# Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis Authors

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**Title**

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**Abstract**

Background

To eliminate mother-to-child transmission (MTCT) of hepatitis B virus (HBV), peripartum antiviral prophylaxis (PAP) may be required for HBV-infected pregnant women with a high risk of MTCT despite infant immunoprophylaxis. We conducted a systematic review and meta-analysis for the efficacy and safety of PAP, in order to inform the 2020 WHO guidelines.

Methods

We searched four English-language (PubMed/EMBASE/Scopus/CENTRAL) and two Chinese-language (CNKI/Wanfang) databases for randomized (RCT) and non-randomized controlled trials (non-RCT) of PAP versus placebo or no PAP published through March 28th, 2019. Two reviewers independently extracted data. Odds ratios (OR) were pooled for the efficacy of PAP to reduce the risk of MTCT. Subgroup analyses were performed on the timing of initiating/stopping antivirals.

Findings

Of 7463 articles identified, 129 studies were included. The pooled ORs for RCTs were similar, at 0.10 (95% CI: 0.03-0.35) for 19 studies of tenofovir disoproxil fumarate (TDF), 0.16 (0.10-0.26) for 40 studies of lamivudine, and 0.14 (0.09-0.21) for 83 studies of telbivudine. The results were similar for non-RCTs. Subgroup analysis identified that initiation in the second trimester may be more beneficial than the third trimester (OR 0.23, 95% CI: 0.09-0.59). We found no increased risk of any infant or maternal safety measures following PAP, except for studies of lamivudine and telbivudine that detected drug-resistant mutations in some treated mothers.

Interpretation

PAP is highly effective at reducing the risk of HBV MTCT. Our findings support the 2020 WHO recommendation of administering antivirals during pregnancy, specifically TDF, for the prevention of HBV MTCT.

Funding

WHO

**Research in context**

*Evidence before this study.*

Major international guidelines for the management of chronic hepatitis B virus (HBV) infection recommend the administration of peripartum antiviral prophylaxis (PAP) to pregnant women with high HBV viral load to prevent mother-to-child transmission (MTCT). The 2015 WHO guidelines utilized a systematic review and meta-analysis on the efficacy, safety, and cost-effectiveness of PAP for the prevention of HBV MTCT. The systematic review only identified limited and low-quality evidence at that time; consequently, the WHO could not make a formal recommendation for use of PAP. Furthermore, only English-language databases were searched, although the majority of studies investigating the efficacy of PAP have been conducted in China and reported in Chinese journals that are not indexed in the English-language databases. Also, since that time, the results of several high-quality clinical trials have been published, especially for tenofovir disoproxil fumarate (TDF), a key first-line anti-HBV therapy.

*Added value of this study.*

Through a comprehensive search that widely covered both the English- and Chinese-language databases, this is the largest and most up-to-date systematic review and meta-analysis on this topic, including more than twice the number of studies compared to previously published systematic reviews. Furthermore, we thoroughly excluded studies with potentially overlapping patient populations. We found high efficacy of three antiviral therapy regimens, including TDF 300 mg (19 studies), lamivudine 100-150 mg (40 studies), and telbivudine 600 mg (83 studies), with protective ORs between 0.10 and 0.16 for RCTs and between 0.09 and 0.17 for non-RCTs. The large number of studies included enabled subgroup analysis on possible sources of

heterogeneity. Although efficacy did not vary by the timing of PAP discontinuation, we found that starting earlier in the second trimester might be more efficacious than in the third trimester. There was no evidence that the use of PAP is associated with an increased risk of fetal death, neonatal death, preterm birth, congenital abnormalities, postpartum hemorrhage, or postpartum hepatitis flare. Almost all studies sysmatically provided both hepatitis B birth dose vaccine (HepB-BD) and immune globulin (HBIG) to neonates, and no study evaluated an HBIG-free strategy.

*Implications of all the available evidence.*

In light of the findings of this meta-analysis, the WHO has made a recommendation for administration of TDF 300 mg starting from the 28$^{th}$ week of pregnancy until at least birth, in addition to the recommendation for at least three doses of hepatitis B vaccination including HepB-BD. Most studies were conducted in Asia, potentially limiting the applicability of findings to other regions with high HBV prevalence such as Africa. Research on the efficacy of PAP without HBIG is urgently needed, given the limited access to HBIG in many low- and middle-income countries.

