World Health Organization

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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Contents

ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
ADV	adefovir dipivoxil
ALT	alanine aminotransferase
ANC	antenatal care
APASL	Asian Pacific Association for the Study of the Liver
CI	confidence interval
CK	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
HCC	hepatocellular carcinoma
HDV	hepatitis D virus
HIV	human immunodeficiency virus
ITT	intention to treat
LdT	telbivudine
MTCT	mother-to-child transmission
OR	odds ratio
PICO	Population, Intervention, Comparison, Outcome
PMTCT	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).

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

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

+: 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
    - 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)
    - emtricitabine (FTC)
    - entecavir (ETV)
    - lamivudine (3TC/LAM)
    - telbivudine (LdT)
    - tenofovir alafenamide fumarate (TAF)
    - TDF.

Comparison

Table 2. Comparison groups considered in PICO1

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

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, 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*** – I^2<30%= "not serious", I^2>=30% and <60%="serious", I^2>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 >=0.5 and <1.0 was considered as "serious", and a range of >=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 I^2 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).

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

	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

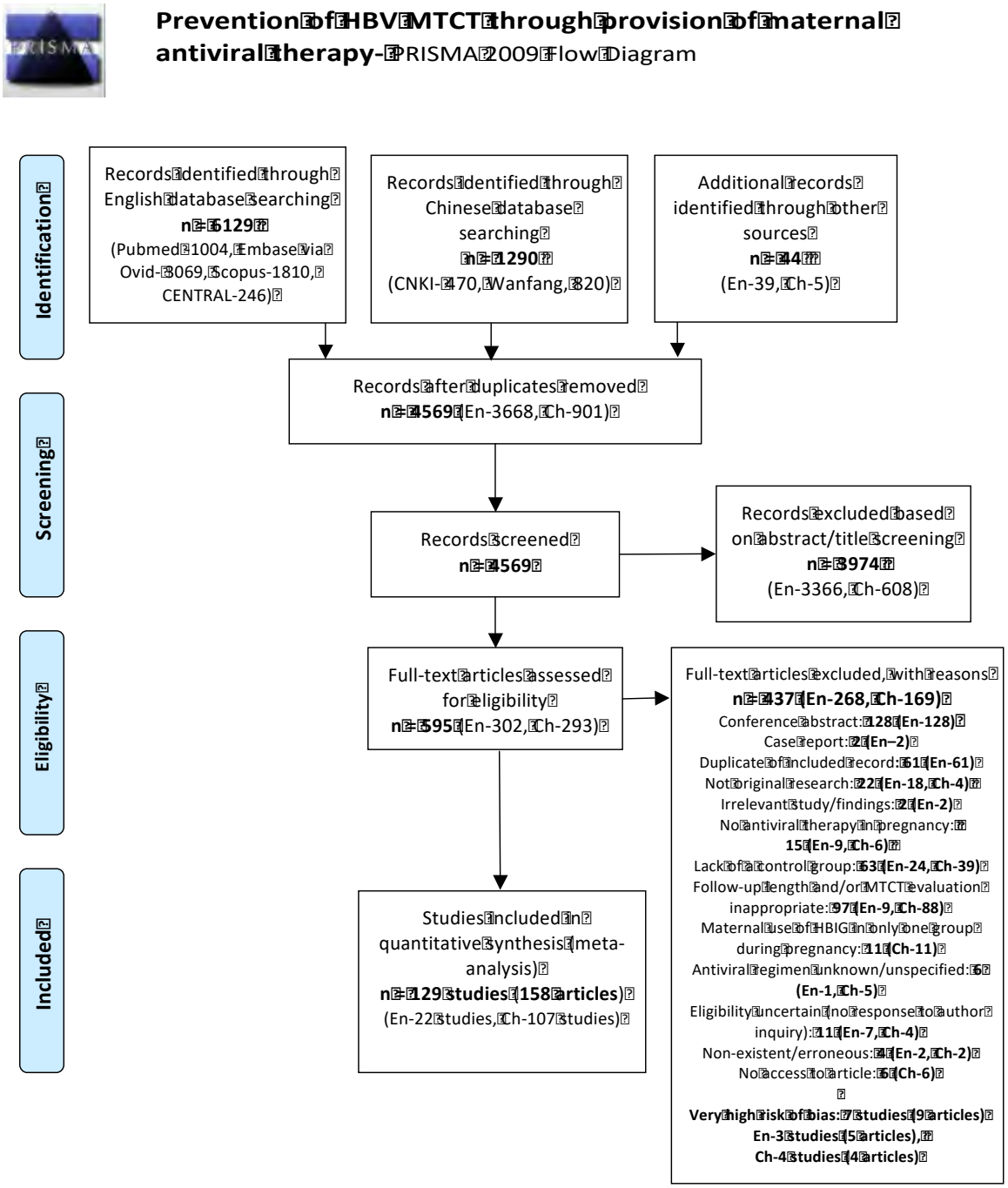
*The total number of original studies is 129. However, this adds up to 146 due to the fact that some studies included multiple types of treatment.

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).

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

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

Fig. 1. PRISMA diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: 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 meta-analysis 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)**.

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

# 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

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).

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

General study details and design				**Treated (TDF 300 mg) pregnant women (tx)**							**Untreated pregnant women (control)**					**Infant treatment (all infants)**		
Author, year	**Country**	**Recruit -ment period**	**HBV DNA level (as inclusion criterion)**	**#**	**Treatment weeks Start during pregnancy | End postpartum**		**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, *timing***	**Birth dose vaccine, *timing***	**Infant vaccine, *dose 1 /dose 2… in months***
Randomized controlled trials (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

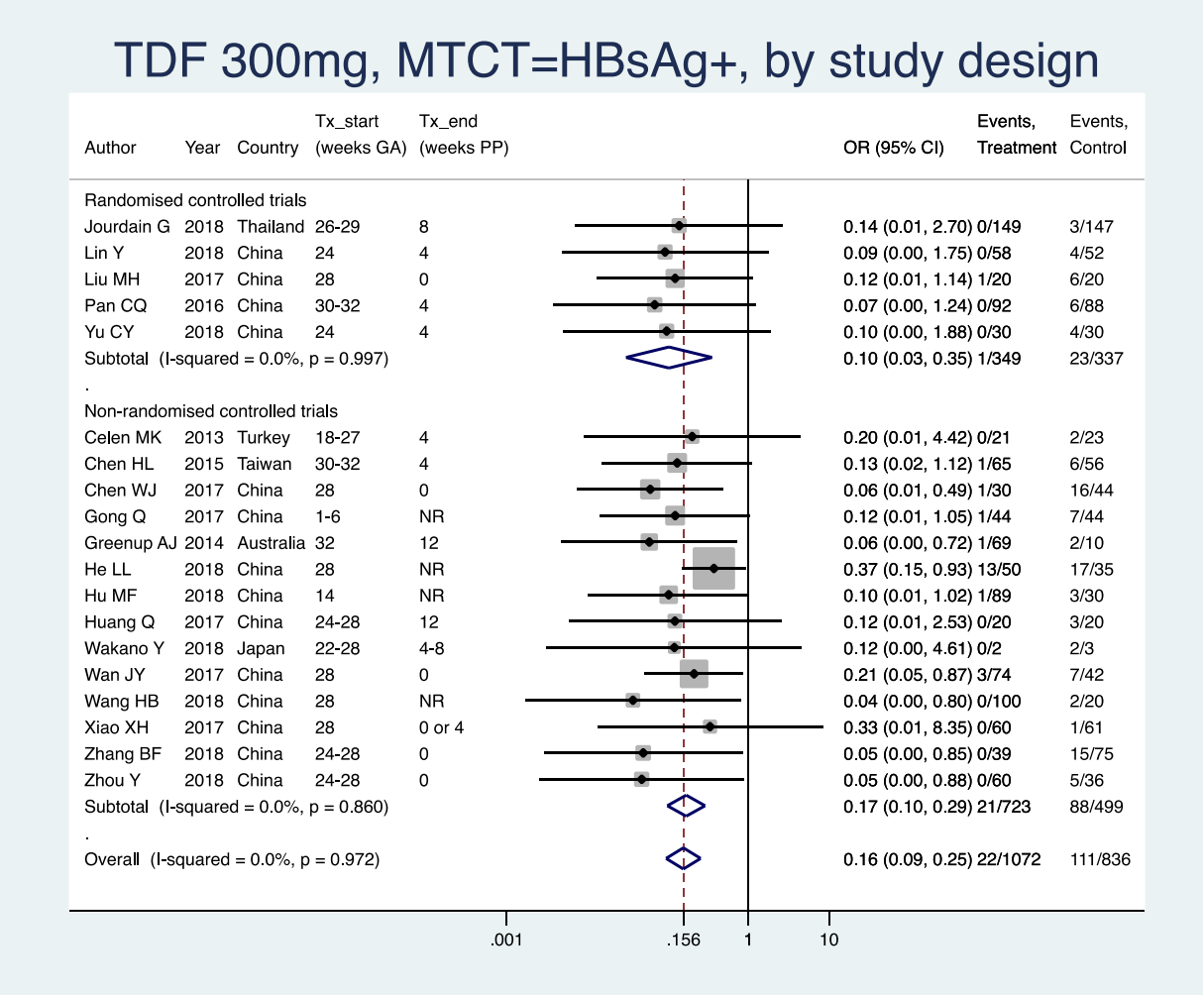
Liu MH, 2017b	China	2014–2016	> 5.3 log10 IU/mL	**20**	28–30	0	30 [22–38]	100	6.5 log10 IU/mL	20	**20**	29 [21–38]	100	6.5 log10 IU/mL	20	Yes, <24 h	Yes, <24 h	Yes, 1/6
Pan CQ, 2016	China	2012–2013	> 5.3 log10 IU/mL	**100**	30–32	4	27.4 ±3.0	100	8.2 log10 IU/mL	92	**100**	26.8 ±3.0	100	8.0 log10 IU/mL	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-randomized controlled 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
Hu MF, 2018	China	2016–2018	>6 log10 IU/mL	**30**	Pre-pregnancy	Various post-pregnancy	28.4 ±1.4	NR	7.4 log10 IU/mL	29	**30**	26.3 ±2.1	NR	7.5 log10 IU/mL	30	Yes, Unclear	Yes, Unclear	Yes, 1/6
				30	14	Various post-pregnancy	23.2 ±3.3	NR	7.5 log10 IU/mL	30						Yes, Unclear	Yes, Unclear	Yes, 1/6
				30	28	Various post-pregnancy	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
Wang HB, 2018	China	2013–2016	NR	**20**	20	NR	NR	NR	7.0 log10 IU/mL	20	**20**	NR	NR	7.2 log10 IU/mL	20	Unclear	Unclear	Unclear
					24	NR	NR	NR	7.1 log10 IU/mL	20						Unclear	Unclear	Unclear
					28	NR	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

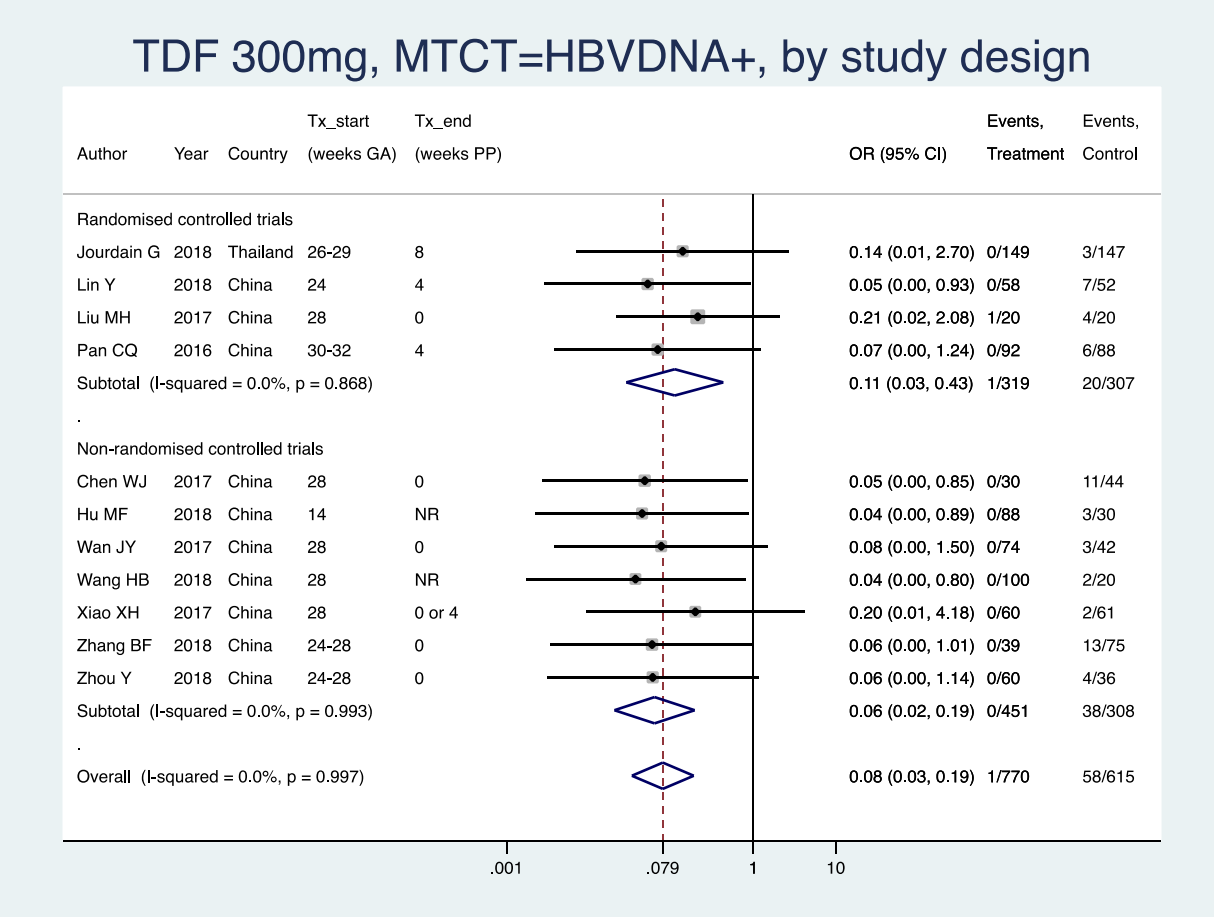
NR=not reported in article *Age and HBV DNA at baseline presented as mean ± SD or median with either (interquartile range [IQR]) or [Range]

Primary efficacy analysis, narrative descriptions and forest plots

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=0.16 (95% CI: 0.10–0.26), *P*<0.001, I^2=0%
     - RCTs only: pooled OR=0.10 (95% CI: 0.03–0.35), *P*<0.001, I^2=0%
     - Non-RCTs only: pooled OR=0.17 (95% CI: 0.10–0.29), *P*<0.001, I^2=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.



2. 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, I^2=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.

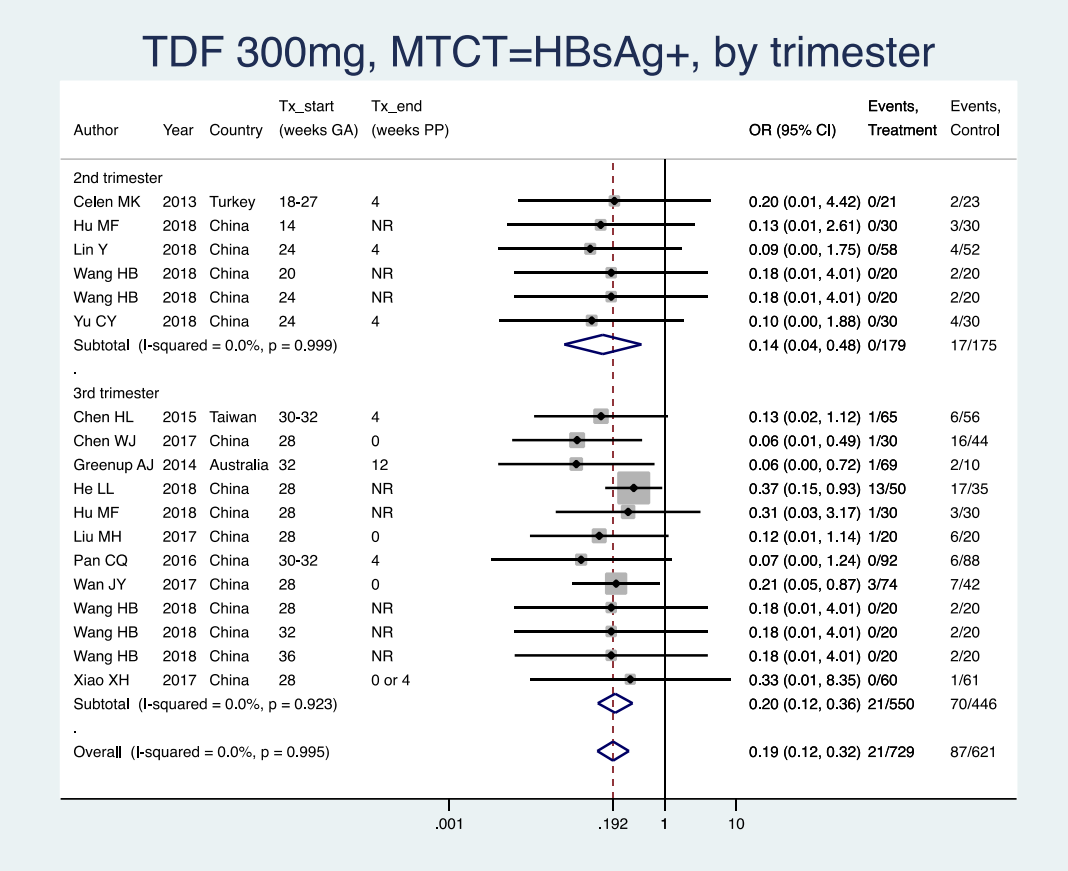


Subgroup analysis

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.

1. 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**

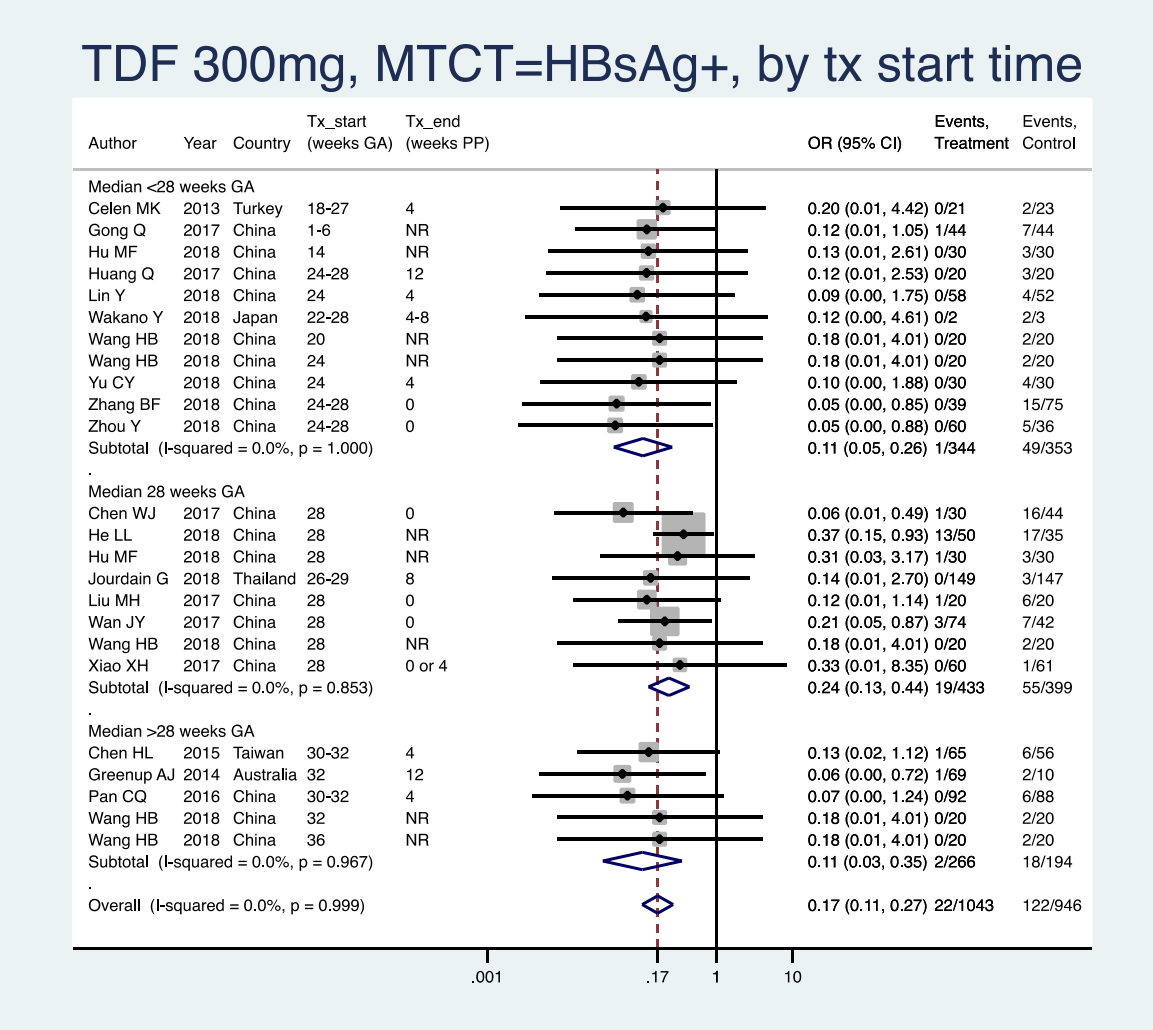
- 1st trimester: not enough studies for meta-analysis (i.e. n<3)
- 2nd trimester: pooled OR=0.14 (95% CI: 0.04–0.48), *P*=0.002, I^2=0.0%
- 3rd trimester: pooled OR=0.21 (95% CI: 0.12–0.36), *P*<0.001, I^2=0.0%
- The *P* value for heterogeneity between 2nd and 3rd trimester was 0.57.



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),

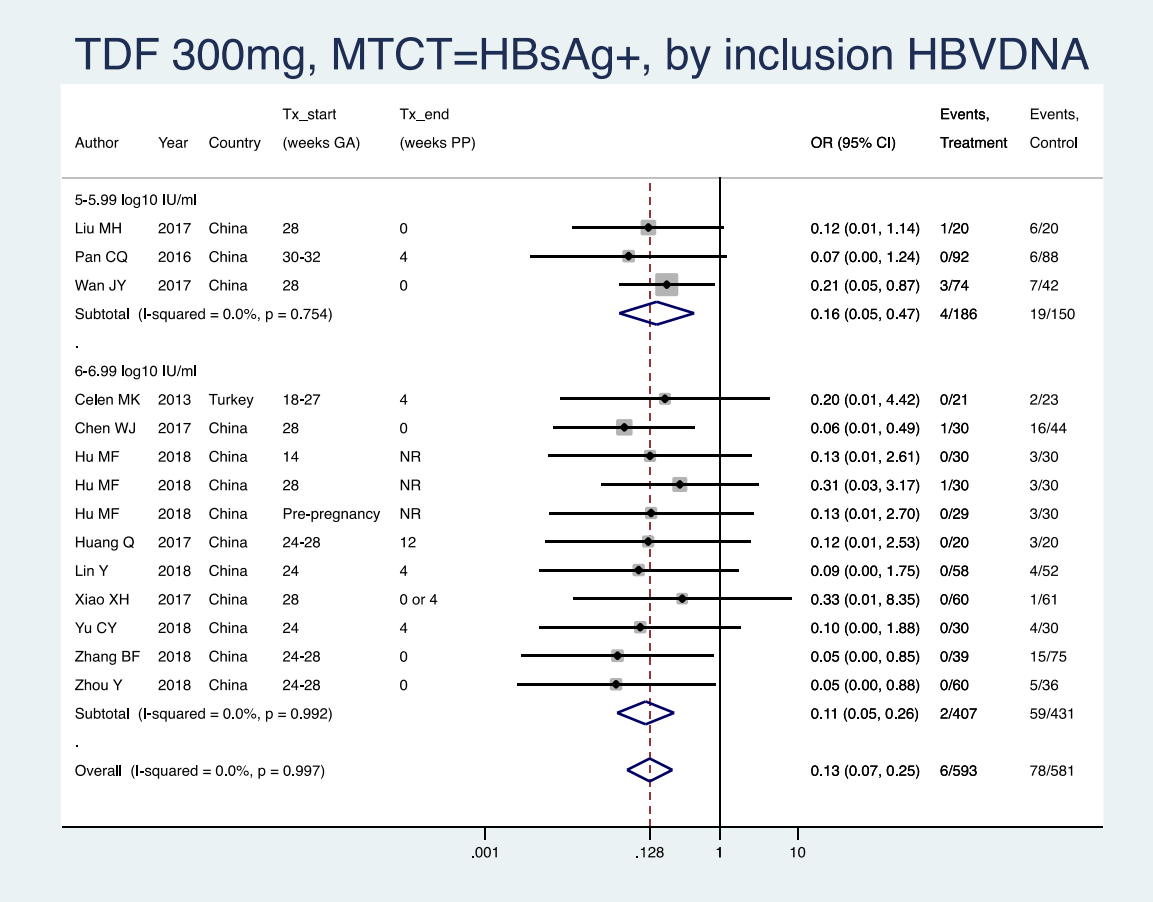
stratified by median weeks' gestation at the time of treatment start (<28 weeks, 28 weeks, >28 weeks)

- <28 weeks: pooled OR=0.11 (95% CI: 0.05–0.26), *P*<0.001, I^2=0.0%
- 28 weeks: pooled OR=0.24 (95% CI: 0.13–0.44), *P*<0.001, I^2=0.0%
- >28 weeks: pooled OR=0.11(95% CI: 0.03–0.35), *P*<0.001, I^2=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).



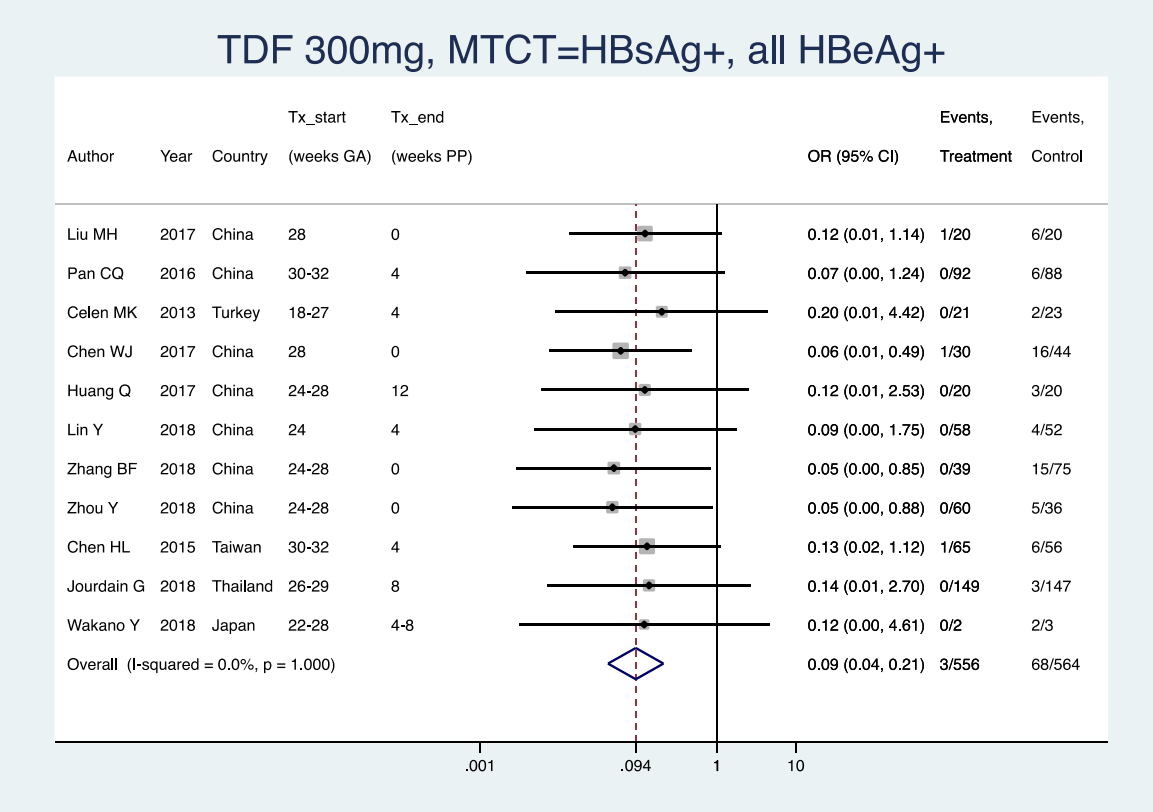
3. PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all study designs merged (i.e. RCT and non-RCT), **stratified by the minimum HBV DNA level specified in the study inclusion criteria**

- >4–4.99 log10 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 log10 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.



4. 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), **only including studies where all women were confirmed HBeAg positive**

- Pooled OR=0.09 (95% CI: 0.04–0.21), *P*<0.001, I^2=0.0%



5. 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).**

Table 7. Infant immunoprophylaxis regimens seen in studies investigating TDF

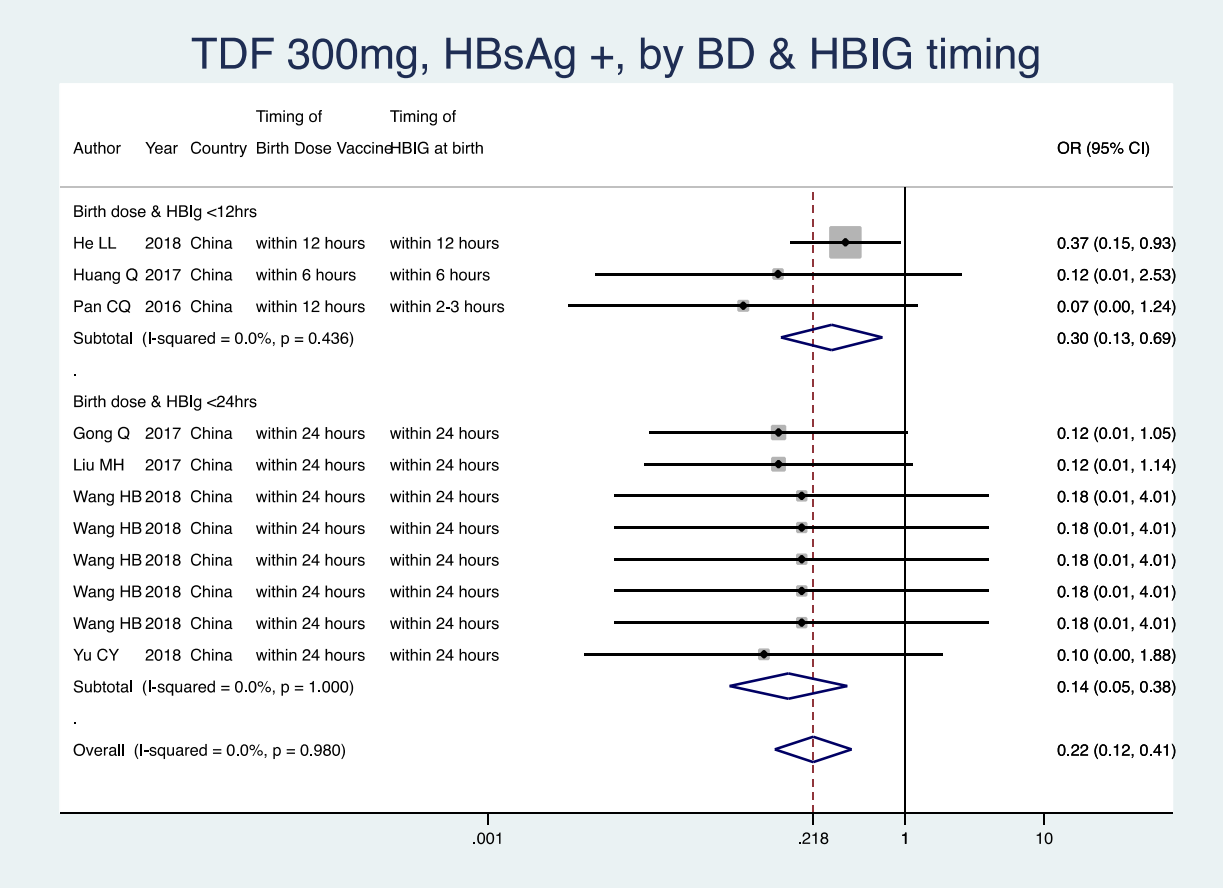
Birth dose vaccine	HBIG at birth	2–4 infant HBV vaccines (not at birth)	# studies (treatment arms)
Yes*	Yes	Yes	15 (21)
Yes	Yes	NR	1 (1) (*Yu CY, 2018*)
No	Yes	Yes	1 (1) (*Celen MK et al., 2013*)
NR	Yes	NR	1 (1) (*Xiao XH et al., 2017*)
NR	NR	NR	1 (1) (*Wan JY et al., 2017*)

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

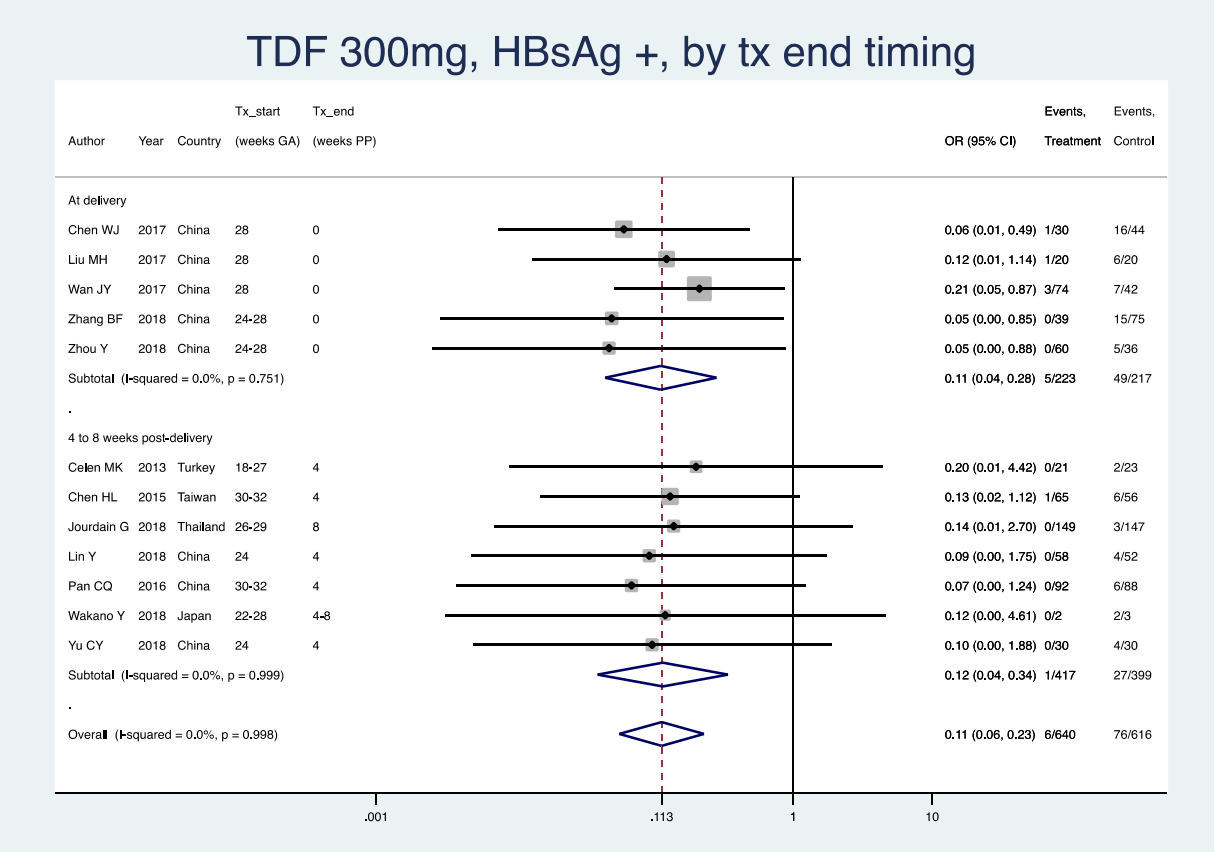
- As most studies provided all of the infant immunoprophylaxis measures (birth dose vaccine, HBIG at birth and subsequent infant vaccinations), stratification by type or combination of infant immunoprophylaxis was not possible in this meta-analysis.

- Therefore, we **<u>stratified by whether or not *both* birth dose vaccine and 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, I^2=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.



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), **stratified by the timing that treatment was discontinued postpartum**
   - At delivery: pooled OR=0.11 (95% CI: 0.04–0.28), *P*<0.001, I^2=0.0%
   - 4–8 weeks postpartum: pooled OR=0.12 (95% CI: 0.04–0.34), *P*<0.001, I^2=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.



