adverse events not addressed.	High risk Comment: same numbers used as for MTCT outcome. Women considered until delivery. Only postpartum haemorrhage reported. Other key adverse events not addressed	High risk Comment: the protocol is available in the method section of the article. But one or more reported primary outcomes were not pre- specified (e.g. maternal HBV DNA and ALT)
Shi QW (2017)	Low risk/Unclear Quotes: "200 cases of pregnant women with chronic	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received HBIG" "The observation group received telbivudine on the basis of HBIG for	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not	High risk Comment: Though all the infants were included in this	High risk Comment: Though all women were included in	High risk Comment: the protocol is available in the method section of the

		hepatitis B were randomly divided into experimental group and control group, 100 cases in each group" <i>Comment:</i> the study did not describe the exact random component in the sequence generation process		the control group" <i>Comment</i> : the study did not address this outcome and no mention of placebo		mentioning clearly that there were no cases LFU)	analysis, some key adverse events including neonatal death and bone density were not reported.	this analysis, some key adverse events were not addressed (e.g. antiviral resistance, postpartum haemorrhage)	article. But one or more reported primary outcomes were not pre- specified (mainly maternal adverse reactions)
Zhao	Y	Low risk	Low risk	High risk	Unclear	Low risk	High risk	High risk	Low risk
(2017)		<i>Quotes:</i> "Referring to random number table, the patients were divided into the observation group and the control group, with 40 cases in each group"	Quotes: "sealed and opaque envelopes were used for concealment of the random allocation."	Quotes: "The control group received compound glycyrrhizin" "The observation group received antiviral treatment with telbivudine on the basis of compound glycyrrhizin" <i>Comment</i> : the study did not address this outcome and no mention of placebo	<i>Comment:</i> the study did not address this outcome	Comment: 100% follow up in both treated and control group	<i>Comment:</i> same numbers used as for MTCT outcome. Only Apgar score reported. Other key adverse events not addressed.	<i>Comment:</i> same numbers used as for MTCT outcome. Women considered until 12 weeks after delivery. Only fever, chill and rash reported. Other key adverse events not addressed	<i>Comment:</i> the protocol is available in the method section of the article. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol.
Zhu	J	Low risk	Unclear Comment: the	High risk <i>Quotes:</i> "The control	Unclear	Unclear	High risk	High risk	Low risk
(2017)		<i>Quotes:</i> "Referring to random number table, the patients were divided into the observation group and the control group, with 60 cases in each group"	comment: the method of concealment not described	<i>Quotes:</i> The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine" <i>Comment:</i> the study did not address this outcome and no	<i>Comment:</i> the study did not address this outcome	<i>Comment:</i> no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU); 6 cases of fetal death in	<i>Comment:</i> same numbers used as for MTCT outcome. Only Apgar score and neonatal asphyxia reported. Other key adverse events not addressed	<i>Comment:</i> same numbers used as for MTCT outcome. Women considered until delivery. Only foetal death and	<i>Comment:</i> the protocol is available in the method section of the article. The current outcomes of interest that this meta-

Fu PX (2016)	Low risk/Unclear Quotes: "200 cases of pregnant women chronically infected with HBV were randomly divided into treated group and control group, with 100 cases in each group"	Unclear Comment: the method of concealment not described	mention of placebo High risk Quotes: "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine" Comment: the study did not address this outcome and no mention of placebo	Unclear Comment: the study did not address this outcome	control group Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear Comment: the study did not address this outcome	postpartum haemorrhage reported. Other key adverse events not addressed High risk <i>Comment:</i> same numbers used as for MTCT outcome. Women considered until delivery. Only CK elevation reported. Other key	analysis is recording were pre- specified in that protocol. High risk <i>Comment:</i> the protocol is available in the method section of the article. But not all of the study's pre- specified primary outcomes have been
	<i>Comment:</i> the study did not describe the exact random component in the sequence generation process						adverse events not addressed	reported (e.g. maternal liver function, viral variants). One or more reported primary outcomes were not pre- specified (e.g. maternal CK)
Huang HY (2016)	Low risk Quotes: "Referring to random number table, the patients were divided into the observation group 1, 2, 3 and the control group, with 30 cases in	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group 1, 2 and 3 received antiviral treatment with telbivudine at 20, 24 and 28 weeks, respectively"	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear Comment: the study did not address this outcome	Unclear <i>Comment:</i> the study did not address this outcome	Low risk Comment: the protocol is available in the method section of the article. The current outcomes of interest that

Xie PY (2016)	each group" Low risk <i>Quotes:</i> "Referring to random number table, the patients were divided into the observation group and the control group, with 60 cases in each group"	Unclear Comment: the method of concealment not described	Comment: the study did not address this outcome and no mention of placebo High risk Quotes: "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine" Comment: the study did not address this outcome and no mention of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear Comment: the study did not address this outcome	Unclear Comment: the study did not address this outcome	this meta- analysis is recording were pre- specified in that protocol. Low risk <i>Comment:</i> the protocol is available in the method section of the article. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol
Lu QY (2016)	Low risk/Unclear Quotes: "The patients were randomly divided into the observation group and the control group, with 152 cases in the observation group and 132 cases in the control group" Comment: the study did not describe the exact random component in the sequence	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received HBIG" "The observation group received telbivudine on the basis of HBIG for the control group" Comment: the study did not address this outcome and no mention of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	High risk Comment: Though all the infants were included in this analysis, some key adverse events including Apgar and bone density were not reported.	High risk Comment: Though all women were included in this analysis, some key adverse events were not addressed (e.g. antiviral resistance, postpartum haemorrhage)	High risk Comment: the protocol is available in the method section of the article. But one or more reported primary outcomes were not pre- specified (mainly maternal and infantile adverse reactions)

Ji (2015)		generation process; and importantly, there's a huge disparity between the number of cases in the observation group and that of the control group Low risk <i>Quotes:</i> "Referring to random number table, the patients were divided into telbivudine group, lamivudine group, with 65 cases in each group"	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine or lamivudine" Comment: the study did not address this outcome and no mention of placebo	Unclear <i>Comment:</i> the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear <i>Comment:</i> the study did not address this outcome	Unclear Comment: the study did not address this outcome	High risk Comment: the protocol is available in the method section of the article. But not all of the study's pre- specified primary outcomes have been reported (e.g. maternal liver function after antiviral treatment).
Li	SF.	Low risk/unclear <i>Quotes:</i> "The	Unclear Comment: the	High risk Quotes: "The control	Unclear Comment: the	Unclear Comment: no	High risk Comment: same	High risk Comment:	High risk Comment: the
(2015)		patients were randomly divided into the observation group and the control group, with 60 cases in each group" <i>Comment:</i> the	method of concealment not described	group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine" <i>Comment</i> : the study did not address this outcome and no	study did not address this outcome	statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	numbers used as for MTCT outcome. Only Apgar score reported. Other key adverse events not addressed	same numbers used as for MTCT outcome. Women considered until 6 months after delivery. Only adverse	protocol is available in the method section of the article. But one or more reported primary outcomes

	study did not describe the exact random component in the sequence generation process		mention of placebo				reactions, abnormal pregnancy, and CK elevation reported. Other key adverse events not addressed	were not pre- specified (e.g. abnormal pregnancy). One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis (e.g. Apgar score).
Yang HW (2015)	Low risk/Unclear Quotes: "The patients were randomly divided into the intervention group and the control group, with 50 cases in each group" Comment: the study did not describe the exact random component in the sequence generation process	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine" <i>Comment</i> : the study did not address this outcome and no mention of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear Comment: the study did not address this outcome	High risk Comment: same numbers used as for MTCT outcome. Women considered until delivery. Only adverse reactions reported. Other key adverse events not addressed.	High risk Comment: the protocol is available in the method section of the article. But one or more reported primary outcomes were not pre- specified (e.g. maternal adverse reactions)
Peng ML (2014)	Low risk/Unclear <i>Quotes:</i> "60 cases of	Unclear Comment: the method of concealment not	High risk Quotes: "The control group received HBIG" "The observation group	Unclear Comment: the study did not address this	Unclear Comment: no statement about LFU (not	Unclear Comment: the study did not address this	Unclear Comment: the study did not address this	Low risk Comment: the protocol is available in

	pregnant women with chronic hepatitis B were randomly divided into experimental group and control group, 30 cases in each group" <i>Comment:</i> the study did not describe the exact random component in the sequence generation	described	received telbivudine on the basis of HBIG for the control group" <i>Comment</i> : the study did not address this outcome and no mention of placebo	outcome	reporting any LFU, and also not mentioning clearly that there were no cases LFU)	outcome	outcome	the method section of the article. The current outcomes of interest that this meta- analysis is recording were pre- specified in that protocol.
Zhu LP (2014)	process Low risk/Unclear Quotes: "The patients were randomly divided into the observation group and the control group, with 30 cases in each group" Comment: the study did not describe the exact random component in the sequence generation process	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine" Comment: the study did not address this outcome and no mention of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear Comment: the study did not address this outcome	High risk Comment: same numbers used as for MTCT outcome. Women considered until delivery. Only adverse reactions, renal function and CK elevation reported. Other key adverse events not addressed	High risk Comment: the protocol is available in the method section of the article. But one or more reported primary outcomes were not pre- specified (e.g. maternal adverse effects)
Bai HL (2013)	Low risk/Unclear Quotes: "The patients were randomly divided	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group	Unclear Comment: the study did not address this outcome	Low risk Comment: 100% follow up in both treated and control group	High risk Comment: same numbers used as for MTCT outcome. Only	High risk Comment: same numbers used as for MTCT	High risk Comment: the protocol is available in the method

	into the observation group and the control group, with 30 cases in each group" <i>Comment:</i> the study did not describe the exact random component in the sequence generation process		received antiviral treatment with telbivudine" <i>Comment</i> : the study did not address this outcome and no mention of placebo			CK elevation reported. Other key adverse events not addressed.	outcome. Women considered until delivery. Only adverse reactions, renal function, and CK elevation reported. Other key adverse events not addressed.	section of the article. But one or more reported primary outcomes were not pre- specified (e.g. maternal and infantile adverse effects). One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis (e.g. postpartum haemorrhage)
Guo HJ (2011)	Low risk/Unclear Quotes: "The patients were randomly divided into the observation group and the control group, with 25 cases in each group" Comment: the study did not describe the exact random	Unclear Comment: the method of concealment not described	Unclear Quotes: "The control group received placebo provided by the manufacturer" "The observation group received antiviral treatment with telbivudine" Comment: the study did not address this outcome, though mention of placebo	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	Unclear Comment: the study did not address this outcome	Unclear Comment: the study did not address this outcome	High risk Comment: the protocol is available in the method section of the article. But one or more reported primary outcomes were not pre- specified (e.g. maternal liver function, total

Zhao DB (2010)	component in the sequence generation process Low risk/Unclear Quotes: "The patients were randomly divided into the observation group and the control group, with 30	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine" Comment: the study did	Unclear Comment: the study did not address this outcome	Unclear Comment: no statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases	Unclear Quotes: "no adverse reactions found in two groups of mothers and infants" Comment: insufficient reporting	Unclear Quotes: "no adverse reactions found in two groups of mothers and infants" Comment:	bilirubin, and HBV DNA). High risk Comment: the protocol is available in the method section of the article. But one or more reported
	cases in each group" <i>Comment:</i> the study did not describe the exact random component in the sequence generation process		not address this outcome and no mention of placebo		LFU)		insufficient reporting	primary outcomes were not pre- specified (e.g. maternal and infantile adverse reactions). One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis (e.g. maternal and infantile adverse reactions).
Zhang LJ (2009)	Low risk/Unclear Quotes: "The patients were randomly divided	Unclear Comment: the method of concealment not described	High risk Quotes: "The control group received no antiviral treatment" "The observation group	Unclear Comment: the study did not address this outcome	Low risk Comment: 96.8% and 100.0% with full follow up in treated and	High risk Comment: all infants included in this analysis from both treated and	High risk Comment: all women considered until delivery.	High risk Comment: the protocol is available in the method

into the observation grou and the control group, with 31 cases in the observation grou and 30 cases in the control grou <i>Comment:</i> the study did not describe the exa random component in th sequence generation process	p " t	received antiviral treatment with telbivudine" <i>Comment:</i> the study did not address this outcome and no mention of placebo		control groups, respectively. Similar follow-up proportions in each group	control groups. Only CK elevation reported. Other key adverse events not addressed	Only adverse reactions, renal function and CK elevation reported. Other key adverse events not addressed.	section of the article. But one or more reported primary outcomes were not pre- specified (e.g. maternal and infantile adverse effects). One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis (e.g. postpartum haemorrhage).
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APPENDIX F: Newcastle–Ottawa Risk of Bias Assessment Tool