## Introduction

Chronic infection with hepatitis B virus (CHB) represents a serious global health problem, affecting 257 million persons worldwide and causing 900,000 deaths annually due to chronic liver diseases such as cirrhosis and liver cancer.[1] In 2016, the World Health Organization (WHO) developed a global strategy to eliminate hepatitis B as a public health threat by 2030, with a goal to reduce its incidence by 90%, and its mortality by 65%.[2] To meet these objectives, it is crucial to eliminate mother-to-child transmission (MTCT) of HBV, because chronic infection is more likely to develop when infection occurs early in life, particularly at birth through MTCT.[3] Moreover, the risk of developing chronic liver diseases may be higher in those who acquired HBV infection through MTCT compared to those who acquire it through horizontal transmission later in life.[4,5]

To prevent MTCT, the WHO recommends that all infants receive at least three doses of hepatitis B vaccine, with the first dose administered within 24 hours of life.[6] However, the birth dose of hepatitis B vaccine (HepB-BD), even if given to neonates along with combined passive immunoprophylaxis using hepatitis B immune globulin (HBIG), does not prevent all MTCT,[7] particularly in those born to mothers with high viremia, as reported in a companion systematic review (*Boucheron P et al.*).[8-10] Consequently, MTCT remains a significant contributor to HBV incidence globally, and supplementary interventions to further decrease MTCT are needed.[11]

In 2014, the WHO commissioned a systematic review to examine the efficacy and safety of antiviral therapy administered during pregnancy for the prevention of MTCT. This review was restricted to English-language articles and identified only one observational study assessing the efficacy of tenofovir disoproxil fumarate (TDF), a key first-line anti-HBV therapy. Moreover,

there was limited evaluation of potential harms associated with the use of antivirals during pregnancy. Consequently, the WHO did not make a formal recommendation at that time.[12] Since then, several clinical trials using TDF have been published, and further evidence has become available regarding the risk of postpartum hepatitis flare in mothers after cessation of antivirals as well as for changes in bone mineral density in the infant.[13-16] We thus conducted an updated systematic review, searching both English- and Chinese-langauge databases, and meta-analysis on the efficacy and safety of peripartum antiviral prophylaxis (PAP) for prevention of MTCT, in order to inform the new WHO guidelines.[17]

## Methods

### Search strategy and selection criteria

We followed a protocol pre-registered in PROSPERO (CRD42019134614), and reported according to PRISMA guidelines.[18] Because many studies on HBV MTCT have been published in Chinese-language articles not indexed in Engligh-language databases, we searched four English-language (PubMed/EMBASE/Scopus/CENTRAL) and two Chinese-language (CNKI/Wanfang) databases from inception until March 28$^{th}$, 2019. The search strategies used terms covering HBV AND antiviral therapy AND pregnancy (Appendix A). We also manually searched the references of included studies. There were no language restrictions. Conference abstracts were not considered.

We considered randomized controlled trials (RCT) or non-randomized controlled trials (non-RCT) that enrolled pregnant women with CHB, who received antiviral prophylaxis anytime during pregnancy, and reported the following outcomes: (i) MTCT, indicated by infant HBsAg positivity and/or HBV DNA positivity at 6-12 months of age; and (ii) any infant/maternal adverse events. The following antivirals were considered: adefovir (ADV), emtricitabine (FTC), entecavir (ETV), lamivudine (LAM), telbivudine (LdT), tenofovir alafenamide fumarate (TAF), and TDF. Control groups received no intervention or placebo. Non-RCTs were eligible if they were described as prospective or retrospective cohort studies, with control populations composed of pregnant women with CHB followed during the same time period but who did not receive antiviral prophylaxis (e.g. unwilling). Non-RCTs with a high risk of bias on the Newcastle Ottawa scale (i.e. score $\leq$5) were excluded.[19] Throughout the paper, we used the term "peripartum antiviral prophylaxis (PAP)" rather than "peripartum antiviral therapy" in order to distinguish between antivirals that are given only for a few months surrounding pregnancy and delivery to prevent MTCT (the former) and antivirals given to women/mothers over a longer period, most often lifelong, for their own health benefit (the latter).

Two investigators independently: screened titles and abstracts for all publications identified through the English-language (AF and KY) and Chinese-language databases (YL and TZ); reviewed identified full-text papers; extracted data using a pre-piloted form (Appendix B); and assessed risk of bias using the Cochrane Collaboration tool for RCTs and the Newcastle-Ottawa Scale for non-RCTs (Appendix C).[19,20] A third reviewer resolved any discrepancies (YS). The following data were extracted: study characteristics, primary endpoint (HBsAg detected in infants at 6-12 months of age), secondary endpoint (HBV DNA in infants at 6-12 months), and maternal and infant safety outcomes including fetal/neonatal death, preterm birth, congenital

abnormalities, postpartum hemorrhage, postpartum hepatitis flare, antiviral resistance, and infant bone mineral density. Articles from the same study sites that had overlapping recruitment periods, enrolment criteria, and treatment types were considered to evaluate the same study population unless specifically indicated otherwise by corresponding authors, who we attempted to contact in all cases. Where multiple articles of the same study population were published, only the most recent article was included unless the risk of bias was lower in a different article.