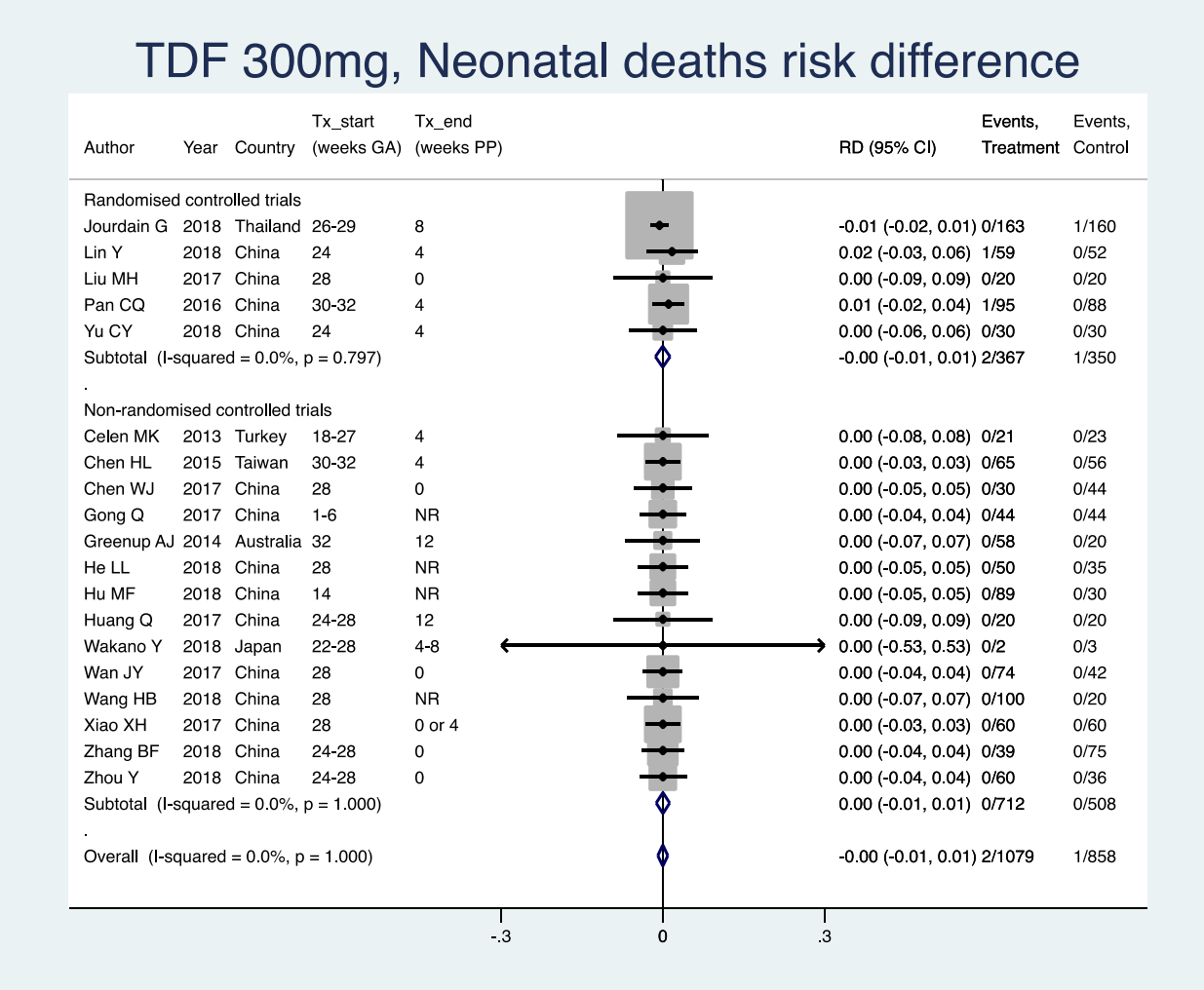
Safety analysis, narrative descriptions and selected forest plots

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.

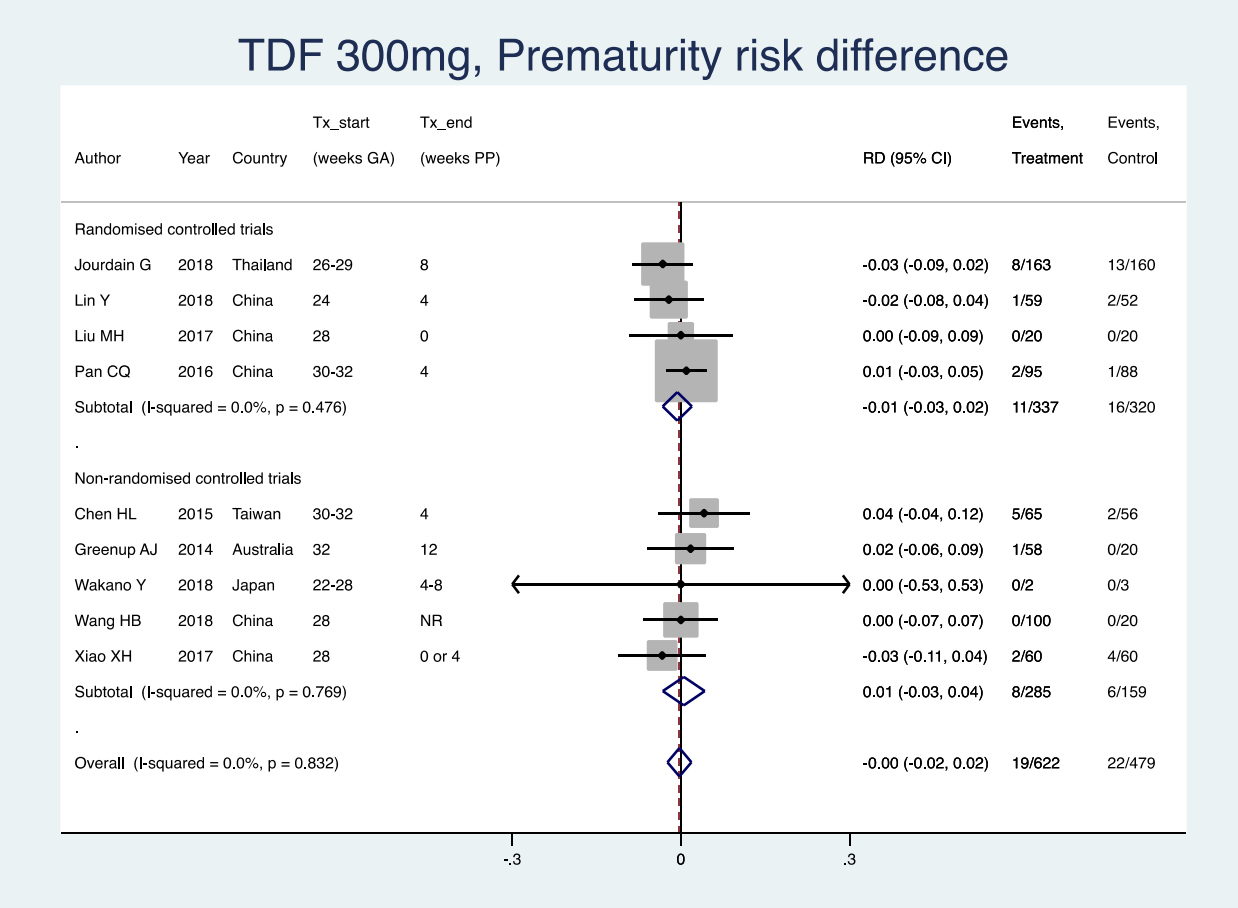
1. **Neonatal deaths** (*death within 28 days of life*)

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 I^2 statistics for the overall pooled OR, as well for RCTs and non-RCTs separately, were all 0%.



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

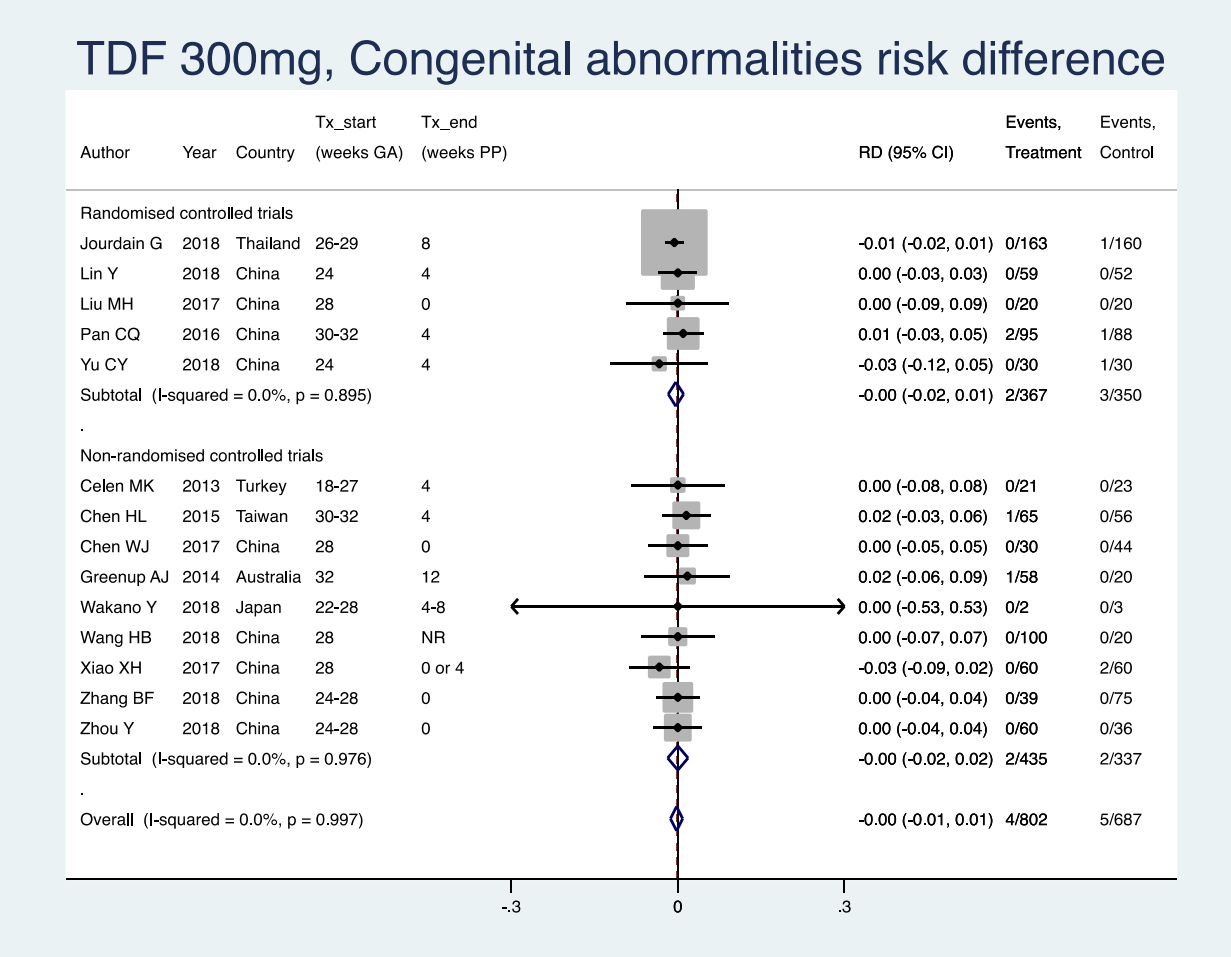
Information on this outcome was available for nine of the 19 included studies that administered TDF to mothers. Within these studies, 19 of 622 (non-weighted average 3.1%) infants whose mothers were treated with TDF during pregnancy were born prematurely, whereas 22 of 479 (non-weighted average 4.6%) 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 I^2 statistics for the overall pooled OR, as well as for RCTs and non-RCTs separately, were all 0%.



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 I^2 statistics for the overall pooled OR, as well as for RCTs and non-RCTs separately, were all 0%.



4. **Bone mineral density**

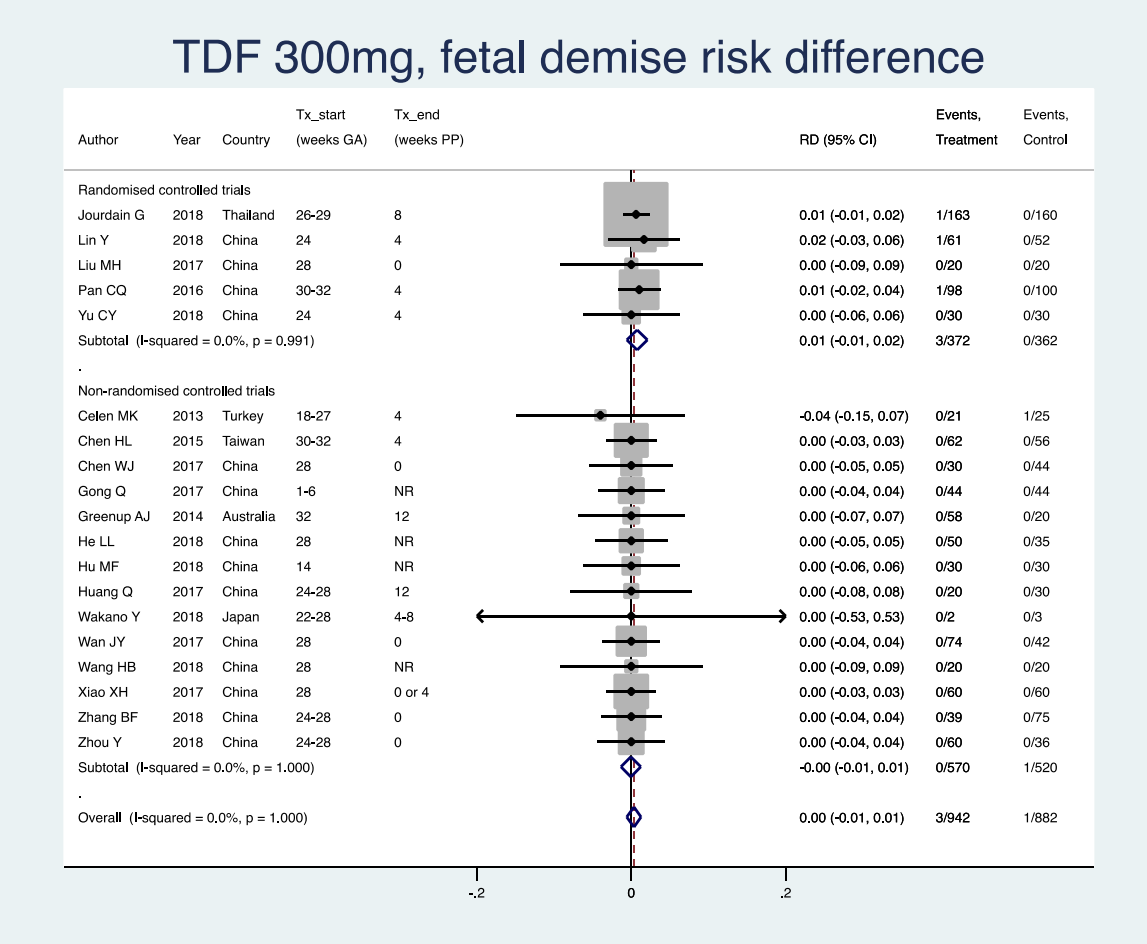
This outcome was investigated only for one of the 19 included studies, an RCT, that administered TDF to mothers. In this study, infant lumbar spine bone mineral density was measured in 62 infants from the treatment group, and 53 infants from the control group at 1 year of age (i.e. not the entire original 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.

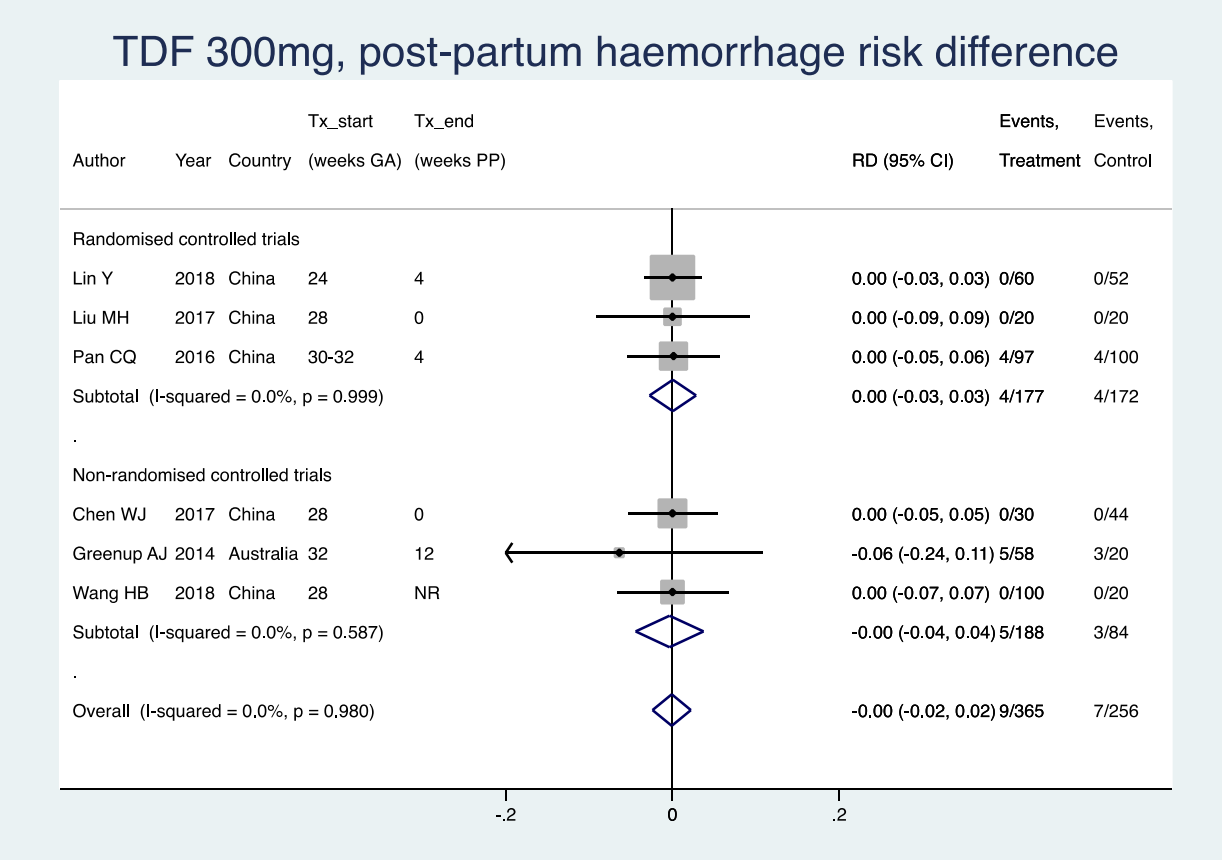
1. **Fetal demise** (miscarriage [<28 weeks], stillbirth [>=28 weeks])

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 I^2 statistics for the overall pooled risk difference estimate, and RCTs and non-RCTs separately, were all 0%.



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 I^2 statistics for the overall pooled risk difference estimates, as well as for RCTs and non-RCTs separately, were all 0%.



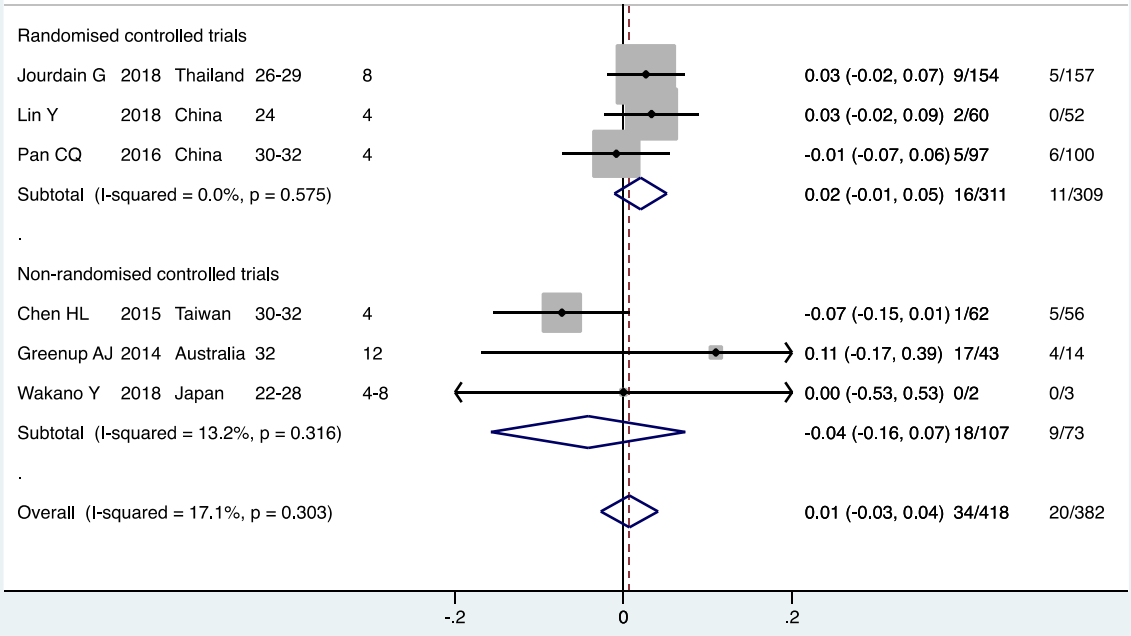
3. **Antiviral resistance**

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 (non-weighted 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. I^2=0%), however, in non-RCTs and in the overall pooled risk difference estimate, there was an I^2 of 13.2% and 17.1%, respectively.

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)

Number of studies	Design	Quality assessment						Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	
HBsAg positivity 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 safety: neonatal deaths												
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 safety: prematurity												
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 safety: congenital abnormalities												
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 safety: bone mineral 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/cm²** (−0.019 to 0.007 g/cm²); p=0.38)	Low[k]
Maternal safety: miscarriage and stillbirth												
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[l]
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: postpartum haemmorhage												
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 flare after treatment discontinuation												
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)	Very low[q]

[a]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[b]Downgrading due to possible publication bias/small study effects, upgrading due to magnitude of effect.
[c]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[d]Upgrading due to magnitude of effect
[e]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[f]No upgrading or downgrading
[g]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[h]No upgrading or downgrading
[i]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[j]No upgrading or downgrading
[k]Downgrading due to inability to examine certain elements (e.g. inconsistency), and for imprecision due to the fact that there was only one RCT included.
[l]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[m]No upgrading or downgrading
[n]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[o]No upgrading or downgrading
[p]Downgrading due to imprecision
[q]Downgrading 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).

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

# 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

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).

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

General study details and design				Treated (TDF 300 mg) pregnant women (tx)							Untreated pregnant women (control)					Infant treatment (all infants)		
Author, year	**Country**	**Recruit -ment period**	**HBV DNA level (inclusion)**	**#**	**Treatment weeks Start during pregnancy | End postpartum**		**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, *timing***	**Birth dose vaccine, *timing***	**Non-birthdose vaccine, *dose 1 /dose 2… in months***
Randomized controlled trials (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

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, Philippines	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-randomized controlled trials (non-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	27.4±4.6 (low HBV DNA group)25.7 ±4.3 (diagnosed too late for tx)	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

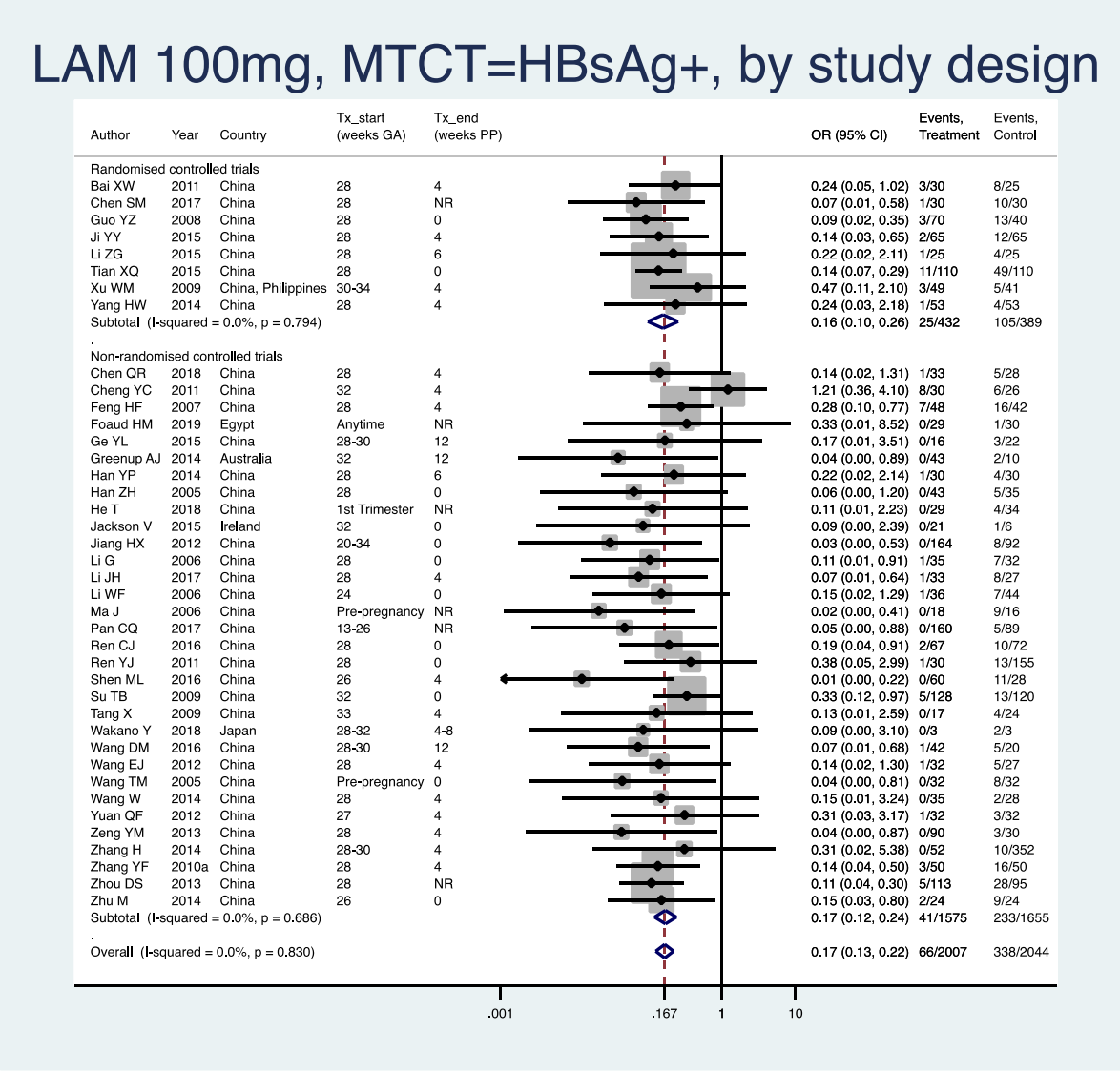
He T, 2018	China	2008–2016	NR	27	1st trimester	NR	29.2±2.9	74	6.3 log10 IU/mL	29	35	29.0±3.6	80	6.25 log10 IU/mL	34	Yes, <6 h	Yes, <12 h	Yes, 1/6
Jackson V, 2015	Ireland	2007–2012	7.2 log10 IU/mL	36	32	0	26 (16–40)	100	8.1 log10 IU/mL	21	9	NR	100	NR	6	Yes, <2–3 h	Yes, <2–3 h	Yes, 2/4/6
Jiang HX, 2012	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, 2017	China	2008–2015	5.3 log10 IU/mL	66	13–26	NR	27.5±3.8	100	6.5 log10 IU/mL	66	89	27.1±4.2	100	6.6 log10 IU/mL	89	Yes, <6 h	Yes, <12 h	Yes, 1/6
				94	28–30	NR	27.5±3.8	100	6.5 log10 IU/mL	94								
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
Zeng YM, 2013	China	2008–2010	4.3 log10 IU/mL	30	28	0	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	4	NR	100	6.6 log10 IU/mL	30								
				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, 2013	China	2009–2012	5.3 log10 IU/mL	49	20	NR	27.4±6.7	NR	6.8 log10 IU/mL	49	95	29.2±6.1	NR	6.9 log10 IU/mL	95	Yes, <12 h	Yes, at birth	Yes, 1/6
				64	28	NR	28.1±5.3	NR	6.7 log10 IU/mL	64								
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

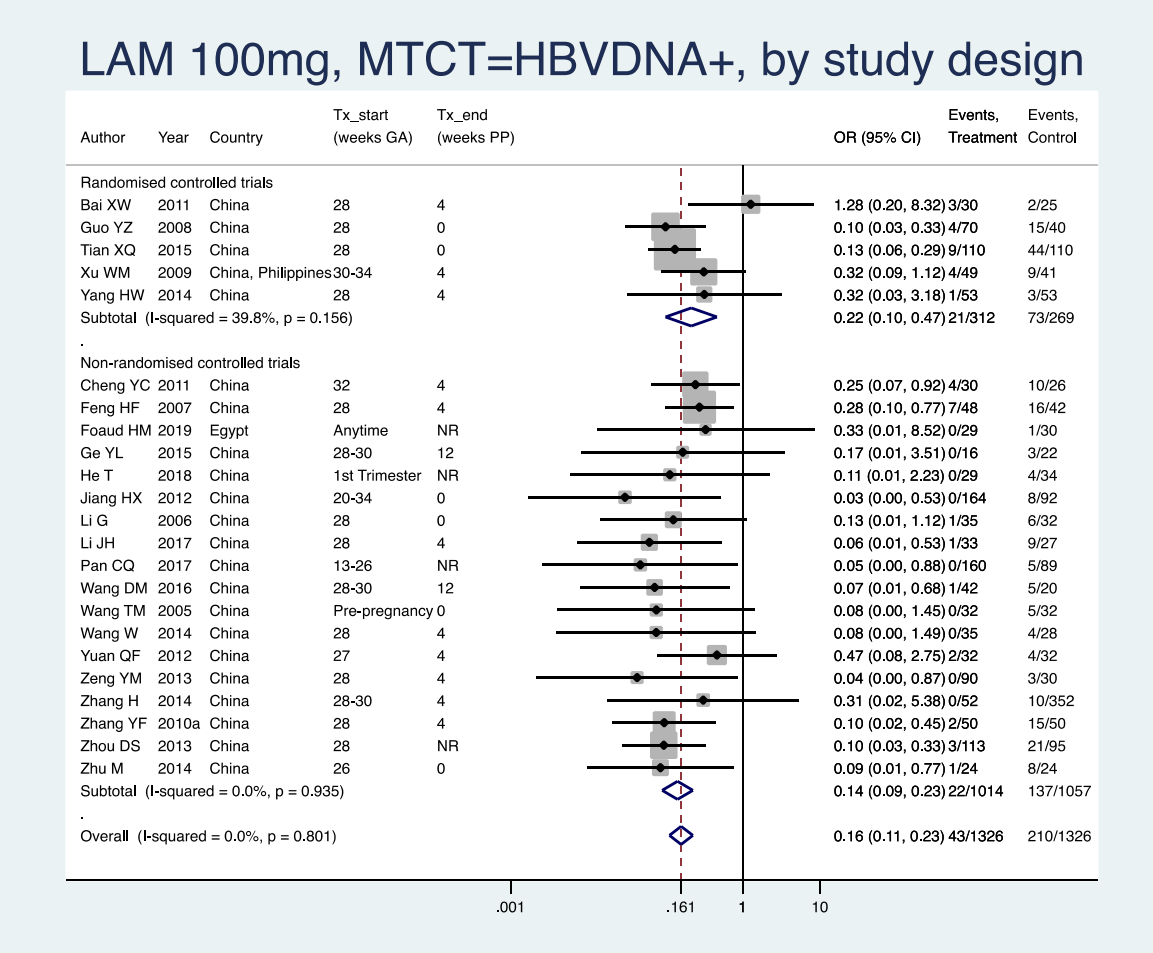
NR=not reported in article *Age and HBV DNA at baseline presented as mean ± SD or median with either (IQR) or [range]

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, I^2=0%
     - RCTs only: pooled OR=0.16 (95% CI: 0.10–0.26), *P*<0.001, I^2=0%
     - Non-RCTs only: pooled OR=0.17 (95% CI: 0.12–0.24), *P*<0.001, I^2=0%
     - When looking at heterogeneity between RCTs and non-RCTs, we arrive at a *P* value of 0.80, indicating no difference between the estimates.



2. 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, I^2=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, I^2=0%
     - When looking at heterogeneity between RCTs and non-RCTs, we arrive at a *P* value of 0.47.



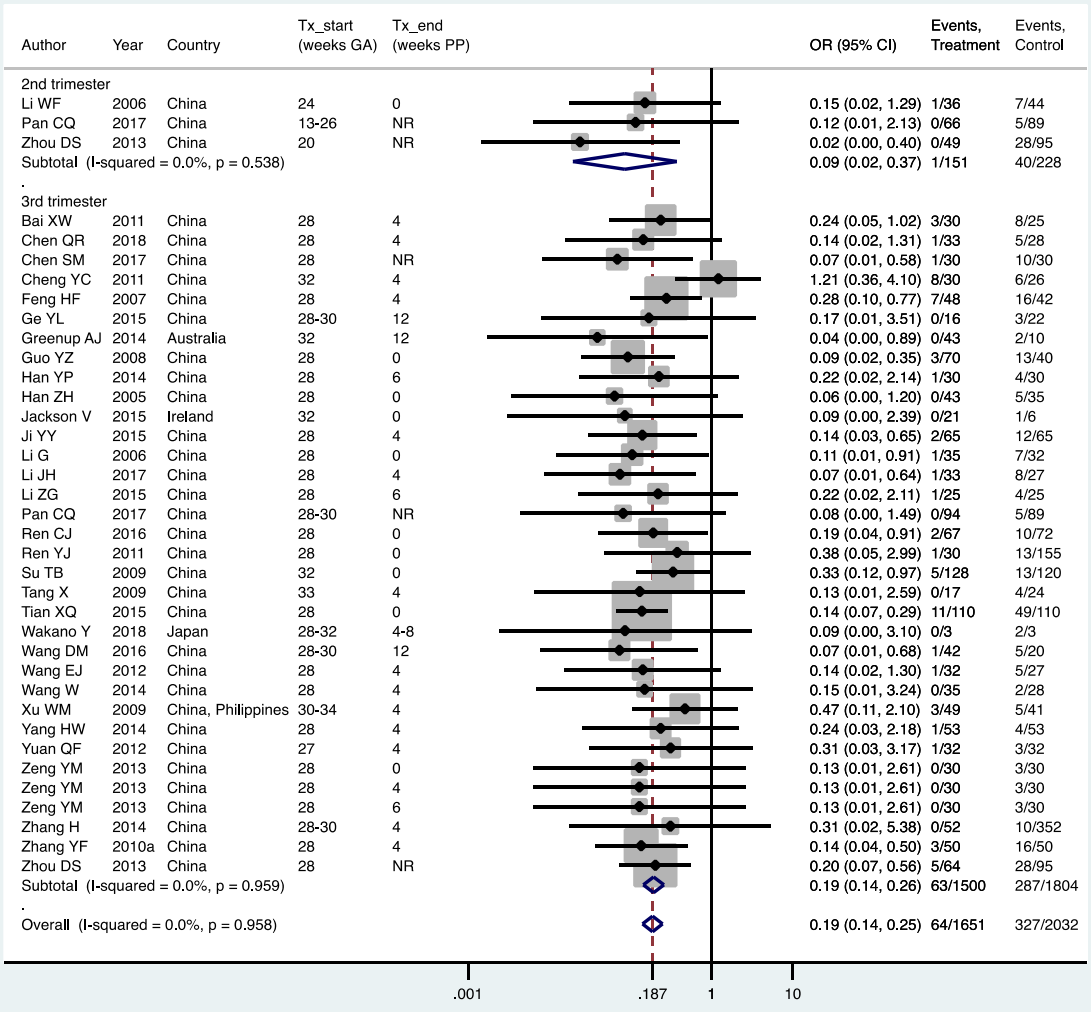
Subgroup analysis

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.

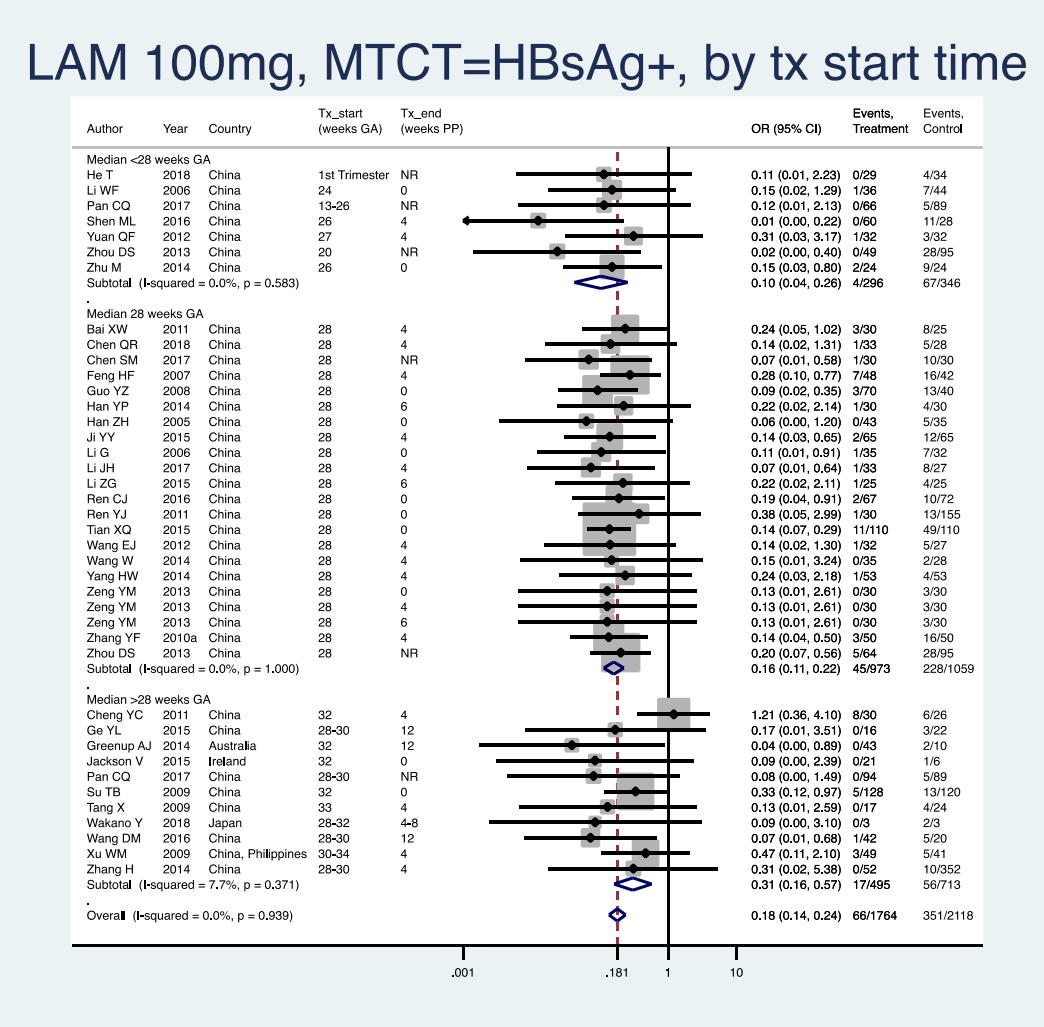
1. PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all HBV DNA levels at inclusion, all study designs merged (i.e. RCT and non-RCT), **stratified by trimester of treatment start.**

- 1st trimester: not enough studies for meta-analysis (i.e. $n<3$)
- 2nd trimester: pooled OR=0.09 (95% CI: 0.02–0.37), P=0.001, I^2=0.0%
- 3rd trimester: pooled OR=0.19 (95% CI: 0.14–0.25), P<0.001, I^2=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.