TDF 300 mg

A. English language observational studies

				Demonstration			Was follow		Total
	Representat	Selection of		that outcome of	Comparability of		up long		number
	iveness of	the non-		interest was not	cohorts on the basis		enough for	Adequacy of	of stars
	the exposed	exposed	Ascertainment	present at	of the design or	Assessment of	outcomes	follow up of	(risk of
Study (year)	cohort	cohort	of exposure	baseline	analysis	outcomes	to occur	cohorts	bias) ^a
Celen MK	4	*	Does not provide	*	女女	*	*	None reported	7 (low)
(2013)	At least somewhat representativ e of the average HBV- infected pregnant woman	Drawn from the same community (same inclusion and exclusion criteria also)	many details on decrease of HBV DNA levels, no other discussion of maternal adherence.	Always the case	Comparable for HBV DNA level and comparable HBeAg positive. Same regimen for infant immunoprophylaxis	Describes testing done and refers to a central laboratory employed for this study	Yes	(retrospective)	
Greenup AJ (2014)	At least somewhat representativ e of the average HBV-	★ Drawn from the same community (same inclusion	★ Reporting on adherence within the paper, reduction of load used to	★ Always the case	Comparable for HBV DNA level and comparable HBeAg positive. Same regimen for infant immunoprophylaxis and	No details given on laboratory methods for infants, and no details of which	≮ Yes	>20% LFU in control group, although <20% LFU in two treatment groups	7 (low)

	infected	and exclusion	assess women's		confirmation that all	assay was used for			
	pregnant	criteria also)	response to		infants received it	testing HBsAg			
	woman		treatment.						
Chen HL	4	*	*	*	**	*	4	*	9 (low)
(2015) Kochaksarei GS (2016)	At least somewhat representativ e of the average HBV- infected pregnant woman At least somewhat representativ e of the average HBV- infected average HBV- infected pregnant	Drawn from the same community (same inclusion and exclusion criteria also) Not same population, the untreated did not have high viraemia or pre- existing liver disease, whereas the treated did	Regular testing (and pre-delivery testing) of HBV DNA levels were correlated with duration of treatment in mothers Adherence is mentioned but was ascertained in 16/23 women (<70%), and only 2/3 had good adherence.	Always the case ★ Always the case	Comparable for HBV DNA level and comparable HBeAg positive. Same regimen for infant immunoprophylaxis Not comparable for HBV DNA level or HBeAg positive. Apparently, the same regimen for infant immunoprophylaxis; however, very few details stated	Describes test assays used for HBsAg and HBV DNA and acknowledges a study laboratory ★ Testing done centrally, and methods/assays for testing described	Yes ★ Yes	LFU reported and <20% LFU in all treatment and control groups <80% follow up in both treated and control groups	5 (high)
Wakano Y (2018)	Not representativ e of the general population (women who	★ Drawn from the same community with same inclusion	★ >2 log reduction of HBV DNA levels in all treated women	★ Always the case	Comparable for HBV DNA level and comparable HBeAg positive. Different immunoprophylaxis regimens mixed among	Laboratory assays not well described	★ Yes	★ 100% retention	6 (high)

ſ	have had a	and exclusion		the groups of treated		
	child infected	criteria		and non-treated		
	previously)					

^aRisk of bias assessments should be classified as being either low (\geq 7) or high (<7) by the Newcastle–Ottawa scale

B. Chinese language observational studies

	00			Demonstration					
		Selection of		that outcome of	Comparability of		Was follow up	Adequacy	Total
	Representative	the non-		interest was not	cohorts on the	Assessment	long enough	of follow	number of
	-ness of the	exposed	Ascertainment	present at	basis of the	of	for outcomes	up of	stars (risk of
Study (year)	exposed cohort	cohort	of exposure	baseline	design or analysis	outcomes	to occur	cohorts	bias)ª
He LL (2018)	🛠 At least	🖈 Drawn	₩Valid method	🛠 Always the	🛠 Comparable	*	🛠 Yes	No statement	7 (low)
	somewhat	from the same	was used to	case	for HBV DNA levels	Laboratory		on LFU	
	representative of	community	ascertain		at baseline but	methods			
	the average HBV-	(same inclusion	adherence to the		HBeAg serostatus	described in			
	infected pregnant	and exclusion	antiviral therapy		not described. Same	detail (which			
	woman	criteria also)	(decrease in viral		regimen for infant	assay used),			
			load levels		immunoprophylaxis	indicating use			
			subsequent to the		at birth	of a central			
			treatment)			laboaratory			
						and/or record			
						linkage			
Hu MF (2018)	🛠 At least	🗱 Drawn	≭ Valid method	🛠 Always the	🛠 Comparable	*	🛠 Yes	No statement	7 (low)
	somewhat	from the same	was used to	case	for HBV DNA levels	Laboratory		on LFU	
	representative of	community(sam	ascertain		at baseline but	methods			
	the average HBV-	e inclusion and	adherence to the		HBeAg serostatus	described in			

	infected pregnant	exclusion	antiviral therapy		not described. Same	detail (which			
	woman	criteria also)	(decrease in viral		regimen for infant	assay used),			
			load levels		immunoprophylaxis	indicating use			
			subsequent to the		at birth	of a central			
			treatment)			laboaratory			
						and/or record			
						linkage			
Wang HB	🛠 At least	🖈 Drawn	≭ Valid method	🛠 Always the	¥Same threshold	≵ Laboratory	🛠 Yes	No statement	7 (low)
(2018)	somewhat	from the same	was used to	case	for HBV DNA level	methods		on LFU	
	representative of	community	ascertain		but HBeAg	described in			
	the average HBV-	(same inclusion	adherence to the		serostatus not	detail (which			
	infected pregnant	and exclusion	antiviral therapy		described. Same	assay used),			
	woman	criteria also)	(decrease in viral		regimen for infant	indicating use			
			load levels		immunoprophylaxis	of a central			
			subsequent to the		at birth	laboaratory			
			treatment)			and/or record			
						linkage			
Zhang BF	🛠 At least	🖈 Drawn	¥Valid method	🛠 Always the	≭ Same HBeAg	No description	★ Yes	No statement	6 (high)
(2018)	somewhat	from the same	was used to	case	serostatus but	accomption		on LFU	
	representative of	community	ascertain		different thresholds				
	the average HBV-	(same inclusion	adherence to the		for HBV DNA level.				
	infected pregnant	and exclusion	antiviral therapy		Same regimen for				
	woman	criteria also)	(decrease in viral		infant				
			load levels		immunoprophylaxis				
			subsequent to the		at birth				
			treatment)						

Zhou Y (2018)	🛠 At least	🛠 Drawn	★Valid method	*	Always the	☆ ☆ Same HBeAg	*	★ Yes	No	8 (low)
		from the core			·		Laboratory.		statement	
	somewhat	from the same	was used to	case		serostatus and same	Laboratory		on LFU	
	representative of	community	ascertain			thresholds for HBV	methods			
	the average HBV-	(same inclusion	adherence to the			DNA level. Same	described in			
	infected pregnant	and exclusion	antiviral therapy			regimen for infant	detail (which			
	woman	criteria also)	(decrease in viral			immunoprophylaxis	assay used),			
			load levels			at birth	indicating use			
			subsequent to the				of a central			
			treatment)				laboaratory			
							and/or record			
							linkage			
Chen WJ	🗱 At least	🖈 Drawn	₩Valid method	4	Always the	₩¥Same HBeAg	≵ Laboratory	🛠 Yes	No statement	8 (low)
(2017)	somewhat	from the same	was used to	case		serostatus and same	methods		on LFU	
	representative of	community	ascertain			thresholds for HBV	described in			
	the average HBV-	(same inclusion	adherence to the			DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy			regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral			immunoprophylaxis	indicating use			
			load levels			at birth	of a central			
			subsequent to the				laboaratory			
			treatment)				and/or record			
							linkage			
Gong Q (2017)	🛠 At least	🛠 Drawn	∜ Valid method	4	Always the	≭ Both HBeAg	No description	🛠 Yes	No statement	6 (high)
	somewhat	from the same	was used to	case		serostatus and			on LFU	
	representative of	community	ascertain			threshold for HBV				
	the average HBV-	(same inclusion	adherence to the			DNA level not				
	infected pregnant	and exclusion	antiviral therapy			described. Same				
	woman	criteria also)	(decrease in viral			regimen for infant				

			load levels subsequent to the			immunoprophylaxis at birth				
Huang Q (2017) (140)	At least somewhat representative of the average HBV- infected pregnant woman	Trawn from the same community (same inclusion and exclusion criteria also)	treatment) ★Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the	Always case	s the	Same HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement on LFU	7 (low)
Wan JY (2017)	At least somewhat representative of the average HBV- infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	treatment) ★Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always case	5 the	Same thresholds for HBV DNA level but HBeAg serostatus not described. Regimen for infant immunoprophylaxis at birth not described	★Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record	★ Yes	No statement on LFU	6 (high)
Xiao XH (2017)	At least somewhat representative of the average HBV-	Drawn from the same community (same inclusion	★Valid method was used to ascertain adherence to adherence to the antiviral therapy	Always Always	s the	Same thresholds for HBV DNA level but HBeAg serostatus not described. Regimen for infant	linkage ★ Laboratory methods described in detail (which	★ Yes	There is a description of LFU for the exposed	6 (high)

infected pregnant	and exclusion	(decrease in viral	immunoprophylaxis	assay used),	but not for
woman	criteria also)	load levels	at birth not clearly	indicating use	the control
		subsequent to the	described	of a central	group
		treatment)		laboaratory	
				and/or record	
				linkage	

^aRisk of bias assessments should be classified as being either low (≥7) or high (<7) by the Newcastle–Ottawa scale

LAM 100–150 mg

A. English language observational studies

				Demonstration			Was follow		Total
	Representat	Selection of		that outcome of	Comparability of		up long		number
	-iveness of	the non-		interest was not	cohorts on the basis		enough for	Adequacy of	of stars
	the exposed	exposed	Ascertainment	present at	of the design or	Assessment of	outcomes	follow up of	(risk of
Study (year)	cohort	cohort	of exposure	baseline	analysis	outcomes	to occur	cohorts	bias) ^a
Greenup AJ (2014)	At least somewhat representativ e of the average HBV- infected pregnant	★ Drawn from the same community (same inclusion and exclusion criteria also)	Reporting on adherence within the paper, reduction of viral load used to assess women's response to	★ Always the case	Comparable for HBV DNA level and comparable HBeAg positive. Same regimen for infant immunoprophylaxis and confirmation that all infants received it	No details given on laboratory methods for infants, and no details of which assay was used for testing HBsAg	★ Yes	> 20% LFU in control group, although <20% LFU in two treatment groups	7 (low)
Zhang II	woman		treatment						0 (10,00)
Zhang H	*	*	*	*	女女	*	*	な	9 (low)
(2014)	At least somewhat representativ e of the average HBV- infected pregnant woman	Drawn from the same community (same inclusion and exclusion criteria also)	Monthly HBV DNA level testing was done to check maternal adherence	Always the case	Comparable for HBV DNA level and comparable HBeAg positive. Same regimen for infant immunoprophylaxis	Describes testing done and refers to a central laboratory employed for this study	Yes	LFU reported and <20% LFU in all treatment and control groups	

Jackson V	4	*	*	*	HBV DNA level and	*	4	<80% retention in	6
(2015)	At least somewhat representativ e of the average HBV- infected pregnant woman	Jx Drawn from the same community (same inclusion and exclusion criteria also)	Mentions good treatment compliance in all but one patient, and measures decrease in viral load in 35/36 women taking treatment just prior to delivery and saw a significant decrease in most patients (also show these results in a figure in the paper)	₹ Always the case	HBeAg not described in control group. Mentions that all infants received the same regimen for infant immunoprophylaxis; however, in the control group, many women defaulted from care/moved to other maternities, so this does not seem well verified	★ Laboratory assays described, with indication of record linkage (results viewed retrospectively in medical records)	₹ ¥ Yes	both treated and control groups	(high)
Liu CP (2015)	★ least somewhat representativ e of the average HBV- infected pregnant woman	Many more women included in the control group (highly disproportionat e, which could indicate non- similarity with the treated)	Some limited data presented on decrease of maternal viral load, but no mention of linking this with compliance/adher ence/time on treatment, and no	☆ Always the case	★ HBV DNA level and/or HBeAg not described for both treated and control groups. Similar infant prophylaxis between treated and control groups	↓ Laboratory assays described, with indication of record linkage (results viewed retrospectively in medical records)	≮ Yes	No loss to follow up described because it was a retrospective cohort study (or listed as such) where the infants needed to have had test results at the testing time-point (this is therefore	5 (high)