Data analysis

The efficacy of PAP was assessed by pooling odds ratios (OR) for RCTs and non-RCTs separately. The primary and secondary endpoints were MTCT based on infant HBsAg positivity and HBV DNA positivity, respectively. The safety of PAP was assessed by pooling risk differences (RDs), rather than ORs, in order to include studies without events. Per-protocol analysis, with the denominator being the number of children with complete follow-up, was performed. If ≥3 studies were eligible for the analysis/sub-analysis, then estimates were pooled using the DerSimonian-Laird random-effects model. Statistical heterogeneity was assessed using the $I^2$ statistic. Subgroup analyses were performed for the primary endpoint on the following potential sources of heterogeneity: study design (RCT vs non-RCT), WHO region, timing of treatment start/discontinuation, maternal characteristics (mean viral load at inclusion, HBeAg, HIV/HCV/HDV co-infections, HBV genotypes), infant immunoprophylaxis regimen (HBIG, HepB-BD), language used to report the work, quality of the study for non-RCTs, sample size (smaller studies with N≤30 in either treated or control group versus larger studies with N>30 in both treated and control group), and maternal viral load criteria (pre-specified viral load threshold of ≥5.3 log10 IU/mL and mean HBV DNA level reported for participating women

versus other than that). The presence of subgroup effects was evaluated using the fixed-effects inverse-variance method. In addition to *a priori* defined subgroup analysis looking at differences by the time of treatment initiation, and in order to further explore optimal timing of PAP, *post hoc* meta-analyses were performed including only studies with multiple treatment arms. These analyses directly compared the efficacy, viral load prior to treatment initiation, and viral load prior to delivery, for participants with earlier ($2^{nd}$ trimester) versus later ($3^{rd}$ trimester) start. The latter two analyses involved pooling mean differences in viral load at the various timepoints in order to generate the standardized mean difference (SMD). Also *post hoc*, where possible we examined differences in safety outcomes as per timing of treatment initiation. Where there were ≥10 studies,[21] small sample effects, a potential marker for publication bias, were evaluated using funnel plots and Egger's test. Analyses were done using STATA 13 (StataCorp LP, CollegeStation, TX). The evidence quality for primary efficacy analyses and safety analyses were evaluated using the GRADE framework,[22] based on risk of bias, inconsistency, imprecision, indirectness, and reporting bias.

Role of the funding source

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

**Results**

Study selection

Of 7463 articles identified, 595 were assessed in full text, and 129 original studies (reported in 158 articles) ultimately met eligibility criteria: 33 RCTs and 96 non-RCTs (Figure 1). These studies initially enrolled a total of 18,112 HBV-infected mothers (9573 treated, 8539 untreated) and 17,582 of the infants that born to these mothers had complete follow-up (9411 from treated mothers, 8171 from non-treated mothers). The following antivirals were evaluated using meta-analysis: TDF 300 mg (19 studies, 1092 mothers/1072 infants), [13-15,23-44] LAM 100-150 mg (40 studies, 2080 mothers/2007 infants),[32-35.39,45-88] LdT 600 mg (83 studies, 6036 mothers/5971 infants).[30,38,42,43,46,50,56,60,62,64,76,79,80,85,89-173] No meta-analysis was done for the two eligible studies on LdT 100 mg (65 mothers/65 infants)[51,174] or for the one study each on ADV 10 mg (42 mothers/42 infants)[175] and ADV 500 mg (258 mothers/254 infants);[176] these results are summarized in Appendix D.

Study characteristics (Appendix E)

Most studies (121/129, 93.8%) took place in China. One study was conducted in both China and the Philippines, and one study each was conducted in Japan, Taiwan, Thailand, Australia, Egypt, Turkey, and Ireland. Only eight studies reported HBV genotypes for all enrolled mothers: genotypes B/C in seven Asian studies;[24,29,39,76,128,139,160] and genotypes B/C/D/E in one Irish study.[67] In 79/129 studies (61.2%), the inclusion criteria specified a high (>5.0 log10 IU/mL) maternal viral load threshold at baseline for all participants. Most studies exclusively included HBeAg-positive women (83/129, 64.3%), 9 studies included a mix of HBeAg-positive and HBeAg-negative women, and one study exclusively included HBeAg-negative women;[165] the remaining 36 studies (27.9%) did not report on HBeAg positivity. All of the included studies

either excluded women co-infected with HIV, HCV, or HDV, or did not report on their prevalence. In most studies (102/129, 79.1%), timely HepB-BD and HBIG were provided to neonates; 27 studies did not clearly indicate timely administration of HepB-BD and HBIG.