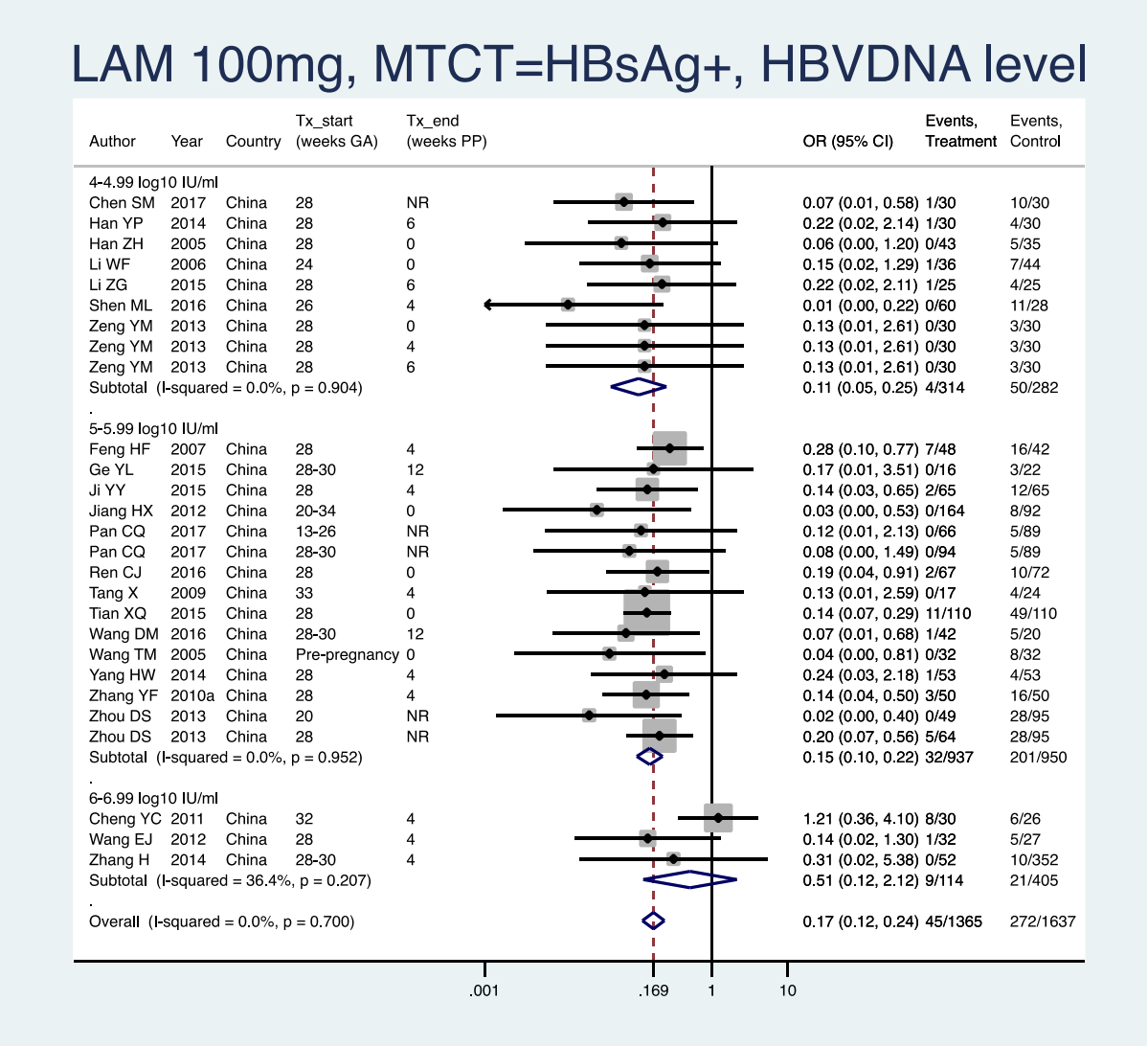
LAM 100mg, MTCT=HBsAg+, by trimester



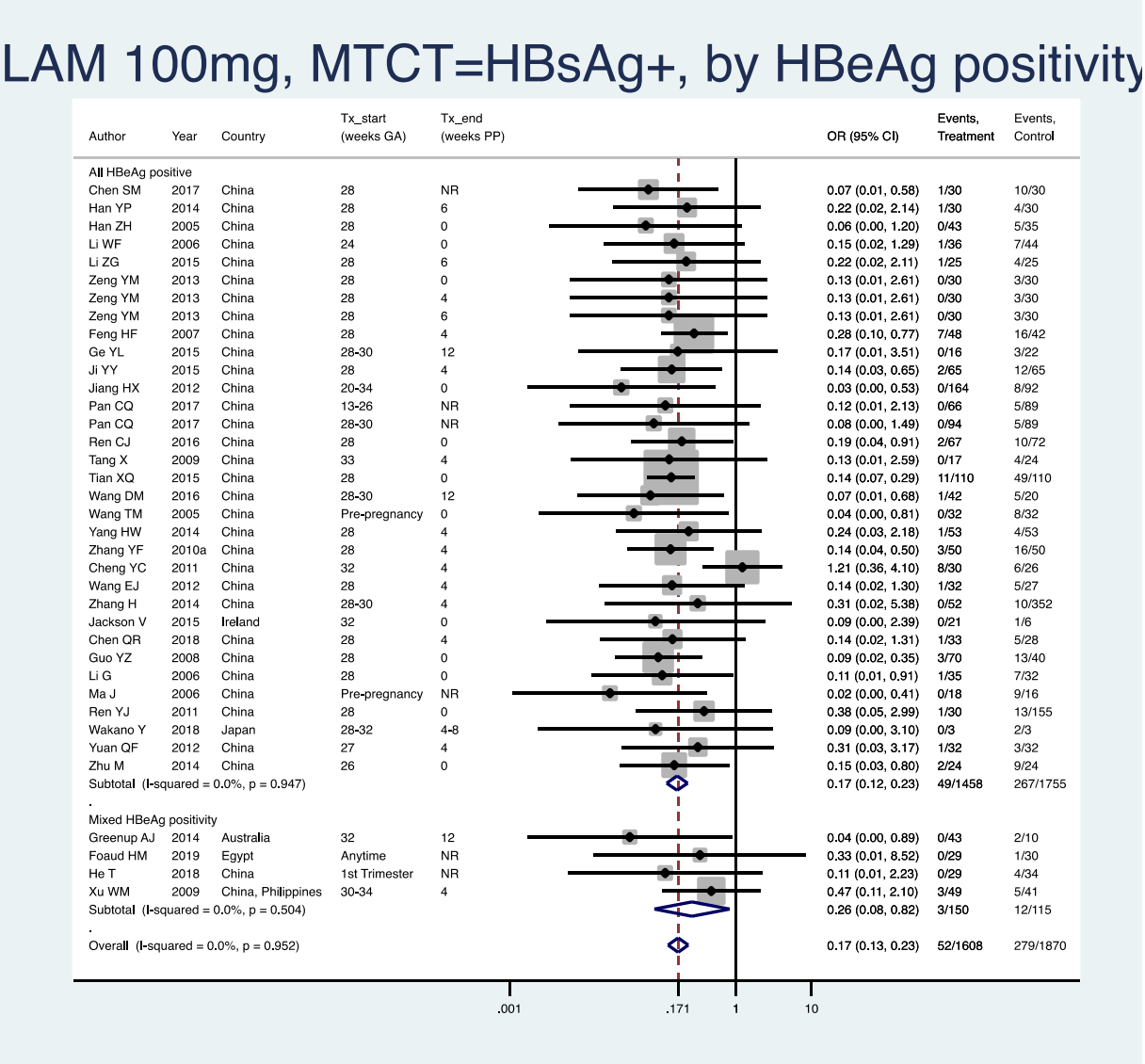
2. PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all HBV DNA levels at inclusion, all study designs merged (i.e. RCT and non-RCT), **stratified by median weeks of gestation at the time of start of treatment (<28 weeks, 28 weeks, >28 weeks).**
    - <28 weeks: pooled OR=0.10 (95% CI: 0.04–0.26), $P<0.001$, $I^2=0.0\%$
    - 28 weeks: pooled OR=0.16 (95% CI: 0.11–0.23), $P<0.001$, $I^2=0.0\%$
    - >28 weeks: pooled OR=0.31(95% CI: 0.16–0.57), $P<0.001$, $I^2=7.7\%$
    - 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.



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 inclusion criteria of the study.**
    - >4–4.99 log10 IU/mL: pooled OR=0.11 (95% CI: 0.05–0.25), *P*<0.001, I^2=0.0%
    - >5–5.99 log10 IU/mL: pooled OR=0.15 (95% CI: 0.10–0.22), *P*<0.001, I^2=0.0%
    - >6–6.99 log10 IU/mL: pooled OR=0.51 (95% CI: 0.12–2.12), *P*=0.357, I^2=36.4%
    - >7–7.99 log10 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.



4. 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), **stratified by whether or not all women were HBeAg-positive.**
    - All HBeAg-positive: pooled OR=0.17 (95% CI: 0.12–0.23), $P<0.001$, $I^2=0.0\%$
    - Mixed HBeAg positivity: pooled OR=0.26 (95% CI: 0.08–0.82), $P=0.022$, $I^2=0.0\%$
    - 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.



5. 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).**

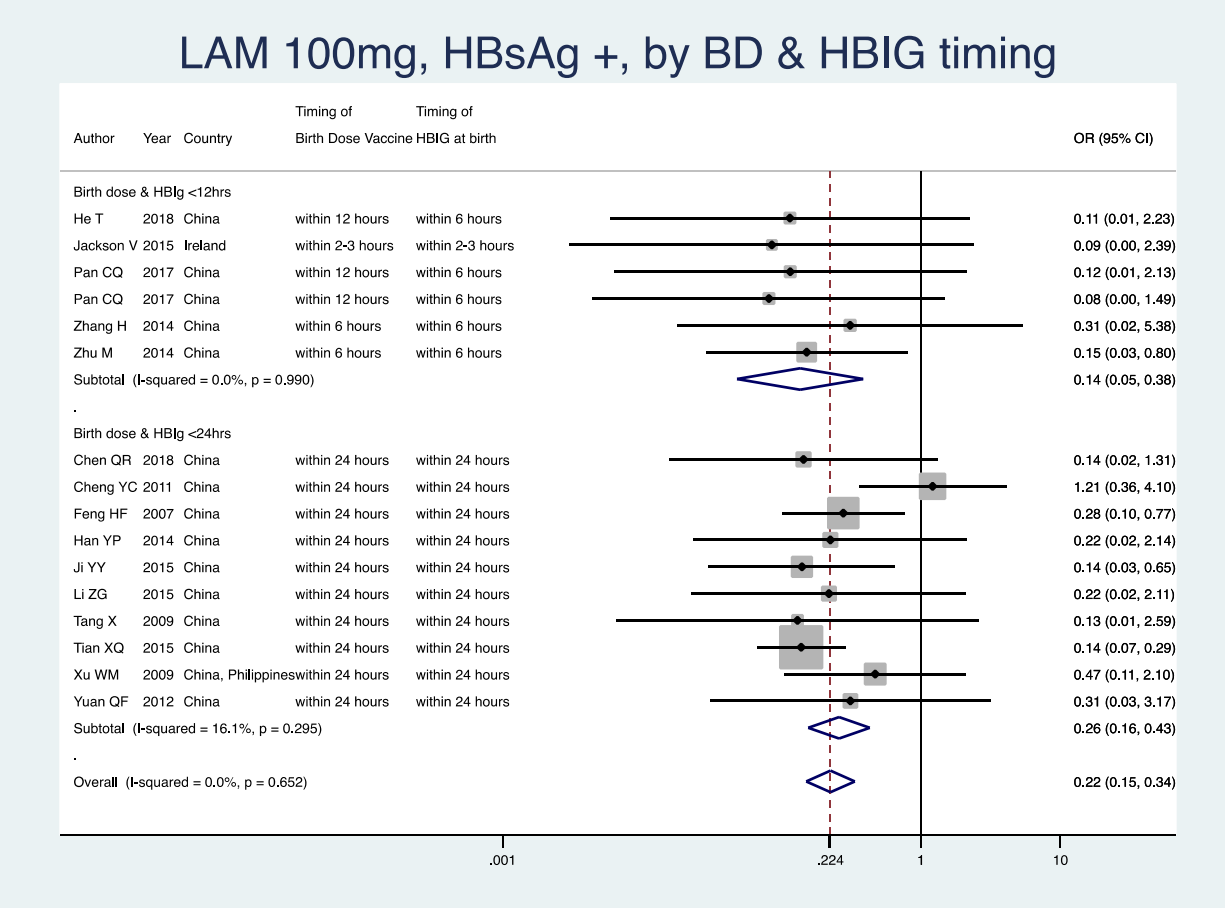
Table 11. Infant immunoprophylaxis regimens seen in studies investigating LAM

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*)

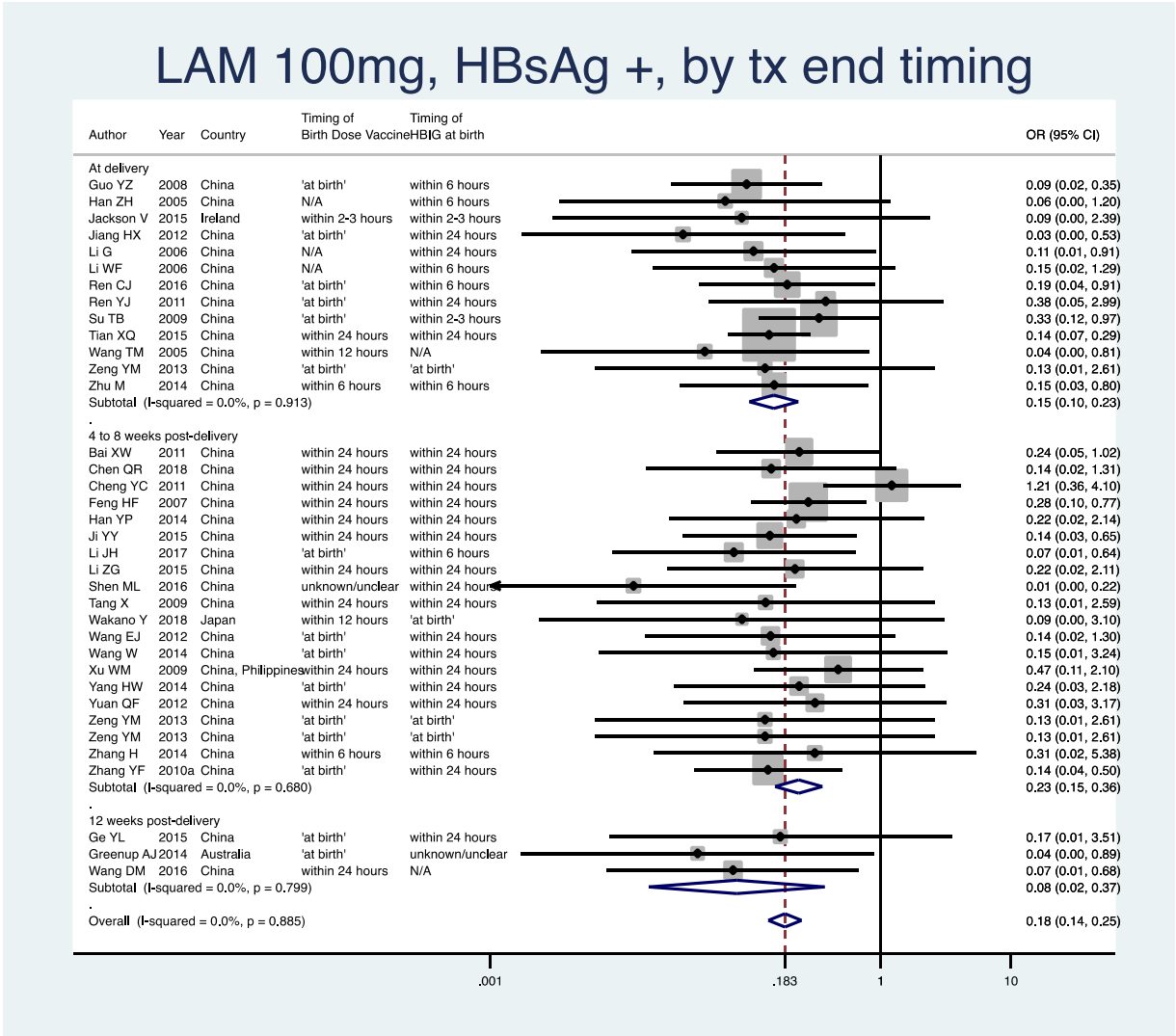
No	Yes	Yes	3 (3) (*Han ZH et al., 2005; Li G et al., 2006; Li WF et al., 2006*)
Yes	NR	Yes	2 (2) (*Wang DM et al., 2016; Wang TM et al., 2005*)

*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.**
  - <12 hours: pooled OR=0.14 (95% CI: 0.05–0.39), P<0.001, I^2=0.0%
  - <24 hours: pooled OR=0.26 (95% CI: 0.16–0.43), P<0.001, I^2=16.1%
  - The P value for heterogeneity between the two subgroups was 0.31.



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), **stratified by the timing that treatment was discontinued postpartum.**
    - At delivery: pooled OR=0.15 (95% CI: 0.10–0.23), *P*<0.001, I^2=0.0%
    - 4–8 weeks postpartum: pooled OR=0.23 (95% CI: 0.15–0.36), *P*<0.001, I^2=0.0%
    - 12 weeks postpartum: pooled OR=0.08 (95% CI: 0.02–0.37), *P*=0.001, I^2=0.0%
    - 24+ weeks postpartum: no studies within this subgroup
    - When looking at heterogeneity across the four subgroups, the *P* value was 0.20.



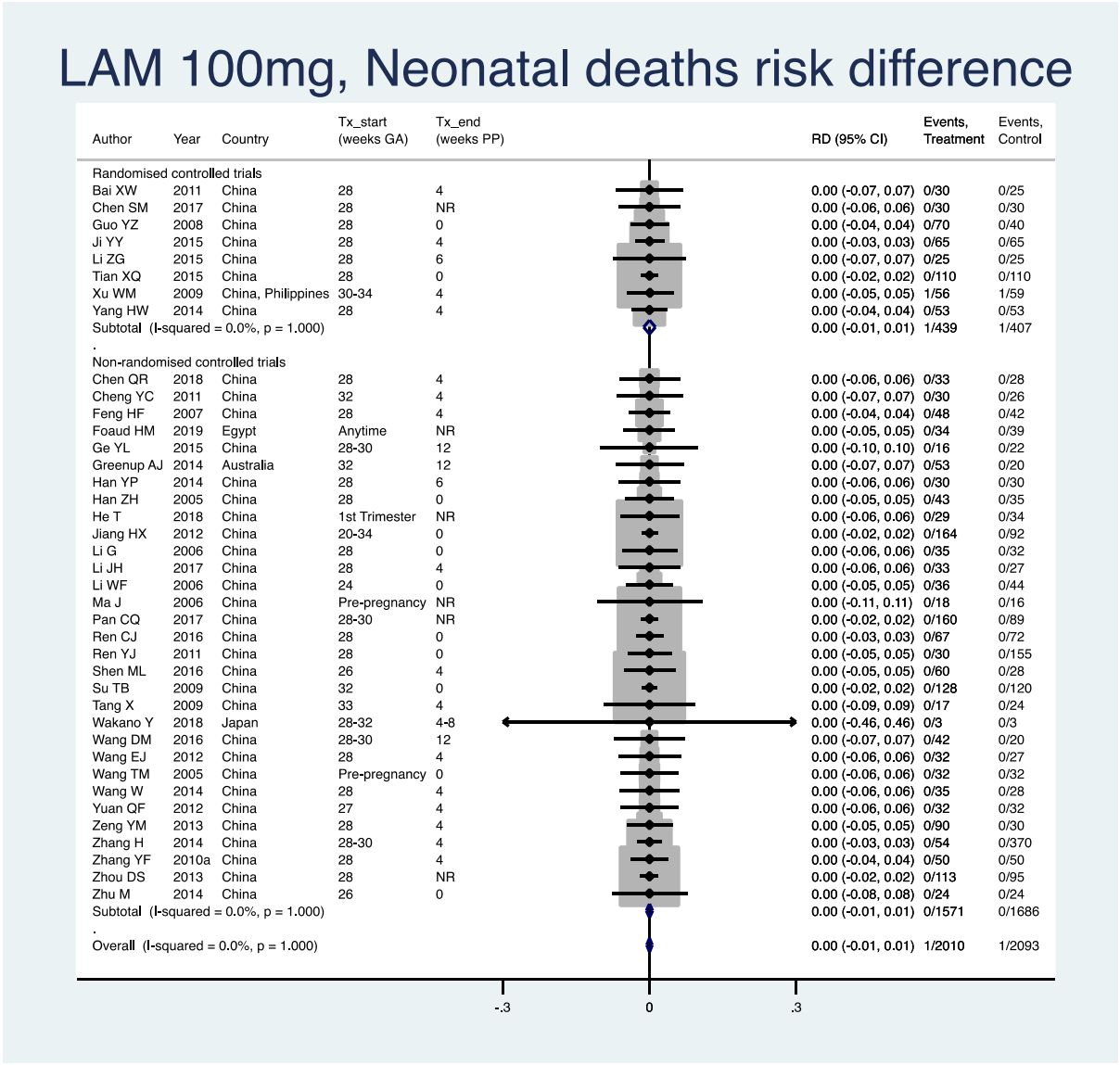
Safety analysis, narrative descriptions and selected forest plots

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.

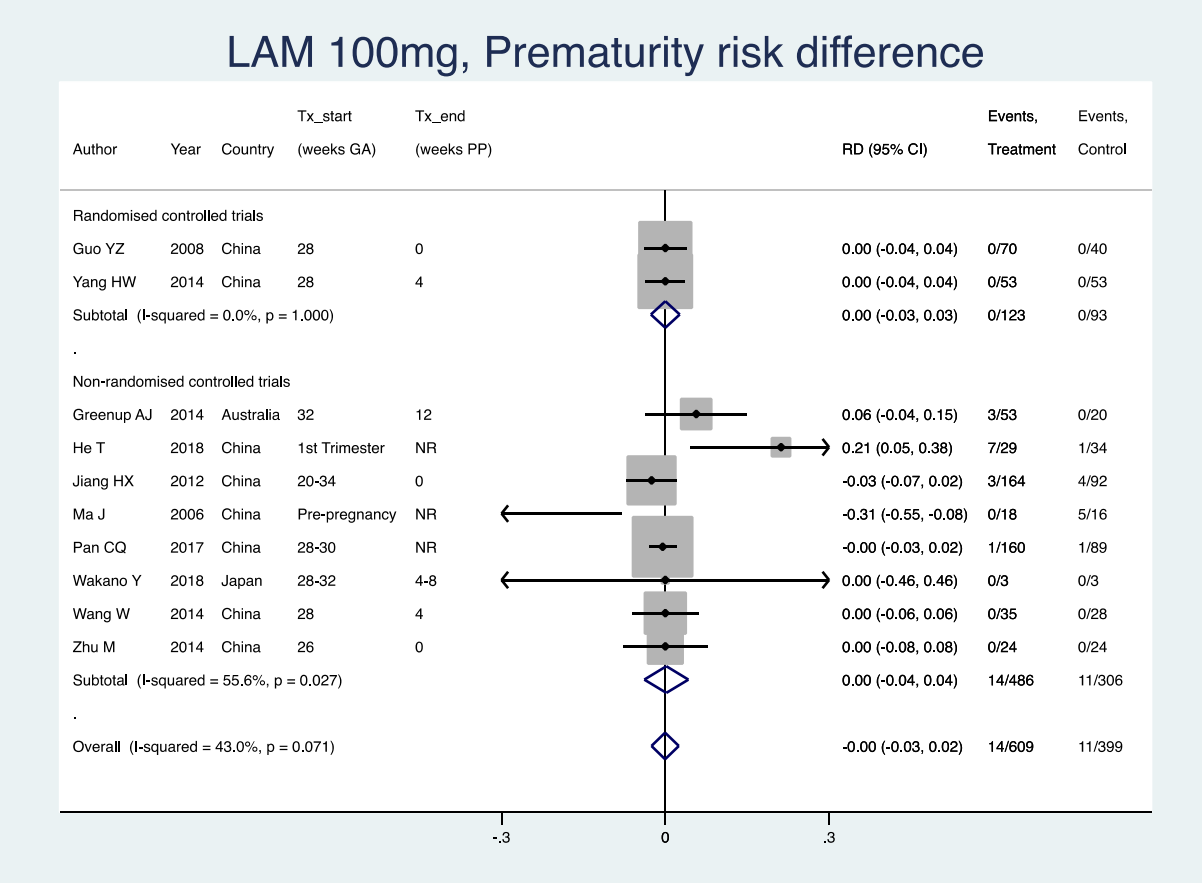
1. **Neonatal deaths** (*death within 28 days of life*)

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 I^2 statistics for the overall pooled risk difference, as well as for RCTs and non-RCTs separately, were all 0.0%.



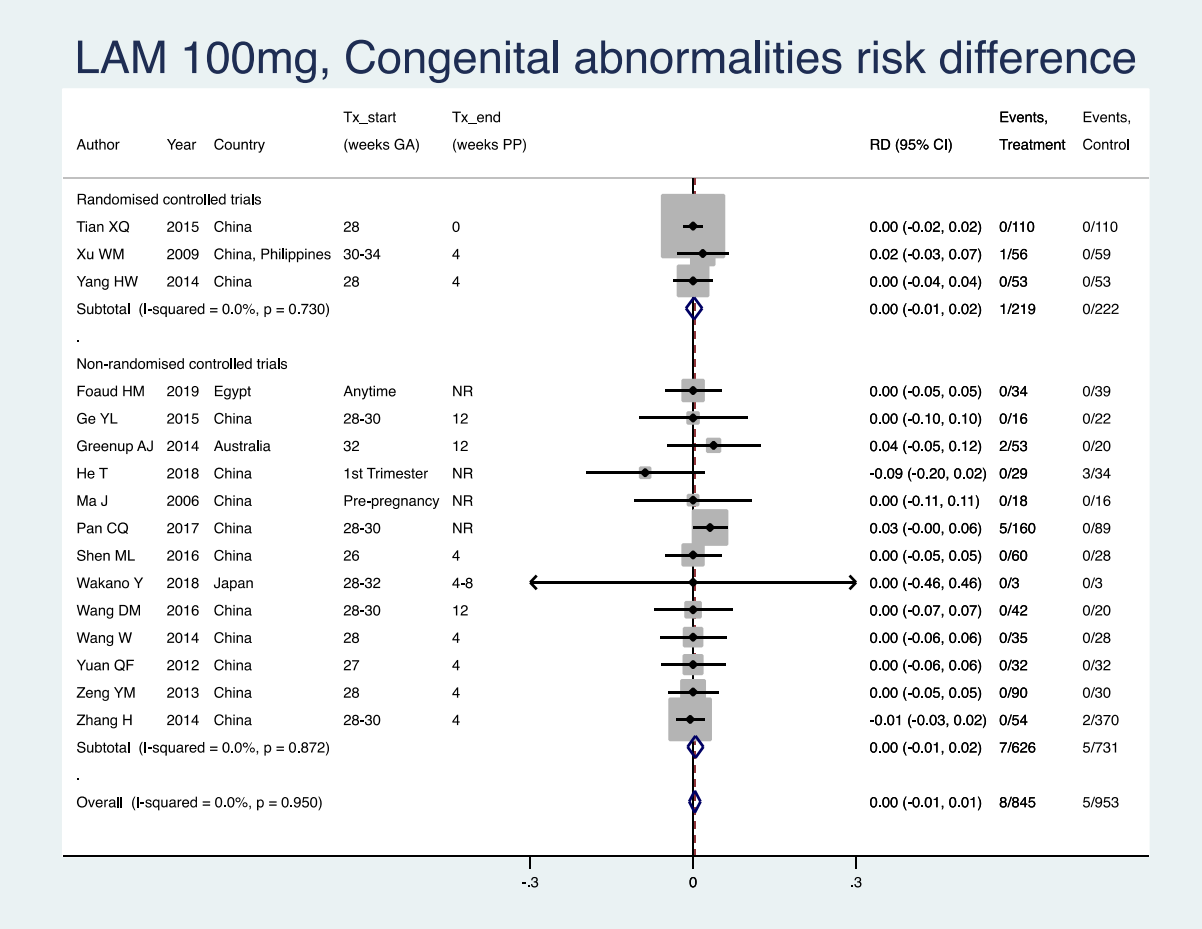
2. **Prematurity** (*typically defined as birth earlier than 37 weeks of gestation*)

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 I^2 statistics for the overall pooled risk difference estimated was 43.0%. The I^2 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.



3. **Congenital abnormalities**

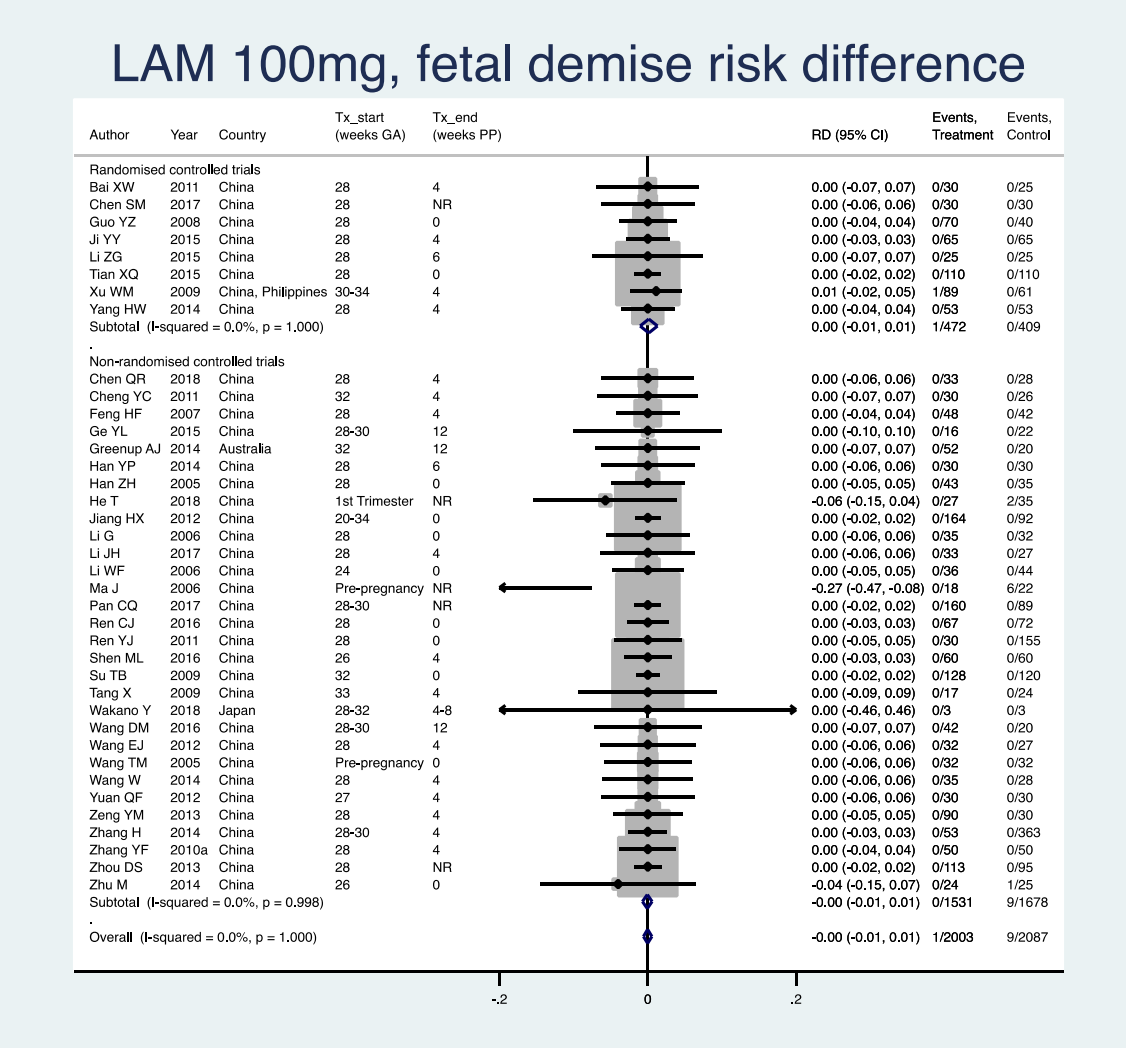
Information on this outcome was available for 16 of the 40 included studies that administered LAM to mothers. Within these studies, eight of 845 (non-weighted average 0.9%) infants whose mothers were treated with LAM during pregnancy were noted to have some sort of congenital abnormality, including: 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 (non-weighted 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 I^2 statistics for the overall pooled risk, as well as for RCTs and non-RCTs separately, were all 0%.



Maternal safety outcomes

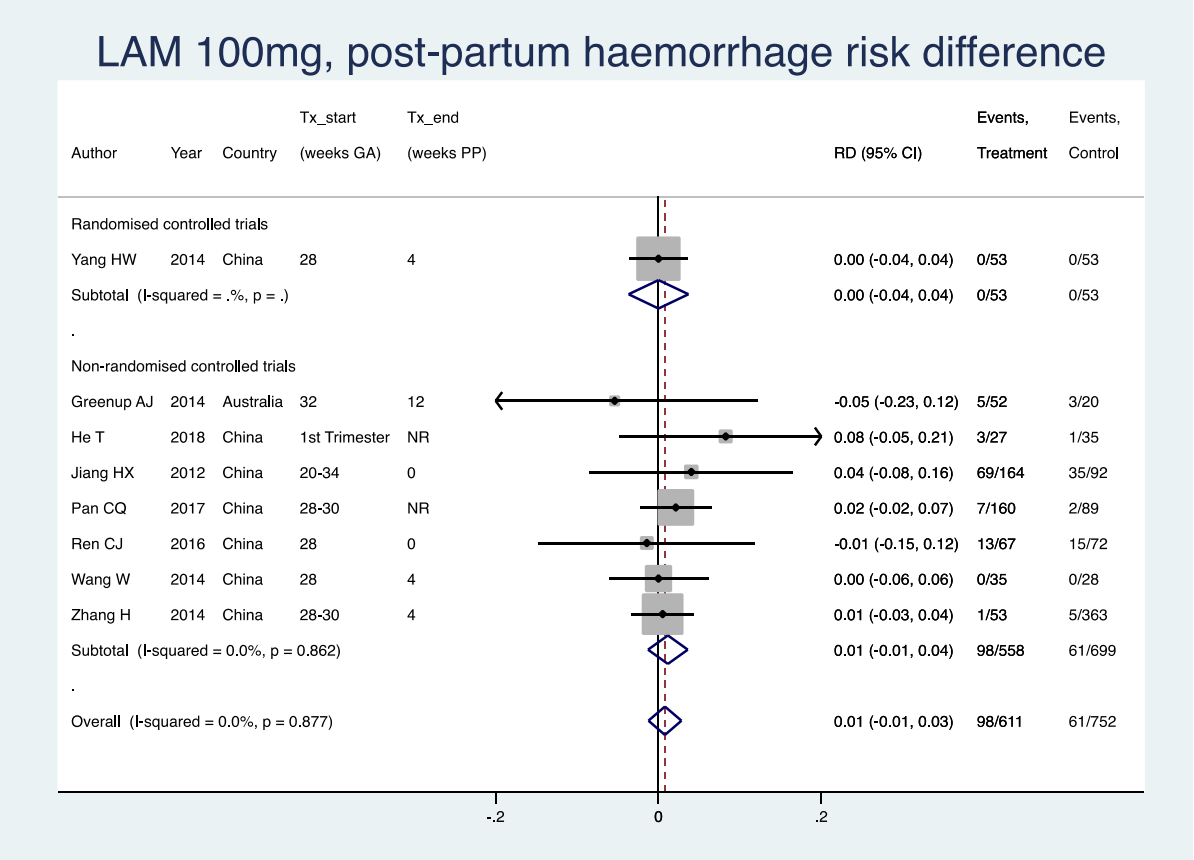
1. **Fetal demise** (miscarriage [<28 weeks], stillbirth [>=28 weeks])

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 I^2 statistics for the overall pooled risk difference estimate as well as for RCTs and non-RCTs separately, were all 0%.



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 I^2 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.

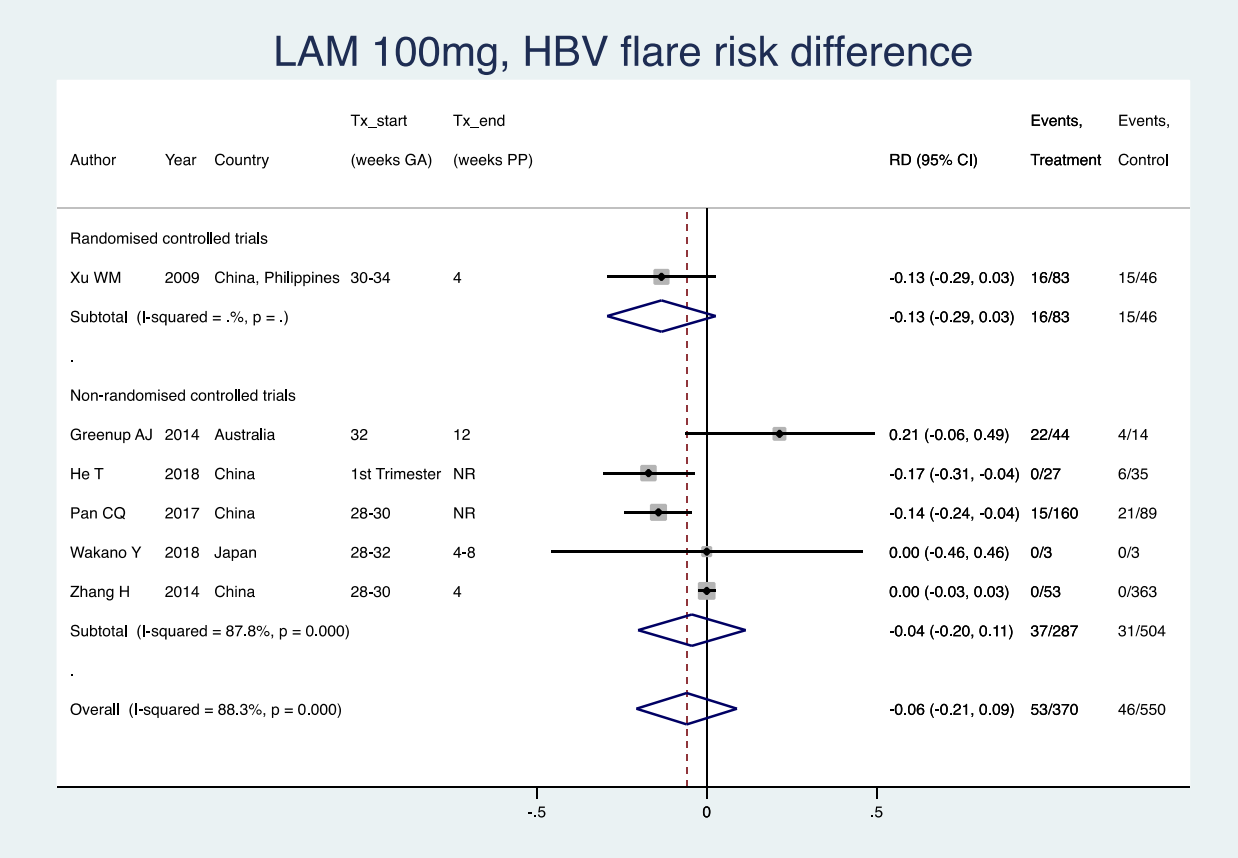


3. **Antiviral resistance**

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 (I^2 of 88.3%), as well as within the non-RCTs only, the I^2 was 87.8%. It was not possible to examine the RCTs alone as a subgroup as there was only one study.