			detailed results					misclassified as a	
			provided					cohort study, and	
								has a high risk of bias	
								for loss to follow up)	
Pan CQ	4	Same	Some data	*	衣衣	*	*	No loss to follow up	6
(2017)		population and	presented on			, ,		described because it	(high)
(2017)	At least	criteria,	decrease of	Always the case	Comparable for HBV	Reference to the	Yes	was a retrospective	('''8'')
	somewhat	however, no	maternal viral		DNA level and	hospital's		cohort study (or	
	representativ	indication of	load, but no		comparable HBeAg	centralized		listed as such) where	
	e of the	how this group	mention of linking		positive. Same regimen	laboratory and		the infants needed	
	average HBV-	was chosen	this with		for infant	linkage to medical		to have had test	
	infected	(usually says	compliance/adher		immunoprophylaxis	records for		results at the testing	
	pregnant	"unwillingness",	ence/time on			assessing infant		time-point (this is	
	woman	for example)	treatment.			outcome		therefore	
			Additionally,					misclassified as a	
			because of study					cohort study, and	
			design					has a high risk of bias	
			(retrospective)					for loss to follow up)	
			there is low/no						
			chance of						
			adherence						
			monitoring						
He T (2018)	*	な	A	*	**	*	な	Retrospective	8 (low)
								cohort mentioned	
	At least	Drawn from the	Detailed	Always the case	Comparable for HBV	Linkage to medical	Yes	but no loss to follow	
	somewhat	same	information on		DNA level and	records		up described, no	
	representativ	community with	reduction of viral		comparable HBeAg			mention of how	
	e of the	same inclusion	load given,		positive. Same regimen			there was perfect	
	average HBV		including specific					retention	

	infected	and exclusion	data for each		for infant				
	pregnant	criteria	woman (every one		immunoprophylaxis				
	woman		had a -6 to -8 log						
			reduction)						
Wakano Y	Not	*	*	*	*	Laboratory assays	4	*	6
(2018)	representativ	,	,	,		not well described	,	ŗ	(high)
(2010)	e of the	Drawn from	>2 log reduction of	Always the case	Comparable for HBV		Yes	100% retention	(יישיי)
	general	the same	HBV DNA levels in		DNA level and				
	population	community with	all treated women		comparable HBeAg				
	(women who	same inclusion			positive. Different				
	have had a	and exclusion			immunoprophylaxis				
	child infected	criteria			regimens mixed among				
	previously)				the groups of treated				
	previously				and non-treated				
Foaud HM	*	Control group	*	\$	A	*	4	<80% follow up at 6–	6
(2019)		comprised	, .	, -	, .	, *	x -	12 months in control	(high)
(2015)	Truly	women who	States that	Always the case	HBeAg proportion not	Lab testing done	Yes	group, though ~86%	(11811)
	representativ	were not	women were		comparable, and HBV	centrally as part of		follow up in treated	
	e of the	candidates for	given lamivudine		DNA at baseline not	the study,		group at that time-	
	average HBV-	lamivudine	monthly and were		given. Same regimen for	laboratory assays		point. (Note: at later	
	infected	(likely to be	questioned		infant	for defining infant		time-point that	
	pregnant	quite different	regarding		immunoprophylaxis	outcome		study defined, there	
	woman	from those who	compliance at			described		was >80% follow up)	
		received it)	each visit						

^aRisk of bias assessments should be classified as being either low (≥7) or high (<7) by the Newcastle–Ottawa scale

B. Chinese language observational studies

				Demonstration					
		Selection of		that outcome of	Comparability of		Was follow up	Adequacy	Total
	Representative	the non-		interest was not	cohorts on the	Assessment	long enough	of follow	number of
	-ness of the	exposed	Ascertainment	present at	basis of the	of	for outcomes	up of	stars (risk of
Study (year)	exposed cohort	cohort	of exposure	baseline	design or analysis	outcomes	to occur	cohorts	bias)ª
Chen QR (2018)	🖈 At least	🛠 Drawn	No description	🖈 Always the	₩¥Same HBeAg	No description	🛠 Yes	No statement	6 (high)
(2010)	somewhat	from the same		case	serostatus and			on LFU	
	representative of	community			comparable HBV				
	the average HBV-	(same inclusion			DNA levels at				
	infected pregnant	and exclusion			baseline. Same				
	woman	criteria also)			regimen for infant				
					immunoprophylaxis				
					at birth				
Li JH (2017)	*	A	≭ Valid method	*	🛠 Comparable	*	*	None reported	7 (low)
	At least	Drawn from	was used to	Always the case	for HBV DNA levels	Indication of	Yes (always	(retrospecti	
	somewhat	the same	ascertain		at baseline but	record linkage	the case)	ve)	
	representative of	community	adherence to the		HBeAg serostatus	(results			
	the average HBV-	(same inclusion	antiviral therapy		not described. Same	viewed			
	infected pregnant	and exclusion	(decrease in viral		regimen for infant	retrospectivel			
	woman	criteria also)	load levels		immunoprophylaxis	y in medical			
			subsequent to the			records)			
			treatment)						
Ren CJ (2016)	🛠 At least	🗱 Drawn	≭ Valid method	🛠 Always the	₩¥Same HBeAg	*	🛠 Yes	No statement	8 (low)
	somewhat	from the same	was used to	case	serostatus and same	Laboratory		on LFU	
	representative of	community	ascertain		thresholds for HBV	methods			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	described in			

	infected pregnant	and exclusion	antiviral therapy		regimen for infant	detail (which			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	assay used),			
			load levels		at birth	indicating use			
			subsequent to the			of a central			
			treatment)			laboratory			
						and/or record			
						linkage			
Shen ML (2016)	★ At least somewhat representative of the average HBV- infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	Same thresholds for HBV DNA level but HBeAg serostatus not described. Regimen for infant immunoprophylaxis at birth not clearly described	↓ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage	★ Yes	No statement on LFU	6 (high)
Wang DM	🖈 At least	🖈 Drawn	≭ Valid method	🛠 Always the	☆ ≵Same HBeAg		★ Yes	No	8 (low)
(2016)	somewhat representative of the average HBV- infected pregnant woman	from the same community (same inclusion and exclusion criteria also)	was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	case	serostatus and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	Laboratory methods described in detail (which assay used), indicating use of a central laboratory		statement on LFU	

							and/or record			
							linkage			
Ge YL (2015)	🗱 At least	🖈 Drawn	≭ Valid method	*	Always the	☆☆ Same HBeAg	No description	🛠 Yes	No statement	7 (low)
	somewhat	from the same	was used to	case		serostatus and same			on LFU	
	representative of	community	ascertain			thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the			DNA level. Same				
	infected pregnant	and exclusion	antiviral therapy			regimen for infant				
	woman	criteria also)	(decrease in viral			immunoprophylaxis				
			load levels			at birth				
			subsequent to the							
			treatment)							
Han YP (2014)	🛠 At least	🖈 Drawn	≭ Valid method	*	Always the	₩¥Same HBeAg	No description	🛠 Yes	No statement	7 (low)
	somewhat	from the same	was used to	case		serostatus and same			on LFU	
	representative of	community	ascertain			thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the			DNA level. Same				
	infected pregnant	and exclusion	antiviral therapy			regimen for infant				
	woman	criteria also)	(decrease in viral			immunoprophylaxis				
			load levels			at birth				
			subsequent to the							
			treatment)							
Wang W	🛠 At least	★ Drawn	∜ Valid method	*	Always the	Comparable for	*	★ Yes	No	7 (low)
(2014)		from the core			,		Laboratori		statement	
	somewhat	from the same	was used to	case		HBV DNA levels but	Laboratory		on LFU	
	representative of	community	ascertain			HBeAg serostatus	methods			
	the average HBV- infected pregnant	(same inclusion and exclusion	adherence to the			not described. Same	described in			
	woman	criteria also)	antiviral therapy (decrease in viral			regimen for infant immunoprophylaxis	detail (which assay used),			
	woman	Cifteria disuj	load levels			at birth	indicating use			
			ioau ieveis				mulcating use			

			subsequent to the			of a central			
			treatment)			laboratory			
			(leathent)			and/or record			
						linkage			
								No	
Zhu M (2014)	女 文	*	本 Valid method	*	✤ Comparable for	*	な	No statement	6 (high)
	At least	Drawn from	was used to	Always the case	HBeAg serostatus	Laboratory	Yes (always	on LFU	
	somewhat	the same	ascertain		but HBV DNA levels	assays	the case)		
	representative of	community	adherence to the		not described. Same	described			
	the average HBV-		antiviral therapy		regimen for infant				
	infected pregnant		(decrease in viral		immunoprophylaxis				
	woman		load levels						
			subsequent to the						
			treatment)						
Zeng YM	🛠 At least	🖈 Drawn	↓ Valid method	🖈 Always the	★ Same HBeAg	*	★ Yes	No	7 (low)
(2013)	somewhat	from the same	was used to	case	serostatus and same	Laboratory		statement	
	representative of	community	ascertain	Case	thresholds for HBV	methods		on LFU	
	the average HBV-	(same inclusion	adherence to the		DNA level. Regimen	described in			
	infected pregnant	and exclusion	antiviral therapy		for infant	detail (which			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	assay used),			
		,	load levels		at birth not	indicating use			
			subsequent to the		described clearly	of a central			
			treatment)		,	laboratory			
			,			and/or record			
						linkage			
Zhou DS (2013)	🖈 At least	★ Drawn	No description	Always the	★Same thresholds	*	★ Yes	No	6 (high)
								statement	
	somewhat	from the same		case	for HBV DNA level	Laboratory		on LFU	
	representative of	community			but HBeAg	methods			

	the average HBV- infected pregnant woman	(same inclusion and exclusion criteria also)			serostatus not described. Same regimen for infant immunoprophylaxis	described in detail (which assay used), indicating use			
					at birth	of a central laboratory and/or record linkage			
Jiang HX (2012)		★ Drawn from the same community (same inclusion and exclusion criteria also)	✓Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	Same HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	↓ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage	⊀ Yes	No statement on LFU	8 (low)
Wang EJ (2012)	★Atleastsomewhatrepresentativeofthe averageHBV-infectedpregnantwoman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels	★ Always the case	Same HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	↓ Laboratory methods described in detail (which assay used), indicating use of a central	⊀ Yes	No statement on LFU	8 (low)

Yuan QF (2012)	At least somewhat representative of the average HBV- infected pregnant woman	→ Drawn from the same community (same inclusion and exclusion criteria also)	subsequent to the treatment) Adherence/compl iance not mentioned and no data presented on decrease in HBV DNA levels	★ Always the case	Comparable for HBeAg serostatus but HBV DNA level not described. Same regimen for infant immunoprophylaxis	laboratory and/or record linkage ★ Indication of record linkage	★ Yes (always the case)	No statement on LFU	6 (high)
Cheng YC (2011)	At least somewhat representative of the average HBV- infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★Valid method was used to ascertain	★ Always the case	★★Same HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	↓ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage	⊀ Yes	No statement on LFU	8 (low)
Ren YJ (2011)	★ least somewhat representative of the average HBV-	→ Drawn from the same community	★Valid method was used to ascertain	★ Always the case	Comparable for HBeAg serostatus but not for HBV DNA level. Same regimen for infant immunoprophylaxis	↓ Laboratory assays described	★ Yes (always the case)	No statement on LFU	7 (low)

	infected pregnant		load levels						
	woman		subsequent to the						
			treatment)						
Zhang YF	🛠 At least	🖈 Drawn	≮ Valid method	🖈 Always the	₩ ★ ★ Same HBeAg	No description	🛠 Yes	No statement	7 (low)
(2010)	somewhat	from the same	was used to	case	serostatus and same	accomption		on LFU	
	representative of	community	ascertain		thresholds for HBV			0.1.2.0	
	the average HBV-	(same inclusion	adherence to the		DNA level. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth				
			subsequent to the						
			treatment)						
Su TB (2009)	な	À	Does not provide any details on	X	🛠 Both HBeAg	*	*	No statement	6 (high)
	At least	Drawn from	adherence	Always the case	serostatus and HBV	Testing done	Yes (always	on LFU	
	somewhat	the same			DNA not described.	centrally in	the case)		
	representative of	community			Same regimen for	the hospital			
	the average HBV-	(same inclusion			infant	that study			
	infected pregnant	and exclusion			immunoprophylaxis	staff worked			
	woman	criteria also)				in			
Tang X (2009)	🛠 At least	🖈 Drawn	₩Valid method	🗚 Always the	★★Same HBeAg	*	🛠 Yes	No statement	8 (low)
	somewhat	from the same	was used to	case	serostatus and same	Laboratory		on LFU	
	representative of	community	ascertain		thresholds for HBV	methods			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	described in			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	detail (which			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	assay used),			
			load levels		at birth	indicating use			
						of a central			

			subsequent to the treatment)			laboratory and/or record			
			treatment)			linkage			
Feng HF (2007)	🛠 At least	🛠 Drawn	≭ Valid method	🖈 Always the	☆☆ Same HBeAg	*	🛠 Yes	No statement	8 (low)
	somewhat	from the same	was used to	case	serostatus and same	Laboratory		on LFU	
	representative of	community	ascertain		thresholds for HBV	methods			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	described in			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	detail (which			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	assay used),			
			load levels		at birth	indicating use			
			subsequent to the			of a central			
			treatment)			laboratory			
						and/or record			
						linkage			
Li G (2006)	*	*	≭ Valid method	*	🛠 Comparable	*	*	*	8 (low)
	At least	Drawn from	was used to	Always the case	HBeAg serostatus	Laboratory	Yes (always	LFU	
	somewhat	the same	ascertain		but HBV DNA levels	assays	the case)	reported	
	representative of	community	adherence to the		not described. Same	described		and <20%	
	the average HBV-	(same inclusion	antiviral therapy		regimen for infant			LFU in both	
	infected pregnant	and exclusion	(decrease in viral		immunoprophylaxis			treatment	
	woman	criteria also)	load levels					group and	
			subsequent to the					control	
			treatment)					group	
Li WF (2006)	🛠 At least	🖈 Drawn	⊀ Valid method	🛠 Always the	☆☆ Same HBeAg	*	🛠 Yes	No	8 (low)
	somewhat	from the same	was used to	case	serostatus and same	Laboratory		statement	
	representative of	community	ascertain	Case	thresholds for HBV	methods		on LFU	
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	described in			

	infected pregnant	and exclusion	antiviral therapy		regimen for infant	detail (which			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	assay used),			
			load levels		at birth	indicating use			
			subsequent to the			of a central			
			treatment)			laboratory			
						and/or record			
						linkage			
Ma J (2006)	*	*	≮ Valid method	*	Comparable HBeAg serostatus but HBV	*	*	No statement	6 (high)
	At least	Drawn from	was used to	Always the case	DNA levels not	Laboratory	Yes (always	on LFU	
	somewhat	the same	ascertain		described. Regimen	assays	the case)		
	representative of	community	adherence to the		for infant	described			
	the average HBV-	(same inclusion	antiviral therapy		immunoprophylaxis				
	infected pregnant	and exclusion	(decrease in viral		not described				
	woman	criteria also)	load levels						
			subsequent to the						
			treatment)						
Han ZH (2005)	🛠 At least	🗱 Drawn	¥Valid method	🛠 Always the	☆ ⋠Same HBeAg	*	🛠 Yes	No statement	8 (low)
	somewhat	from the same	was used to	case	serostatus and same	Laboratory		on LFU	
	representative of	community	ascertain		thresholds for HBV	methods			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	described in			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	detail (which			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	assay used),			
			load levels		at birth	indicating use			
			subsequent to the			of a central			
			treatment)			laboratory			
						and/or record			
						linkage			

Wang	ΤM	🛠 At least	🛠 Drawn	≯ Valid method	🛠 Always the	≭ Same HBeAg	No	≮ Yes	No	6 (high)
(2005)							description		statement	
(,		somewhat	from the same	was used to	case	serostatus but HBV			on LFU	
		representative of	community	ascertain		DNA level not				
		the average HBV-	(same inclusion	adherence to the		described. Same				
		infected pregnant	and exclusion	antiviral therapy		regimen for infant				
		woman	criteria also)	(decrease in viral		immunoprophylaxis				
				load levels		at birth				
				subsequent to the						
				treatment)						

^aRisk of bias assessments should be classified as being either low (≥7) or high (<7) by the Newcastle–Ottawa scale

LDT 600 mg

A. English language observational studies

	Representat iveness of	Selection of the non-		Demonstration that outcome of interest was not	Comparability of cohorts on the basis		Was follow up long enough for	Adequacy of	Total number of stars
	the exposed	exposed	Ascertainment	present at	of the design or	Assessment of	outcomes	follow up of	(risk of
Study (year)	cohort	cohort	of exposure	baseline	analysis	outcomes	to occur	cohorts	bias) ^a
			•		•				9 (low)
0	*	*	*	×	女 女	×	*	*	9 (IOW)
(2014)	At least	Drawn from	Monthly HBV DNA	Always the case	Comparable for HBV	Describes testing	Yes	LFU reported and	
	somewhat	the same	level testing was		DNA level and	done and refers to		<20% LFU in all	
	representativ	community	done to check		comparable HBeAg	a central		treatment and	
	e of the	(same inclusion	maternal		positive. Same regimen	laboratory		control groups	
	average HBV-	and exclusion	adherence		for infant	employed for this			
	infected	criteria also)			immunoprophylaxis	study			
	pregnant								
	woman								
Han GR	*	な	な	*	女女	*	*	*	9 (low)
(2015)	At least	Drawn from	Regular testing	Always the case	Comparable for HBV	Describes test	Yes	LFU reported and	
	somewhat	the same	(and pre-delivery		DNA level and	assays used for		<20% LFU in all	
	representativ	community	testing) of HBV		comparable HBeAg	HBsAg and HBV		treatment and	
	e of the	(same inclusion	DNA levels were		positive. Same regimen	DNA of infants and		control groups	
	average HBV-	and exclusion	done in mothers		for infant	describes that			
	infected	criteria also)	and each treated		immunoprophylaxis	samples were			
	pregnant		mother had at			taken by study			
	woman		least a 3-log			personnel			
			decrease in HBV			themselves			
			DNA level prior to			(meaning they			
			delivery			would have direct			
						linkage to results)			

Liu CP	*	Many more	Some limited data	*	*	*	*	No loss to follow up	5
(2015)	At least somewhat representativ e of the average HBV- infected pregnant woman	women in the control group when compared to the treated group – this could indicate dissimilarity between the two groups	presented on decrease of maternal viral load, but no mention of linking this with compliance/adher ence/time on treatment, and no detailed results provided	Always the case	HBV DNA level and/or HBeAg not described for both treated and control groups. Similar infant prophylaxis between treated and control groups.	Laboratory assays described, with indication of record linkage (results viewed retrospectively in medical records)	Yes	described because it was a retrospective cohort study (or listed as such) where the infants needed to have had test results at the testing time-point (this is therefore misclassified as a cohort study, and has a high risk of bias for loss to follow up)	(high)
Wu Q (2015)	At least somewhat representativ e of the average HBV- infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Fairly detailed data provided on maternal viral load decrease. >80% of women taking treatment had >2 log decrease in viral load compared to none of the controls.	★ Always the case	★★ Comparable for DNA level and comparable HBeAg positive. Same regimen for infant immunoprophylaxis	↓ Laboratory assays described in detail with indication that testing (and viewing of medical records, was done by study personnel)	☆ Yes	<80% follow up for both treated and control groups	8 (low)
Liu Y (2016)	4	*	Some limited data presented on	*	*	*	4	Loss to follow up not mentioned and	6 (high)

	A+ a	Durauna farra	daamaa - C				Vee	flaur about - f	
	At least	Drawn from	decrease of	Always the case	HBV DNA level and	Laboratory assays	Yes	flow-chart of	
	somewhat	the same	maternal viral		HBeAg comparable	described in detail		patients not given.	
	representativ	community	load, but no		between treated and	with indication		This may indicate	
	e of the	(same inclusion	mention of linking		non-treated groups.	that testing (and		omitting of loss to	
	average HBV-	and exclusion	this with		Infant	viewing of medical		followup details	
	infected	criteria also)	compliance/adher		immunoprophylaxis not	records, was done		rather than perfect	
	pregnant		ence/time on		described clearly (no	by study		(100%) retention,	
	woman		treatment, and no		timing of HBIG)	personnel)		and does not allow	
			detailed results					one to assume the	
			provided					latter	
Tan Z (2016)	× ×	None (Arm 1)	Adherence or	*	☆(Arm 1) ☆☆(Arm 2)	*	*	*	6 (high)
		☆ (Arm 2)	compliance to				,		(Arm 1)
	Truly	, (AIII 2)	treatment not	Always the case	Comparable for HBV	Lab testing done	Yes	>80% follow up in	
	representativ	For arm 2 it is	examined, little		DNA level and	centrally as part of		across all treatment	8 (low)
	e of the	drawn from the	data on tracking of		comparable HBeAg	the study,		arms and control	(Arm 2)
	average HBV-	same	viral load decrease		positive for the second	laboratory assays		groups	
	infected	community			treatment arm	for defining infant			
	pregnant	(same inclusion			compared to the control	outcome			
	woman	and exclusion			arm. For the first arm of	described			
		criteria also).			the study they are not				
		However, arm 1			comparable. Same				
		is not			regimen for infant				
		comparable			immunoprophylaxis				
		with the control							
		group							
Chen ZX	*	4	Adherence/compl	☆	*	*	4	Loss to follow up not	6
(2017)	r *		iance not				F -	mentioned and	(high)
(2017)	At least	Drawn from the	mentioned and no	Always the case	Comparable for HBV	Lab testing done	Yes	flow-chart of	1,
	somewhat	same	data presented on		DNA level but more than	centrally as part of		patients not given.	
			1		l	I		I	

	representativ	community	decrease in HBV		10 % points different for	the study,		This may indicate	
	e of the	(same inclusion	DNA levels		HBeAg-positive. Same	laboratory assays		omitting of loss to	
	average HBV-	and exclusion			regimen for infant	for defining infant		follow up details	
	infected	criteria also)			immunoprophylaxis	outcome		rather than perfect	
	pregnant					described		(100%) retention,	
	woman							and does not allow	
								one to assume the	
								latter	
Sun W	*	*	X	4	**	Laboratory assays	\$	Loss to follow up not	7 (low)
(2017)	,					used not well	,	mentioned and	
(/	At least	Drawn from the	HBV DNA changes	Always the case	Comparable for HBV	described	Yes	flow-chart of	
	somewhat	same	specified with		DNA level and			patients not given.	
	representativ	community with	some detail. ~7 log		comparable HBeAg-			This may indicate	
	e of the	same inclusion	decrease in both		positive. Same regimen			omitting of loss to	
	average HBV-	and exclusion	treatment groups		for infant			follow up details	
	infected	criteria.	compared to the		immunoprophylaxis			rather than perfect	
	pregnant	Mentions	control group					(100%) retention,	
	woman	allocation of						and does not allow	
		women into						one to assume the	
		three groups						latter	
He T (2018)	4	な	*	4	**	*	*	Retrospective	8 (low)
	·							cohort mentioned	
	At least	Drawn from the	Detailed	Always the case	Comparable for HBV	Linkage to medical	Yes	but no loss to follow	
	somewhat	same	information on		DNA level and	records		up described, no	
	representativ	community with	reduction of viral		comparable HBeAg-			mention of how	
	e of the	same inclusion	load given,		positive. Same regimen			there was perfect	
	average HBV-	and exclusion	including specific		for infant			retention	
	infected	criteria	data for each		immunoprophylaxis				
			woman (every one						

	pregnant		had a -6 to -8 log						
	woman		reduction)						
Hu Y (2018)	*	*	*	な	**	*	*	Only~70% follow up between 7 and 12	8 (low)
	At least somewhat representativ e of the average HBV- infected pregnant woman	Drawn from the same community with same inclusion and exclusion criteria	Detailed info on reduction of viral load given, only ~5% of women in the treated group did not have a reduction below 2x10^7 log	Always the case	Comparable for HBV DNA level and comparable HBeAg- positive. Same regimen for infant immunoprophylaxis	Lab testing done centrally as part of the study, laboratory assays for defining infant outcome described	Yes	months (although some others were included and tested at 13–14 months not actually completely lost to follow up)	
Sheng QJ	*	*	*	*	**	*	*	A	9 (low)
(2018a)	At least somewhat representativ e of the average HBV- infected pregnant woman	Drawn from the same community with same inclusion and exclusion criteria	Mentions careful monitoring of HBV DNA level for checking maternal adherence/changi ng treatment regimen when needed	Always the case	Comparable for HBV DNA level and comparable HBeAg- positive. Same regimen for infant immunoprophylaxis	Lab testing done centrally as part of the study, laboratory assays for defining infant outcome described	Yes	>80% follow up in both treatment and control groups	
Sheng QJ (2018b)	At least somewhat representativ e of the average HBV- infected	★ Drawn from the same community with same inclusion and exclusion criteria	★ Mentions that all treated women received 8 weeks of therapy. Provides detailed information on	★ Always the case	Comparable for HBV DNA level. HBeAg comparability not clear as they only give the proportion overall of women who were HBeAg	★ Lab testing done centrally as part of the study, laboratory assays for defining infant	★ Yes	No description of any loss to follow up or confirmation that there was no loss to follow up	7 (low)

pregnant	decrease in HBV	positive.	Same regime	en	outcome		
woman	DNA level for	for	infa	nt	described		
	treated cohort	immunop	prophylaxis				

^aRisk of bias assessments should be classified as being either low (\geq 7) or high (<7) by the Newcastle–Ottawa scale