GRADE summary of findings

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

Number of studies	Design	Quality assessment						Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	
HBsAg positivity 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 safety: neonatal deaths												
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]

Infant safety: prematurity												
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 safety: congenital abnormalities												
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 safety: miscarriage and stillbirth												
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[l]
Maternal safety: postpartum haemmorhage												
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 safety: HBV flare after treatment discontinuation												

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]

[a]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[b]Downgrading due to evidence of possible publication bias, however, upgrading due to magnitude of effect.
[c]Downgrading 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%.
[d]Upgrading due to magnitude of effect
[e]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[f]No upgrading or downgrading
[g]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[h]Downgrading 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%.
[i]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[j]No upgrading or downgrading
[k]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[l]No upgrading or downgrading
[m]Downgrading 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
[n]No upgrading or downgrading
[o]Downgrading 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.
[p]Downgrading 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).

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

# 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

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).

Table 14. Characteristics of included studies investigating LdT 600 mg

General study details and design				**Treated (TDF 300 mg) pregnant women (tx)**						**Untreated pregnant women (control)**					**Infant treatment (all infants)**		
Author, year	**Country**	**Recruit-ment period**	**HBV DNA level (inclusion)**	**#**	**Treatment weeks Start during pregnancy | End postpartum**	**Age, in years**	**HBeAg %**	**Mean or median HBV DNA at baseline**	**# Infants assessed for MTCT**	**#**	**Age, in years**	**HBeAg %**	**Mean or median HBV DNA at baseline**	**# Infants assessed for MTCT**	**HBIG at birth, *timing***	**Birth dose vaccine, *timing***	**Non-birth dose vaccine, *dose 1 /dose 2… in months***
Randomized controlled trials (RCTs)																	

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	28 ± 3	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
Huang HY, 2016	China	2012–2013	5.3 log10 IU/mL	30	20	0	28.2 ± 3.5	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	24	0	28.6 ± 3.4	100	7.3 log10 IU/mL	30								
				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-randomized controlled trials (non-RCTs)																		
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, 2015	China	2008–2010	5.3 log10 IU/mL	257	20–27	NR	27 (20–35)	100	7.9 log10 IU/mL	256	92	26 (20-35)	100	7.9 log10 IU/mL	86	Yes, <2–3 h	Yes, <12 h	Yes, 1/6
				105	28–32	NR	28 (20–38)	100	7.8 log10 IU/mL	102								
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, 2016	China	2012–2015	4.3 log10 IU/mL	30	28	NR	NR	NR	5.1 log10 IU/mL	30	25	NR	NR	5.0 log10 IU/mL	25	Yes, <6 h	Yes, <6 h	Yes, 1/6
				35	Pre-pregnant	NR	NR	NR	5.1 log10 IU/mL	35								
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, 2016	China	2010–2012	6 log10 IU/mL	32	28–32	4	27.9 ± 3.7	97	7.4 log10 IU/mL	32	78	27.5 ±3.5	97	7.5 log10 IU/mL	78	Yes, NR	Yes, At birth	Yes, 1/6
				50	4–27	4	28.3 ±3.8	94	7.6 log10 IU/mL	50								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, 2016	China	2009–2014	5.3 log10 IU/mL	60	Pre-pregnant	0	NR	NR	6.9 log10 IU/mL	60	60	NR	NR	6.8 log10 IU/mL	60	Yes, <12 h	Yes, <12 h	Yes, 1/6
				60	24	0	NR	NR	6.9 log10 IU/mL	60								
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, 2017	China	2013–2015	6.3 log10 IU/mL	61	20–28	12	28.9 ± 11.8	100	7.1 log10 IU/mL	62	65	27.5 ± 12.9	100	7.0 log10 IU/mL	65	Yes, <6 h	Yes, <12 h	Yes, 1/6
				62	12	12	29.7 ± 9.8	100	7.1 log10 IU/mL	61								

Sun WH, 2015	China	2009–2013	6.3 log10 IU/mL	42	12	12	28.9 ± 11.8	100	7.1 log10 IU/mL	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	29.7 ±9.8	100	7.2 log10 IU/mL	41								
Tan J, 2019	China	2013–2015	NR	41	28	0	NR	NR	7.6 log10 IU/mL	41	59	NR	NR	7.5 log10 IU/mL	59	Yes, <24 h	Yes, At birth	Yes, 1/6
Tan Z, 2016	nhina	2012–2015	6 log10 IU/mL	145	14–28	NR	29 (23-39)	90	7.6 log10 IU/mL	137	334	28 (20-41)	85	7.6 log10 IU/mL	320	Yes, <6 h	Yes, At birth	Yes, 1/6
			NR	37	<14	NR	29 (20-38)	65	2 log10 IU/mL	34								
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
Wang HB, 2016	China	2013–2016	NR	20	20	NR	NR	NR	6.9 log10 IU/mL	20	20	NR	NR	7.2 log10 IU/mL	20	Yes, <24 h	Yes, <24 h	Yes, 1/6
				20	24	NR	NR	NR	7.2 log10 IU/mL	20								
				20	28	NR	NR	NR	7.1 log10 IU/mL	20								
				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

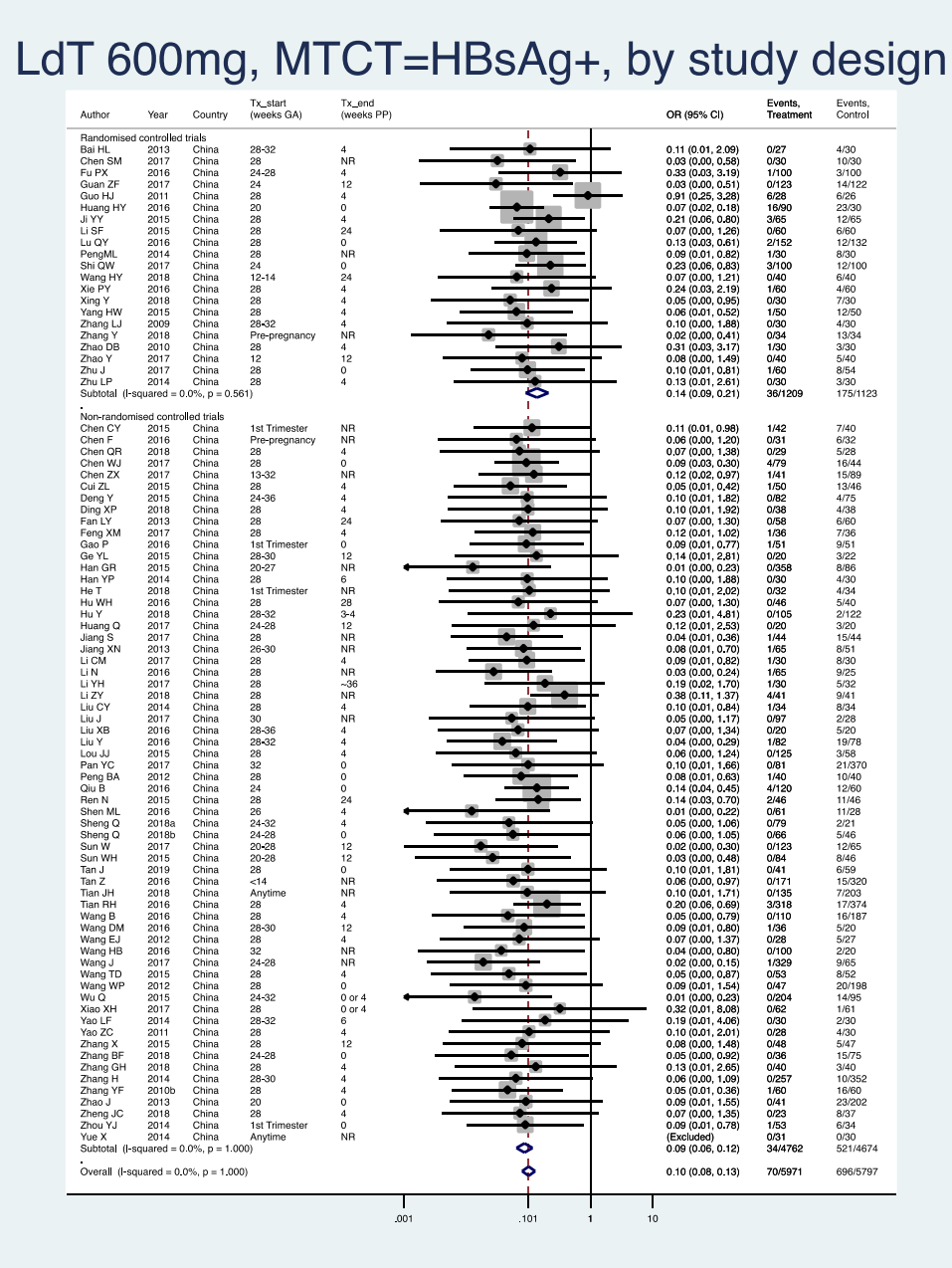
Wang TD, 2015	China	2012–2013	6.3 log10 IU/mL	53	28	4	26.3 ± 3.1	100	7.3 log10 IU/mL	53	52	25.8 ± 3.9	100	7.5 log10 IU/mL	52	Yes, <24 h	Yes, <24 h	Yes, 1/6
Wang WP, 2012	China	2010–2011	4.3 log10 IU/mL	25	28	0	NR	100	6.7 log10 IU/mL	25	198	NR	100	6.3 log10 IU/mL	198	Yes, <6 h	Yes, <6 h	Yes, 1/6
				22	<27	0	NR	100	6.8 log10 IU/mL	22								
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]

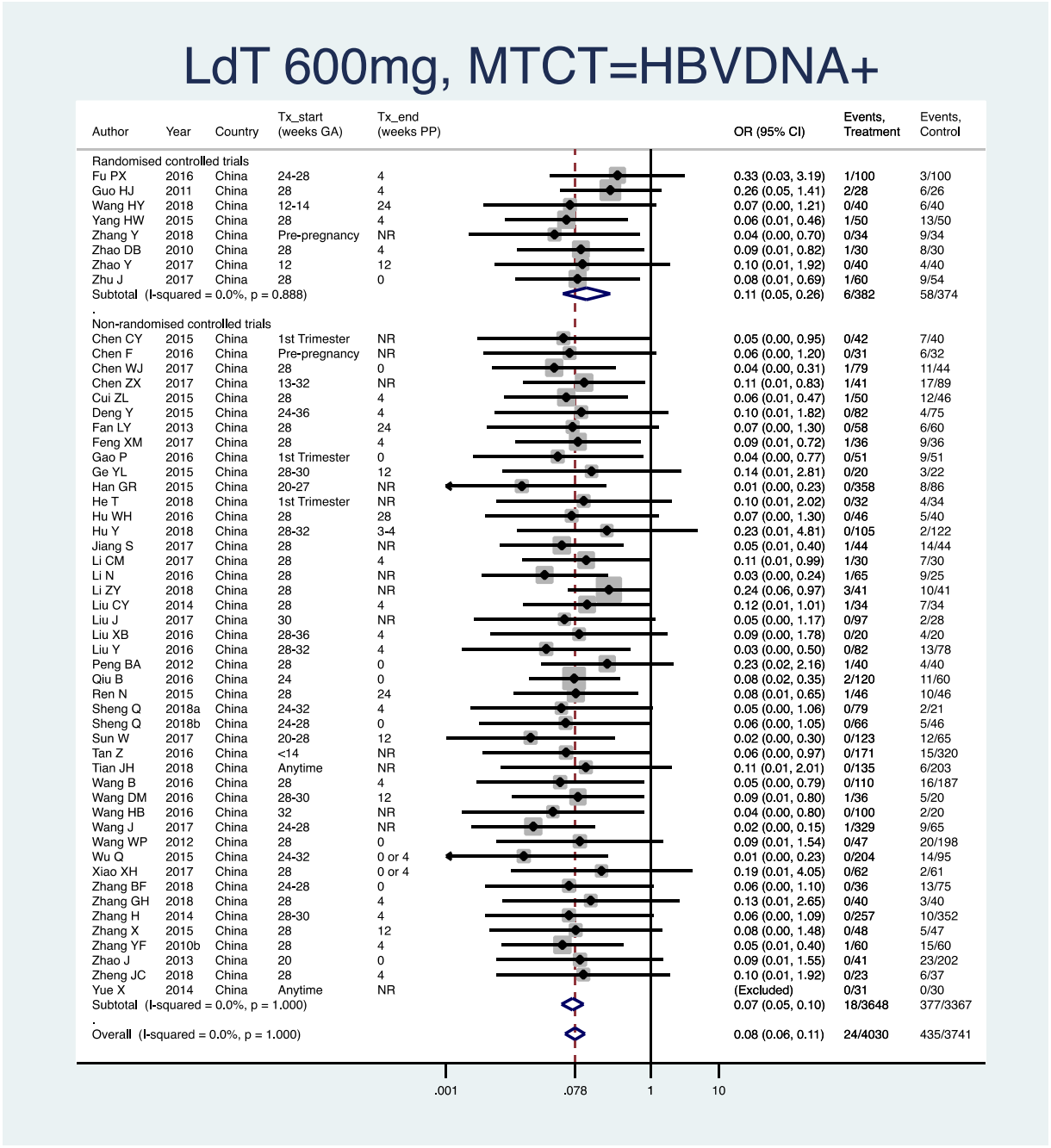
Primary efficacy analysis, narrative descriptions and forest plots

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=0.10 (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, I^2=0%
  - The P value for heterogeneity between RCTs and non-RCTs was 0.08.



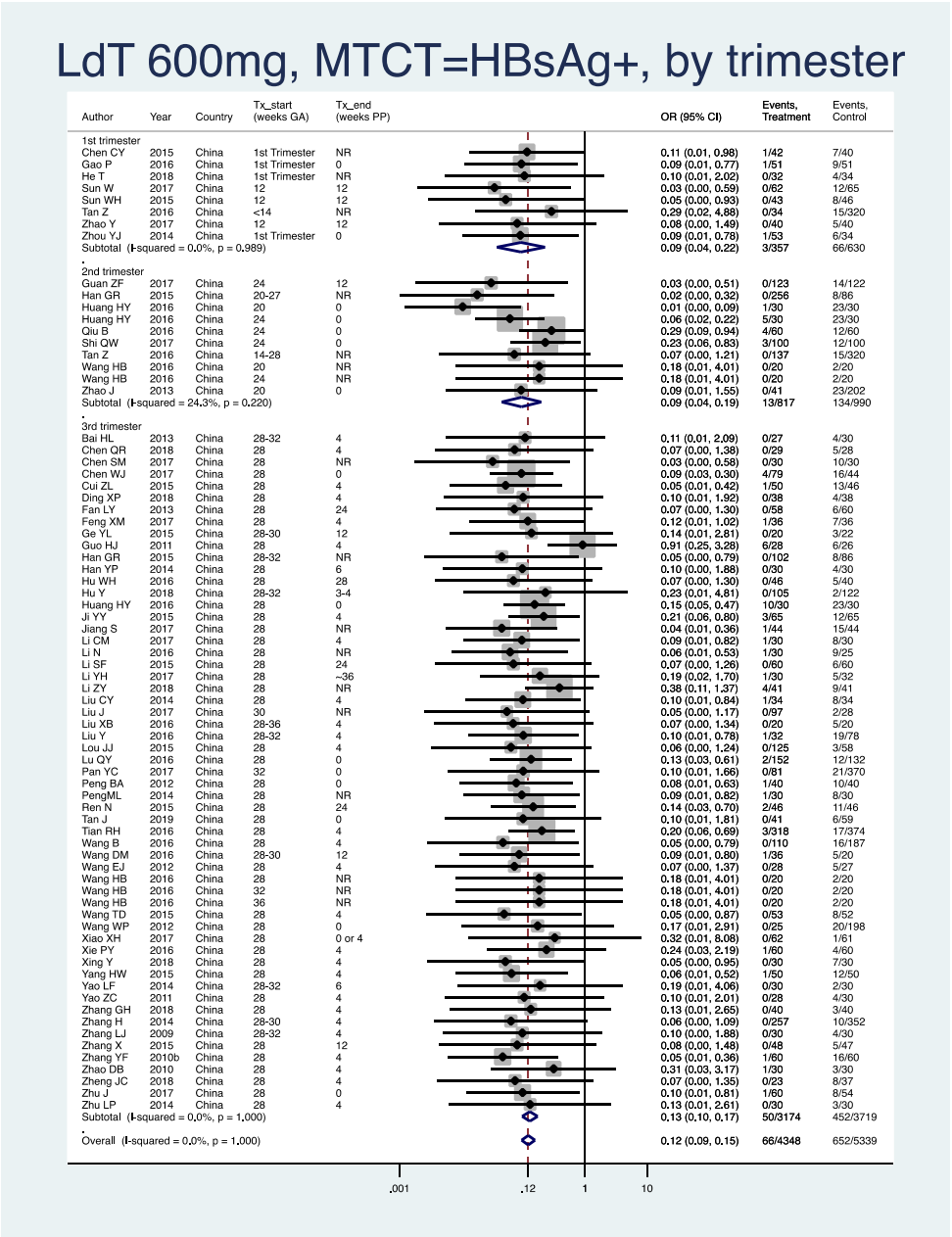
2. PMTCT, as indicated by detection of HBV DNA at 6–12 months of age, all treatment start times, all HBV DNA levels at inclusion, stratified by study design (RCT and non-RCT).
    - Overall pooled OR=0.08 (95% CI: 0.06–0.11), $P<0.001$, $I^2=0.0\%$
        - RCTs only: pooled OR=0.12 (95% CI: 0.05–0.26), $P<0.001$, $I^2=0\%$
        - Non-RCTs only: pooled OR=0.07 (95% CI: 0.05–0.10), $P<0.001$, $I^2=0\%$
        - The P value for heterogeneity between RCTs and non-RCTs was 0.29.



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.

1. 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: pooled OR=0.09 (95% CI: 0.04–0.22), *P*=0.001, I^2=0.0%
    - 2nd trimester: pooled OR=0.09 (95% CI: 0.05–0.20), *P*=0.001, I^2=24.3%
    - 3rd trimester: pooled OR=0.13 (95% CI: 0.10–0.17), *P*<0.001, I^2=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.

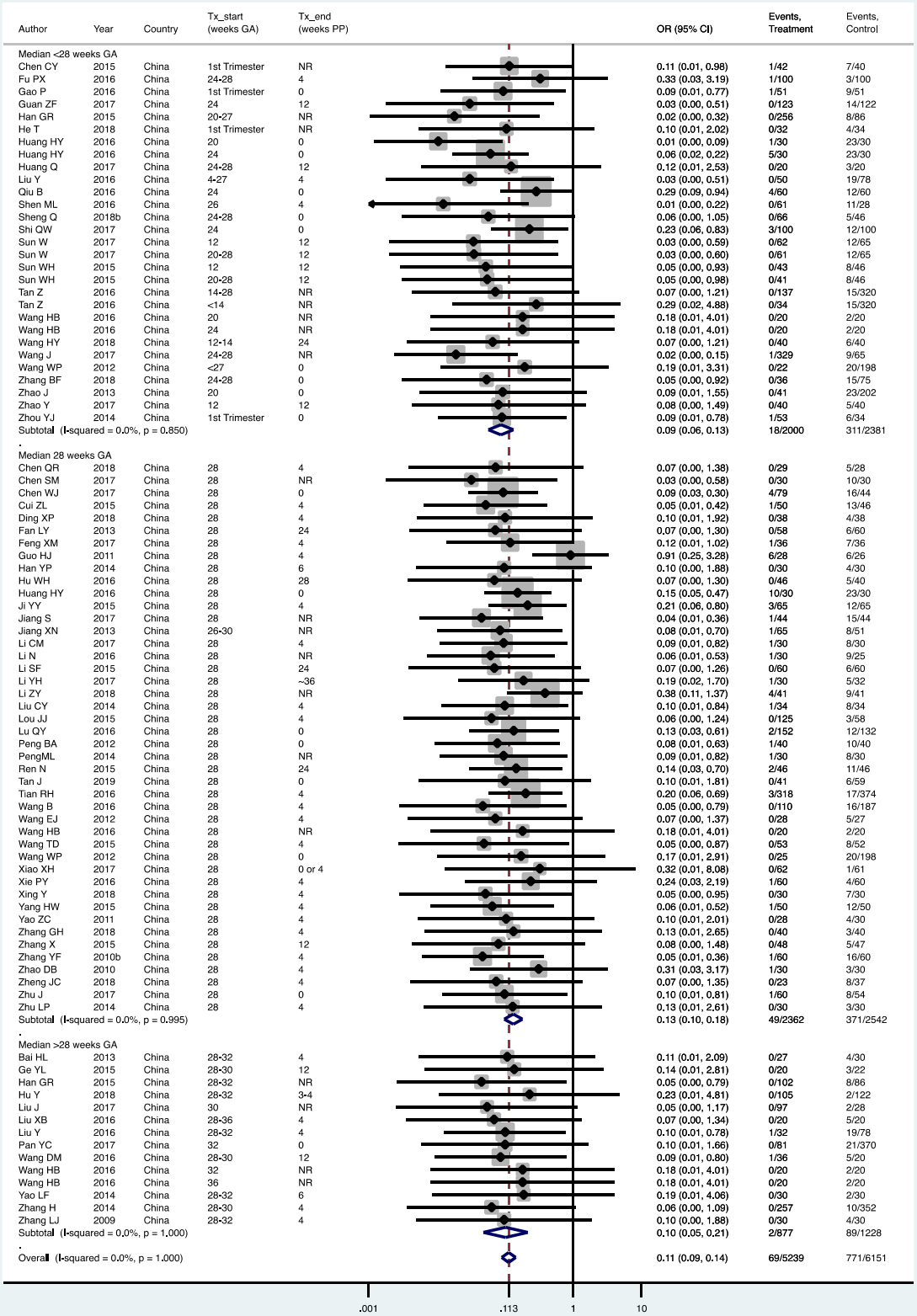


2. PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all HBV DNA levels at inclusion, all study designs merged (i.e. RCT and non-RCT), **stratified by median weeks of gestation at the time of treatment start (<28 weeks, 28 weeks, >28 weeks).**

- <28 weeks: pooled OR=0.09 (95% CI: 0.06–0.13), P<0.001, I^2=0.0%
- 28 weeks: pooled OR=0.13 (95% CI: 0.10–0.18), P<0.001, I^2=0.0%
- >28 weeks: pooled OR=0.10 (95% CI: 0.05–0.21), P<0.001, I^2=0.0%

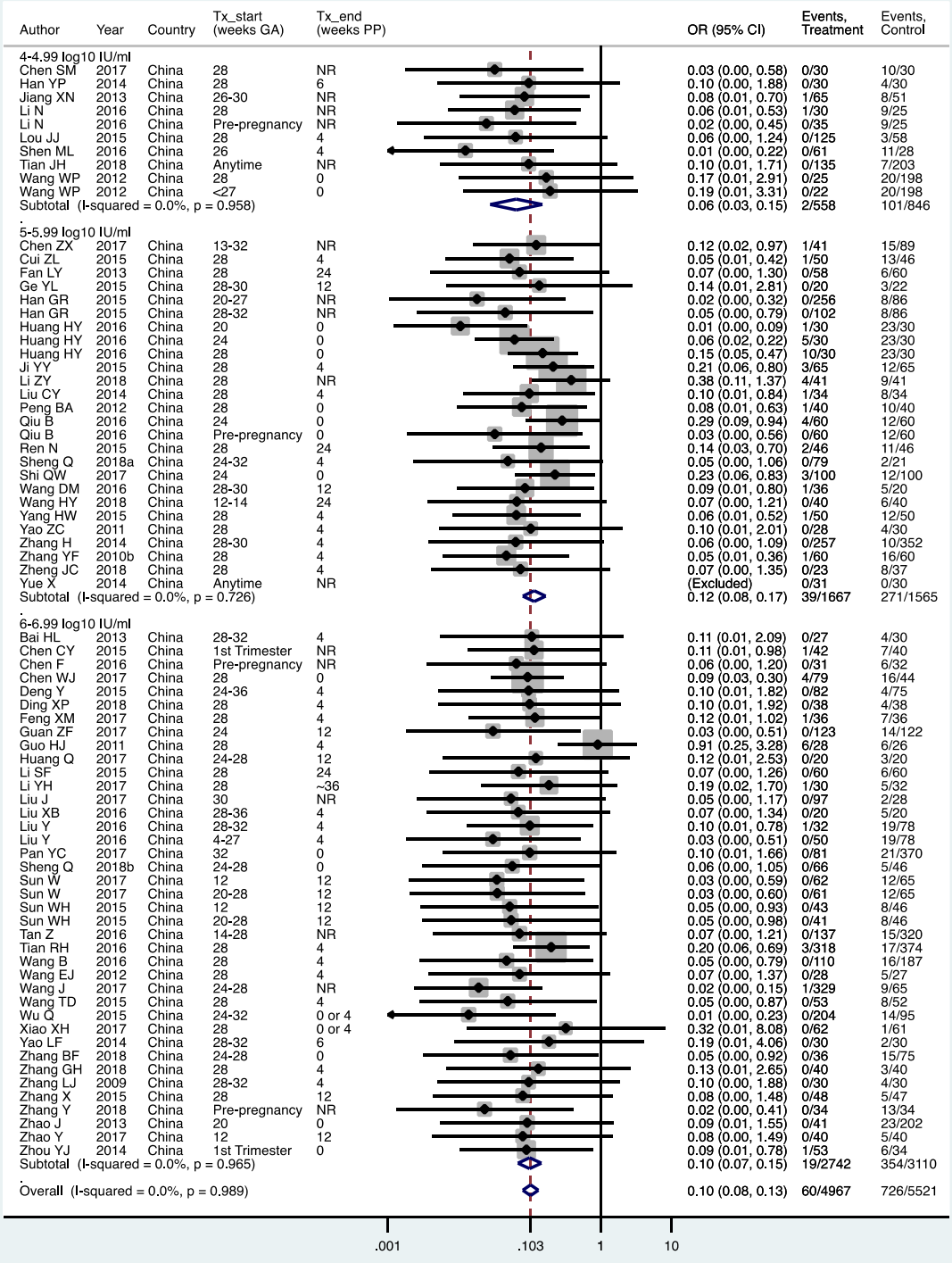
- When looking at heterogeneity across the three subgroups, the *P* value was 0.28. If comparing <28 weeks median with 28 weeks median, there was no heterogeneity (p=0.12). If comparing <28 weeks median with >28 weeks median for treatment start, there was no evidence of heterogeneity (*P*=0.72). If comparing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

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



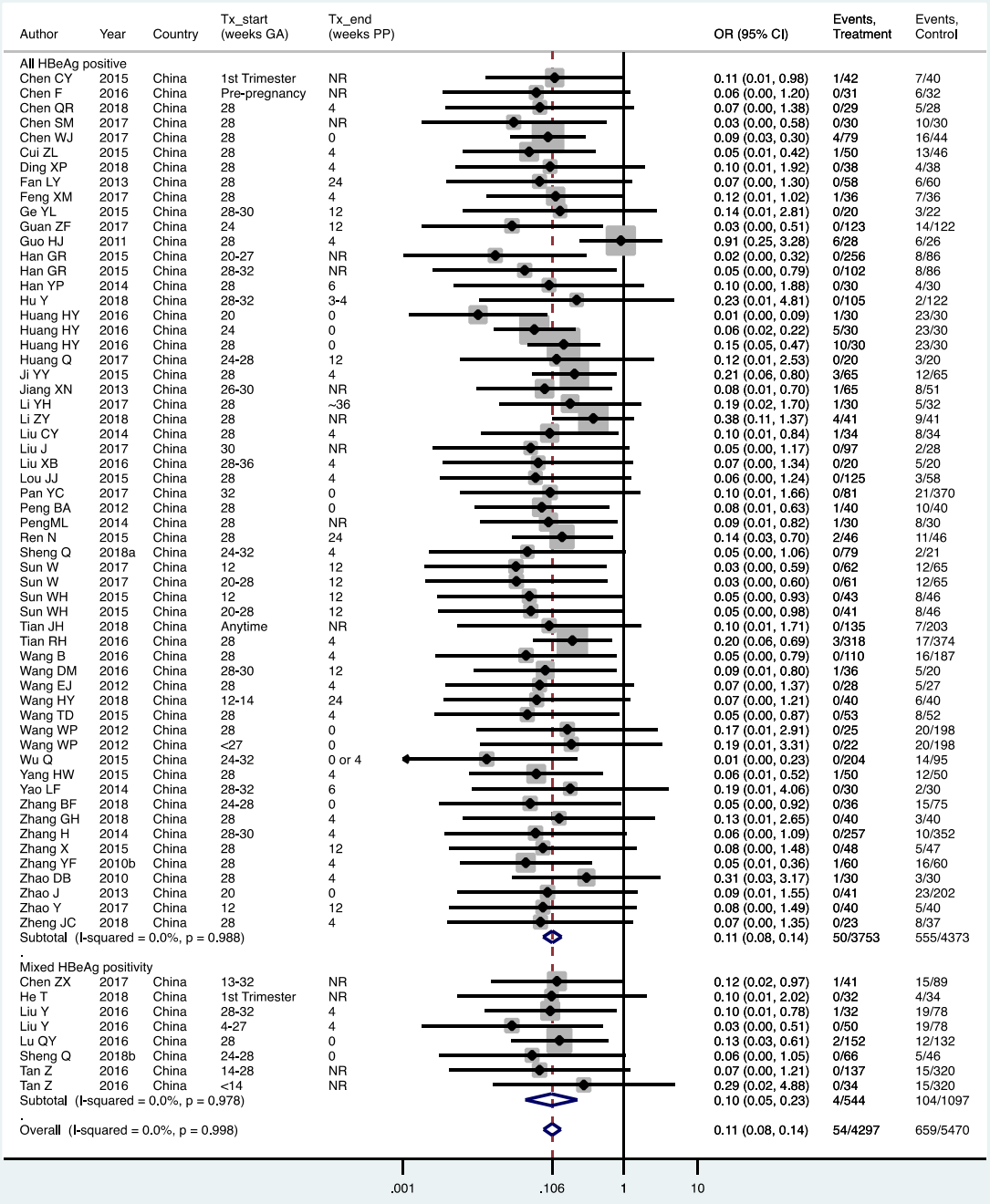
3. PMTCT, as indicated by detection of HBsAg at 6–12 months of age, all treatment start times, all study designs merged (i.e. RCT and non-RCT), **stratified by the minimum HBV DNA level specified in the study inclusion criteria.**
   - >4–4.99 log10 IU/mL: pooled OR=0.07 (95% CI: 0.03–0.15), *P*<0.001, I^2=0.0%
   - >5–5.99 log10 IU/mL: pooled OR=0.12 (95% CI: 0.08–0.17), *P*<0.001, I^2=0.0%
   - >6–6.99 log10 IU/mL: pooled OR=0.10 (95% CI: 0.07–0.15), *P*<0.001, I^2=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. 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), **stratified by whether or not all women were HBeAg-positive.**
    - All HBeAg-positive: pooled OR=0.11 (95% CI: 0.08–0.14), $P<0.001$, $I^2=0.0\%$
    - Mixed HBeAg-positive: pooled OR=0.10 (95% CI: 0.05–0.23), $P<0.001$, $I^2=0.0\%$
    - There was no heterogeneity ($P=0.94$) between the two subgroups.

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



Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	OR (95% CI)	Events, Treatment	Events, Control
All HBeAg positive							
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	2018	China	28	4	0.10 (0.01, 1.92)	0/38	4/38
Fan LY	2013	China	28	24	0.07 (0.00, 1.30)	0/58	6/60
Feng XM	2017	China	28	4	0.12 (0.01, 1.02)	1/36	7/36
Ge YL	2015	China	28-30	12	0.14 (0.01, 2.81)	0/20	3/22
Guan ZF	2017	China	24	12	0.03 (0.00, 0.51)	0/123	14/122
Guo HJ	2011	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
Han YP	2014	China	28	6	0.10 (0.00, 1.88)	0/30	4/30
Hu Y	2018	China	28-32	3-4	0.23 (0.01, 4.81)	0/105	2/122
Huang HY	2016	China	20	0	0.01 (0.00, 0.09)	1/30	23/30
Huang HY	2016	China	24	0	0.06 (0.02, 0.22)	5/30	23/30
Huang HY	2016	China	28	0	0.15 (0.05, 0.47)	10/30	23/30
Huang Q	2017	China	24-28	12	0.12 (0.01, 2.53)	0/20	3/20
Ji YY	2015	China	28	4	0.21 (0.06, 0.80)	3/65	12/65
Jiang XN	2013	China	26-30	NR	0.08 (0.01, 0.70)	1/65	8/51
Li YH	2017	China	28	~36	0.19 (0.02, 1.70)	1/30	5/32
Li ZY	2018	China	28	NR	0.38 (0.11, 1.37)	4/41	9/41
Liu CY	2014	China	28	4	0.10 (0.01, 0.84)	1/34	8/34
Liu J	2017	China	30	NR	0.05 (0.00, 1.17)	0/97	2/28
Liu XB	2016	China	28-36	4	0.07 (0.00, 1.34)	0/20	5/20
Lou JJ	2015	China	28	4	0.06 (0.00, 1.24)	0/125	3/58
Pan YC	2017	China	32	0	0.10 (0.01, 1.66)	0/81	21/370
Peng BA	2012	China	28	0	0.08 (0.01, 0.63)	1/40	10/40
PengML	2014	China	28	NR	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
Tian JH	2018	China	Anytime	NR	0.10 (0.01, 1.71)	0/135	7/203
Tian RH	2016	China	28	4	0.20 (0.06, 0.69)	3/318	17/374
Wang B	2016	China	28	4	0.05 (0.00, 0.79)	0/110	16/187
Wang DM	2016	China	28-30	12	0.09 (0.01, 0.80)	1/36	5/20
Wang EJ	2012	China	28	4	0.07 (0.00, 1.37)	0/28	5/27
Wang HY	2018	China	12-14	24	0.07 (0.00, 1.21)	0/40	6/40
Wang TD	2015	China	28	4	0.05 (0.00, 0.87)	0/53	8/52
Wang WP	2012	China	28	0	0.17 (0.01, 2.91)	0/25	20/198
Wang WP	2012	China	<27	0	0.19 (0.01, 3.31)	0/22	20/198
Wu Q	2015	China	24-32	0 or 4	0.01 (0.00, 0.23)	0/204	14/95
Yang HW	2015	China	28	4	0.06 (0.01, 0.52)	1/50	12/50
Yao LF	2014	China	28-32	6	0.19 (0.01, 4.06)	0/30	2/30
Zhang BF	2018	China	24-28	0	0.05 (0.00, 0.92)	0/36	15/75
Zhang GH	2018	China	28	4	0.13 (0.01, 2.65)	0/40	3/40
Zhang H	2014	China	28-30	4	0.06 (0.00, 1.09)	0/257	10/352
Zhang X	2015	China	28	12	0.08 (0.00, 1.48)	0/48	5/47
Zhang YF	2010b	China	28	4	0.05 (0.01, 0.36)	1/60	16/60
Zhao DB	2010	China	28	4	0.31 (0.03, 3.17)	1/30	3/30
Zhao J	2013	China	20	0	0.09 (0.01, 1.55)	0/41	23/202
Zhao Y	2017	China	12	12	0.08 (0.00, 1.49)	0/40	5/40
Zheng JC	2018	China	28	4	0.07 (0.00, 1.35)	0/23	8/37
Subtotal (I-squared = 0.0%, p = 0.988)					0.11 (0.08, 0.14)	50/3753	555/4373
.							
Mixed HBeAg positivity							
Chen ZX	2017	China	13-32	NR	0.12 (0.02, 0.97)	1/41	15/89
He T	2018	China	1st Trimester	NR	0.10 (0.01, 2.02)	0/32	4/34
Liu Y	2016	China	28-32	4	0.10 (0.01, 0.78)	1/32	19/78
Liu Y	2016	China	4-27	4	0.03 (0.00, 0.51)	0/50	19/78
Lu QY	2016	China	28	0	0.13 (0.03, 0.61)	2/152	12/132
Sheng Q	2018b	China	24-28	0	0.06 (0.00, 1.05)	0/66	5/46
Tan Z	2016	China	14-28	NR	0.07 (0.00, 1.21)	0/137	15/320
Tan Z	2016	China	<14	NR	0.29 (0.02, 4.88)	0/34	15/320
Subtotal (I-squared = 0.0%, p = 0.978)					0.10 (0.05, 0.23)	4/544	104/1097
.							
Overall (I-squared = 0.0%, p = 0.998)					0.11 (0.08, 0.14)	54/4297	659/5470

5. 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).**

Table 15. Infant immunoprophylaxis regimens seen in studies investigating LdT

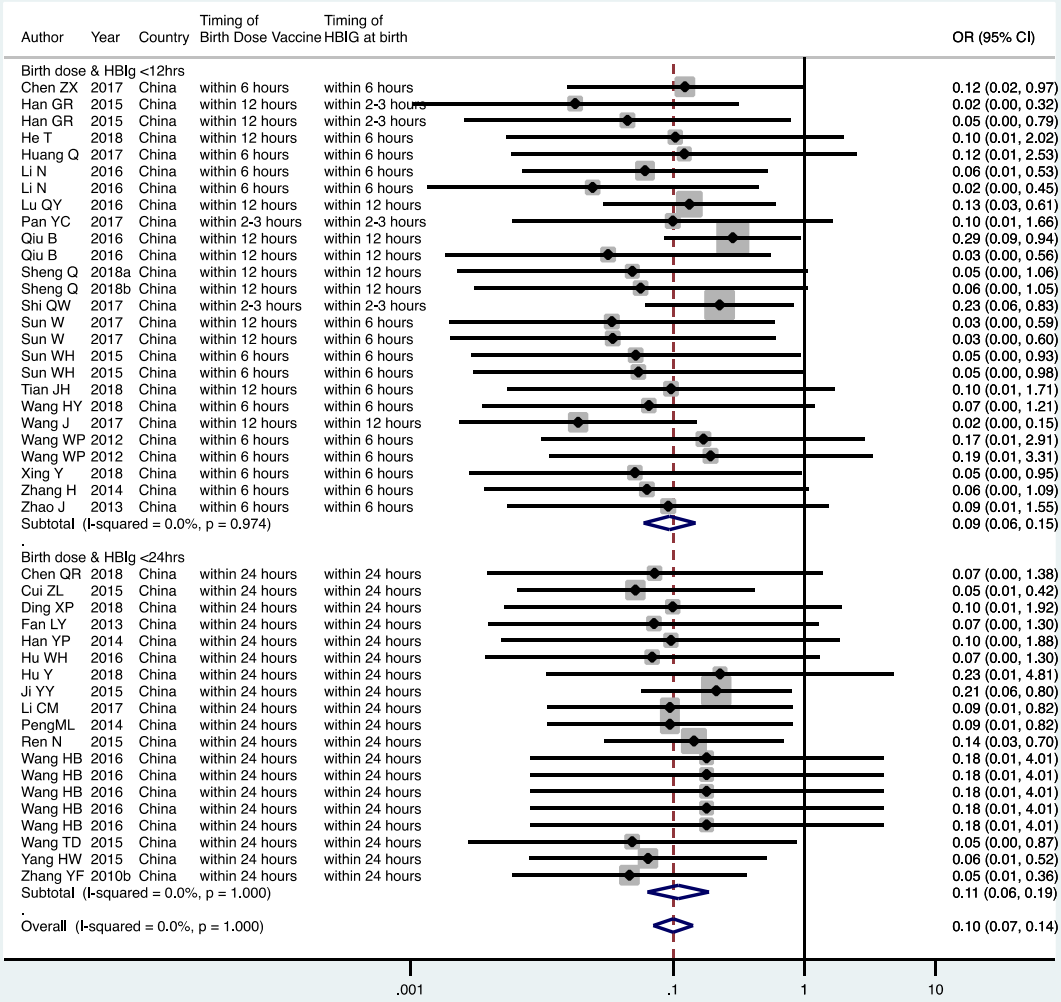
Birth dose vaccine	HBIG at birth	2–4 infant vaccines (not at birth)	# studies (treatment arms)
Yes	Yes	Yes	76 (88)
Yes	NR	NR	2 (2) (*Liu J et al., 2017; Wang DM et al. 2016*),
No	Yes	Yes	2 (2) *(Li SF et al., 2015; Li ZY et al., 2018)*
NR	Yes	NR	2 (2) *(Xiao XH et al., 2017; Yao LF et al., 2014)*
NR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

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.

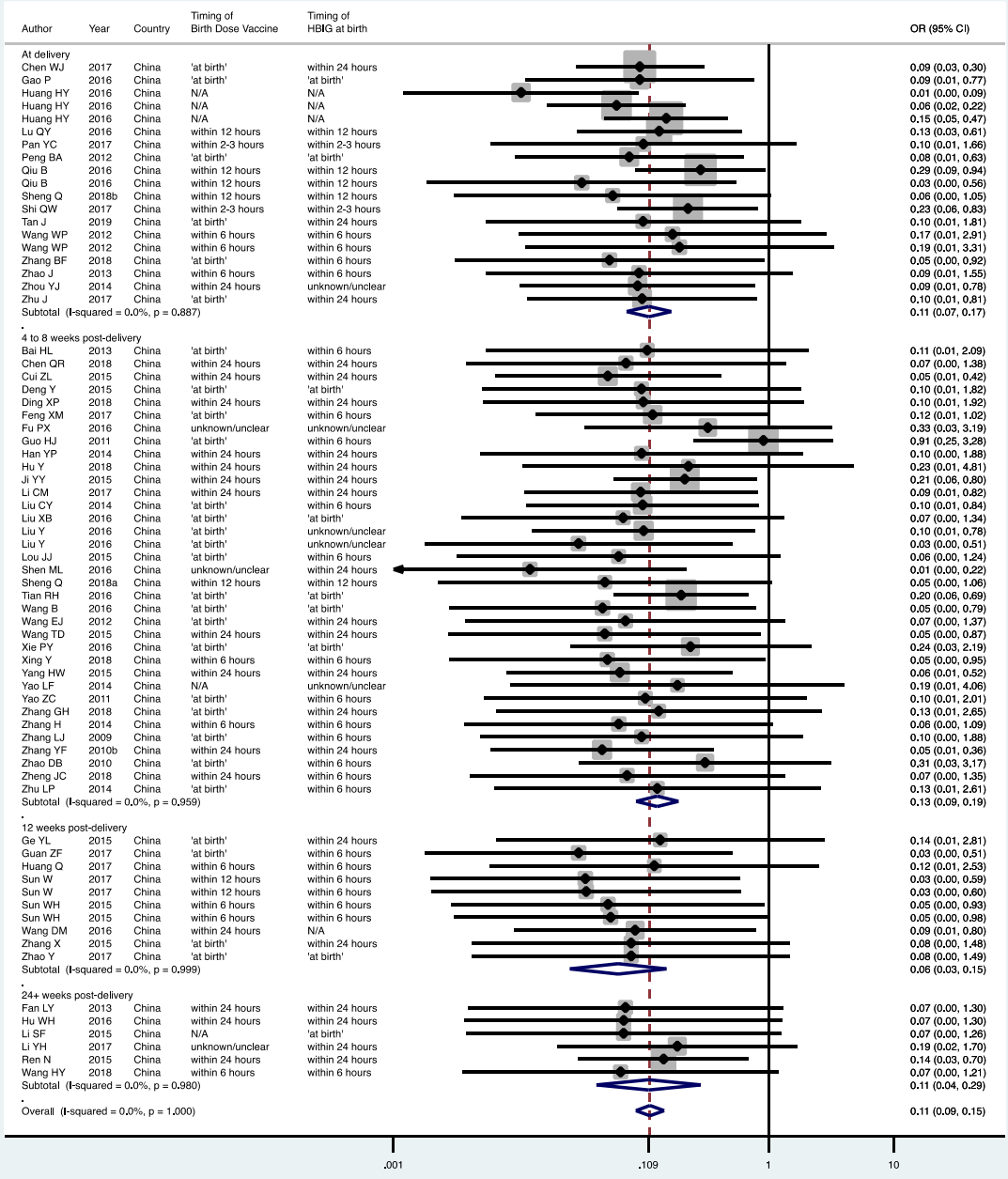
- Therefore, we **<u>stratified by whether or not *both* birth dose vaccine and HBIG were given within 12 hours of life, versus within 24 hours of life.</u>**
    - <12 hours: pooled OR=0.09 (95% CI: 0.06–0.15), *P*<0.001, I^2=0.0%
    - <24 hours: pooled OR=0.11 (95% CI: 0.06–0.19), *P*<0.001, I^2=0.0%
    - The *P* value for heterogeneity between the two subgroups was 0.67.

LdT 600mg, 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), **stratified by the timing that treatment was discontinued postpartum.**
    - At delivery: pooled OR=0.11 (95% CI: 0.07–0.17), $P<0.001$, $I^2=0.0\%$
    - 4–8 weeks postpartum: pooled OR=0.13 (95% CI: 0.09–0.19), $P<0.001$, $I^2=0.0\%$
    - 12 weeks postpartum: pooled OR=0.06 (95% CI: 0.3–0.15), $P<0.001$, $I^2=0.0\%$
    - 24+ weeks postpartum: pooled OR=0.11 (95% CI: 0.04–0.29), $P<0.001$, $I^2=0.0\%$
    - When looking at heterogeneity across the four subgroups, the *P* value was 0.55.

LdT 600mg, HBsAg +, by tx end timing



Safety analysis, narrative descriptions and selected forest plots

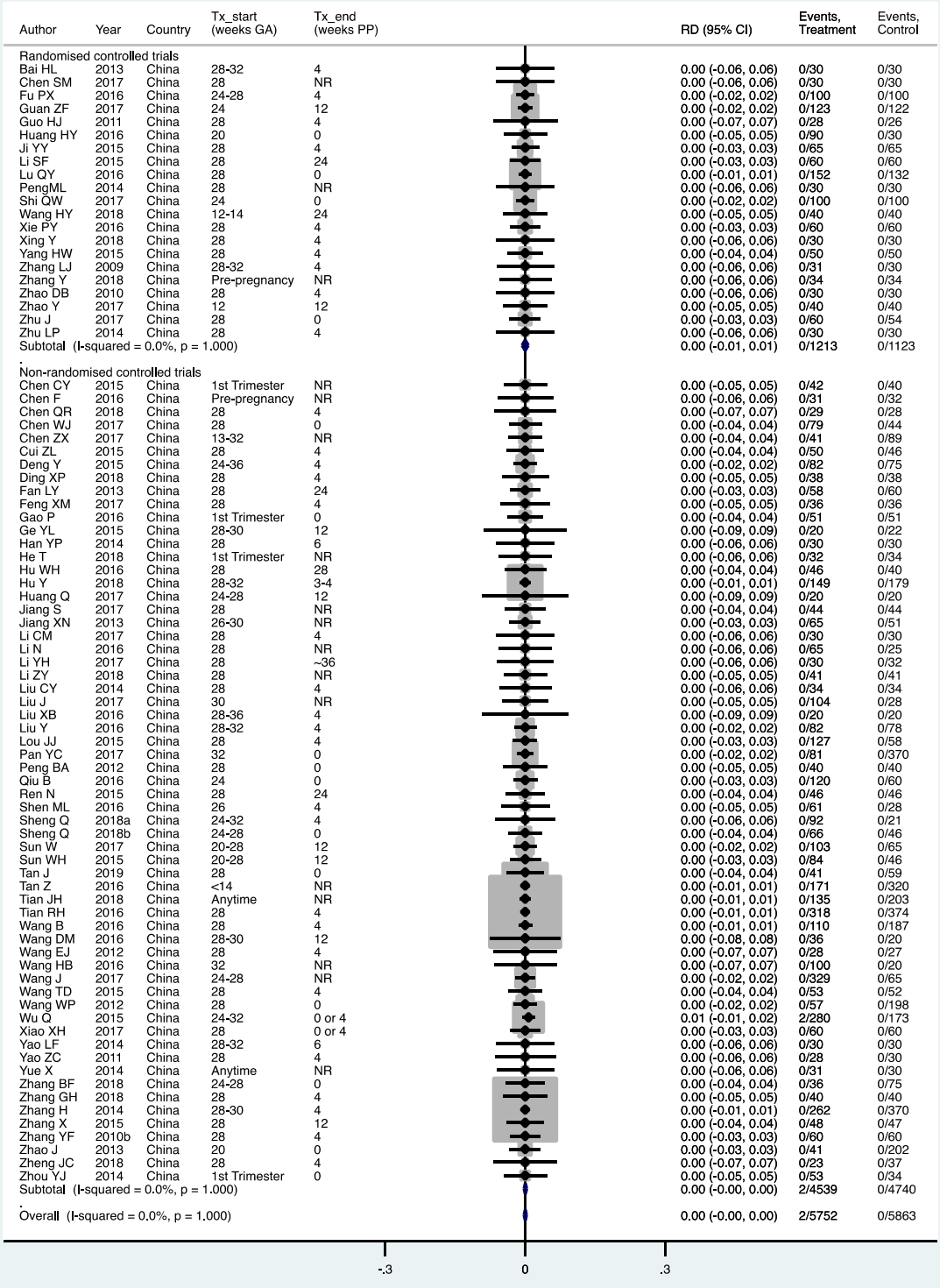
Infant safety outcomes

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. **Neonatal deaths** (*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 I^2 statistics for the overall pooled risk difference, as well as for RCTs and non-RCTs separately, were all 0.0%.

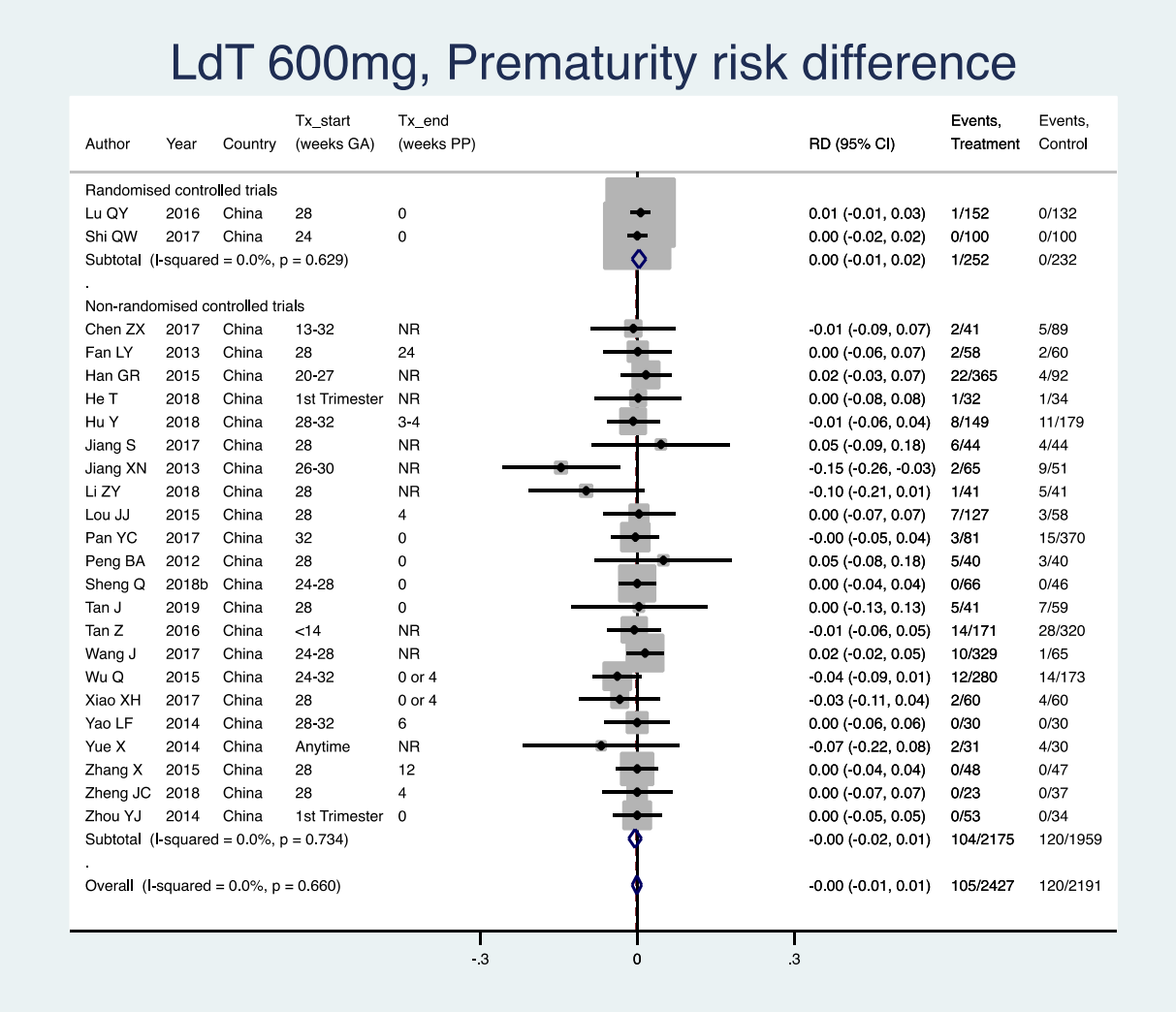
LdT 600mg, Neonatal deaths risk difference



Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	RD (95% CI)	Events, Treatment	Events, Control
Randomised controlled trials							
Bai HL	2013	China	28-32	4	0.00 (-0.06, 0.06)	0/30	0/30
Chen SM	2017	China	28	NR	0.00 (-0.06, 0.06)	0/30	0/30
Fu PX	2016	China	24-28	4	0.00 (-0.02, 0.02)	0/100	0/100
Guan ZF	2017	China	24	12	0.00 (-0.02, 0.02)	0/123	0/122
Guo HJ	2011	China	28	4	0.00 (-0.07, 0.07)	0/28	0/26
Huang HY	2016	China	20	0	0.00 (-0.05, 0.05)	0/90	0/30
Ji YY	2015	China	28	4	0.00 (-0.03, 0.03)	0/65	0/65
Li SF	2015	China	28	24	0.00 (-0.03, 0.03)	0/60	0/60
Lu QY	2016	China	28	0	0.00 (-0.01, 0.01)	0/152	0/132
PengML	2014	China	28	NR	0.00 (-0.06, 0.06)	0/30	0/30
Shi QW	2017	China	24	0	0.00 (-0.02, 0.02)	0/100	0/100
Wang HY	2018	China	12-14	24	0.00 (-0.05, 0.05)	0/40	0/40
Xie PY	2016	China	28	4	0.00 (-0.03, 0.03)	0/60	0/60
Xing Y	2018	China	28	4	0.00 (-0.06, 0.06)	0/30	0/30
Yang HW	2015	China	28	4	0.00 (-0.04, 0.04)	0/50	0/50
Zhang LJ	2009	China	28-32	4	0.00 (-0.06, 0.06)	0/31	0/30
Zhang Y	2018	China	Pre-pregnancy	NR	0.00 (-0.06, 0.06)	0/34	0/34
Zhao DB	2010	China	28	4	0.00 (-0.06, 0.06)	0/30	0/30
Zhao Y	2017	China	12	12	0.00 (-0.05, 0.05)	0/40	0/40
Zhu J	2017	China	28	0	0.00 (-0.03, 0.03)	0/60	0/54
Zhu LP	2014	China	28	4	0.00 (-0.06, 0.06)	0/30	0/30
Subtotal (I-squared = 0.0%, p = 1.000)					0.00 (-0.01, 0.01)	0/1213	0/1123
.							
Non-randomised controlled 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)	0/31	0/32
Chen QR	2018	China	28	4	0.00 (-0.07, 0.07)	0/29	0/28
Chen WJ	2017	China	28	0	0.00 (-0.04, 0.04)	0/79	0/44
Chen ZX	2017	China	13-32	NR	0.00 (-0.04, 0.04)	0/41	0/89
Cui ZL	2015	China	28	4	0.00 (-0.04, 0.04)	0/50	0/46
Deng Y	2015	China	24-36	4	0.00 (-0.02, 0.02)	0/82	0/75
Ding XP	2018	China	28	4	0.00 (-0.05, 0.05)	0/38	0/38
Fan LY	2013	China	28	24	0.00 (-0.03, 0.03)	0/58	0/60
Feng XM	2017	China	28	4	0.00 (-0.05, 0.05)	0/36	0/36
Gao P	2016	China	1st Trimester	0	0.00 (-0.04, 0.04)	0/51	0/51
Ge YL	2015	China	28-30	12	0.00 (-0.09, 0.09)	0/20	0/22
Han YP	2014	China	28	6	0.00 (-0.06, 0.06)	0/30	0/30
He T	2018	China	1st Trimester	NR	0.00 (-0.06, 0.06)	0/32	0/34
Hu WH	2016	China	28	28	0.00 (-0.04, 0.04)	0/46	0/40
Hu Y	2018	China	28-32	3-4	0.00 (-0.01, 0.01)	0/149	0/179
Huang Q	2017	China	24-28	12	0.00 (-0.09, 0.09)	0/20	0/20
Jiang S	2017	China	28	NR	0.00 (-0.04, 0.04)	0/44	0/44
Jiang XN	2013	China	26-30	NR	0.00 (-0.03, 0.03)	0/65	0/51
Li CM	2017	China	28	4	0.00 (-0.06, 0.06)	0/30	0/30
Li N	2016	China	28	NR	0.00 (-0.06, 0.06)	0/65	0/25
Li YH	2017	China	28	~36	0.00 (-0.06, 0.06)	0/30	0/32
Li ZY	2018	China	28	NR	0.00 (-0.05, 0.05)	0/41	0/41
Liu CY	2014	China	28	4	0.00 (-0.06, 0.06)	0/34	0/34
Liu J	2017	China	30	NR	0.00 (-0.05, 0.05)	0/104	0/28
Liu XB	2016	China	28-36	4	0.00 (-0.09, 0.09)	0/20	0/20
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 (-0.03, 0.03)	0/127	0/58
Pan YC	2017	China	32	0	0.00 (-0.02, 0.02)	0/81	0/370
Peng BA	2012	China	28	0	0.00 (-0.05, 0.05)	0/40	0/40
Qiu B	2016	China	24	0	0.00 (-0.03, 0.03)	0/120	0/60
Ren N	2015	China	28	24	0.00 (-0.04, 0.04)	0/46	0/46
Shen ML	2016	China	26	4	0.00 (-0.05, 0.05)	0/61	0/28
Sheng Q	2018a	China	24-32	4	0.00 (-0.06, 0.06)	0/92	0/21
Sheng Q	2018b	China	24-28	0	0.00 (-0.04, 0.04)	0/66	0/46
Sun W	2017	China	20-28	12	0.00 (-0.02, 0.02)	0/103	0/65
Sun WH	2015	China	20-28	12	0.00 (-0.03, 0.03)	0/84	0/46
Tan J	2019	China	28	0	0.00 (-0.04, 0.04)	0/41	0/59
Tan Z	2016	China	<14	NR	0.00 (-0.01, 0.01)	0/171	0/320
Tian JH	2018	China	Anytime	NR	0.00 (-0.01, 0.01)	0/135	0/203
Tian RH	2016	China	28	4	0.00 (-0.01, 0.01)	0/318	0/374
Wang B	2016	China	28	4	0.00 (-0.01, 0.01)	0/110	0/187
Wang DM	2016	China	28-30	12	0.00 (-0.08, 0.08)	0/36	0/20
Wang EJ	2012	China	28	4	0.00 (-0.07, 0.07)	0/28	0/27
Wang HB	2016	China	32	NR	0.00 (-0.07, 0.07)	0/100	0/20
Wang J	2017	China	24-28	NR	0.00 (-0.02, 0.02)	0/329	0/65
Wang TD	2015	China	28	4	0.00 (-0.04, 0.04)	0/53	0/52
Wang WP	2012	China	28	0	0.00 (-0.02, 0.02)	0/57	0/198
Wu Q	2015	China	24-32	0 or 4	0.01 (-0.01, 0.02)	2/280	0/173
Xiao XH	2017	China	28	0 or 4	0.00 (-0.03, 0.03)	0/60	0/60
Yao LF	2014	China	28-32	6	0.00 (-0.06, 0.06)	0/30	0/30
Yao ZC	2011	China	28	4	0.00 (-0.06, 0.06)	0/28	0/30
Yue X	2014	China	Anytime	NR	0.00 (-0.06, 0.06)	0/31	0/30
Zhang BF	2018	China	24-28	0	0.00 (-0.04, 0.04)	0/36	0/75
Zhang GH	2018	China	28	4	0.00 (-0.05, 0.05)	0/40	0/40
Zhang H	2014	China	28-30	4	0.00 (-0.01, 0.01)	0/262	0/370
Zhang X	2015	China	28	12	0.00 (-0.04, 0.04)	0/48	0/47
Zhang YF	2010b	China	28	4	0.00 (-0.03, 0.03)	0/60	0/60
Zhao J	2013	China	20	0	0.00 (-0.03, 0.03)	0/41	0/202
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
Subtotal (I-squared = 0.0%, p = 1.000)					0.00 (-0.00, 0.00)	2/4539	0/4740
.							
Overall (I-squared = 0.0%, p = 1.000)					0.00 (-0.00, 0.00)	2/5752	0/5863

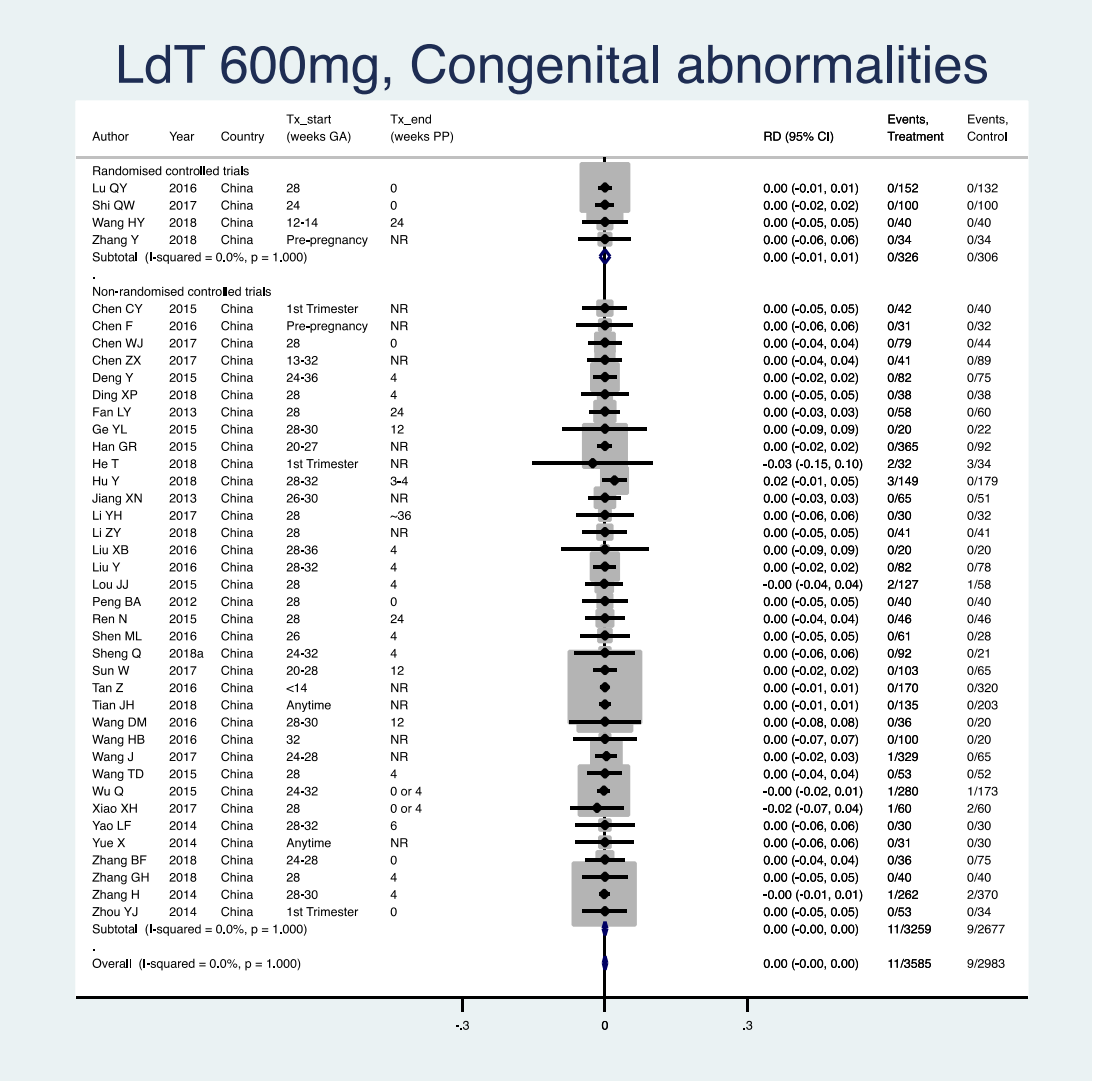
2. **Prematurity** (*typically defined as birth earlier than 37 weeks gestation*)

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 I^2 statistics for the overall pooled risk difference estimated was 0.0%. The I^2 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.



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 I^2 statistics for the overall pooled risk, as well as for RCTs and non-RCTs separately, were all 0%.

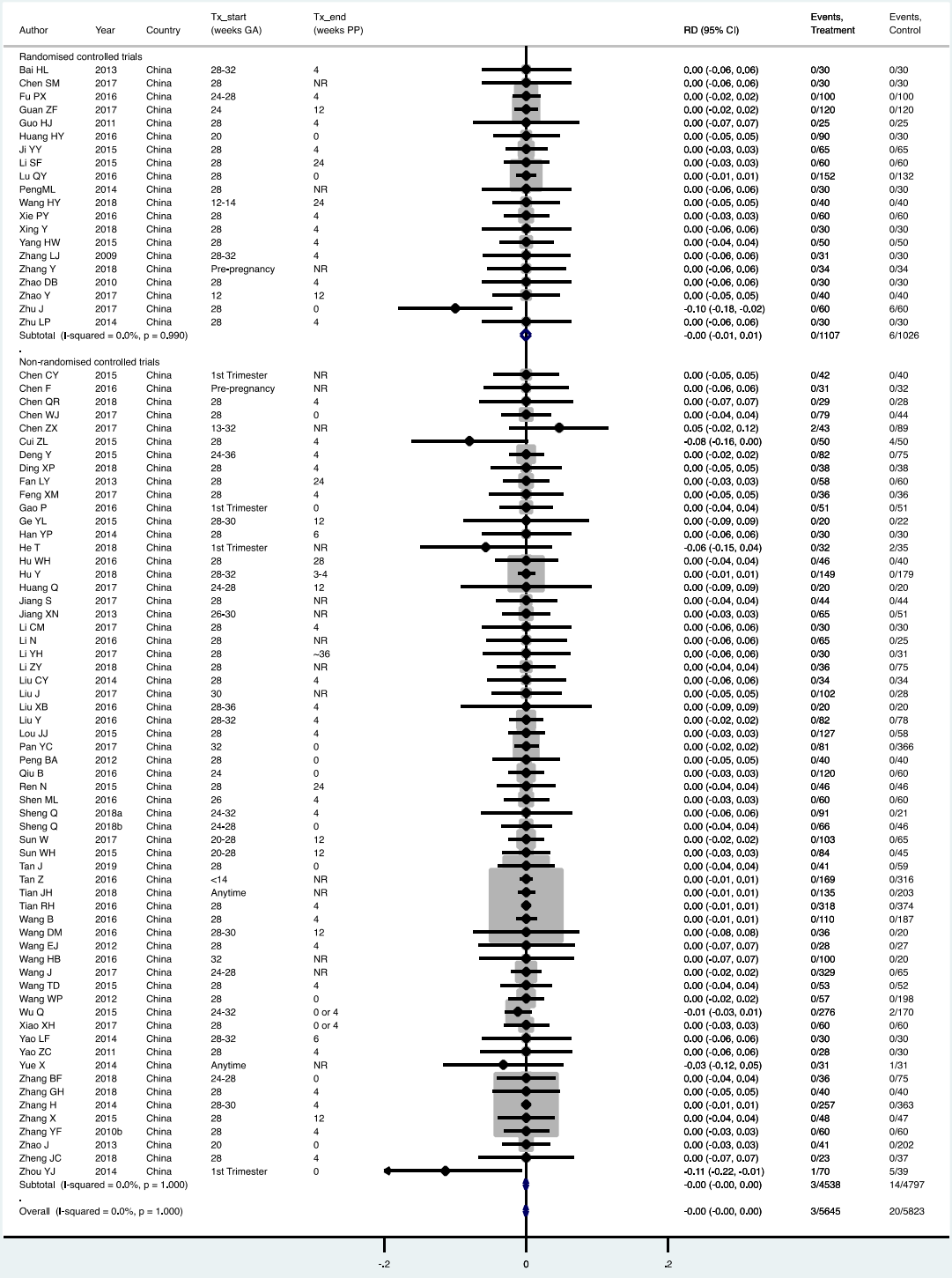


Maternal safety outcomes

1. **Fetal demise** (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 I^2 statistics for the overall pooled risk difference estimate, as well as for RCTs and non-RCTs separately, were all 0%.

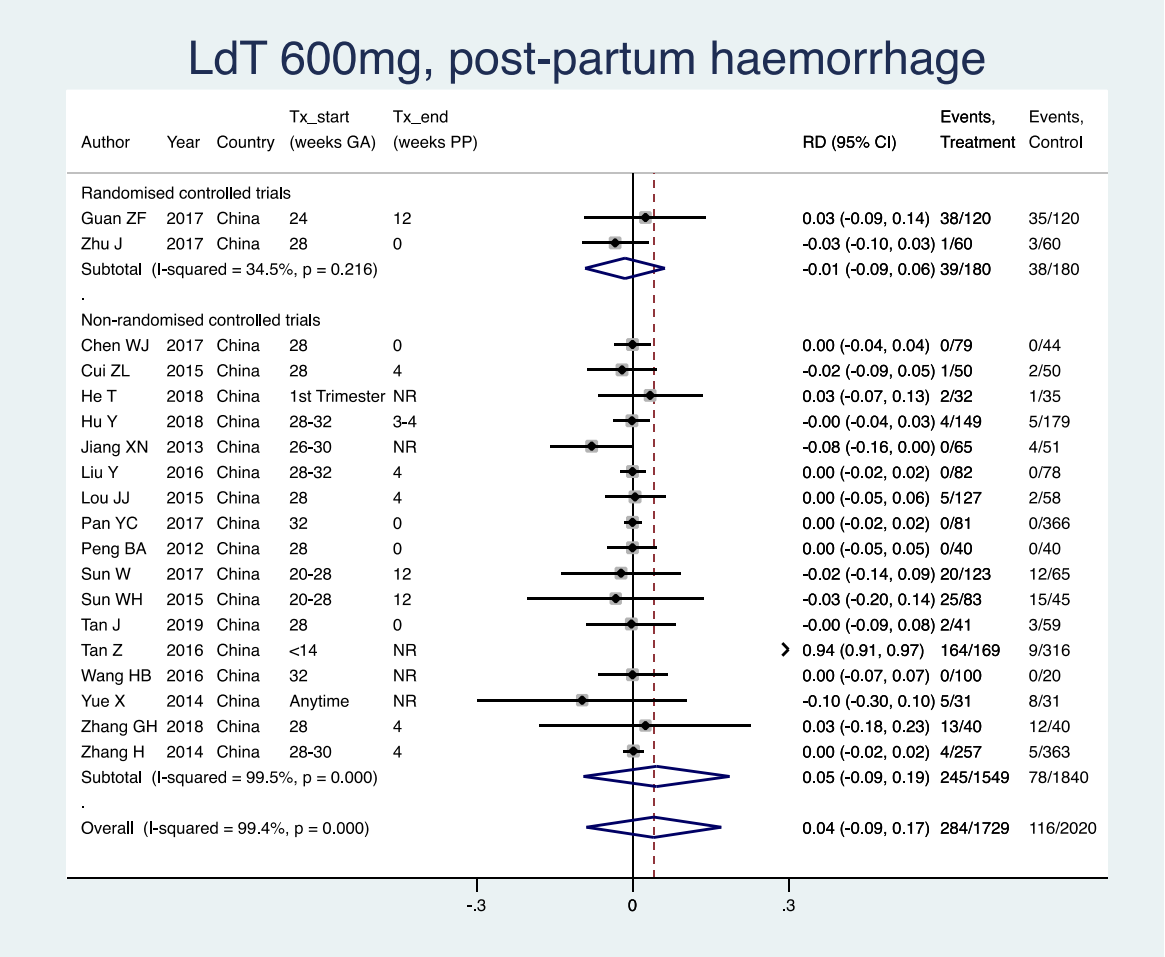
LdT 600mg, fetal demise risk difference



Author	Year	Country	Tx_start (weeks GA)	Tx_end (weeks PP)	RD (95% CI)	Events, Treatment	Events, Control
Randomised controlled trials							
Bai HL	2013	China	28-32	4	0.00 (-0.06, 0.06)	0/30	0/30
Chen SM	2017	China	28	NR	0.00 (-0.06, 0.06)	0/30	0/30
Fu PX	2016	China	24-28	4	0.00 (-0.02, 0.02)	0/100	0/100
Guan ZF	2017	China	24	12	0.00 (-0.02, 0.02)	0/120	0/120
Guo HJ	2011	China	28	4	0.00 (-0.07, 0.07)	0/25	0/25
Huang HY	2016	China	20	0	0.00 (-0.05, 0.05)	0/90	0/30
Ji YY	2015	China	28	4	0.00 (-0.03, 0.03)	0/65	0/65
Li SF	2015	China	28	24	0.00 (-0.03, 0.03)	0/60	0/60
Lu QY	2016	China	28	0	0.00 (-0.01, 0.01)	0/152	0/132
PengML	2014	China	28	NR	0.00 (-0.06, 0.06)	0/30	0/30
Wang HY	2018	China	12-14	24	0.00 (-0.05, 0.05)	0/40	0/40
Xie PY	2016	China	28	4	0.00 (-0.03, 0.03)	0/60	0/60
Xing Y	2018	China	28	4	0.00 (-0.06, 0.06)	0/30	0/30
Yang HW	2015	China	28	4	0.00 (-0.04, 0.04)	0/50	0/50
Zhang LJ	2009	China	28-32	4	0.00 (-0.06, 0.06)	0/31	0/30
Zhang Y	2018	China	Pre-pregnancy	NR	0.00 (-0.06, 0.06)	0/34	0/34
Zhao DB	2010	China	28	4	0.00 (-0.06, 0.06)	0/30	0/30
Zhao Y	2017	China	12	12	0.00 (-0.05, 0.05)	0/40	0/40
Zhu J	2017	China	28	0	-0.10 (-0.18, -0.02)	0/60	6/60
Zhu LP	2014	China	28	4	0.00 (-0.06, 0.06)	0/30	0/30
Subtotal (I-squared = 0.0%, p = 0.990)					-0.00 (-0.01, 0.01)	0/1107	6/1026
.							
Non-randomised controlled 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)	0/31	0/32
Chen QR	2018	China	28	4	0.00 (-0.07, 0.07)	0/29	0/28
Chen WJ	2017	China	28	0	0.00 (-0.04, 0.04)	0/79	0/44
Chen ZX	2017	China	13-32	NR	0.05 (-0.02, 0.12)	2/43	0/89
Cui ZL	2015	China	28	4	-0.08 (-0.16, 0.00)	0/50	4/50
Deng Y	2015	China	24-36	4	0.00 (-0.02, 0.02)	0/82	0/75
Ding XP	2018	China	28	4	0.00 (-0.05, 0.05)	0/38	0/38
Fan LY	2013	China	28	24	0.00 (-0.03, 0.03)	0/58	0/60
Feng XM	2017	China	28	4	0.00 (-0.05, 0.05)	0/36	0/36
Gao P	2016	China	1st Trimester	0	0.00 (-0.04, 0.04)	0/51	0/51
Ge YL	2015	China	28-30	12	0.00 (-0.09, 0.09)	0/20	0/22
Han YP	2014	China	28	6	0.00 (-0.06, 0.06)	0/30	0/30
He T	2018	China	1st Trimester	NR	-0.06 (-0.15, 0.04)	0/32	2/35
Hu WH	2016	China	28	28	0.00 (-0.04, 0.04)	0/46	0/40
Hu Y	2018	China	28-32	3-4	0.00 (-0.01, 0.01)	0/149	0/179
Huang Q	2017	China	24-28	12	0.00 (-0.09, 0.09)	0/20	0/20
Jiang S	2017	China	28	NR	0.00 (-0.04, 0.04)	0/44	0/44
Jiang XN	2013	China	26-30	NR	0.00 (-0.03, 0.03)	0/65	0/51
Li CM	2017	China	28	4	0.00 (-0.06, 0.06)	0/30	0/30
Li N	2016	China	28	NR	0.00 (-0.06, 0.06)	0/65	0/25
Li YH	2017	China	28	~36	0.00 (-0.06, 0.06)	0/30	0/31
Li ZY	2018	China	28	NR	0.00 (-0.04, 0.04)	0/36	0/75
Liu CY	2014	China	28	4	0.00 (-0.06, 0.06)	0/34	0/34
Liu J	2017	China	30	NR	0.00 (-0.05, 0.05)	0/102	0/28
Liu XB	2016	China	28-36	4	0.00 (-0.09, 0.09)	0/20	0/20
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 (-0.03, 0.03)	0/127	0/58
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
Qiu B	2016	China	24	0	0.00 (-0.03, 0.03)	0/120	0/60
Ren N	2015	China	28	24	0.00 (-0.04, 0.04)	0/46	0/46
Shen ML	2016	China	26	4	0.00 (-0.03, 0.03)	0/60	0/60
Sheng Q	2018a	China	24-32	4	0.00 (-0.06, 0.06)	0/91	0/21
Sheng Q	2018b	China	24-28	0	0.00 (-0.04, 0.04)	0/66	0/46
Sun W	2017	China	20-28	12	0.00 (-0.02, 0.02)	0/103	0/65
Sun WH	2015	China	20-28	12	0.00 (-0.03, 0.03)	0/84	0/45
Tan J	2019	China	28	0	0.00 (-0.04, 0.04)	0/41	0/59
Tan Z	2016	China	<14	NR	0.00 (-0.01, 0.01)	0/169	0/316
Tian JH	2018	China	Anytime	NR	0.00 (-0.01, 0.01)	0/135	0/203
Tian RH	2016	China	28	4	0.00 (-0.01, 0.01)	0/318	0/374
Wang B	2016	China	28	4	0.00 (-0.01, 0.01)	0/110	0/187
Wang DM	2016	China	28-30	12	0.00 (-0.08, 0.08)	0/36	0/20
Wang EJ	2012	China	28	4	0.00 (-0.07, 0.07)	0/28	0/27
Wang HB	2016	China	32	NR	0.00 (-0.07, 0.07)	0/100	0/20
Wang J	2017	China	24-28	NR	0.00 (-0.02, 0.02)	0/329	0/65
Wang TD	2015	China	28	4	0.00 (-0.04, 0.04)	0/53	0/52
Wang WP	2012	China	28	0	0.00 (-0.02, 0.02)	0/57	0/198
Wu Q	2015	China	24-32	0 or 4	-0.01 (-0.03, 0.01)	0/276	2/170
Xiao XH	2017	China	28	0 or 4	0.00 (-0.03, 0.03)	0/60	0/60
Yao LF	2014	China	28-32	6	0.00 (-0.06, 0.06)	0/30	0/30
Yao ZC	2011	China	28	4	0.00 (-0.06, 0.06)	0/28	0/30
Yue X	2014	China	Anytime	NR	-0.03 (-0.12, 0.05)	0/31	1/31
Zhang BF	2018	China	24-28	0	0.00 (-0.04, 0.04)	0/36	0/75
Zhang GH	2018	China	28	4	0.00 (-0.05, 0.05)	0/40	0/40
Zhang H	2014	China	28-30	4	0.00 (-0.01, 0.01)	0/257	0/363
Zhang X	2015	China	28	12	0.00 (-0.04, 0.04)	0/48	0/47
Zhang YF	2010b	China	28	4	0.00 (-0.03, 0.03)	0/60	0/60
Zhao J	2013	China	20	0	0.00 (-0.03, 0.03)	0/41	0/202
Zheng JC	2018	China	28	4	0.00 (-0.07, 0.07)	0/23	0/37
Zhou YJ	2014	China	1st Trimester	0	-0.11 (-0.22, -0.01)	1/70	5/39
Subtotal (I-squared = 0.0%, p = 1.000)					-0.00 (-0.00, 0.00)	3/4538	14/4797
.							
Overall (I-squared = 0.0%, p = 1.000)					-0.00 (-0.00, 0.00)	3/5645	20/5823

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 I^2 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.