B. Chinese language observational studies

	00			Demonstration					
		Selection of		that outcome of	Comparability of		Was follow up	Adequacy	Total
	Representative	the non-		interest was not	cohorts on the	Assessment	long enough	of follow	number of
	-ness of the	exposed	Ascertainment	present at	basis of the	of	for outcomes	up of	stars (risk of
Study (year)	exposed cohort	cohort	of exposure	baseline	design or analysis	outcomes	to occur	cohorts	bias)ª
Tan J (2019)	☆ At least	*Drawn from	≭ Valid method	★Always the case	★Comparable for	*Laborator	₩Yes	No statement	7 (low)
	somewhat	the same	was used to		HBV DNA levels at	y methods		on LFU	
	representative of	community	ascertain		baseline but HBeAg	described in			
	the average HBV-	(same inclusion	adherence to the		serostatus not	detail (which			
	infected pregnant	and exclusion	antiviral therapy		described. Same	assay used),			
	woman	criteria also)	(decrease in viral		regimen for infant	indicating use			
			load levels		immunoprophylaxis	of a central			
			subsequent to the		at birth	laboratory			
			treatment)			and/or record			
						linkage			
Chen QR	₩ At least	*Drawn from	No description	★Always the case	₩¥Same HBeAg	No description	₩Yes	No statement	6 (high)
(2018)	somewhat	the same			serostatus and	•		on LFU	
	representative of	community			comparable HBV				
	the average HBV-	(same inclusion			DNA levels at				
					baseline. Same				

	infected pregnant	and exclusion			regimen for infant				
	woman	criteria also)			immunoprophylaxis				
					at birth				
Ding XP (2018)	☆ At least	*Drawn from	≭ Valid method	★Always the case	₩¥Same HBeAg	No description	₩Yes	No statement	7 (low)
	somewhat	the same	was used to		serostatus and			on LFU	
	representative of	community	ascertain		comparable HBV				
	the average HBV-	(same inclusion	adherence to the		DNA levels at				
	infected pregnant	and exclusion	antiviral therapy		baseline. Same				
	woman	criteria also)	(decrease in viral		regimen for infant				
			load levels		immunoprophylaxis				
			subsequent to the		at birth				
			treatment)						
Li ZY (2018)	*	な	★ Valid method	な	☆ ★Comparable	4	な	None	8 (low)
								reported	
	At least	Drawn from	was used to	Always the case	for HBeAg	Indication of	Yes (always	(retrospecti	
	somewhat	the same	ascertain		serostatus and HBV	record linkage	the case)	ve)	
	representative of	community	adherence to the		DNA level. Same	(results			
	the average HBV-	(same inclusion	antiviral therapy		regimen for infant	viewed			
	infected pregnant	and exclusion	(decrease in viral		immunoprophylaxis	retrospectivel			
	woman	criteria also)	load levels			y in medical			
			subsequent to the treatment)			records)			
T: (2010)								No	7/1)
Tian JH (2018)	≯ At least	★Drawn from	No description	★Always the case	☆☆ Same	★Laboratory	⊀¥Yes	statement	7 (low)
	somewhat	the same			threshold for HBV	methods		on LFU	
	representative of	community			DNA level and same	described in			
	the average HBV-	(same inclusion			HBeAg serostatus	detail (which			
	infected pregnant	and exclusion			used. Same regimen	assay used),			
	woman	criteria also)			for infant	indicating use			

						immunoprophylaxis	of a central			
						at birth	laboratory			
							and/or record			
							linkage			
Zhang	BF	⊀ At least	☆ Drawn from	≯ Valid method	★Always the case	₩ Same HBeAg	No description	₩Yes	No statement	6 (high)
(2018)		somewhat	the same	was used to		serostatus but			on LFU	
		representative of	community	ascertain		different thresholds				
		the average HBV-	(same inclusion	adherence to the		for HBV DNA level.				
		infected pregnant	and exclusion	antiviral therapy		Same regimen for				
		woman	criteria also)	(decrease in viral		infant				
				load levels		immunoprophylaxis				
				subsequent to the		at birth				
				treatment)						
0	GH	∤ At least	☆ Drawn from	≭ Valid method	★Always the case	₩¥Same HBeAg	No description	₩Yes	No statement	7 (low)
(2018)		somewhat	the same	was used to		serostatus and same			on LFU	
		representative of	community	ascertain		thresholds for HBV				
		the average HBV-	(same inclusion	adherence to the		DNA level. Same				
		infected pregnant	and exclusion	antiviral therapy		regimen for infant				
		woman	criteria also)	(decrease in viral		immunoprophylaxis				
				load levels		at birth				
				subsequent to the						
				treatment)						
Zheng	JC	∤ At least	★Drawn from	No description	★Always the case	☆ ☆Same HBeAg	*Laboratory	₩Yes	No statement	7 (low)
(2018)		somewhat	the same			serostatus and same	methods		on LFU	
		representative of	community			thresholds for HBV	described in		511 21 0	
		the average HBV-	(same inclusion			DNA level. Same	detail (which			
						regimen for infant	assay used),			

		infected pregnant	and exclusion			immunoprophylaxis	indicating use			
		woman	criteria also)			at birth	of a central			
							laboratory			
							and/or record			
							linkage			
Chen	WJ	≮ At least	☆ Drawn from	≮ Valid method	Always the case	☆☆ Same HBeAg	☆ Laboratory	₩Yes	No statement	8 (low)
(2017)		somewhat	the same	was used to		serostatus and same	methods		on LFU	
		representative of	community	ascertain		thresholds for HBV	described in		0.1. 2. 0	
		the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
		infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
		woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
				load levels		at birth	of a central			
				subsequent to the			laboratory			
				treatment)			and/or record			
							linkage			
Feng	XM	⊀At least	★Drawn from	↓ Valid method	★Always the case	★★Same HBeAg	≮Laboratory	₩Yes	No	8 (low)
(2017)		somewhat				serostatus and same	methods		statement	
		representative of		was used to ascertain		thresholds for HBV	described in		on LFU	
			community (same inclusion	adherence to the		DNA level. Same	detail (which			
		the average HBV-	•							
		infected pregnant		antiviral therapy		regimen for infant	assay used),			
		woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
				load levels		at birth	of a central			
				subsequent to the			laboratory			
				treatment)			and/or record			
							linkage			

Huang Q	≵ At least	★Drawn from	≯ Valid method	Always the case	☆ ‡XSame HBeAg	No	≮γ _{es}	No	7 (low)
(2017)	somewhat	the same	was used to		serostatus and same	description		statement on LFU	
	representative of	community	ascertain		thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the		DNA level. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth				
			subsequent to the						
			treatment)						
Jiang S (2017)	⊀ At least	★Drawn from	∜ Valid method	★Always the case	🛠 Comparable for	No description <mark>a</mark>	₩Yes	No statement	6 (high)
	somewhat	the same	was used to		HBV DNA level but			on LFU	
	representative of	community	ascertain		HBeAg serostatus				
	the average HBV-	(same inclusion	adherence to the		not described. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth				
			subsequent to the						
			treatment)						
Li CM (2017)	*	*	≭ Valid method	*	★Comparable for	Laboratory assays used	*	No statement	6 (high)
	At least	Drawn from	was used to	Always the case	HBV DNA level but	not well	Yes (always	on LFU	
	somewhat	the same	ascertain		HBeAg serostatus	described	the case)		
	representative of	community	adherence to the		not described. Same				
	the average HBV-	(same inclusion	antiviral therapy		regimen for infant				
	infected pregnant	and exclusion	(decrease in viral		immunoprophylaxis				
	woman	criteria also)	load levels						
			subsequent to the						
			treatment)						

Li YH (2017)	☆ At least	★Drawn from	★Valid method	Always the case	☆ ☆Same HBeAg	≮Laboratory	₩Yes	No	8 (low)
	somewhat	the same	was used to		serostatus and same	methods		statement	
	representative of	community	ascertain		thresholds for HBV	described in		on LFU	
	the average HBV	(same inclusion	adherence to the		DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth	of a central			
			subsequent to the			laboratory			
			treatment)			and/or record			
						linkage			
Liu J (2017)	≯ At least	*Drawn from	≭ Valid method	★Always the case	≭ ≭Same HBeAg	No description	≮Yes	There is a description	7 (low)
	somewhat	the same	was used to		serostatus and	description		of LFU for	
	representative of	community	ascertain		comparable for HBV			the	
	the average HBV-	(same inclusion	adherence to the		DNA levels. Same			exposed	
	infected pregnant	and exclusion	antiviral therapy		regimen for infant			but not for	
	woman	criteria also)	(decrease in viral		immunoprophylaxis			the control	
			load levels		at birth			group	
			subsequent to the						
			treatment)						
Luo DX (2017)	☆ At least	*Drawn from	★Valid method	Always the case	Comparable for HBV DNA levels but	No description	₩Yes	No statement	5 (high)
	somewhat	the same	was used to		HBeAg serostatus			on LFU	
	representative of	community	ascertain		not described.				
	the average HBV-	(same inclusion	adherence to the		Regimen for infant				
	infected pregnant	and exclusion	antiviral therapy		immunoprophylaxis				
	woman	criteria also)	(decrease in viral		at birth not clearly				
			load levels		described				

			subsequent to the						
Pan YC (2017)	t least	★Drawn from	treatment) No description	★Always the case	₩¥Same HBeAg	≭ Laboratory	₩Yes	⊀ Subject	8 (low)
	somewhat representative of	the same community		·	serostatus and same thresholds for HBV	methods described in		s lost to follow up	
	the average HBV infected pregnant woman	(same inclusion and exclusion criteria also)			DNA level. Same regimen for infant immunoprophylaxis	detail (which assay used), indicating use		unlikely to introduce bias, small	
					at birth	of a central laboratory and/or record linkage		number lost	
Wang J (2017)	★At least somewhat representative of the average HBV infected pregnant woman	↓ Drawn from the same community (same inclusion and exclusion criteria also)	★Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★Always the case	★Same thresholds for HBV DNA level but HBeAg serostatus not described. Same regimen for infant immunoprophylaxis at birth	No description	≮Yes	No statement on LFU	6 (high)
Xiao XH (2017)	At least somewhat representative of the average HBV- infected pregnant woman	*Drawn from the same community (same inclusion and exclusion criteria also)	★Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral	☆Always the case	Same thresholds for HBV DNA level but HBeAg serostatus not described. Regimen for infant immunoprophylaxis	★Laboratory methods described in detail (which assay used), indicating use	₩Yes	There is a description of LFU for the exposed but not for	6 (high)

			load levels		at birth not clearly	of a central		the control	
			subsequent to the		described	laboratory		group	
			treatment)			and/or record			
						linkage			
Chen F (2016)	★At least	★Drawn from	☆ Valid method	★Always the case	★ Same HBeAg	☆ Laboratory	☆ Yes	No statement	7 (low)
	somewhat	the same	was used to		sero-status and	methods		of LFU	
	representative of	community(sam	ascertain		same thresholds for	described in			
	the average HBV-	e inclusion and	adherence to the		HBV DNA level.	detail (which			
	infected pregnant	exclusion	antiviral therapy (decrease in viral		Regimen for infant	assay used),			
	woman	criteria also)	load levels		immunoprophylaxis at birth not clearly	indicating use of a central			
			subsequent to the		described	laboaratory			
			treatment)		described	and/or record			
			treatment)			linkage			
					Comparable for HBV	lilikage		No	<i>c</i> (1 : 1)
Gao P (2016)	☆ At least	★Drawn from	₩Valid method	★Always the case	DNA levels but	★Laboratory	☆ Yes	statement	6 (high)
	somewhat	the same	was used to		HBeAg serostatus	methods		on LFU	
	representative of	community	ascertain		not described.	described in			
	the average HBV-	(same inclusion	adherence to the		Regimen for infant	detail (which			
	infected pregnant	and exclusion	antiviral therapy		immunoprophylaxis	assay used),			
	woman	criteria also)	(decrease in viral		at birth not clearly	indicating use			
			load levels		described	of a central			
			subsequent to the			laboratory			
			treatment)			and/or record			
						linkage			
			M	Always the case	Comparable for	₩Laboratory	₩Yes	No	7 (low)
Hu WH (2016)	☆ At least	★Drawn from	★Valid method	Always the case			123	statement	
Hu WH (2016)	≮At least somewhat	[‡] XDrawn from the same	★Valid method was used to	Always the case	HBV DNA levels but	methods	1103	statement on LFU	

	the average HBV-	(same inclusion	adherence to the		not described. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth	of a central			
			subsequent to the			laboratory			
			treatment)			and/or record			
						linkage			
Li N (2016)	⊀ At least	★Drawn from	≭ Valid method	Always the case	★Comparable for	No description	≮γ _{es}	No statement	6 (high)
	somewhat	the same	was used to		HBV DNA levels but			on LFU	
	representative of	community	ascertain		HBeAg serostatus				
	the average HBV-	(same inclusion	adherence to the		not described. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth				
			subsequent to the						
			treatment)						
Liu XB (2016)	₩ At least	≭ Drawn from	≭ Valid method	★Always the case	₩¥Same HBeAg	No description	₩Yes	No statement	7 (low)
	somewhat	the same	was used to		serostatus and same			of LFU	
	representative of	community	ascertain		thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the		DNA level. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth				
			subsequent to the						
			treatment)						