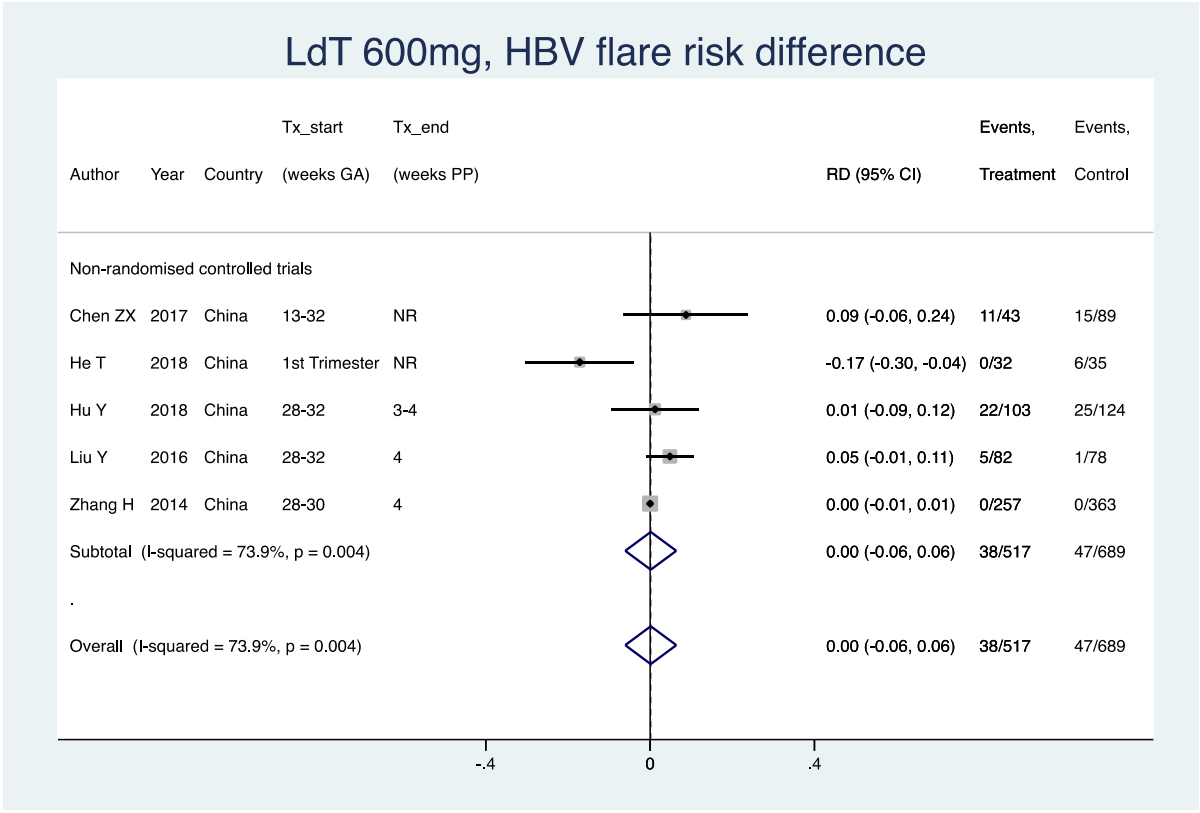


3. **Antiviral resistance**

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 time-point. The weighted pooled risk difference for this safety outcome seen following meta-analysis 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%).


LdT 600mg, HBV flare risk difference
Author
Year
Country
Tx_start (weeks GA)
Tx_end (weeks PP)
RD (95% CI)
Events, Treatment
Events, Control
Non-randomised controlled trials
Chen ZX 2017 China 13-32 NR 0.09 (-0.06, 0.24) 11/43 15/89
He T 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 25/124
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-squared = 73.9%, p = 0.004) 0.00 (-0.06, 0.06) 38/517 47/689
.
Overall (I-squared = 73.9%, p = 0.004) 0.00 (-0.06, 0.06) 38/517 47/689
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GRADE summary of findings

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

Number of studies	Design	Quality assessment						Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	
HBsAg positivity 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 safety: neonatal deaths												
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 safety: prematurity												
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 safety: congenital abnormalities												
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 safety: miscarriage and stillbirth												
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[l]
Maternal safety: postpartum haemorrhage												
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]

[a]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[b]Downgrading due to possible evidence of publication bias/small study effects, upgrading due to magnitude of effect.
[c]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high.
[d]Downgrading due to possible evidence of publication bias/small study effects, upgrading due to magnitude of effect.
[e]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[f]No upgrading or downgrading
[g]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[h]No upgrading or downgrading
[i]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[j]No upgrading or downgrading
[k]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[l]No upgrading or downgrading
[m]Downgrading 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 (I^2>30%), downgrading due to imprecision.
[n]Downgrading due to "very serious" inconsistency (I^2>60%), downgrading due to imprecision, downgrading due to evidence of possible publication bias/small study effects.
[o]Downgrading 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).

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

	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

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

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 HBeAg-negative 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 ≥5 log10 IU/mL and 2.2% of women with viraemia ≥7 log10 IU/mL are negative for HBeAg.

REFERENCES

- AASLD, 2018. American Association for the Study of Liver Disease Practice Guidelines. Accessed at: https://www.aasld.org/publications/practice-guidelines. Last accessed on September 2nd, 2019.
- APASL, 2016. Asian Pacific Association for the Study of the Liver Guidelines. Accessed at: http://apasl.info/guidelines/ Last accessed on September 2nd, 2019.
- Bai H, Shang H, Li Z. Clinical investigation on telbivudine preventing intrauterine hepatitis B virus infection during late pregnancy. China Medical Engineering 2013; 21 (6): 53-54
- Bai XW, Wang X, Li J, Wang L. Effects of different maternal and child block modes on mother-to-child transmission of neonatal hepatitis B virus. Maternal and Child Health Care of China 2011; 26 (21): 3265-3266
- Cao Y. The curative effect of telbivudine throughout pregnancy in pregnant women with chronic hepatitis B and its efficacy to prevent mother-to-child transmission of hepatitis B virus. World of Mother and Infant 2018; (1): 83
- Celen MK, Mert D, Ay M, Dal T, Kaya S, Yildirim N et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. World J Gastroenterol 2013 December 28; 19(48): 9377-9382
- Chang MH. Natural History and clinical management of chronic hepatitis B virus infection in children. Hepatol Int 2008; 2: S28-S36.
- Chen CY, Tu X, Cheng Q, Chen F, Dai Y, Gong F, et al. Clinical observation of telbivudine's antiviral efficacy and protection against mother-to-infant transmission of chronic hepatitis B during the first trimester of pregnancy. Chin J Hepatol 2015; 23 (1): 9-12
- Chen F, Tu X, Chen C, Cheng Q, Li X, Lin X, et al. Clinical observation on antiviral efficacy and blocking of mother-to-infant transmission by telbivudine in women with chronic hepatitis B throughout pregnancy. Journal of Practical Medicine 2016; 32 (4): 636-639

- Chen HL, Lee CN, Chang CH, Ni YH, Shyu MK, Chen SM et al. Efficacy of Maternal Tenofovir Disoproxil Fumarate in Interrupting Mother-to-Infant Transmission of Hepatitis B Virus. HEPATOLOGY, Vol. 62, No. 2, 2015, 375-386
- Chen HL, Lin LH, Hu FC, Lee JT, Lin WT, Yang YJ, et al. Effects of Maternal Screening and Universal Immunization to Prevent Mother-to-Infant Transmission of HBV. Gastroenterology 2012; 142: 773-781.
- Chen QR, Li J, Chen L, Meng L. Clinical study on blocking of mother-to-child transmission of chronic hepatitis B virus via nucleoside analogues. Maternal and Child Health Care of China 2018; 33 (24): 5719-5721
- Chen SM. Comparison of the efficacy of antiviral therapy with lamivudine and telbivudine during pregnancy to prevent mother-to-child transmission of hepatitis B virus. Journal of China Prescription Drug 2017; 15 (1): 54-55
- Chen WJ, Song S, He H, Liang Q. Comparison of efficacy and safety of tenofovir and telbivudine during pregnancy to prevent mother-to-child transmission of HBV. Shandong Medicine 2017; 57 (22): 73-75
- Chen YL, Gao X, Li J. The prevention of intrauterine hepatitis B virus infection by telbivudine combined with hepatitis B vaccine. Acta Universitatis Medicinalis Nanjing 2014; 34 (1): 67-68
- Chen ZX, Gu GF, Bian ZL, Cai WH, Shen Y, Hao YL et al. Clinical course and perinatal transmission of chronic hepatitis B during pregnancy in a real-life setting: A prospective cohort study. J Infect. 2017 Aug;75(2):146-154. doi: 10.1016/j.jinf.2017.05.012
- Cheng YC. Observation on the efficacy of lamivudine to prevent mother-to-child transmission in chronically HBV-infected pregnant women with high viral load. Zhejiang Practical Medicine 2011; 16 (1): 28-30
- Clinical observation on lamivudine preventing mother-to-child transmission of hepatitis B virus. Jiangxi Medical Journal 2009; 44 (3): 250-251
- The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. 2008. Published by John Wiley & Sons Ltd, West Sussex, England.
- Cui ZL. The effect of telbivudine on liver function and pregnancy outcome in pregnant women with chronic hepatitis B. IMHGN 2015; 21 (21): 3202-3204

- Deng Y, Wu W, Zhang D, Hu P, Kang J, Yang Y, et al. The safety of telbivudine in preventing mother-to-infant transmission of hepatitis B virus in pregnant women after discontinuation. Chin J Hepatol 2015; 23 (8): 586-589
- Ding XP, Jin Hai. The curative effect of telbivudine to interrupt mother-to-child transmission in pregnant women with chronic hepatitis B and its influence on the transplacental transfer rate of hepatitis B virus antigen. Health Research 2018; 38 (5): 574-576
- EASL. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. (2017)Accessible at : https://easl.eu/wp-content/uploads/2018/10/HepB-English-report.pdf. Last retrieved September 2nd, 2019.
- Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. Proc. R. Soc. Lond. B 1993; 253:197-201
- Evans AA, O'Connell AP, Pugh JC, Mason WS, Shen F, Chen GC, et al. Geographic variation in viral load among Hepatitis B Carriers with differing risks of hepatocellular carcinoma. Cancer Epidemiology, Biomarkers & Prevention 1998; 7:559-565.
- Fan LY, Jiang X, Wan J, Ye J, Zhou W. Efficacy and safety of telbivudine in the perinatal transmission of hepatitis B virus. J Med Res 2013; 42 (9): 103-106
- Fang H, Xiao D, Fang C. Case report of 42 pregnant women receiving adefovir combined with hepatitis B immunoglobulin to prevent mother-to-child transmission of hepatitis B virus. Chinese Medicine Modern Distance Education of China 2011; 9 (6): 25-26
- Feng HF, Zhang S. Effect on interruption of hepatitis B virus vertical transmission by lamivudine. J Appl Clin Pediatr 2007; 22 (13): 1019-1020
- Feng XM. Clinical efficacy of telbivudine combined with hepatitis B vaccine to prevent mother-to-child transmission of HBV. Clinical Research and Practice 2017; 2 (7): 48-49

- Feng Y, Xu C, Zhang H, Huang Y, Wei W. Effect of adefovir dipivoxil on blocking the mother-to-infant vertical transmission in chronic hepatitis B virus infected women. Chin J Nosocomiol 2018; 28 (16): 2439-2454
- Foaud HM, Maklad S, Gmal El Din A, Mahmoud F. Lamivudine use in pregnant HBsAg-females effectively reduces maternal viremia. Arab J Gastroenterol. 2019 Mar;20(1):8-13. doi: 10.1016/j.ajg.2019.02.003
- Fu P. The efficacy and safety of telbivudine to prevent mother-to-child transmission of HBV during late pregnancy. Psychologist 2016; 22 (16): 109-110
- Gao P. Clinical observation of individual antiviral efficacy of chronic hepatitis B patients in early pregnancy and mother to child block. J Medical Forum 2016; 37 (6): 50-52
- Ge J, Hu J. The awareness towards and intervention against telbivudine combined with passive-active immunoprophylaxis to prevent mother-to-child transmission of HBV during late pregnancy. Medical Aesthetics and Cosmetology 2015; 24 (6): 726
- Ge YL, Sun H, Lv J. Efficacy of lamivudine or telbivudine administered to prevent hepatitis B virus vertical transmission. Chin J Clin Pharmacol 2015; 31 (2): 83-85
- Gong Q, Zhai D. The efficacy of TDF in patients with chronic hepatitis B during pregnancy and the effectiveness of mother-to-infant blocking transmission. China Continuing Medical Education 2017; 9 (21): 173-174
- The GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490– 4.
- Greenup AJ, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of Hepatitis B Virus. J Hepatol. 2014 Sep;61(3):502-7. doi: 10.1016/j.jhep.2014.04.038
- Greenup AJ, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U et al. Corrigendum to ‘‘Efficacy and safety of tenofovir disoproxil fumarate (TDF) in pregnancy to prevent perinatal transmission of hepatitis B virus’’ [J Hepatol 2014;61:502–507]. Journal of Hepatology 2015 vol. 63: 1054

- Guan Z, Song R, Wang L, Wang Y. Effect of taking telbivudine in second or third-trimester pregnancy on placental penetration. Acta Med Univ Sci Technol Huazhong 2017; 46 (4): 475-479
- Guo H, Zhang Y. Observation on the effect of telbivudine to interrupt mother-to-child transmission of HBV in pregnant women with high viral load. Journal of Changzhi Medical College 2011; 25 (5): 368-370
- Guo YZ, Li S, Ge S, Wang J. The clinical application of lamivudine in interdiction of maternal-to-child transmission for the HBsAg, HBeAg-positive pregnant women. Chin J of Clinical Rational Drug Use 2008; 1 (1): 8-9
- Han GR, Jiang HX, Yue X, Ding Y, Wang CM, Wang GJ et al. Efficacy and safety of telbivudine treatment: an open-label, prospective study in pregnant women for the prevention of perinatal transmission of hepatitis B virus infection. J Viral Hepat. 2015 Sep;22(9):754-62. doi: 10.1111/jvh.12379
- Han ZH, Chen Y, Li L, Sun X, Sun Y, Zhao H, et al. Observation on efficacy and safety of lamivudine to interrupt mother-to-child transmission of hepatitis B virus. Chin J Intern Med 2005; 44 (5): 378
- Han YP. The comparison of efficacy of antiviral therapy with lamivudine and telbivudine during pregnancy to prevent mother-to-child transmission of hepatitis B virus. Hebei Medical Journal 2014; 36 (3): 389-390
- He L, Tang Z. Clinical study on HBV-DNA quantification in pregnant women and mother-to-fetus vertical transmission. Maternal and Child Health Care of China 2018; 33 (6): 1239-1241
- He T, Bai Y, Cai H, Ou X, Liu M, Yi W et al. Safety and efficacy of lamivudine or telbivudine started in early pregnancy for mothers with active chronic hepatitis B. Hepatol Int. 2018 Mar;12(2):118-125. doi: 10.1007/s12072-017-9839-5.
- Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane handbook for systematic reviews of interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011. (www.cochrane-handbook.org. Accessed 13th March 2019).

- Hu M, Zhuang L, Wang J, Li L, Yang Y, Bai B, et al. The efficacy and safety of tenofovir on blocking mother-infant transmission of hepatitis B. Chin J Drug Depend 2018; 27 (5): 379-383
- Hu WH, Zhang X, Liao Y. Efficacy evaluation of interventions to prevent mother-to-child transmission of hepatitis B virus in Yunfu City. Journal of Qiqihar University of Medicine 2016; 37 (16): 2081-2083
- Hu Y, Xu C, Xu B, Hu L, Liu Q, Chen J et al. Safety and efficacy of telbivudine in late pregnancy to prevent mother-to-child transmission of hepatitis B virus: A multicenter prospective cohort study. J Viral Hepat. 2018;25:429–437
- Huang HY, Wang M, Zhou J. Effect of antiviral therapy during different periods of pregnancy on the immune efficiency of maternal and infant transmission blocking of high HBV-DNA viral load in pregnant women. Chinese Journal of Eugenics and Genetics 2016; 24 (11): 72-73, 96
- Huang Q, Zhao X. The observation on the curative effect of antiviral treatment in the middle and late pregnancy to prevent mother-to-infant transmission of HBV. Qinghai Medical Journal 2017; 47 (7): 6-8
- Hutin Y, Desai S, Bulterys M. Preventing hepatitis B virus infection: milestones and targets. Bull World Health Organ. 2018; 96(7):443-A.
- Jackson V, Ferguson W, Kelleher TB, Lawless M, Eogan M, Nusgen U et al. Lamivudine treatment and outcome in pregnant women with high hepatitis B viral loads. Eur J Clin Microbiol Infect Dis. 2015 Mar;34(3):619-23. doi: 10.1007/s10096-014-2270-0.
- Ji YY. Efficacy comparison of lamivudine and telbivudine combined with hepatitis B vaccine in blocking vertical transmission of hepatitis B virus. Chin J Postgrad Med 2015; 38 (1): 41-43
- Jiang HX, Han G, Wang C, Ji Y. Maternal-fetal outcomes of lamivudine treatment administered during late pregnancy to highly viremic mothers with HBeAg+ chronic hepatitis B. Chin J Hepatol 2012; 20 (12): 888-891
- Jiang S. The efficacy and safety of telbivudine to prevent mother-to-child transmission of hepatitis B virus. Diet Health 2017; 4 (23): 99-100

- Jiang XN, Fan L, Li D, Wan J, Ye J. Clinical trial of telbivudine in the treatment of chronic hepatitis B in patients during the third trimester of pregnancy. J Clin Hepatol 2013; 29 (2): 101-103
- Jourdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khamduang W, Tierney C, et al., Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. N Engl J Med. 2018;378 (10):911–23.
- Keane E, Funk A, Shimakawa Y. Systematic review with meta-analysis: the risk of mother-to-child transmission of hepatitis B virus infection in sub-Saharan Africa. Aliment Pharmacol Ther 2016; 44 (10):1005-1017
- Kochaksaraei GS, Castillo E, Osman M, Simmonds K, Scott AN, Oshiomogho JI et al. Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant patients in a low hepatitis B virus endemic region. Journal of Viral Hepatitis, 2016, 23, 15–2
- Kourtis AP, Wiener J, Wang L, Fan B, Shepherd J, Chen L et al., Tenofovir Disoproxil Fumarate Use during Pregnancy and Infant Bone Health: the Tenofovir in Pregnancy Pilot Study. Pediatr Infect Dis J 2018; 37 (11): e264-e268
- Li CM, Xie R. The efficacy and safety of telbivudine to prevent mother-to-child transmission of hepatitis B virus. Northern Pharmacy 2017; 14 (8): 153-154
- Li G, Du W. Observation on effect of combined treatment to interrupt mother-to-child transmission of hepatitis B virus. Journal of Wenzhou Medical College 2006; 36 (5): 493-495
- Li JH. Clinical study of combined application of lamivudine, hepatitis B vaccine and immunoglobulin in blocking mother-to-child transmission of hepatitis B. Chinese General Practice 2017; 20 (S1): 128-130
- Li N, Cui W. Effects of hepatitis B virus transmission blocked by telbivudine on different period of pregnancy women. Medical Innovation of China 2016; 13 (1): 89-92
- Li SF, Zhai Z, Cui Q. Pharmacy analysis of telbivudine to prevent mother-to-child transmission of hepatitis B virus. World of Mother and Infant 2015; (6): 144-145
- Li WF, Jiang R, Wei Z, Li Y. Clinical effect and safety of lamivudine to interrupt mother-to-child transmission of hepatitis B virus in pregnant women chronically infected with hepatitis B. Chinese Hepatology 2006; 11 (2): 106-107

- Li YH, Wang D, Chen M. Observation on the curative effect of telbivudine to prevent mother-to-child transmission of HBV. Northern Pharmacy 2017; 14 (11): 103-104
- Li ZY, Guo B, Wang S, Ping H, Lin X. Efficacy and safety of telbivudine for maternal-infant blockade in pregnant women with high-load chronic hepatitis B virus infection. Drug Evaluation Research 2018; 41 (11): 2073-2077
- Li ZG, Liu X. The comparison of efficacy of antiviral therapy with lamivudine and telbivudine during pregnancy to prevent mother-to-child transmission of hepatitis B virus. World Latest Medicine Information 2015; 15 (55): 72
- Liu CY, Gao X, Pang Q. Clinical studies on telbivudine blocking mother-to-infant transmission of high load pregnant women with chronic hepatitis B virus. Journal of Yanan University 2014; 12 (4): 18-20, 42
- Liu CP, Zeng YL, Zhou M, Chen LL, Hu R, Wang L et al. Factors Associated with Mother-to-child Transmission of Hepatitis B Virus Despite Immunoprophylaxis. Intern Med 54: 711-716, 2015
- Liu J, Wang C. Effect of telbivudine in treatment of hyperplasma viremia pregnant women during immune tolerant phase of hepatitis B virus infection and during the second and the third trimesters of pregnancy and observation on the proportion of pregnant women with increased alanine aminotransferase level after drug withdrawal. Maternal and Child Health Care of China 2017; 32 (15): 3477-3480
- Liu M, Chen H, Tang H. The curative effect of tenofovir dipivoxil fumarate to interrupt mother-to-child transmission of hepatitis B virus. Chinese Journal of Woman and Child Health Research 2017; 28 (4): 378-379
- Liu XB, Li Y, Wang L. The clinical application of telbivudine to prevent mother-to-child transmission of chronic hepatitis B infection. Journal of Contemporary Clinical Medicine 2016; 29 (6): 2649-2650
- Lin Y, Liu Y, Ding G, Touqui L, Wang W, Xu N et al. Efcacy of tenofovir in preventing perinatal transmission of HBV infection in pregnant women with high viral loads. Nature Scientific Reports 2018; 8:15514
- Liu Y, Wang M, Yao S, Yuan J, Lu J, Li H et al. Efficacy and safety of telbivudine in different trimesters of pregnancy with high viremia for interrupting perinatal transmission of hepatitis B virus. Hepatology Research 2016; 46: E181–E188

- Lu Q. The efficacy and safety of antiviral drugs joint with hepatitis B immunoglobulin in treatment of HBV mother-to-child transmission block in maternal late-pregnancy. Henan J Prev Med 2016; 27 (3): 171-173, 176
- Lou JJ, Zhang J, Wang Y, Yu R. Efficacy and safety of telbivudine in preventing the transmission of HBV from mother to child in late pregnancy in women with high viral load. Chinese Journal of Microecology 2015; 27 (12): 1464-1467
- Luo DX, He K. The exploration on the efficacy of telbivudine to prevent mother-to-child transmission of hepatitis B virus and its nursing intervention. Chinese Journal of Woman and Child Health Research 2017; 28 (2): 626
- Ma J, Sui J, Bai B, Yang Z, Fu L. Observations on virus development intervention efficacy and safety of lamivudine in treatment of chronic hepatitis B patients with pregnancy. China Practical Medical 2006; 1 (1): 19-21
- Machaira M, Papaevangelou V, Vouloumanou EK, Tansarli GS, Falagas ME. Hepatitis B vaccine alone or with hepatitis B immunoglobulin in neonates of HBsAg+/HBeAg- mothers: a systematic review and meta-analysis. J Antimicrob Chemother 2015; 70: 396-404.
- Miyahara R, Jasseh M, Gomez P, Shimakawa Y, Greenwood B, Keita K, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. Vaccine 2016; 34: 3335-3341.
- Nayagam S, Thursz M, Sicuri E, Conteh L, Wiktor S, Low-Beer D, et al. Requirements for global elimination of hepatitis B: a modelling study. Lancet Infect Dis 2016; 16(12):1399-408.
- Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med 2016;374:2324-34
- Pan CQ, Yi W, Liu M, Wan G, Hu YH, Zhou MF. Lamivudine therapy during the second vs the third trimester for preventing transmission of chronic hepatitis B. J Viral Hepat. 2017 Mar;24(3):246-252. doi: 10.1111/jvh.12640.
- Pan YC, Wang C, Wen S, Wang C, Kong F, Niu J, et al. Clinical effect and short-term safety of telbivudine in blocking mother-to-child transmission of HBV. J Clin Hepatol 2017; 33 (9): 1707-1712

- ~~Pan Y, Wang C, Wen S, Wang C, Kong F, Niu J, et al. Clinical effect and short-term safety of telbivudine in blocking mother-to-child transmission of HBV. J Clin Hepatol 2017; 33 (9): 1707-1712~~
- Peng BA, Zhao Y, Yang X, Miao M, Zhu L, Yu H. Evaluation of the efficacy and safety of telbivudine in preventing mother-to-infant HBV transmission. Chin Pharm J 2012; 47 (11): 855-857
- Peng M, Liu W, Lv W, Pang Y. Effect of telbivudine combined with hepatitis B vaccine and immune globulin on blocking mother-infant vertical transmission of hepatitis B virus. Chin J Nosocomiol 2014; 24 (1): 15-16, 33
- Qiu B, Zhu L, Chen Y, Wu X, Liu X, Wang T, et al. Application of telbivudine before or after pregnancy in blocking intrauterine mother-to-child transmission of hepatitis B virus in human. J Prac Hepatol 2016; 19 (4): 428-431
- Ren CJ, Xiong Y. Efficacy and safety of lamivudine in preventing mother-to-infant transmission of hepatitis B virus in pregnant women with high virus load. J Med Theor & Prac 2016; 29 (4): 436-438
- Ren N, Hu S. Clinical studies on telbivudine blocking effect of mother-to-infant transformation of pregnant women with chronic hepatitis B virus and its safety analysis. China Medicine and Pharmacy 2015; 5 (16): 7-9, 62
- Ren YJ, Guo J, Chen W, Jiao R. Observation on antiviral therapy interrupting mother-to-child transmission of hepatitis B virus. Hebei Medical Journal 2011; 33 (24): 3721-3722
- Salvadori N, Fan B, Teeyasoontranon W, Ngo-Giang-Huong N, Phanomcheong S, Luvira A et al. Maternal and Infant Bone Mineral Density 1 Year After Delivery in a Randomized, Controlled Trial of Maternal Tenofovir Disoproxil Fumarate to Prevent Mother-to-child Transmission of Hepatitis B Virus. Clin Infect Dis. 2019 Jun 18;69(1):144-146. doi: 10.1093/cid/ciy982.
- Shen ML, Xu H, Ju H, Xian J, Yang X. Sequential telbivudine/lamivudine and hepatitis B immunoglobulin therapy for preventing mother-to-infant transmission of hepatitis B virus. WCJD 2016; 24 (23): 3517-3522
- Sheng Q, Ding Y, Li B, Han C, Li Y, Zhang C et al. Efficacy and safety of nucleos(t)ide analogues to prevent hepatitis B virus mother-to-child transmission in

pregnant women with high viremia: real life practice from China. Int. J. Med. Sci. 2018; 15(8): 796-801

- Sheng QJ, Wang SJ, Wu YY, Dou XG, Ding Y. Hepatitis B virus serosurvey and awareness of mother-to-child transmission among pregnant women in Shenyang, China: An observational study. Medicine. 2018; 97:22
- Shi Q. Standard interruption of mother-to-child transmission of hepatitis B virus with prenatal intervention and postnatal combined immunoprophylaxis. Mod Diagn Treat 2017; 28 (1): 100-102
- Shimakawa Y, Hong-Jing Y, Tsuchiya N, BottomLey C, Hall AJ. Association of early age at establishment of Hepatitis B infection with persistent viral replication, liver cirrhosis, and hepatocellular carcinoma: a systematic review. PLOS ONE 2013;8(7):e69430.
- Song J, Yang F, Wang S, Tikande S, Deng Y et al., Efficacy and safety of antiviral treatment on blocking the mother-to-child transmission of hepatitis B virus: A meta-analysis. Journal of Viral Hepatitis 2019;26:397–406
- Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, et al., Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002
- Su TB, Liu J. Observation on the effect of lamivudine combined with hepatitis B immunoglobulin and hepatitis B vaccine to prevent mother-to-child transmission of hepatitis B virus. Chinese Journal of Coal Industry Medicine 2009;12(1):104
- Sun WH, Ma L, Hao A, Liu W, Song M, Li M, et al. Predictive value of telbivudine in preventing mother-to-infant transmission of hepatitis B virus in pregnant women with high viremia. Chin J Hepatol 2015; 23(3):180-183
- Sun W, Zhao S, Ma L, Hao A, Zhao B, Zhou L et al. Telbivudine treatment started in early and middle pregnancy completely blocks HBV vertical transmission. BMC Gastroenterology 2017; 17:51
- Tan J, Ye X, Wang H. Efficacy of telbivudine in blocking mother-to-child transmission of hepatitis B virus infection in pregnant women with serum HBsAg positive and its influence on infant's response to hepatitis B vaccination. J Prac Hepatol 2019; 22 (1): 49-52

- Tan Z, Yin Y, Zhou J, Wu L, Xu C, Hou H. Telbivudine treatment of hepatitis B virus-infected pregnant women at different gestational stages for the prevention of mother-to-child transmission: Outcomes of telbivudine treatment during pregnancy. Medicine 2016; 95:40
- Tavakolpour S, Darvishi M, Mirsafaei HS, Ghasemiadl. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B infection during pregnancy: a systematic review. Infectious Diseases, 2018; 50 (2); 95–106.
- Tian JH, Wang H, Huang C, Chen Y, Liu M. Study on curative effect and safety of telbivudine in blocking the maternal-neonatal transmission of hepatitis B virus. China & Foreign Medical Treatment 2018; 37 (2): 134-136
- Tian RH, Li R, Lv J, Zhang L, Zhang H. Nursing management of pregnant women receiving antiviral therapy during pregnancy to interrupt intrauterine transmission of hepatitis B virus. Chinese Journal of Clinical Research 2016; 29 (4): 566-568
- Tian XQ, Han Y. Clinical research and nursing on hepatitis B immunoglobulin combined with lamivudine to prevent mother-to-child transmission of hepatitis B virus. Shanxi Med J 2015; 44 (18): 2186-2188
- van Zonneveld M, van Nunen AB, Niesters HGM, de Man RA, Schalm SW, Janssen HLA. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. Journal of Viral Hepatitis, 2003, 10, 294–297
- Wakano Y, Sugiura T, Endo T, Ito K, Suzuki M, Tajiri H et al. Antiviral therapy for hepatitis B virus during second pregnancies. J. Obstet. Gynaecol. Res. Vol. 44, No. 3: 566–569, March 2018
- Wan JY, Cai Q, Wang M. Efficacy and safety of tenofovir on blocking mother to child transmission of hepatitis B virus in virus high load pregnant women. China Tropical Medicine 2017; 17 (8): 828-830
- Wang B, Rong J. Clinical observation on telbivudine interrupting mother-to-child transmission of hepatitis B virus. Chinese Remedies & Clinics 2016; 16 (3): 386-388
- Wang DM. The efficacy and safety of lamivudine and telbivudine to prevent mother-to-child transmission of hepatitis B virus. Chinese Hepatology 2016; 21 (11): 972-974

- Wang EJ. Comparison of efficacy and safety between lamivudine and telbivudine in blocking vertical transmission ofhepatitis B virus in late stage of pregnancy. Chinese General Practice 2012; 15 (11): 3628-3630
- Wang HB, Li H, Yang X, Gong M, Gao S, Zhang F, et al. Clinical observation of effectiveness and safety on blocking HBV vertical transmission via oral telbivudine treatment in middle-late pregnancy. Journal of Practical Medicine 2016; 32 (23): 3928-3931
- Wang H, Li H, Yang X, Gong M, Gao S, Zhang F, et al. Efficacy and safety on blocking HBV vertical transmission by oral tenofovir disoproxil treatment in middle-late pregnancy. Chin J Exp Clin Infect Dis 2018; 12 (1): 51-55
- Wang H, Lu R, Zhong C, Xun S. Clinical studies on telbivudine blocking effect of mother-to-infant transformation of pregnant women with chronic hepatitis B virus. Contemporary Medicine 2018; 24 (10): 70-72
- Wang J, Liu J, Zhao F, Li H, Sheng H, Liu N, et al. To explore remedial strategy for gravidas with high HBV DNA load to prevent mother-to-infant transmission during late gestation. Chinese Journal of Woman and Child Health Research 2017; 28 (12): 1570-1573
- Wang TD. The effect of telbivudine on interrupting mother-to-child transmission of hepatitis B virus and on viral serology. China Pharmaceuticals 2015; 24 (12): 54-56
- Wang TM, Qiu B, Chen Y, Wu X. Clinical investigation on lamivudine interrupting mother-to-child transmission of hepatitis B virus. Chinese Journal of Eugenics and Genetics 2005; 13 (12): 68-69
- Wang W, Yang H, Gao H, Wang H. The evaluation of efficacy and safety of lamivudine to prevent mother-to-child transmission of hepatitis B virus. Hebei Medical Journal 2014; 36 (15): 2325-2326
- Wang WP, Zhao J. The study of efficacy and side effects of telbivudine and for treatment of patients with chronic hepatitis B in pregnant women. Prog Obstet Gynecol 2012; 21 (9): 697-699
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle–Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. 2014. Available at:

www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Last accessed on March 13, 2019.

- Wen WH, Chang MH, Zhao LL, Ni Y, Hsu HY, Wu JF, et al. Mother-to-infant transmission of hepatitis B virus infection: Significance of maternal viral load and strategies for intervention. J Hepatol 2013; 59: 24-30.
- World Health Organization. Neonatal and perinatal mortality: country, regional and global estimates. WHO library 2006. Available at: https://apps.who.int/iris/bitstream/handle/10665/43444/9241563206_eng.pdf?sequence=1. Last access on March 13, 2019.
- World Health Organization. Hepatitis B vaccines. Wkly Epidemiol Rec. 2009; 84(40):405-19.
- World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. WHO-Geneva 2015. Available at: http://apps.who.int/medicinedocs/documents/s21813en/s21813en.pdf. Last accessed on March 13th 2019.
- World Health Organization. Combating hepatitis B and C to reach elimination by 2030: advocacy brief. WHO-Geneva 2016. Available at: https://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/. Last accessed on March 13th 2019.
- World Health Organization. Global Hepatitis Report 2017. WHO-Geneva 2017a. Available at: https://apps.who.int/iris/rest/bitstreams/1082592/retrieve. Last accessed on March 13th 2019.
- World Health Organization. Hepatitis B vaccines: WHO position paper - July 2017. Wkly Epidemiol Rec 2017b; 27(92): 369–392
- World Health Organization. Preterm Birth. Available at: https://www.who.int/news-room/fact-sheets/detail/preterm-birth. WHO-Geneva 2018. Last accessed on March 13th, 2019.
- World Health Organization. Maternal, newborn, child and adolescent health. Available at: https://www.who.int/maternal_child_adolescent/epidemiology/stillbirth/en/. Last accessed on: March 13th, 2019.

- Wu Q, Huang H, Sun X, Pan M, He Y, Tan S et al. Telbivudine Prevents Vertical Transmission of Hepatitis B Virus From Women With High Viral Loads: A Prospective Long-Term Study. Clinical Gastroenterology and Hepatology 2015;13:1170–1176
- Xiao XH, Gao X. The effect of telbivudine and tenofovir in HBV-infected women during late pregnancy. Maternal and Child Health Care of China 2017; 32 (18): 4567-4570
- Xie P. Nursing management of pregnant women receiving antiviral therapy during pregnancy to interrupt intrauterine transmission of hepatitis B virus. Psychologist 2016; 22 (12): 151-152
- Xing Y. Effect of telbivudine on neonates and HBV-DNA levels in pregnant women with chronic HBV infection. Clinical Research 2018; 26 (2): 53-55
- Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. Journal of Viral Hepatitis, 2009, 16, 94–103
- Yang H. Effect of telbivudine in blocking the maternal-neonatal transmission of hepatitis B virus and nursing analysis. Journal of Hainan Medical University 2015; 21 (4): 483-485, 488
- Yang HW, Wang W, Gao H. The effect of lamivudine combined with immunoprophylaxis on prevention of mother-to-child transmission of hepatitis B virus. Hebei Medical Journal 2014; 36 (23): 3618-3619
- Yao LF, Yu Q. Clinical observation of effects of telbivudine on pregnant women at third trimester with high viral load of hepatitis B virus. Chin J Obstet Gynecol Pediatr 2014; 10 (4): 499-502
- Yao ZC, Chen M, Liao W, Zhang Y, Wu Y, Li L, et al. The efficacy and safety of telbivudine in blocking intrauterine hepatitis B viral transmission. J Clin Hepatol 2011; 14 (4): 259-261
- Yu CY. Effect of tenofovir dipivoxil fumarate on maternal and fetal blocking of antiviral hepatitis B during pregnancy. J of Pub Health and Prev Med 2018; 29 (5): 122-125

- Yuan QF. Analysis of different strategies to prevent mother-to-child transmission and the rates of neonatal infection with hepatitis B virus. Chinese Manipulation & Rehabilitation Medicine 2012; 3 (12): 481
- Yue X, Han G, Zhang X, Jiang H, He Q, Ding W. Efficacy and safety of telbivudine for pregnant women with hepatitis B e antigen negative chronic hepatitis B. Chin J Infect Dis 2014; 32 (9): 550-553
- Zeng Y, Chen R, Lou G, Shi J. Study of the strategy about cessation of lamivudine used in HBV intrauterine infection. J Med Res 2013; 42 (2): 87-90
- Zhang BF, Cheng M, Zhang Q, Zhao X, Yu L, Yang J, et al. Clinical study on blocking mother-to-child transmission of hepatitis B virus with high viral load and HBeAg positivity during pregnancy in Guizhou province. Chin J Hepatol 2018; 26 (12): 945-950
- Zhang GH. To evaluate the efficacy and safety of telbivudine in preventing mother to child transmission of hepatitis B. China Health Care & Nutrition 2018; 28 (6): 18-19
- Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or Lamivudine Use in Late Pregnancy Safely Reduces Perinatal Transmission of Hepatitis B Virus in Real-Life Practice. Hepatology. 2014; 60 (2): 468-476
- Zhang L, Wang L. Blocking intrauterine infection by telbivudine in pregnant chronic hepatitis B patients. Chin J Hepatol 2009; 17 (8): 561-563
- Zhang R, Lu F, Liu M. Analysis of nursing management of antiviral intrauterine interruption of patients with HBV during pregnancy. China Health Industry 2016; 13 (31): 145-147
- Zhang X. Efficacy and safety of telbivudine in preventing mother-to-infant transmission of hepatitis B viral infection in pregnant women with high serum hepatitis B viral load. J Prac Hepatol 2015; 18 (4): 411-412
- Zhang Y, Bai X, Gu K, Gao J. Effect of telbivudine on pregnancy with CHB and infant development. Chinese Journal of Woman and Child Health Research 2018; 29 (12): 1595-1598

- Zhang YF. Observation on the effect of lamivudine to prevent hepatitis B virus mother-to-child transmission in 50 pregnant women chronically infected with HBV. Journal of Practical Obstetrics and Gynecology 2010; 26 (5): 367-368
- Zhang YF, Hu Y. Efficacy and safety of telbivudine in preventing mother-to-infant HBV transmission. ADRJ 2010; 12 (3): 157-159
- Zhao D, Liao X, Peng G, Liu J, Lin C. Effect analysis of telbivudine combined with hepatitis B vaccine and hepatitis B immunoglobulin to prevent mother-to-child transmission of hepatitis B virus in 60 pregnant women. Chin J Mod Drug Appl 2010; 4 (17): 37-38
- Zhao J, Qiu S, Yang L, Chen L, Gu S, Shi L. The reason of failure to interrupt intrauterine hepatitis B virus infection and its solution. China Clinician 2013; 41 (4): 58-60
- Zhao Y, Cao Y, Fang R, Zhang J. A randomized controlled trial of telbivudine in preventing mother-to-infant transmission of HBV in pregnant women with high serum HBV DNA load. J Prac Hepatol 2017; 20 (2): 157-160
- Zheng JC, Chen H. Observation on the efficacy of telbivudine used in middle-late pregnancy to interrupt HBV mother-to-child transmission. China Rural Medicine 2018; 25 (2): 34-35
- Zhou DS, Lin Q, Jiang J. Effect of lamivudine blocking mother-to-child transmission of HBV in different pregnancy stages. Hainan Med J 2013; 24 (21): 3155-3157
- Zhou YJ, Zheng J, Pan H, Lu C. Long-term efficacy and safety of telbivudine in the treatment of childbearing patients with chronic hepatitis B. Chin J Hepatol 2014; 22 (8): 573-576
- Zhou Y, Zhou H, Lin Y, Guo Y. Clinical efficacy and safety of tenofovir in preventing vertical transmission of hepatitis B virus in women with middle-late pregnancy. New Medical Science 2018; 49 (11): 807-810
- Zhou YH, Correspondence: Prevention of Mother-to-Child Transmission of Hepatitis BVirus by Treating Mothers With High Viral Loads. Hepatology 2016; 64 (5): 1823-1824.

- Zhu J. Blocking effect and safety of telbivudine combined with hepatitis B immunoglobulin and hepatitis B vaccine in HBV maternal-infant vertical transmission. Maternal and Child Health Care of China 2017; 32 (6): 1213-1215
- Zhu L. The efficacy and safety of telbivudine to prevent intrauterine hepatitis B virus infection. Chin J Mod Drug Appl 2014; 8 (9): 142-143
- Zhu M, Zhu S. Clinical application of lamivudine in preventing mother-to-child transmission of hepatitis B virus. Hebei Medicine 2014; 20 (10): 1703-1705

APPENDICES

APPENDIX A: Search strategies

Database: PubMed

Date searched: 28 March 2019

Search strategy:

Item	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 pre-partum[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 vertical*[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 foetus[Text] OR offspring[Text] OR MTCT[Text] OR TME[Text]	**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

Search strategy:

Item	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**

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

Database: Scopus

Date searched: 28 March 2019

Search strategy:

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 “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

Search strategy:

Item	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* 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	**74 080**
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'+'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

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")

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

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

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

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

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)

Note: 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) Representativeness of the exposed cohort (0 or 1 star)

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 ✷
- 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) <u>Comparability of cohorts on the basis of the design or analysis (0 or 1 or 2 star(s))</u>

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) <u>Assessment of outcome (0 or 1 star)</u>

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) <u>Was follow up long enough for outcomes to occur (0 or 1 star)</u>

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) **<u>Adequacy of follow up of cohorts (0 or 1 star)</u>**

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 (year)	Selection bias		Performance bias	Detection bias	Attrition bias			Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data addressed			Selective reporting
					MTCT	Infant safety	Mother safety	
Pan CQ (2016)	**Low risk** *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"	**High risk** *Comment:*no concealment described	**High risk** *Quotes:* "open-label"	**High risk** *Quotes:* "open-label"	**Low risk** *Comment:* 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.	**Low risk** *Comment:* Reports on all infant adverse events of interest for 88% and 97.8% of control and treated group, respectively. This excludes bone density measurements.	**Low risk** *Comment:* Reports on all maternal adverse events of interest for >95% of both treated and control groups, including antiviral resistance testing.	**Low risk** *Comment:* 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 G (2018)	**Low risk** *Quotes:* "participants were randomly assigned in a 1:1	**Low/Unclear risk** *Quotes:* "The participants, the trial staff on site	**Low risk** *Quotes:* "The participants, the trial staff on site and at the coordination	**Low risk** *Quotes:* "The participants, the trial staff on site and at the coordination center,	**Low risk** *Comment:* 88 and 90% with full follow up in treated and	**Low risk** *Comment*: 95 and 98% of infants included in this analysis from	**High risk** *Comment:* although >90% women considered	**Low risk** *Comment:* 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" *Comment:* 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 discontinuation 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.

B. Chinese language studies

Study (year) (No.)	Selection bias		Performance bias	Detection bias	Attrition bias			Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data addressed			
					MTCT	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" *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 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 discontinuation, 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

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

LAM 100–150 mg

A. English language studies

Study (year)	Selection bias		Performance bias	Detection bias	Attrition bias			Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data addressed			Selective reporting
					MTCT	Infant safety	Mother safety	
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 seems that randomization occurred after informed consent.	**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 to preserve blinding with study personnel.	**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" *Comment:* 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, respectively (these proportions also differ by >10 % points)	**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.

B. Chinese language studies

Study (year) (No.)	Selection bias		Performance bias	Detection bias	Attrition bias			Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data addressed			
					MTCT	Infant safety	Mother safety	Selective reporting
Chen SM (2017)	**Low risk/Unclear** *Quotes:* "90 cases of pregnant women chronically infected with HBV were selected and randomly divided into lamivudine group, telbivudine group and 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 groups 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.
Ji YY (2015)	**Low risk** *Quotes:* "Referring to random number table, the patients were divided into telbivudine group, lamivudine 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	**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	**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 not all of the

	and control group, with 65 cases in each group"		lamivudine" *Comment*: 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 ZG (2015)	**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 XQ (2015)	**Low risk** *Quotes:* "Referring to random number table, the patients were divided into the observation group and the control group, with 110 cases in	**Unclear** *Comment:* the method of concealment not described	**High risk** *Quotes:* "The control group received HBIG" "The observation group received lamivudine on the basis of HBIG for the control group" *Comment*: the study did not address this outcome and no	**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	**High risk** *Comment:* though all women were included in this analysis, the adverse events observed were	**High risk** *Comment*: the protocol is available in 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 (2014)	**Low risk/Unclear** *Quotes:* "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" *Comment:* 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	**Unclear** *Comment:* the method of concealment not described	**High risk** *Quotes:* "The experimental II group received HBIG" "The experimental I group received lamivudine on the basis of HBIG" *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)	**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)

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" *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.
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

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

LDT 600 mg

A. Chinese language studies

Study (year) (No.)	Selection bias		Performance bias	Detection bias	Attrition bias			Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data addressed			
					MTCT	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" *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:* 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)	**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" *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:* 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)	**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.
Zhang Y (2018)	**Low risk** *Quotes:* "Referring to random number table, the patients were divided into the observation group and the control group, with 34 cases in each group"	**Unclear** *Comment:* the method of concealment not described	**High risk** *Quotes:* "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" *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:* same numbers used as for MTCT outcome. Only congenital abnormality and Apgar score reported. Other key adverse events not addressed.	**High risk** *Comment:* same numbers used as for MTCT outcome. Only creatine kinase (CK) reported. Key adverse events not addressed	**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 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" *Comment:* the study did not describe the exact random component in the sequence generation process		antiviral treatment with lamivudine or telbivudine" *Comment*: 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" *Comment:* the study did not describe the exact random component in the sequence generation process		the control group" *Comment*: 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 (2017)	**Low risk** *Quotes:* "Referring to random number table, the patients were divided into the observation group and the control group, with 40 cases in each group"	**Low risk** *Quotes:* "…sealed and opaque envelopes were used for concealment of the random allocation."	**High risk** *Quotes:* "The control group received compound glycyrrhizin" "The observation group received antiviral treatment with telbivudine on the basis of compound glycyrrhizin" *Comment*: the study did not address this outcome and no mention of placebo	**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 Apgar score reported. Other key adverse events not addressed.	**High risk** *Comment:* 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	**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.
Zhu J (2017)	**Low risk** *Quotes:* "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	**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	**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); 6 cases of fetal death in	**High risk** *Comment:* same numbers used as for MTCT outcome. Only Apgar score and neonatal asphyxia reported. Other key adverse events not addressed	**High risk** *Comment:* same numbers used as for MTCT outcome. Women considered until delivery. Only foetal death and	**Low risk** *Comment*: the protocol is available in the method section of the article. The current outcomes of interest that this meta-

			mention of placebo		control group		postpartum haemorrhage reported. Other key adverse events not addressed	analysis is recording were pre-specified in that protocol.
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" *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 CK elevation reported. Other key adverse events not addressed	**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, 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** *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

	each group"		*Comment*: the study did not address this outcome and no mention of placebo					this meta-analysis is recording were pre-specified in that protocol.
Xie PY (2016)	**Low risk** *Quotes:* "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	**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	**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
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)

	generation process; and importantly, there's a huge disparity between the number of cases in the observation group and that of the control group							
Ji YY (2015)	**Low risk** *Quotes:* "Referring to random number table, the patients were divided into telbivudine group, lamivudine group and control 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** *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 not all of the study's pre-specified primary outcomes have been reported (e.g. maternal liver function after antiviral treatment).
Li SF. (2015)	**Low risk/unclear** *Quotes:* "The patients were randomly divided into the observation group and the control group, with 60 cases in each group" *Comment:* the	**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	**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 6 months after delivery. Only adverse	**High risk** *Comment:* the 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" *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 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** *Quotes:* "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" *Comment:* the study did not describe the exact random component in the sequence generation process	described	received telbivudine on the basis of HBIG for the control group" *Comment*: 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)	**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" *Comment:* the study did not describe the exact random component in the sequence generation process		received antiviral treatment with telbivudine" *Comment*: 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

	component in the sequence generation process							bilirubin, and HBV DNA).
Zhao DB (2010)	**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** *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:* insufficient reporting	**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 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 group and the control group, with 31 cases in the observation group and 30 cases in the control group" *Comment:* the study did not describe the exact random component in the sequence generation process		received antiviral treatment with telbivudine" *Comment*: 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).

APPENDIX F: Newcastle–Ottawa Risk of Bias Assessment Tool

TDF 300 mg

A. English language observational studies

Study (year)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at baseline	Comparability of cohorts on the basis of the design or analysis	Assessment of outcomes	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total number of stars (risk of bias)[a]
Celen MK (2013)	☆ At least somewhat representative of the average HBV-infected pregnant woman	☆ Drawn from the same community (same inclusion and exclusion criteria also)	Does not provide 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	None reported (retrospective)	7 (low)
Greenup AJ (2014)	☆ At least somewhat representative of the average HBV-	☆ Drawn from the same community (same inclusion	☆ Reporting on adherence within the paper, reduction of viral 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 pregnant woman	and exclusion criteria also)	assess women's response to treatment.		confirmation that all infants received it	assay was used for testing HBsAg			
Chen HL (2015)	☆ At least somewhat representative of the average HBV-infected pregnant woman	☆ Drawn from the same community (same inclusion and exclusion criteria also)	☆ Regular testing (and pre-delivery testing) of HBV DNA levels were correlated with duration of treatment in mothers	☆ Always the case	☆☆ Comparable for HBV DNA level and comparable HBeAg positive. Same regimen for infant immunoprophylaxis	☆ Describes test assays used for HBsAg and HBV DNA and acknowledges a study laboratory	☆ Yes	☆ LFU reported and <20% LFU in all treatment and control groups	9 (low)
Kochaksarei GS (2016)	☆ At least somewhat representative of the average HBV-infected pregnant woman	Not same population, the untreated did not have high viraemia or pre-existing liver disease, whereas the treated did	Adherence is mentioned but was ascertained in 16/23 women (<70%), and only 2/3 had good adherence.	☆ Always the case	☆ Not comparable for HBV DNA level or HBeAg positive. Apparently, the same regimen for infant immunoprophylaxis; however, very few details stated	☆ Testing done centrally, and methods/assays for testing described	☆ Yes	<80% follow up in both treated and control groups	5 (high)
Wakano Y (2018)	Not representative 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)

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

[a]Risk of bias assessments should be classified as being either low (≥7) or high (<7) by the Newcastle–Ottawa scale

B. Chinese language observational studies

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

	infected pregnant woman	exclusion criteria also)	antiviral therapy (decrease in viral load levels subsequent to the treatment)		not described. Same regimen for infant immunoprophylaxis at birth	detail (which assay used), indicating use of a central laboaratory and/or record linkage			
Wang HB (2018)	✯ 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 threshold for HBV DNA level but HBeAg serostatus not described. Same regimen for infant immunoprophylaxis at birth	✯Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage	✯ Yes	No statement on LFU	7 (low)
Zhang BF (2018)	✯ 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 HBeAg serostatus but different thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	✯ Yes	No statement on LFU	6 (high)

Zhou Y (2018)	☆ 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 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 laboaratory and/or record linkage	☆ Yes	No statement on LFU	8 (low)
Chen WJ (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 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 laboaratory and/or record linkage	☆ Yes	No statement on LFU	8 (low)
Gong Q (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	☆Both HBeAg serostatus and threshold for HBV DNA level not described. Same regimen for infant	No description	☆ Yes	No statement on LFU	6 (high)

			load levels subsequent to the treatment)		immunoprophylaxis at birth				
Huang Q (2017) (140)	☆ 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 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)	☆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 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)
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 the antiviral therapy	☆ Always the case	Same thresholds for HBV DNA level but HBeAg serostatus not described. Regimen for infant	☆ Laboratory methods described in detail (which	☆ Yes	There is a description of LFU for the exposed	6 (high)

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

[a]Risk 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

Study (year)	Representat-iveness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at baseline	Comparability of cohorts on the basis of the design or analysis	Assessment of outcomes	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total number of stars (risk of bias)[a]
Greenup AJ (2014)	☆ At least somewhat representative of the average HBV-infected pregnant woman	☆ 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 treatment	☆ 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 H (2014)	☆ At least somewhat representative 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	9 (low)

Jackson V (2015)	✯ At least somewhat representative of the average HBV-infected pregnant woman	✯ 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	HBV DNA level and 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	<80% retention in both treated and control groups	6 (high)
Liu CP (2015)	✯ At least somewhat representative of the average HBV-infected pregnant woman	Many more women included in the control group (highly disproportionate, 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/adherence/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 provided					misclassified as a cohort study, and has a high risk of bias for loss to follow up)	
Pan CQ (2017)	☆ At least somewhat representative of the average HBV-infected pregnant woman	Same population and criteria, however, no indication of how this group was chosen (usually says "unwillingness", for example)	Some data presented on decrease of maternal viral load, but no mention of linking this with compliance/adherence/time on treatment. Additionally, because of study design (retrospective) there is low/no chance of adherence monitoring	☆ Always the case	☆☆ Comparable for HBV DNA level and comparable HBeAg positive. Same regimen for infant immunoprophylaxis	☆ Reference to the hospital's centralized laboratory and linkage to medical records for assessing infant outcome	☆ 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 misclassified as a cohort study, and has a high risk of bias for loss to follow up)	6 (high)
He T (2018)	☆ At least somewhat representative of the average HBV	☆ Drawn from the same community with same inclusion	☆ Detailed information on reduction of viral load given, including specific	☆ Always the case	☆☆ Comparable for HBV DNA level and comparable HBeAg positive. Same regimen	☆ Linkage to medical records	☆ Yes	Retrospective cohort mentioned but no loss to follow up described, no mention of how there was perfect retention	8 (low)

	infected pregnant woman	and exclusion criteria	data for each woman (every one had a -6 to -8 log reduction)		for infant immunoprophylaxis				
Wakano Y (2018)	Not representative of the general population (women who have had a child infected previously)	✯ Drawn from the same community with same inclusion and exclusion criteria	✯ >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 the groups of treated and non-treated	Laboratory assays not well described	✯ Yes	✯ 100% retention	6 (high)
Foaud HM (2019)	✯ Truly representative of the average HBV-infected pregnant woman	Control group comprised women who were not candidates for lamivudine (likely to be quite different from those who received it)	✯ States that women were given lamivudine monthly and were questioned regarding compliance at each visit	✯ Always the case	✯ HBeAg proportion not comparable, and HBV DNA at baseline not given. 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 at 6–12 months in control group, though ~86% follow up in treated group at that time-point. (Note: at later time-point that study defined, there was >80% follow up)	6 (high)

[a]Risk of bias assessments should be classified as being either low (≥7) or high (<7) by the Newcastle–Ottawa scale

B. Chinese language observational studies

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

	infected pregnant woman	and exclusion criteria also)	antiviral therapy (decrease in viral load levels subsequent to the treatment)		regimen for infant immunoprophylaxis at birth	detail (which assay used), indicating use of a central 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 (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 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	✯ Yes	No statement on LFU	8 (low)

						and/or record linkage			
Ge YL (2015)	☆ 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 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)
Han YP (2014)	☆ 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 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)
Wang W (2014)	☆ 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	☆ Always the case	☆Comparable for HBV DNA levels but HBeAg serostatus not described. Same regimen for infant immunoprophylaxis at birth	☆ Laboratory methods described in detail (which assay used), indicating use	☆ Yes	No statement on LFU	7 (low)

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

	the average HBV-infected pregnant woman	(same inclusion and exclusion criteria also)			serostatus not described. Same regimen for infant immunoprophylaxis at birth	described in detail (which assay used), indicating use of a central laboratory and/or record linkage			
Jiang HX (2012)	☆ 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 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)	☆ 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	☆ 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)

			subsequent to the treatment)			laboratory and/or record linkage			
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)	Adherence/compliance 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	☆ 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 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)
Ren YJ (2011)	☆ At least somewhat representative of the average HBV-	☆ Drawn from the same community	☆Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral	☆ 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 woman		load levels subsequent to the treatment)						
Zhang YF (2010)	☆ 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 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)
Su TB (2009)	☆ At least somewhat representative of the average HBV-infected pregnant woman	☆ Drawn from the same community (same inclusion and exclusion criteria also)	Does not provide any details on adherence	☆ Always the case	☆ Both HBeAg serostatus and HBV DNA not described. Same regimen for infant immunoprophylaxis	☆ Testing done centrally in the hospital that study staff worked in	☆ Yes (always the case)	No statement on LFU	6 (high)
Tang X (2009)	☆ 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	☆ 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)

			subsequent to the treatment)			laboratory and/or record linkage			
Feng HF (2007)	☆ 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 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)
Li G (2006)	☆ 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	☆ Comparable HBeAg serostatus but HBV DNA levels not described. Same regimen for infant immunoprophylaxis	☆ Laboratory assays described	☆ Yes (always the case)	☆ LFU reported and <20% LFU in both treatment group and control group	8 (low)
Li WF (2006)	☆ At least somewhat representative of the average HBV-	☆ Drawn from the same community (same inclusion	☆Valid method was used to ascertain adherence to the	☆ Always the case	☆☆Same HBeAg serostatus and same thresholds for HBV DNA level. Same	☆ Laboratory methods described in	☆ Yes	No statement on LFU	8 (low)

	infected pregnant woman	and exclusion criteria also)	antiviral therapy (decrease in viral load levels subsequent to the treatment)		regimen for infant immunoprophylaxis at birth	detail (which assay used), indicating use of a central laboratory and/or record linkage			
Ma J (2006)	☆ 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	Comparable HBeAg serostatus but HBV DNA levels not described. Regimen for infant immunoprophylaxis not described	☆ Laboratory assays described	☆ Yes (always the case)	No statement on LFU	6 (high)
Han ZH (2005)	☆ 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 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 TM (2005)	☆ 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 HBeAg serostatus but HBV DNA level not described. Same regimen for infant immunoprophylaxis at birth	No description	☆ Yes	No statement on LFU	6 (high)

[a]Risk 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

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

Liu CP (2015)	☆ At least somewhat representative of the average HBV-infected pregnant woman	Many more women in the control group when compared to the treated group – this could indicate dissimilarity between the two groups	Some limited data presented on decrease of maternal viral load, but no mention of linking this with compliance/adherence/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	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 misclassified as a cohort study, and has a high risk of bias for loss to follow up)	5 (high)
Wu Q (2015)	☆ At least somewhat representative 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 HBV 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)	☆	☆	Some limited data presented on	☆	☆	☆	☆	Loss to follow up not mentioned and	6 (high)

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

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

	pregnant woman		had a -6 to -8 log reduction)						
Hu Y (2018)	☆ At least somewhat representative 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	Only ~70 % follow up between 7 and 12 months (although some others were included and tested at 13–14 months… not actually completely lost to follow up)	8 (low)
Sheng QJ (2018a)	☆ At least somewhat representative 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/changing 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	9 (low)
Sheng QJ (2018b)	☆ At least somewhat representative 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 woman		decrease in HBV DNA level for treated cohort		positive. Same regimen for infant immunoprophylaxis	outcome described			

[a]Risk of bias assessments should be classified as being either low (≥7) or high (<7) by the Newcastle–Ottawa scale

B. Chinese language observational studies

Study (year)	Representative--ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at baseline	Comparability of cohorts on the basis of the design or analysis	Assessment of outcomes	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total number of stars (risk of bias)[a]
Tan J (2019)	✯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	✯Comparable for HBV DNA levels at baseline but HBeAg serostatus not described. 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	7 (low)
Chen QR (2018)	✯At least somewhat representative of the average HBV-	✯Drawn from the same community (same inclusion	No description	✯Always the case	✯✯Same HBeAg serostatus and comparable HBV DNA levels at baseline. Same	No description	✯Yes	No statement on LFU	6 (high)

	infected pregnant woman	and exclusion criteria also)			regimen for infant immunoprophylaxis at birth				
Ding XP (2018)	☆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 HBeAg serostatus and comparable HBV DNA levels at baseline. Same regimen for infant immunoprophylaxis at birth	No description	☆Yes	No statement on LFU	7 (low)
Li ZY (2018)	☆ 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	☆☆Comparable for HBeAg serostatus and HBV DNA level. Same regimen for infant immunoprophylaxis	☆ Indication of record linkage (results viewed retrospectively in medical records)	☆ Yes (always the case)	None reported (retrospective)	8 (low)
Tian JH (2018)	☆At least somewhat representative of the average HBV-infected pregnant woman	☆Drawn from the same community (same inclusion and exclusion criteria also)	No description	☆Always the case	☆☆Same threshold for HBV DNA level and same HBeAg serostatus used. Same regimen for infant	☆Laboratory methods described in detail (which assay used), indicating use	☆Yes	No statement on LFU	7 (low)

					immunoprophylaxis at birth	of a central laboratory and/or record linkage			
Zhang BF (2018)	☆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 HBeAg serostatus but different thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	☆Yes	No statement on LFU	6 (high)
Zhang GH (2018)	☆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 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)
Zheng JC (2018)	☆At least somewhat representative of the average HBV-	☆Drawn from the same community (same inclusion	No description	☆Always the case	☆☆Same HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant	☆Laboratory methods described in detail (which assay used),	☆Yes	No statement on LFU	7 (low)

	infected pregnant woman	and exclusion criteria also)			immunoprophylaxis at birth	indicating use of a central laboratory and/or record linkage			
Chen WJ (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 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)
Feng XM (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 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)

Huang Q (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 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)
Jiang S (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	✯ Comparable for HBV DNA level but HBeAg serostatus not described. Same regimen for infant immunoprophylaxis at birth	No description a	✯Yes	No statement on LFU	6 (high)
Li CM (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	✯Comparable for HBV DNA level but HBeAg serostatus not described. Same regimen for infant immunoprophylaxis	Laboratory assays used not well described	✯ Yes (always the case)	No statement on LFU	6 (high)

Li YH (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 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)
Liu 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 HBeAg serostatus and comparable for HBV DNA levels. Same regimen for infant immunoprophylaxis at birth	No description	✯Yes	There is a description of LFU for the exposed but not for the control group	7 (low)
Luo DX (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	✯Always the case	Comparable for HBV DNA levels but HBeAg serostatus not described. Regimen for infant immunoprophylaxis at birth not clearly described	No description	✯Yes	No statement on LFU	5 (high)

			subsequent to the treatment)						
Pan YC (2017)	✯At least somewhat representative of the average HBV infected pregnant woman	✯Drawn from the same community (same inclusion and exclusion criteria also)	No description	✯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	✯Subjects lost to follow up unlikely to introduce bias, small number lost	8 (low)
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 subsequent to the treatment)		at birth not clearly described	of a central laboratory and/or record linkage		the control group	
Chen F (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 HBeAg sero-status and same thresholds for HBV DNA level. Regimen for infant immunoprophylaxis at birth not clearly described	✯Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage	✯Yes	No statement of LFU	7 (low)
Gao P (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	Comparable for HBV DNA levels 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)
Hu WH (2016)	✯At least somewhat representative of	✯Drawn from the same community	✯Valid method was used to ascertain	✯Always the case	✯Comparable for HBV DNA levels but HBeAg serostatus	✯Laboratory methods described in	✯Yes	No statement on LFU	7 (low)

	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)		not described. Same regimen for infant immunoprophylaxis at birth	detail (which assay used), indicating use of a central laboratory and/or record linkage			
Li N (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	✯Comparable for HBV DNA levels but HBeAg serostatus not described. Same regimen for infant immunoprophylaxis at birth	No description	✯Yes	No statement on LFU	6 (high)
Liu XB (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 HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	✯Yes	No statement of LFU	7 (low)

Qiu B (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. 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 of LFU	7 (low)
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)
Tian RH (2016)	✯At least somewhat representative of the average HBV-infected pregnant woman	✯Drawn from the same community (same inclusion and exclusion criteria also)	No description	✯Always the case	✯✯Same HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	✯Yes	No statement on LFU	6 (high)

Wang B (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	☆☆Comparable for HBeAg serostatus and HBV DNA level. Same regimen for infant immunoprophylaxis	☆ Laboratory assays described	☆ Yes (always the case)	No statement on LFU	8 (low)
Wang DM (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 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 laboaratory and/or record linkage	☆Yes	No statement on LFU	8 (low)
Wang HB (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	☆Always the case	☆Comparable 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)

			subsequent to the treatment)						
Zhang R (2016)	✯At least somewhat representative of the average HBV-infected pregnant woman	✯Drawn from the same community (same inclusion and exclusion criteria also)	No description	✯Always the case	HBeAg serostatus and threshold for HBV DNA level not described. Regimen for infant immunoprophylaxis at birth not clearly described	No description	✯Yes	No statement on LFU	4 (high)
Chen CY (2015)	✯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 HBeAg serostatus and same thresholds for HBV DNA level. 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	7 (low)
Cui ZL (2015)	✯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	✯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)

			subsequent to the treatment)			laboratory and/or record linkage			
Deng Y (2015)	☆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)
Ge YL (2015)	☆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 HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	☆Yes	No statement on LFU	7 (low)
Lou JJ (2015)	☆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 HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant	☆Laboratory methods described in detail (which assay used), indicating use	☆Yes	No statement on LFU	8 (low)

			load levels subsequent to the treatment)		immunoprophylaxis at birth	of a central laboratory and/or record linkage			
Ren N (2015)	☆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 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)
Sun WH (2015)	☆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 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 TD (2015)	☆At least somewhat representative of	☆Drawn from the same community	☆Valid method was used to ascertain	☆Always the case	☆☆Same HBeAg serostatus and same thresholds for HBV	☆Laboratory methods described in	☆Yes	No statement on LFU	8 (low)

	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)		DNA level. Same regimen for infant immunoprophylaxis at birth	detail (which assay used), indicating use of a central laboratory and/or record linkage			
Zhang X (2015)	✯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 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)
Chen YL (2014)	No description of the derivation of the cohort	No description of the derivation of the non-exposed cohort	✯Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	✯Always the case	✯Comparablefor HBV DNA levels but HBeAg serostatus not described. Same regimen for infant immunoprophylaxis at birth	No description	✯Yes	No statement on LFU	4 (high)

Han YP (2014)	☆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 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)
Liu CY (2014)	☆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 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)
Yao LF (2014)	☆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	☆Always the case	☆Same HBeAg serostatus and same thresholds for HBV DNA level. Regimen for infant immunoprophylaxis at birth not clearly described	☆Laboratory methods described in detail (which assay used), indicating use of a central laboratory	☆Yes	No statement on LFU	7 (low)

			subsequent to the treatment)			and/or record linkage			
Yue X (2014)	✯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 HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	✯Yes	✯Complete follow up	8 (low)
Zhou YJ (2014)	✯At least somewhat representative of the average HBV-infected pregnant woman	✯Drawn from the same community(same inclusion and exclusion criteria also)	No description	✯Always the case	✯Comparable HBeAg serostatus and same thresholds for HBV DNA level. Regimen for infant immunoprophylaxis at birth not described clearly	✯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)
Fan LY (2013)	✯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 HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant	No description	✯Yes	No statement on LFU	7 (low)

			load levels subsequent to the treatment)		immunoprophylaxis at birth				
Jiang XN (2013)	✯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 HBeAg serostatus and same thresholds for HBV DNA level. Regimen for infant immunoprophylaxis at birth not described clearly	No description	✯Yes	✯Complete follow up	7 (low)
Zhao J (2013)	✯At least somewhat representative of the average HBV-infected pregnant woman	✯Drawn from the same community (same inclusion and exclusion criteria also)	No description	✯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	7 (low)
Peng BA (2012)	✯At least somewhat representative of the average HBV-	✯Drawn from the same community (same inclusion	✯Valid method was used to ascertain adherence to the antiviral therapy	✯Always the case	✯✯Same HBeAg serostatus and same thresholds for HBV DNA level. Same regimen for infant	No description	✯Yes	No statement on LFU	7 (low)

	infected pregnant woman	and exclusion criteria also)	(decrease in viral load levels subsequent to the treatment)		immunoprophylaxis at birth				
Wang EJ (2012)	☆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 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 WP (2012)	☆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 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)
Yao ZC (2011)	☆At least somewhat representative of	☆Drawn from the same community	☆Valid method was used to ascertain	☆Always the case	☆Same thresholds for HBV DNA level but HBeAg	☆Laboratory methods described in	☆Yes	No statement on LFU	7 (low)

	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)		serostatus not described. Same regimen for infant immunoprophylaxis at birth	detail (which assay used), indicating use of a central laboratory and/or record linkage			
Zhang YF (2010)	✯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 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)

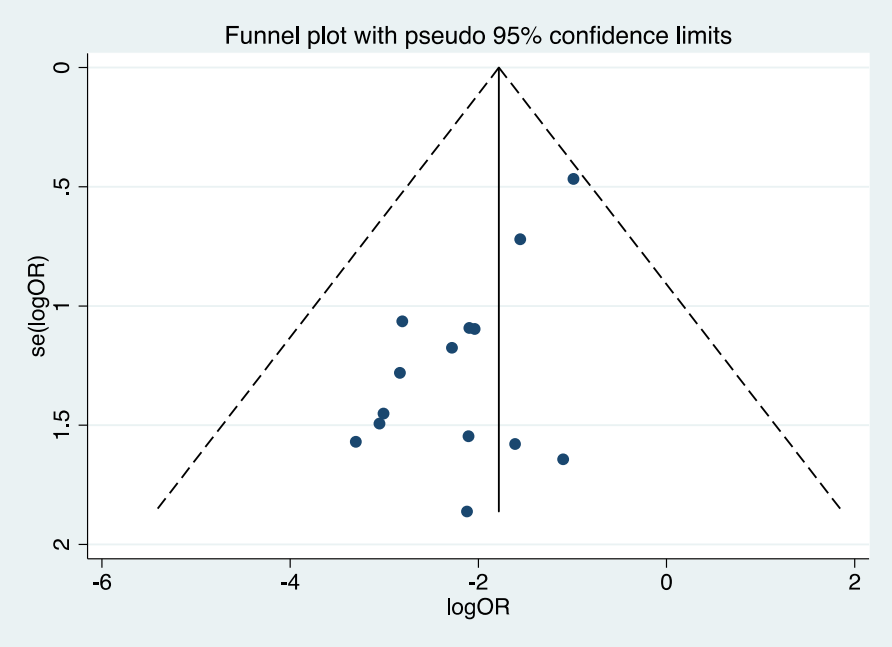
[a]Risk of bias assessments should be classified as being either low (≥7) or high (<7) by the Newcastle–Ottawa scale

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

TDF 300 mg

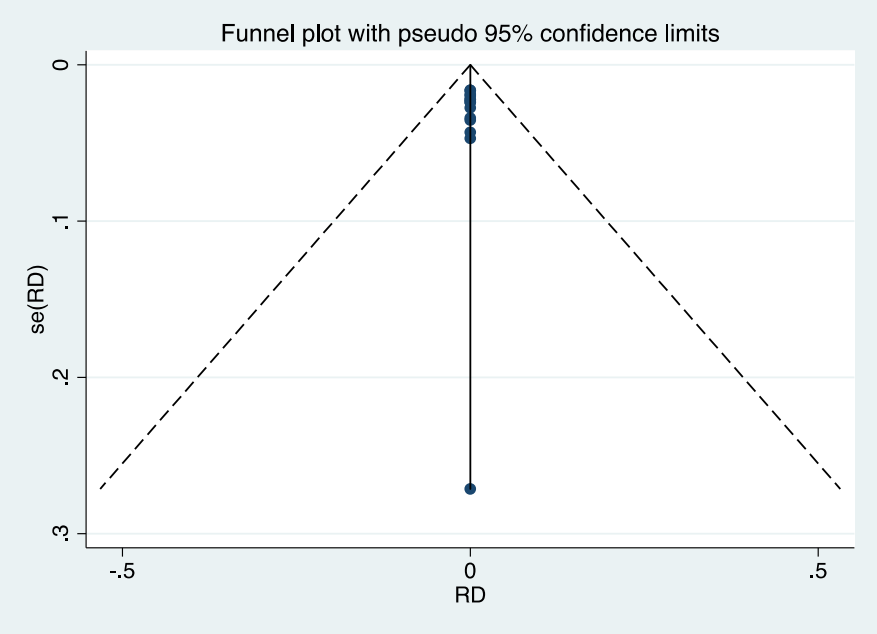
MTCT indicated by HBsAg positivity at 6–12 months, non-RCTs