Qiu B (2016)	⊀ At least	☆ Drawn from	≭ Valid method	Always the case	✿Same thresholds	≮ Laboratory	≮γ _{es}	No statement	7 (low)
	somewhat	the same	was used to		for HBV DNA level	methods		of LFU	
	representative of	community	ascertain		but HBeAg	described in			
	the average HBV-	(same inclusion	adherence to the		serostatus not	detail (which			
	infected pregnant	and exclusion	antiviral therapy		described. Same	assay used),			
	woman	criteria also)	(decrease in viral		regimen for infant	indicating use			
			load levels		immunoprophylaxis	of a central			
			subsequent to the		at birth	laboratory			
			treatment)			and/or record			
						linkage			
Shen ML	⊀ At least	★Drawn from	¥Valid method	*Always the case	Same thresholds for HBV DNA level but	☆ Laboratory	₩Yes	No statement	6 (high)
(2016)	somewhat	the same	was used to		HBeAg serostatus	methods		on LFU	
	representative of	community	ascertain		not described.	described in			
	the average HBV-	(same inclusion	adherence to the		Regimen for infant	detail (which			
	infected pregnant	and exclusion	antiviral therapy		immunoprophylaxis	assay used),			
	woman	criteria also)	(decrease in viral		at birth not clearly	indicating use			
			load levels		described	of a central			
			subsequent to the		405011204	laboratory			
			treatment)			and/or record			
						linkage			
Tian RH (2016)	≮ At least	☆ Drawn from	No description	Always the case	☆☆ Same HBeAg	No	⊀γes	No	6 (high)
	somewhat	the same			serostatus and same	description		statement	
	representative of	community			thresholds for HBV			on LFU	
	the average HBV-	(same inclusion			DNA level. Same				
	infected pregnant	and exclusion			regimen for infant				
		criteria also)							
	woman				immunoprophylaxis				
					at birth				

Wang B (2016)	*	*	∜ Valid method	*	☆☆ Comparable	*	*	No	8 (low)
	At least	Drawn from the same	was used to ascertain	Always the case	for HBeAg serostatus and HBV	Laboratory assays	Yes (always the case)	statement on LFU	
	representative of	community	adherence to the		DNA level. Same	described	the case)		
	the average HBV-	(same inclusion	antiviral therapy		regimen for infant	acochoca			
	infected pregnant	and exclusion	(decrease in viral		immunoprophylaxis				
	woman	criteria also)	load levels		F - F /				
			subsequent to the						
			treatment)						
Wang DM	⊀ At least	★Drawn from	≮ Valid method	Always the case	★★Same HBeAg	☆ Laboratory	☆ Yes	No statement	8 (low)
(2016)	somewhat	the same	was used to		serostatus and same	methods		on LFU	
	representative of	community	ascertain		thresholds for HBV	described in			
	the average HBV	(same inclusion	adherence to the		DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth	of a central			
			subsequent to the			laboaratory			
			treatment)			and/or record			
						linkage			
Wang HB	≮ At least	★Drawn from	≭ Valid method	Always the case	✿Comparable for	No description	≮Yes	No statement	6 (high)
(2016)	somewhat	the same	was used to		HBV DNA level but	-		on LFU	
	representative of	community	ascertain		HBeAg serostatus				
	the average HBV-	(same inclusion	adherence to the		not described. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth				

			subsequent to the						
			treatment)						
Zhang R (2016)	☆ At least	★Drawn from	No description	Always the case	HBeAg serostatus	No	₩Yes	No	4 (high)
				, ,.	and threshold for	description	,	statement	
	somewhat	the same			HBV DNA level not			on LFU	
	representative of	community			described. Regimen				
	the average HBV-	(same inclusion			for infant				
	infected pregnant	and exclusion			immunoprophylaxis				
	woman	criteria also)			at birth not clearly				
					described				
Chen CY (2015)	⊀ At least	*Drawn from	₩Valid method	★Always the case	☆ Same HBeAg	*Laboratory	₩Yes	No statement	7 (low)
	somewhat	the same	was used to		serostatus and same	methods		on LFU	
	representative of	community	ascertain		thresholds for HBV	described in			
	the average HBV-	(same inclusion	adherence to the		DNA level. Regimen	detail (which			
	infected pregnant	and exclusion	antiviral therapy		for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth not clearly	of a central			
			subsequent to the		described	laboratory			
			treatment)			and/or record			
						linkage			
Cui ZL (2015)	≯ At least	*Drawn from	¥Valid method	★Always the case	₩¥Same HBeAg	*Laboratory	₩Yes	No statement	8 (low)
	somewhat	the same	was used to		serostatus and same	methods		on LFU	
	representative of	community	ascertain		thresholds for HBV	described in			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth	of a central			

			subsequent to the			laboratory			
			treatment)			and/or record			
						linkage			
Deng Y (2015)	⊀ At least	*Drawn from	₩Valid method	★Always the case	Same thresholds	No description	₩Yes	No statement	6 (high)
	somewhat	the same	was used to		for HBV DNA level			on LFU	
	representative of	community	ascertain		but HBeAg				
	the average HBV-	(same inclusion	adherence to the		serostatus not				
	infected pregnant	and exclusion	antiviral therapy		described. Same				
	woman	criteria also)	(decrease in viral		regimen for infant				
			load levels		immunoprophylaxis				
			subsequent to the		at birth				
			treatment)						
Ge YL (2015)	≮ At least	*Drawn from	≮ Valid method	Always the case	☆ ≵Same HBeAg	No description	₩Yes	No statement	7 (low)
	somewhat	the same	was used to		sero-status and			on LFU	
	representative of	community(sam	ascertain		same thresholds for				
	the average HBV-	e inclusion and	adherence to the		HBV DNA level.				
	infected pregnant	exclusion	antiviral therapy		Same regimen for				
	woman	criteria also)	(decrease in viral		infant				
			load levels		immunoprophylaxis				
			subsequent to the		at birth				
			treatment)						
Lou JJ (2015)	⊀At least	*Drawn from	₩Valid method	★Always the case	₩¥Same HBeAg	☆ Laboratory	₩Yes	No statement	8 (low)
	somewhat	the same	was used to		serostatus and same	methods		on LFU	
	representative of	community	ascertain		thresholds for HBV	described in			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral			indicating use			

Sum WH (2015) *At least *Drawn from community the average H8V- server as labor (same inclusion antiviral therapy woman *Availul includiu the same criteria also) *Availul includiu adverage h8V- server as labor (decrease in viral load *Availul includiu adverage h8V- (decrease in viral load *Availul includiu adverage h8V- (decrease in viral load *Availul method *Availul method *Availul server as load *Availul includiu munoprophylaxis at birth *Availul method *Availul server as load *Availul s				load levels		immunoprophylaxis	of a central			
Ren N (2015)KAt is least representative of the average HBV ummanKorawn from the same to community (same inclusion and exclusion oriteria also)Kvalid method ascertain adherence to the antiviral therapy (same inclusion and exclusion oriteria also)Kvalid method adherence to the antiviral therapy (same inclusion and exclusion oriteria also)Kvalid method adherence to the antiviral therapy (same inclusion and exclusion oriteria also)Kvalid method adherence to the and exclusion oriteria also)Kvalid method adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)Kvalid method adherence to the and/or record linkageKvalid method adsoratory and/or record linkageKvalid method adsoratory and/or record linkageKvalid methods the same adsoratory and/or record linkageNo statement on LFU8 (low) statement on LFUVUN WH (2015)KAt least somewhat methods somewhat methods infected pregnant womanKvalid method and exclusion and exclusion and exclusion and exclusion and exclusion community (decrease in viral load levelsKalways the case stressed karse in decrease subsequent to the treatment)Kalways the case serostatus and same thresholds for HBV adsoratory adjor record linkageNo statement on LFU8 (low) statement on LFUVAING 2015)KAt least methodsKalways the case subsequent to the treatment subsequent to the treatmentKalways the case serostatus and same at birth serostatus and same thresholds for				subsequent to the		at birth	laboratory			
Nen N (2015)*At teast*Exprawn from the same community (same inclusion and exclusion retresentative of the average HBV- infected pregnant woman*Exprawn from sacetrain and exclusion antiviral therapy (decrease in viral load levels subsequent to the treatment)*Always the case the shore of the average the solution and exclusion and exclusion and exclusion infected pregnant woman*Always the case the solution and exclusion antiviral therapy (decrease in viral load levels subsequent to the treatment)*Always the case the solution and exclusion and exclusion and intriviral therapy (decrease in viral load levels subsequent to the treatment)*Always the case the same the same treatment)*Always the case the same the same the same treatment)*Always the case the same the same treatment)*No terester subsequent to the treatment)& (Iow) terester the same the same the same community treatment)*Always the case the same the same the same thresholds for HBV*Always the case terester the same thresholds for HBV thresholds for HBV*No terester terester terester terester terester terester terester terester to the average HBV- infected pregnant woman*Always the case the same terester te				treatment)			and/or record			
Mat least *Drawn from *Valid *Always the case *X same HBeAg *Laboratory *Kyes statement on LFU statement on LFU somewhat the same was used to ascertain adderence to the on tivinal therapy (decrease in viral load immunoprophylaxis at birth methods #Kyes *Kyes No statement on LFU statement on LFU Sum WH (2015) *At the sorae HBV- (same inclusion woman *Kyes *Kyes No statement on LFU %Iow) Sum WH (2015) *At the same representative of community *Kyes No statement on LFU %Iow) Sum WH (2015) *At the same voman *Kyes *Kyes No statement infected pregnant on LFU %Iow) Sum WH (2015) *At the same voman *Kyes *Korawn from criteria also) *Kyes *Korawn from voman *Kuabi *Korawn from representative of community *Kuabi *Kabi *Korawn from on LFU *Korawn from voman							linkage			
representative of the average HBV- infected pregnant womancommunity criteria also)ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the trestment)thresholds for HB DNA level. Same detail (which regimen for infant assay used), indicating use of a central laboratory and/or record linkageMo statement8 (low)SUN WH (2015)*At least somewhat representative of the average HBV- (same inclusion and exclusion or infant insubsequent to the treatment)*Always the case a service**Same HBeAg service at birth*Laboratory ad/or record linkage*No statement on LFU8 (low)SUN WH (2015)*At least somewhat representative of the average HBV- (same inclusion and exclusion antiviral therapy (decrease in viral) load levels subsequent to the treatment)*Always the case a terving**Same HBeAg serostatus and same at birth**YesNo statement on LFU8 (low)Namg 2015)*At least somewhat the same somewhat**Drawn from the same was used to ascertain adherence to the antiviral therapy (decrease in viral) load levels subsequent to the treatment)**Always the case the same at birth**Asame HBeAg serostatus and same methods**YesNo statement on LFU8 (low)Namg somewhat 2015)**At least somewhat**Valid method was used to a subsequent to the treatment)**Always the case serostatus and same at birth**Asame HBeAg serostatus and same methods*Yes<	Ren N (2015)	⊀At least	★Drawn from	☆ Valid method	★Always the case	☆☆ _{Same} HBeAg	★Laboratory	₩Yes	-	8 (low)
Image: heaverage HBV: woman(same inclusion and exclusion criteria also)adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)DNA level. Same regimen for infant assay used), indicating use of a central linkagedetail (which assay used), indicating use of a central linkageMo statement8 (low)SUN WH (2015)*At least mersentative of the average HBV- infected pregnant woman*Aorawn from the same vasued to adverence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)*Always the case serostatus and same the same vasued to adverence to the attriation adverence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)*Always the case serostatus and same the same vasued to attriation adverence to the attriation adverence to the treatment;*Always the case serostatus and same attriation adverence to the attriation adverence to the attriation adverence to the treatment;*Always the case serostatus and same to the same vasue adverence to the attriation adverence to the treatment;*Always the case serostatus and same to the value adverence to the value adverence to the attriation adverence to the treatment;*Always the case serostatus and same to the value adverence to the value adverence to the attriation adverence to the the same vasue adverence to the the value adverence to the the value adverence to the the val		somewhat	the same	was used to		serostatus and same	methods		on LFU	
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womancriteria also)(decrease in viral load levels subsequent to the treatment)immunoprophylaxis at birthindicating use of a central laboratory and/or record linkageNo statement on LFU8 (low)Sun WH (2015)*At least somewhat representative of the average HBV- linfected pregnant woman*Volid methods*Always the case accertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the trestment)*Always the case accertain adherence to the antiviral therapy (decrease in viral load load levels subsequent to the trestment)*Always the case the same the same accertain adherence to the antiviral therapy (decrease in viral load load levels subsequent to the treatment)*Always the case the same the same the same the same the same trestment*Always the case the same the same the same the same the same the same treatment)*Always the case the same the same <br< td=""><td></td><td>the average HBV-</td><td>(same inclusion</td><td>adherence to the</td><td></td><td>DNA level. Same</td><td>detail (which</td><td></td><td></td><td></td></br<>		the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
Jun WH (2015)*At least somewhat representative of the average HBV- (same inclusion and exclusion criteria also)*Valid method adverage in viral load levels subsequent to the was used to ascertain and verse the same the same community*Always the case ascertain and verse the same infected pregnant woman*Always the case ascertain and exclusion antiviral therapy (decrease in viral load levels subsequent to the treatment)*Always the case ascertain antiviral therapy (decrease in viral load levels subsequent to the treatment)*Always the case ascertain antiviral therapy and/or record limmunoprophylaxis at birth*Always the case asse asse at birth*Alaboratory asse asse at birth*Always the case asse at birth*Always the case asse at birth*Always used, adderence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)*Always the case asse at birth*Always the case serostatus and same at birth*Alaboratory and/or record linkage*Alaboratory serostatus and same the same*Ale least serostatus and same methods*Alaboratory serostatus and same methods*Ala		infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
And least somewhat representative of the average HBV uoman* Drawn from the same community criteria also)* Valid method advence to the antiviral therapy (decrease in viral load levels subsequent to the antiviral therapy the average HBV infected pregnant woman* Drawn from the same community criteria also)* Valid method advence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)* Always the case the same the same to the same to the same the same to the same to		woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
Sun WH (2015)*Atleast*Drawn from the same community somewhat representative of the average HBV- woman*ADia*ADia*Always the case ascertain adherence to the and exclusion criteria also)*Always the case ascertain adherence to the and exclusion criteria also)*Always the case ascertain adherence to the and exclusion criteria also)*Always the case ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)*Always the case accertain at birth*Always the case accertain adportercord linkage*Always the case accertain adportercord laboratory and/or record linkage*Alaboratory accertain adportercord laboratory and/or record linkage*Alaboratory accertain adportercord laboratory and/or record linkage*Alaboratory accertain accertain laboratory adportercord linkage*Alaboratory accertain accertain laboratory adportercord linkage*Alaboratory accertain accertain laboratory adportercord linkage*Always the case accertain accertain laboratory accertain laboratory adportercord linkage*Always the case accertain laboratory adportercord linkage*Always the c				load levels		at birth	of a central			
Sun WH (2015) *At least somewhat representative of the average HBV-infected pregnant woman *Xolid method accrtain adherence to the treatment) *Xolid method accretain adherence to the treatment) *Xolid method accre				subsequent to the			laboratory			
Sun WH (2015) *At least *Drawn from *Valid *Always the case *Always t				treatment)			and/or record			
Main With (2013) KAt least K Drawn from K Valid K Aliways the case K K Same HBeAg K Laboratory K Yes Statement Statement somewhat the same use use <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td>linkage</td><td></td><td></td><td></td></t<>							linkage			
representative of the average HBV, infected pregnant woman community ascertain alderence to the antiviral therapy (decrease in viral load levels subsequent to the treatment) thresholds for HBV described in DNA level. Same detail (which alderence to the antiviral therapy (decrease in viral load levels subsequent to the treatment) immunoprophylaxis at birth indicating use at birth indicating use at birth of a central laboratory and/or record linkage Nang TD 2015) *At least the same was used to *Drawn from the same was used to *Always the case serostatus and same methods *Always the case serostatus and same methods *Alboratory serostatus and same methods *Alboratory serostatus and same methods *Alexapt the serostatus and same methods	Sun WH (2015)	★ At least	★Drawn from	≯ Valid method	★Always the case	★★Same HBeAg	☆ Laboratory	₩Yes	-	8 (low)
Wang 2015)TD *At somewhat*Drawn from the same*Valid was used to*Valid method was used to*Always the case subset to**Always the case serostatus and same**Always the case methods**Always the case serostatus and same**Always the case methods**Always the case methods***Always the case methods*********************************		somewhat	the same	was used to		serostatus and same	methods		on LFU	
infected pregnant womanand exclusion criteria also)antiviral therapy (decrease in viral load levels subsequent to the treatment)regimen for infant immunoprophylaxis at birthassay used), indicating use of a central laboratory and/or record linkagesubsequent of a central laboratory and/or record linkageNo statement8 (low) statementNang 2015)TD somewhat★At te same★ Valid was used to★ Always the case was used to★ ★ Same HBeAg serostatus and same★ YesNo statement on LFU8 (low) statement										
woman criteria also) (decrease in viral load levels subsequent to the treatment) was used to the treatment was used to the was used to the treatment		representative of	community	ascertain		thresholds for HBV	described in			
Nang 2015)TD somewhat★ the same★ xValid was used to★ xValid was used to★ xValid method% xValid method% xValid method% xValid method% xVa										
Ang 2015)TD *At the*Drawn from the*Valid was used to*Always the case the**Same theHaboratory and/or record linkageMo statement8 (low) statement on LFU		the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
Mang TD *At least *Drawn from the same *Valid method was used to *Always the case **Always the		the average HBV- infected pregnant	(same inclusion and exclusion	adherence to the antiviral therapy		DNA level. Same regimen for infant	detail (which assay used),			
Nang TD XAt least XDrawn from XValid Method XAlways the case XAlways the case XAs XAs No 8 (low) 2015) \$		the average HBV- infected pregnant	(same inclusion and exclusion	adherence to the antiviral therapy (decrease in viral		DNA level. Same regimen for infant immunoprophylaxis	detail (which assay used), indicating use			
Wang TD * At least * Drawn from * Valid * Valid * Always the case * * Same * Alboratory * Laboratory * Yes No 8 (low) 2015) somewhat the same was used to to<		the average HBV- infected pregnant	(same inclusion and exclusion	adherence to the antiviral therapy (decrease in viral load levels		DNA level. Same regimen for infant immunoprophylaxis	detail (which assay used), indicating use of a central			
2015) ** At least ** Drawn from ** Valid method ** Always the case ** ** Same HBeAg ** Laboratory ** Yes Statement a somewhat the same was used to serostatus and same methods on LFU		the average HBV- infected pregnant	(same inclusion and exclusion	adherence to the antiviral therapy (decrease in viral load levels subsequent to the		DNA level. Same regimen for infant immunoprophylaxis	detail (which assay used), indicating use of a central laboratory			
somewhat the same was used to serostatus and same methods on LFU		the average HBV- infected pregnant	(same inclusion and exclusion	adherence to the antiviral therapy (decrease in viral load levels subsequent to the		DNA level. Same regimen for infant immunoprophylaxis	detail (which assay used), indicating use of a central laboratory and/or record			
	0	the average HBV- infected pregnant woman	(same inclusion and exclusion criteria also)	adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	DNA level. Same regimen for infant immunoprophylaxis at birth	detail (which assay used), indicating use of a central laboratory and/or record linkage	≮Yes		8 (low)
	Wang TD (2015)	the average HBV- infected pregnant woman ★At least	(same inclusion and exclusion criteria also) ★Drawn from	adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★Always the case	DNA level. Same regimen for infant immunoprophylaxis at birth	detail (which assay used), indicating use of a central laboratory and/or record linkage	≮Yes	statement	8 (low)

	the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth	of a central			
			subsequent to the			laboratory			
			treatment)			and/or record			
						linkage			
Zhang X (2015)	≭ At least	*Drawn from	∜ Valid method	★Always the case	☆☆ Same HBeAg	★ Laboratory	₩Yes	No statement	8 (low)
	somewhat	the same	was used to		serostatus and same	methods		on LFU	
	representative of	community	ascertain		thresholds for HBV	described in			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth	of a central			
			subsequent to the			laboratory			
			treatment)			and/or record			
						linkage			
Chen YL (2014)	No description of the derivation	No description of the	☆ Valid method	Always the case	Comparablefor	No description	≮γ _{es}	No statement	4 (high)
	of the cohort	derivation of	was used to		HBV DNA levels but			on LFU	
		the non-	ascertain		HBeAg serostatus				
		exposed cohort	adherence to the		not described. Same				
			antiviral therapy		regimen for infant				
			(decrease in viral		immunoprophylaxis				
			load levels		at birth				
			subsequent to the						
			treatment)						

Han YP (2014)	∤ At least	☆ Drawn from	≭ Valid method	Always the case	☆ ≵Same HBeAg	No description	≮Yes	No statement	7 (low)
	somewhat	the same	was used to		serostatus and same			on LFU	
	representative of	community	ascertain		thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the		DNA level. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth				
			subsequent to the						
			treatment)						
Liu CY (2014)	☆ At least	Drawn from	≯ Valid method	Always the case	₩¥Same HBeAg	☆ Laboratory	₩Yes	No statement	8 (low)
	somewhat	the same	was used to		serostatus and same	methods		on LFU	
	representative of	community	ascertain		thresholds for HBV	described in			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth	of a central			
			subsequent to the			laboratory			
			treatment)			and/or record			
						linkage			
Yao LF (2014)	≭ At least	☆ Drawn from	≭ Valid method	★Always the case	☆ Same HBeAg	₩Laboratory	₩Yes	No statement	7 (low)
	somewhat	the same	was used to		serostatus and same	methods		on LFU	
	representative of	community	ascertain		thresholds for HBV	described in			
	the average HBV-	(same inclusion	adherence to the		DNA level. Regimen	detail (which			
	infected pregnant	and exclusion	antiviral therapy		for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth not clearly	of a central			
					described	laboratory			

			subsequent to the			and/or record			
			treatment)			linkage			
Yue X (2014)	☆ At least	☆ Drawn from	¥Valid method	★Always the case	₩¥Same HBeAg	No description	₩Yes	≮Comple	8 (low)
	somewhat	the same	was used to		serostatus and same			te follow up	
	representative of	community	ascertain		thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the		DNA level. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth				
			subsequent to the						
			treatment)						
Zhou YJ (2014)	₩ At least	₩ Drawn from	No description	★Always the case	*Comparable	≮ Laboratory	₩Yes	No statement	6 (high)
	somewhat	the same			HBeAg serostatus	methods		on LFU	
	representative of	community(and same thresholds	described in			
	the average HBV-	same inclusion			for HBV DNA level.	detail (which			
	infected pregnant	and exclusion			Regimen for infant	assay used),			
	woman	criteria also)			immunoprophylaxis	indicating use			
					at birth not	of a central			
					described clearly	laboratory			
						and/or record			
						linkage			
Fan LY (2013)	☆ At least	*Drawn from	≭ Valid method	★Always the case	☆ ≵Same HBeAg	No description	☆ Yes	No statement	7 (low)
	somewhat	the same	was used to		serostatus and same			on LFU	
	representative of	community	ascertain		thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the		DNA level. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral						

			load levels		immunoprophylaxis				
			subsequent to the		at birth				
			treatment)						
Jiang XN	≭ At least	☆ Drawn from	≭ Valid method	★Always the case	≭ Same HBeAg	No description	₩Yes	☆ Comple	7 (low)
(2013)	somewhat	the same	was used to		serostatus and same	description		te follow up	
	representative of	community	ascertain		thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the		DNA level. Regimen				
	infected pregnant	and exclusion	antiviral therapy		for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth not				
			subsequent to the		described clearly				
			treatment)						
Zhao J (2013)	⊀ At least	☆ Drawn from	No description	Always the case	≭ ≭Same HBeAg	₩Laboratory	⊀γ _{es}	No	7 (low)
	FAL least	PDrawn from		Maiways the case			ries	statement	
	somewhat	the same			serostatus and same	methods		on LFU	
	representative of	community			thresholds for HBV	described in			
	the average HBV-	(same inclusion			DNA level. Same	detail (which			
	infected pregnant	and exclusion			regimen for infant	assay used),			
	woman	criteria also)			immunoprophylaxis	indicating use			
					at birth	of a central			
						laboratory			
						and/or record			
						linkage			
Peng BA (2012)	⊀ At least	★Drawn from	¥Valid method	Always the case	☆☆ Same HBeAg	No description	⊀¥γes	No statement	7 (low)
	somewhat	the same	was used to		serostatus and same			on LFU	
	representative of	community	ascertain		thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the		DNA level. Same				
			antiviral therapy		regimen for infant				

	infected pregnant	and exclusion	(decrease in viral		immunoprophylaxis				
	woman	criteria also)	load levels		at birth				
			subsequent to the						
			treatment)						
Wang EJ (2012)	≯ At least	☆ Drawn from	≮ Valid method	★Always the case	☆ ≵Same HBeAg	*Laboratory	≮Yes	No statement	8 (low)
	somewhat	the same	was used to		serostatus and same	methods		on LFU	
	representative of	community	ascertain		thresholds for HBV	described in			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth	of a central			
			subsequent to the			laboratory			
			treatment)			and/or record			
						linkage			
Wang WP	⊀ At least	☆ Drawn from	≭ Valid method	★Always the case	₩¥Same HBeAg	₩Laboratory	₩Yes	No statement	8 (low)
(2012)	somewhat	the same	was used to		serostatus and same	methods		on LFU	
	representative of	community	ascertain		thresholds for HBV	described in			
	the average HBV-	(same inclusion	adherence to the		DNA level. Same	detail (which			
	infected pregnant	and exclusion	antiviral therapy		regimen for infant	assay used),			
	woman	criteria also)	(decrease in viral		immunoprophylaxis	indicating use			
			load levels		at birth	of a central			
			subsequent to the			laboratory			
			treatment)			and/or record			
						linkage			
Yao ZC (2011)	⊀ At least	☆ Drawn from	₩ Valid method	Always the case	★Same thresholds	₩Laboratory	≮Yes	No statement	7 (low)
	somewhat	the same	was used to		for HBV DNA level	methods		on LFU	
	representative of	community	ascertain		but HBeAg	described in		-	

	the average HBV-	(same inclusion	adherence to the		serostatus not	detail (which			
	infected pregnant	and exclusion	antiviral therapy		described. Same	assay used),			
	woman	criteria also)	(decrease in viral		regimen for infant	indicating use			
			load levels		immunoprophylaxis	of a central			
			subsequent to the		at birth	laboratory			
			treatment)			and/or record			
						linkage			
Zhang YF	★ At least	★Drawn from	★Valid method	Always the case	☆☆Same HBeAg	No	₩Yes	No	7 (low)
(2010)		, 2.4		, , and jo the cube	, , come moong	description	,	statement	
(2010)	somewhat	the same	was used to		serostatus and same			on LFU	
	representative of	community	ascertain		thresholds for HBV				
	the average HBV-	(same inclusion	adherence to the		DNA level. Same				
	infected pregnant	and exclusion	antiviral therapy		regimen for infant				
	woman	criteria also)	(decrease in viral		immunoprophylaxis				
			load levels		at birth				
			subsequent to the						
			treatment)						