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



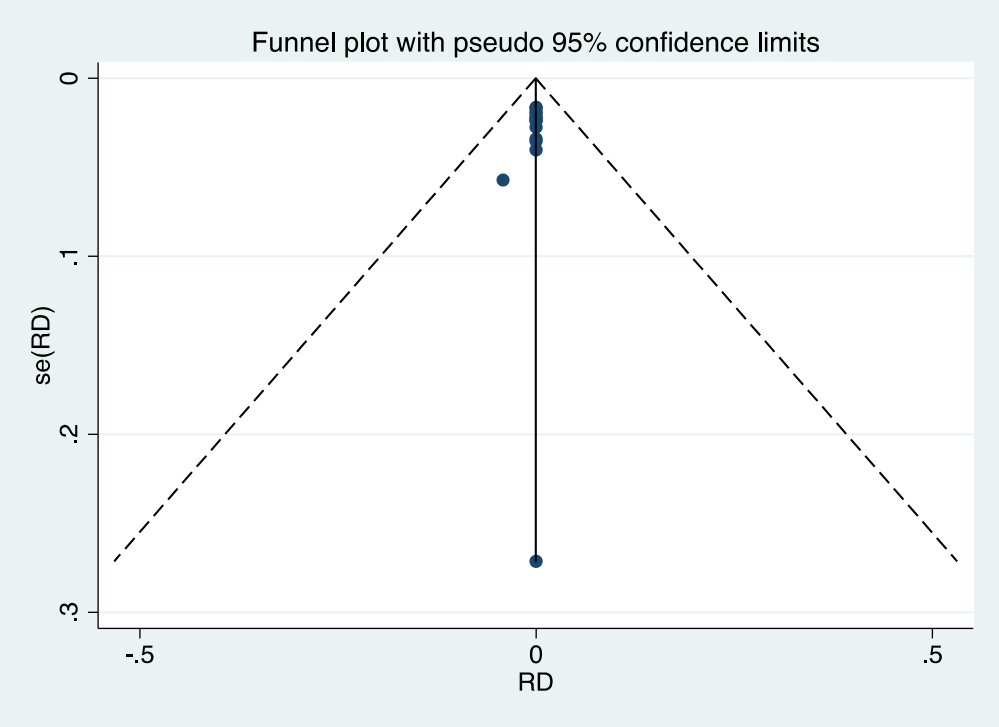
Neonatal deaths, non-RCTs

- No evidence of publication bias



Miscarriages and stillbirths, non-RCTs

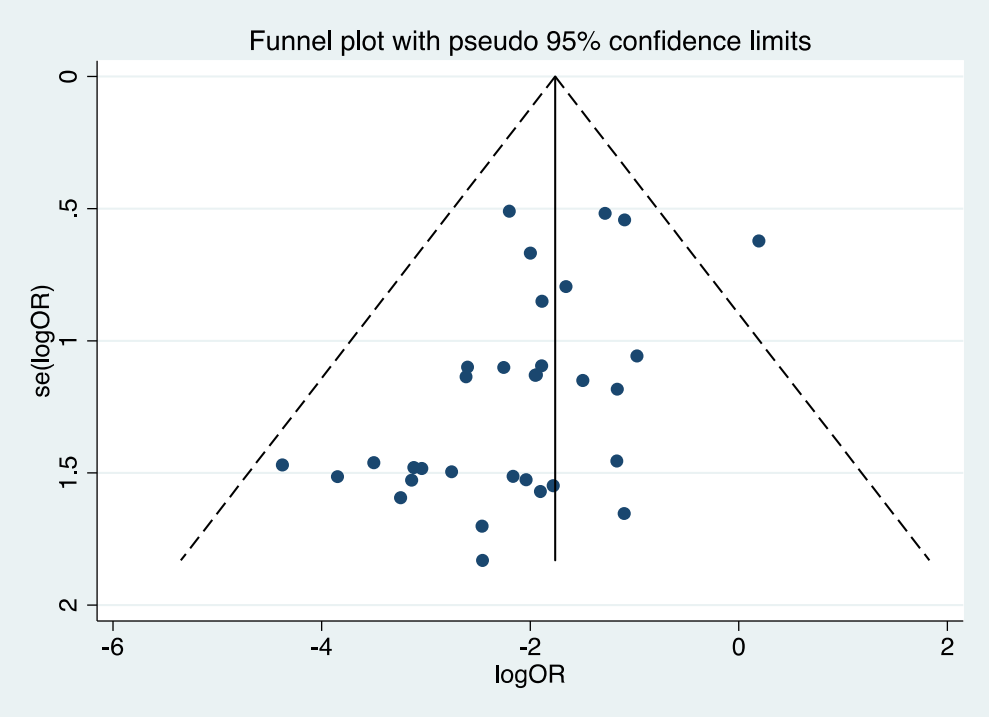
- No evidence of publication bias



LAM 100–150 mg

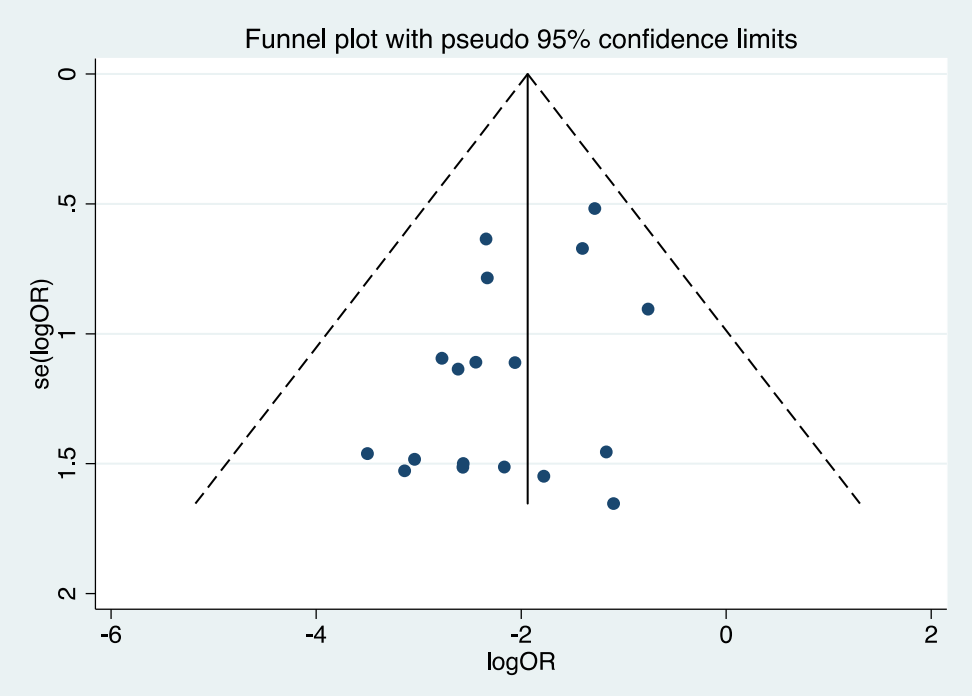
MTCT indicated by HBsAg positivity at 6–12 months, non-RCTs

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



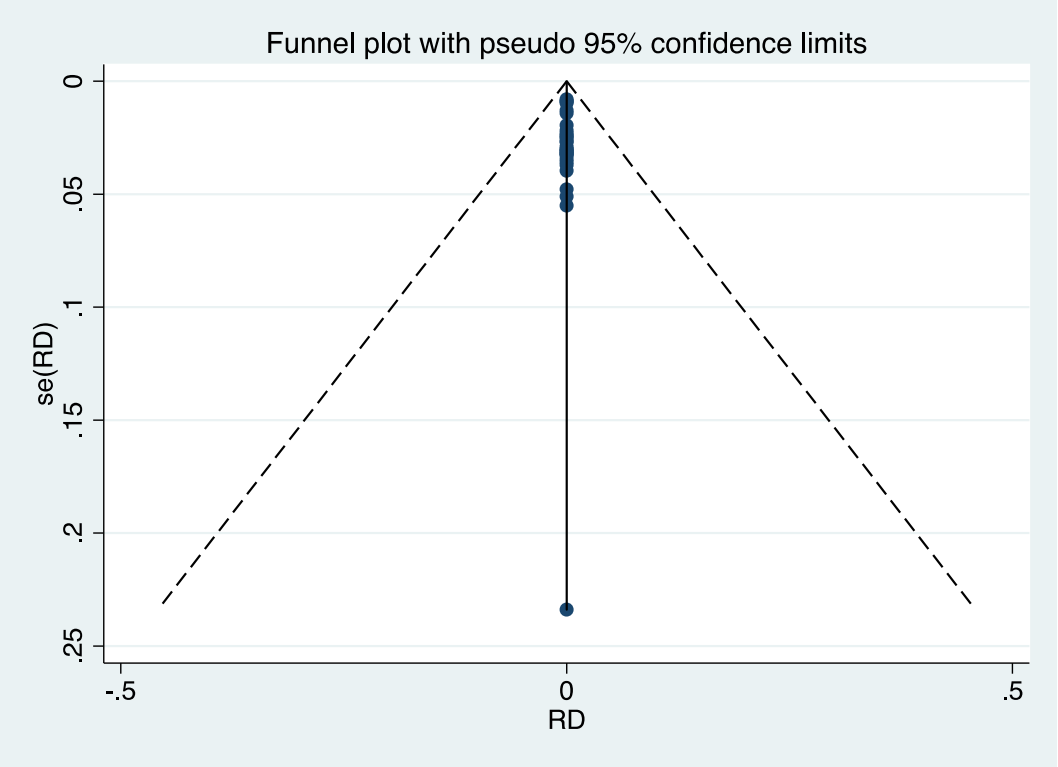
MTCT indicated by HBV DNA positivity at 6–12 months, non-RCTs

- No evidence of publication bias, Egger test *P* value=0.055



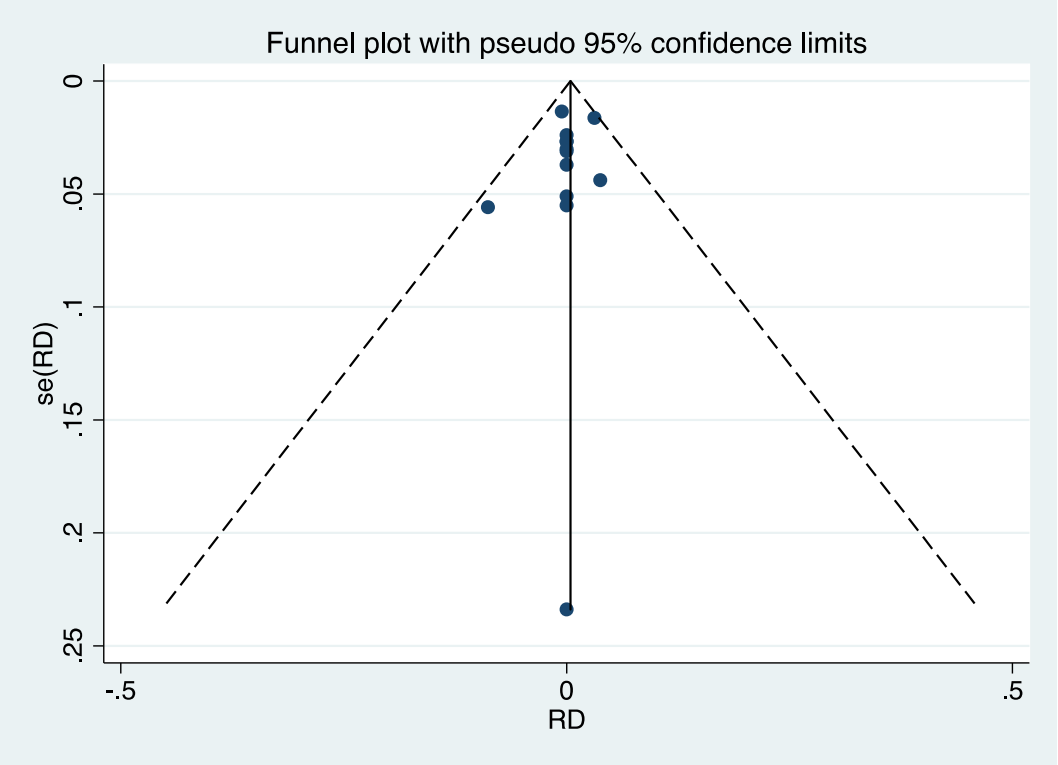
Neonatal deaths, non-RCTs

- No evidence of publication bias



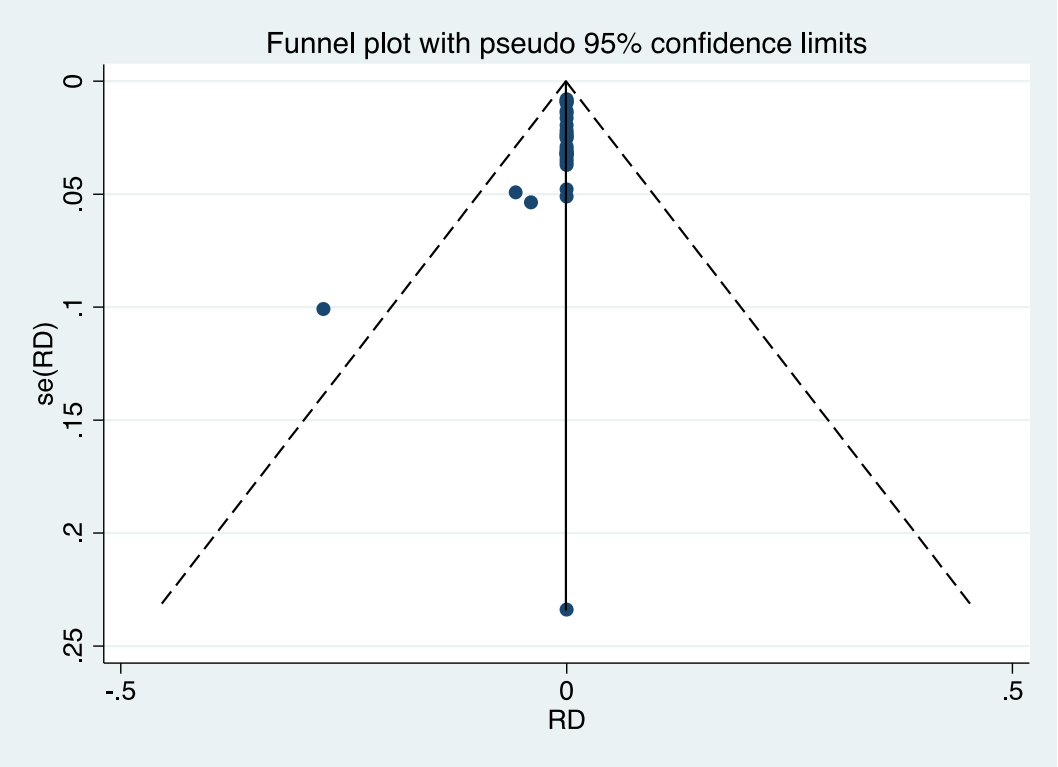
Congenital abnormalities, non-RCTs

- No evidence of publication bias



Miscarriages and stillbirths, non-RCTs

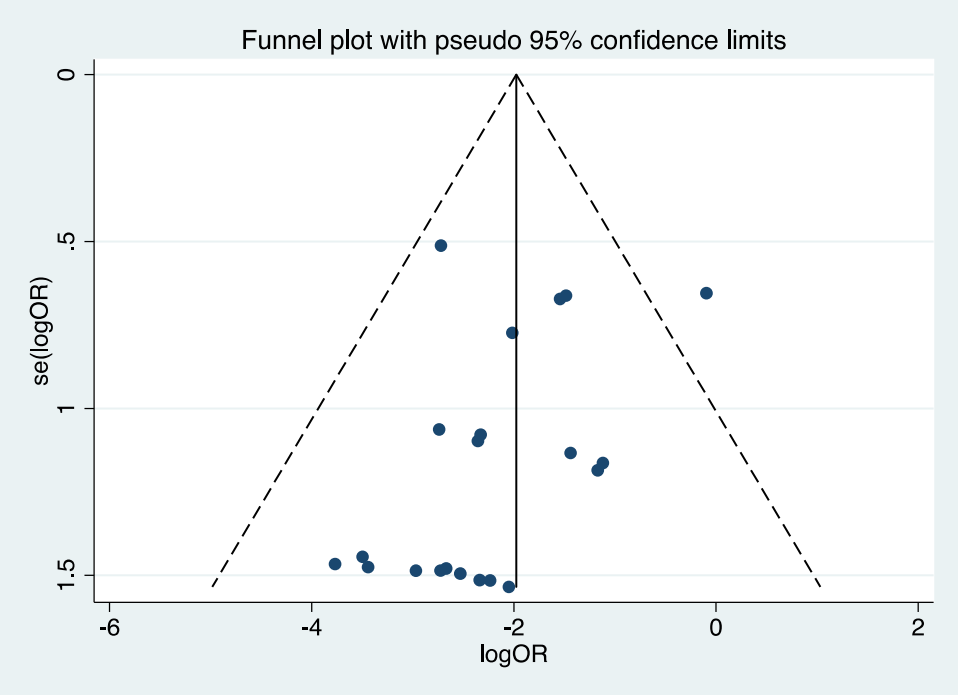
- No evidence of publication bias



LdT 600 mg

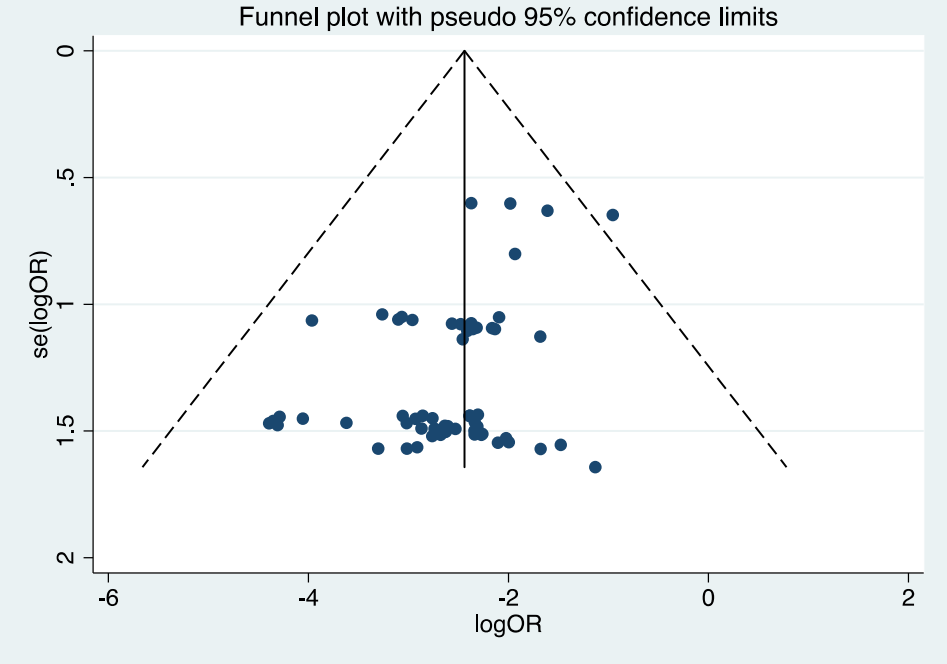
MTCT indicated by HBsAg positivity at 6–12 months, RCTs

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



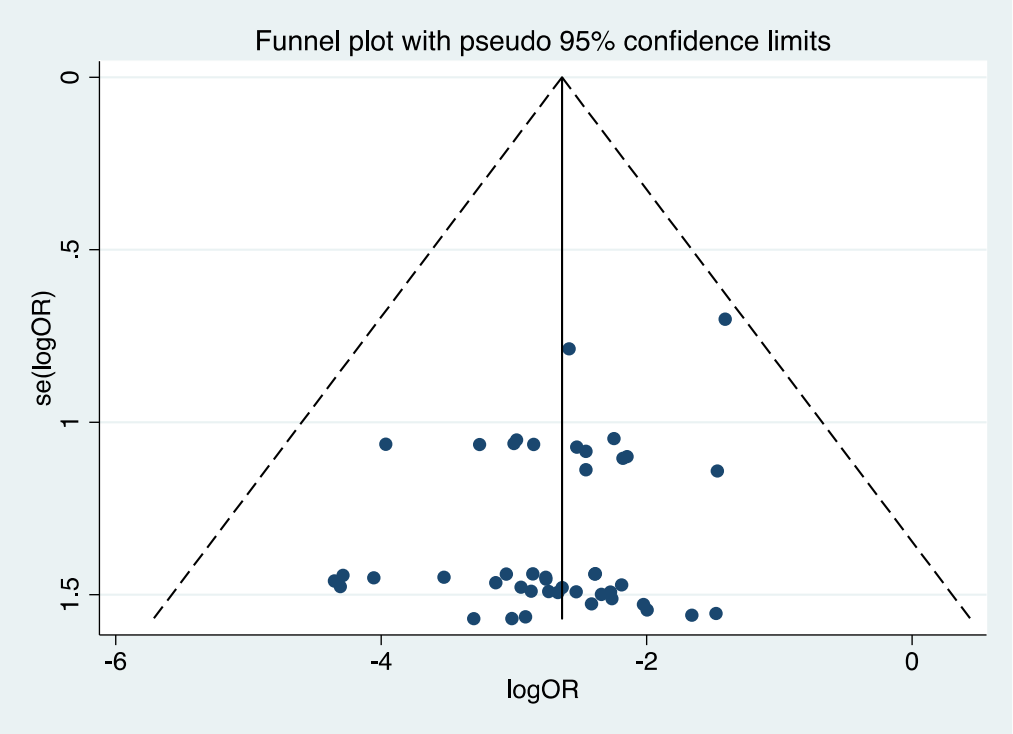
MTCT indicated by HBsAg positivity at 6–12 months, non-RCTs

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



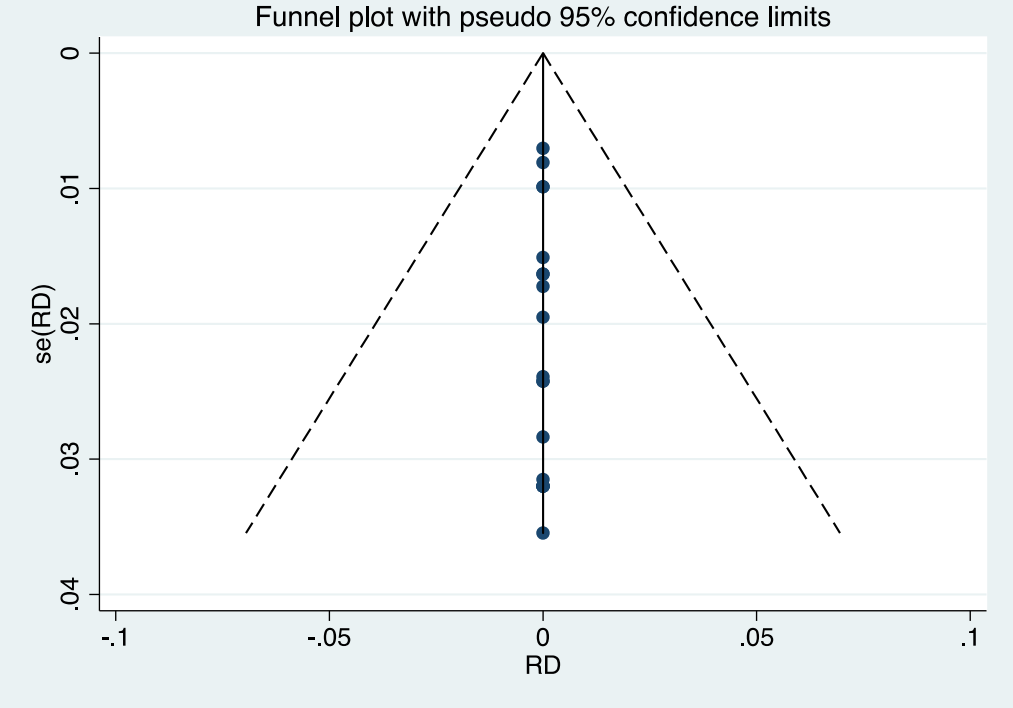
MTCT indicated by HBV DNA positivity at 6–12 months, non-RCTs

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



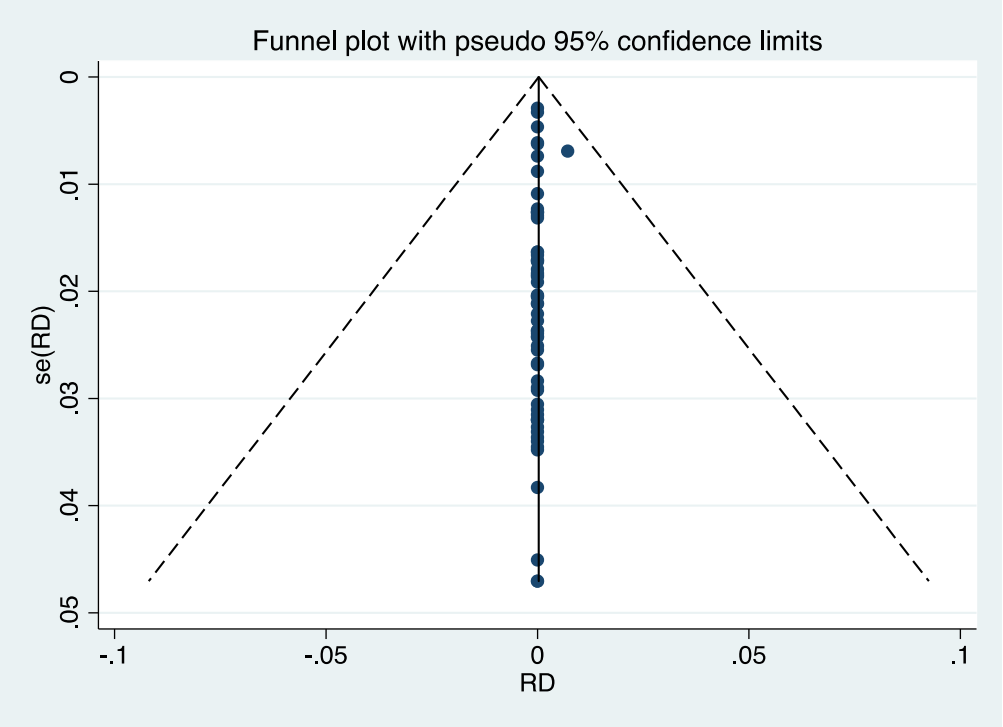
Neonatal deaths, RCTs

- No evidence of publication bias



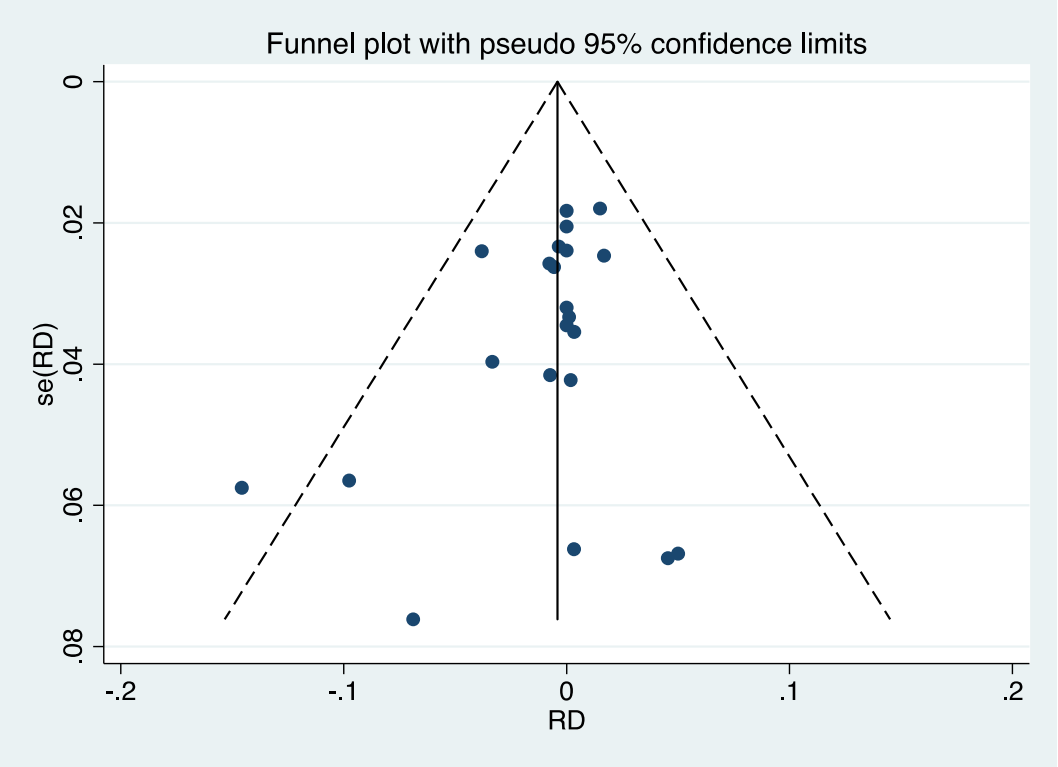
Neonatal deaths, non-RCTs

- No evidence of publication bias



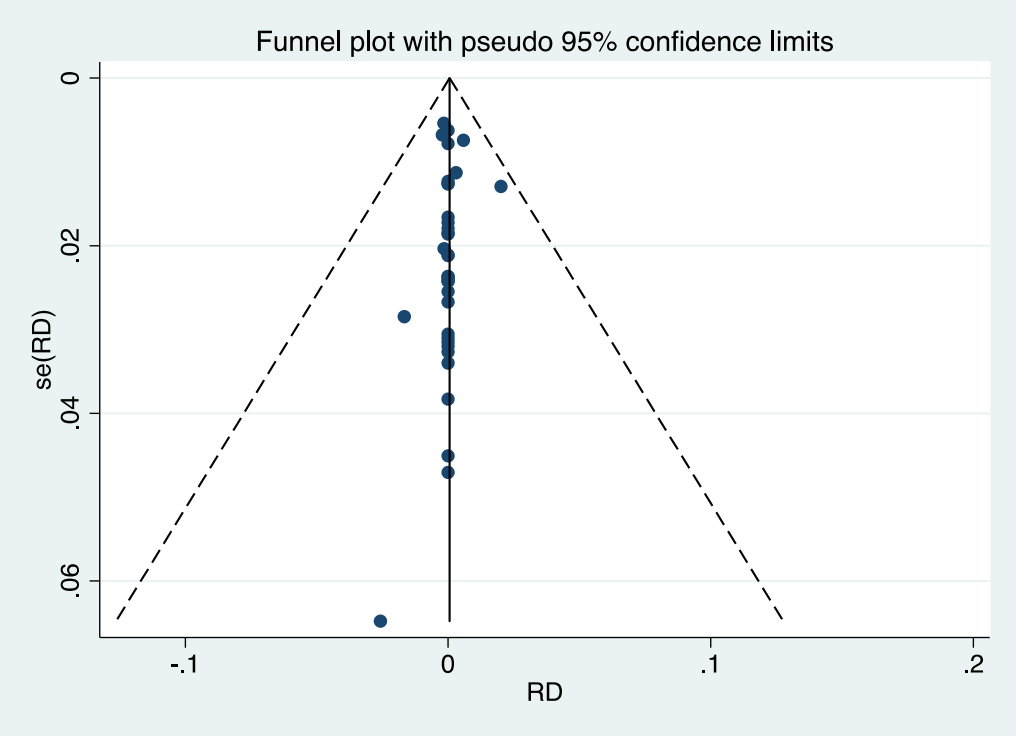
Prematurity, non-RCTs

- Unclear/no evidence of publication bias



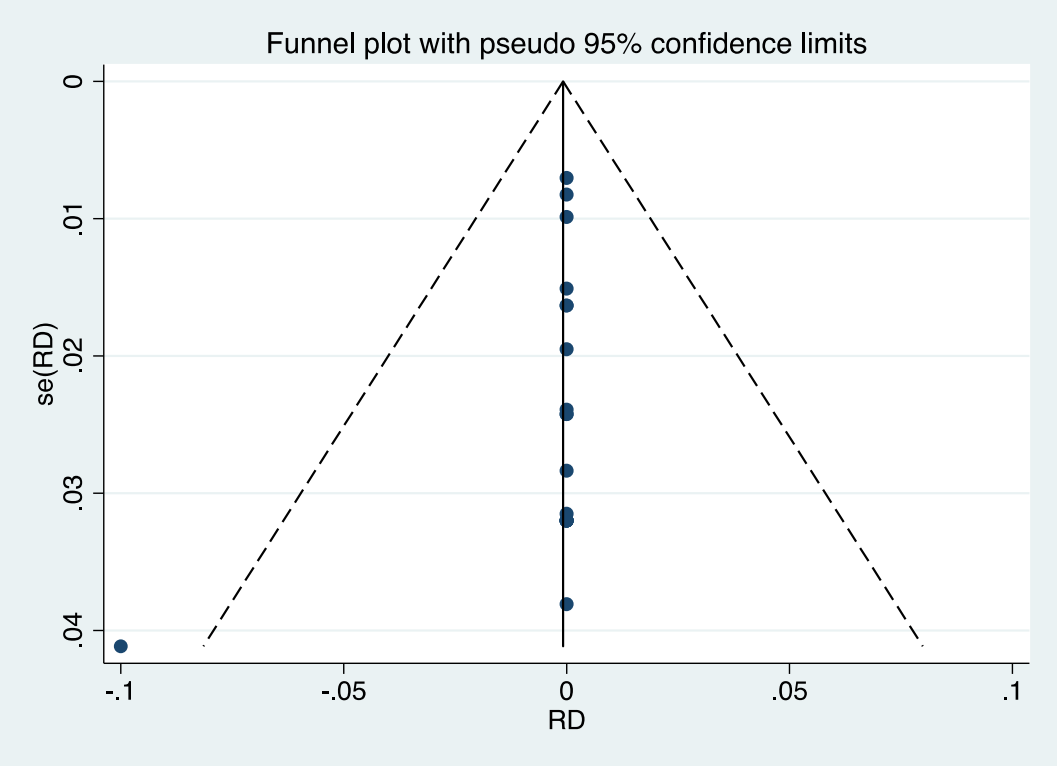
Congenital abnormalities, non-RCTs

- No evidence of publication bias



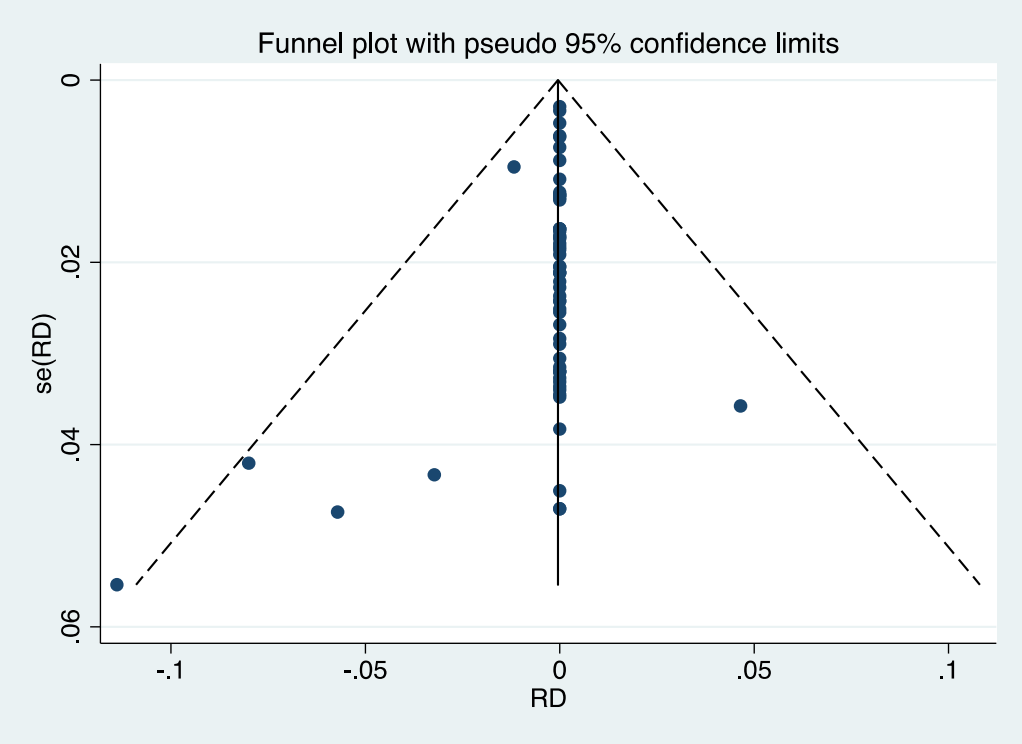
Miscarriages and stillbirths, RCTs

- No evidence of publication bias



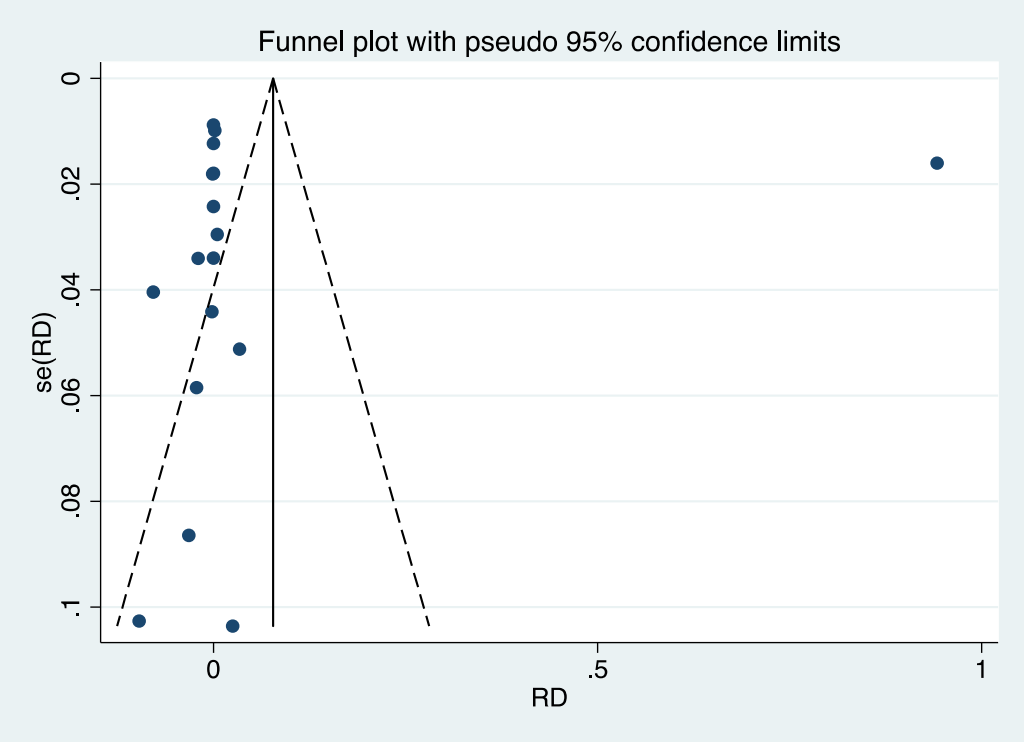
Miscarriages and stillbirths, non-RCTs

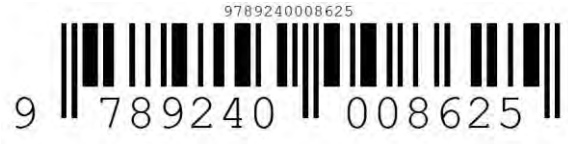
- No evidence of publication bias



Postpartum haemorrhage, non-RCTs

- Possible evidence of publication bias/small study effects

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