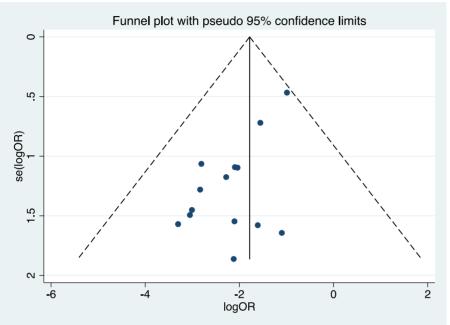
^aRisk of bias assessments should be classified as being either low (≥7) or high (<7) by the Newcastle–Ottawa scale

APPENDIX G: Publication bias assessment (>=10 studies)

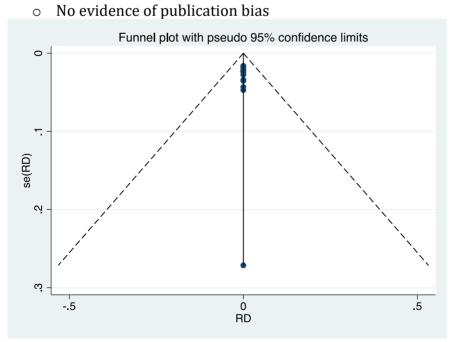
TDF 300 mg

MTCT indicated by HBsAg positivity at 6–12 months, non-RCTs

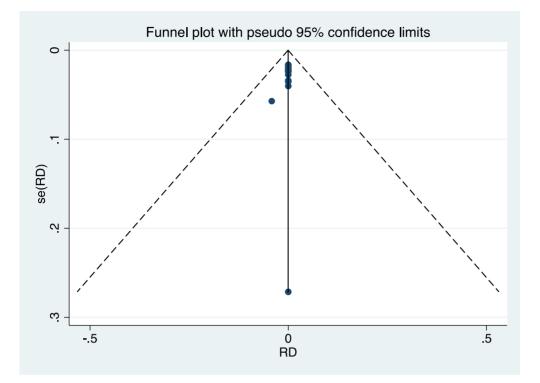
Evidence of possible publication bias/small study effects, Egger test *P* value=0.002



Neonatal deaths, non-RCTs



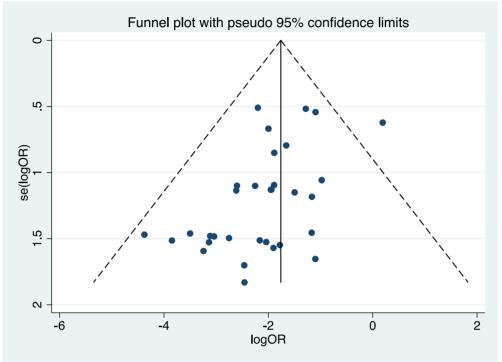
Miscarriages and stillbirths, non-RCTsoNo evidence of publication bias



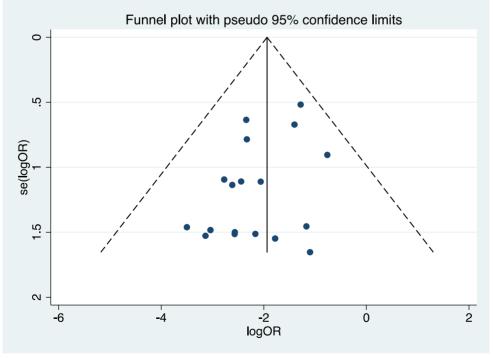
LAM 100-150 mg

MTCT indicated by HBsAg positivity at 6-12 months, non-RCTs

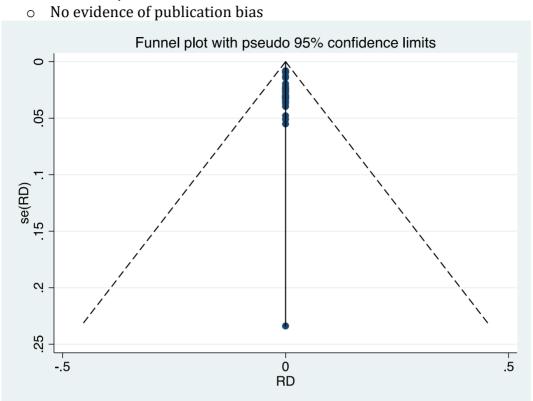
• Evidence of possible publication bias/small study effects, Egger test *P* value=0.002



MTCT indicated by HBV DNA positivity at 6–12 months, non-RCTs o No evidence of publication bias, Egger test *P* value=0.055

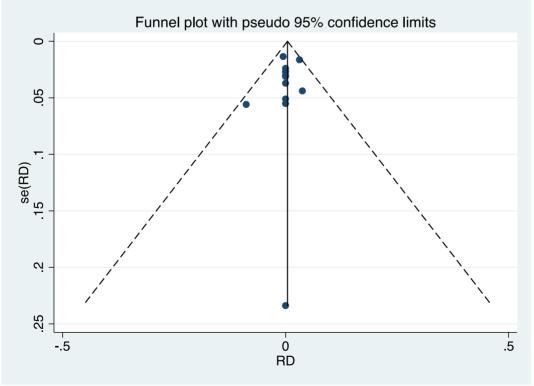


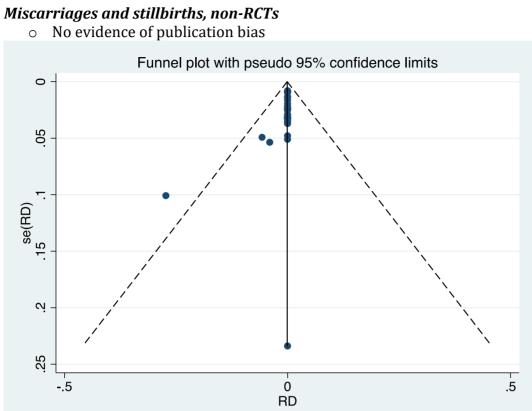
Neonatal deaths, non-RCTs



Congenital abnormalities, non-RCTs

• No evidence of publication bias

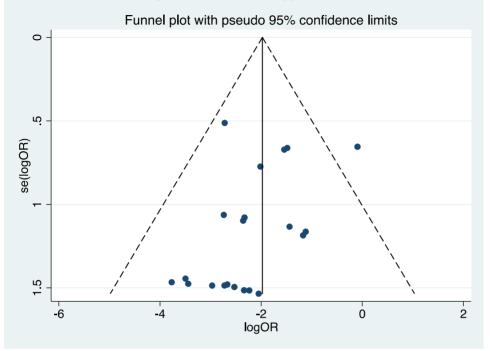




LdT 600 mg

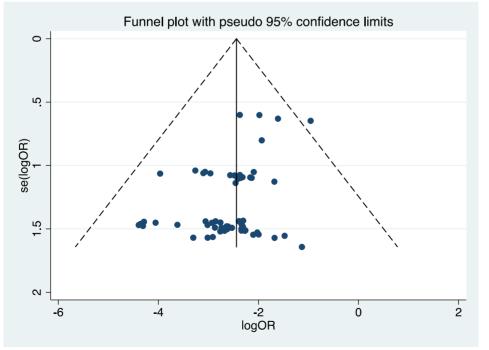
MTCT indicated by HBsAg positivity at 6–12 months, RCTs

• No evidence of publication bias, Egger test *P* value=0.119



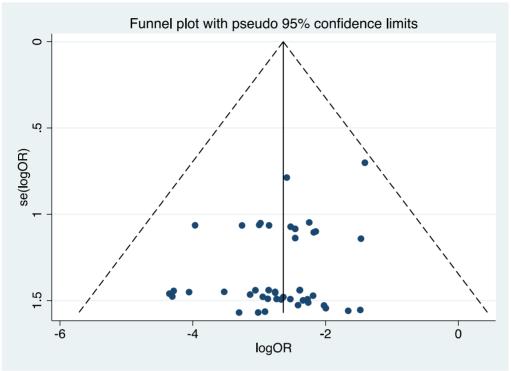
MTCT indicated by HBsAg positivity at 6-12 months, non-RCTs

• Evidence of possible publication bias/small study effects, Egger test *P* value <0.001



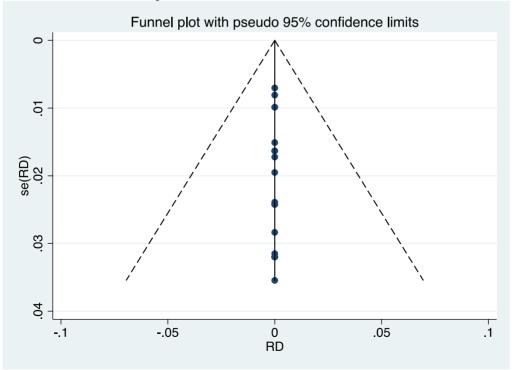
MTCT indicated by HBV DNA positivity at 6–12 months, non-RCTs

• Possible evidence of publication bias/small study effects, Egger test *P* value=0.038

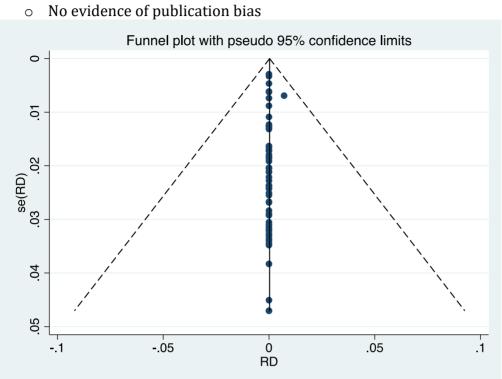


Neonatal deaths, RCTs

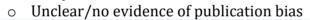
• No evidence of publication bias

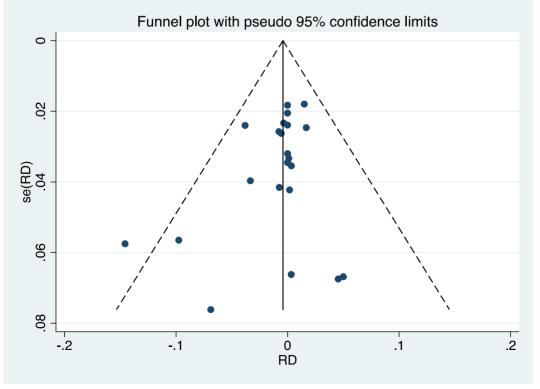


Neonatal deaths, non-RCTs

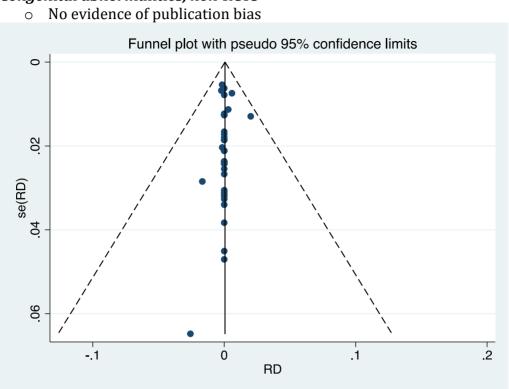


Prematurity, non-RCTs



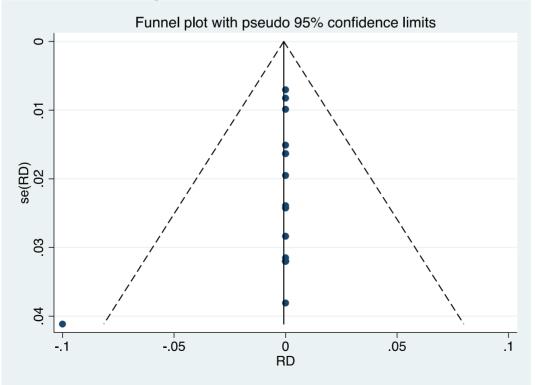


Congenital abnormalities, non-RCTs

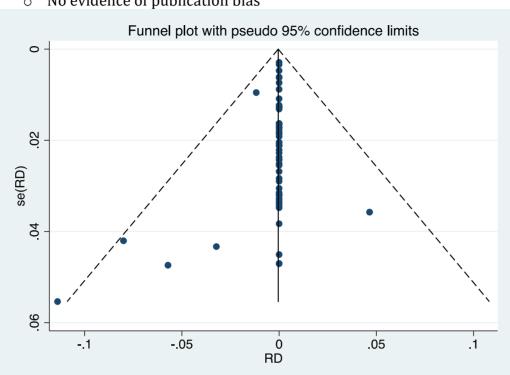


Miscarriages and stillbirths, RCTs

• No evidence of publication bias



Miscarriages and stillbirths, non-RCTs



• No evidence of publication bias

Postpartum haemorrhage, non-RCTs

• Possible evidence of publication bias/small study effects