Risk of bias within studies

Of the five RCTs evaluating TDF, two had low risk of bias for the majority of the main criteria;[13,14] the remaining three had a high/unclear risk of bias for the majority of criteria.[24,26,27] None of the RCTs investigating LAM (n=8) or LdT (n=21) achieved a 'low risk of bias' rating on the majority of the main criteria; most were either high/unclear risk for performance bias (blinding of study personnel), detection bias (blinding of outcome assessment), and attrition bias (high loss to follow-up or no reporting of loss to follow-up) (Appendix F). Of the 96 non-RCTs, 29 had a high risk of bias with a score of 6 while 67 had low risk of bias with a score ranging 7-9. There were no differences in the distributions of risk of bias scores across non-RCTs examining the three main treatment regimens (Appendix G).

Overall efficacy

PAP was associated with a significant reduction in HBsAg positivity in infants aged 6-12 months in both RCTs and non-RCTs. The pooled ORs in RCTs were: 0.10 (95% CI: 0.03-0.35) for TDF, 0.16 (0.10-0.26) for LAM, and 0.14 (0.09-0.21) for LdT (Figure 2). Statistical heterogeneity was not present ($I^2$=0.0%) in any of the analyses, and the three antiviral regimens were similar in efficacy without any statistically significant difference (p=0.78). The pooled ORs in non-RCTs were: 0.17 (95% CI: 0.10-0.29) for TDF, 0.17 (0.12-0.24) for LAM, and 0.09 (0.06-0.12) for LdT. Between RCTs and non-RCTs, no significant differences in treatment efficacy were

observed for each type of antiviral; therefore, these were merged for subsequent subgroup analysis. Similar efficacies were observed when using infant HBV DNA positivity as an endpoint. There was no statistical heterogeneity ($I^2$=0.0%) seen in any of the meta-analyses that used HBV DNA positivity as an endpoint, besides that of RCTs using LAM ($I^2$=39.8%) where only five studies were included and one outlier (OR=1.28, 95%CI: 0.20-8.32)[45] contributed all observed heterogeneity (Appendix H). The individual characteristics (where available) of infants with MTCT despite maternal TDF 300 mg prophylaxis can be found in Appendix I.

Efficacy by subgroups

Efficacy did not vary according to mean maternal viral load at baseline (6.0-6.9, 7.0-7.9, 8.0-8.9 log10 IU/ml), the timing of PAP discontinuation (at delivery, 4-8, 12, 24 weeks postpartum), infant immunoprophylaxis regimen, language used to report the study (English, Chinese), risk of bias score for non-RCTs (high, 6; intermediate, 7; low, 8-9), study sample size (≤30 participants versus >30 participants in each group), or maternal viral load criteria (Appendices J-R). Although LAM 100-150 mg was associated with greater efficacy with earlier initiation, compared with later initiation, the interaction was not statistically significant (p=0.06) (Table 1). *Post hoc meta-analyses* of studies that directly compared different treatment starting times (2nd vs 3rd trimester) suggested that starting in the 2nd trimester might be more effective at reducing MTCT risk (OR 0.23, 95% CI: 0.09-0.59) (Figure 3). In the same set of analyses, while baseline viral load did not differ between women in these two timing groups prior to treatment (SMD=0.01, 95%CI: -0.16-0.19), women starting treatment earlier (in the second trimester) had significantly reduced viral load prior to delivery (SMD=-0.62, 95%CI: -0.77- -0.46) (Appendix S).

Maternal safety

There was no evidence that PAP was associated with an increased risk of fetal death or postpartum hemorrhage, however, the number of events was small and the estimates were imprecise (Table 2, Appendices T-V). There was also no association between cessation of TDF (four studies), LAM (six studies), or LdT (three studies) and increased risk of postpartum flare, based on evaluation for flare at a fixed time in the intervention group and a matched period in the control group. The definition of flare varied across studies; however, most cases were mild and spontaneously recovered, and none progressed to hepatic decompensation (Appendix V). One TDF study investigated antiviral resistance for all women and found no HBV mutations related to antiviral therapy.[24] In contrast, 2/4 studies of LAM and 3/7 studies of LdT detected drug-resistant mutations in some treated mothers; meta-analysis was not possible because of considerable variation in timing of testing and population tested.[32,61,67,76,85,110,119,121,133,139,148] There were no differences in risk of any maternal safety outcomes by timing of treatment initiation (Appendix W).

Infant safety

There was no evidence that PAP was associated with an increased risk of neonatal death, preterm birth, and congenital abnormalities, however, given the small number of events these estimates were imprecise (Table 2, Appendices X-Z). Only one TDF study investigated bone mineral density changes in children in both groups, with no statistically significant difference detected.[14,15] There were no differences in risk of any infant safety outcomes by timing of treatment initiation (Appendix W). There was heterogeneity ($I^2$=43.0%) in the meta-analysis of the risk of preterm birth following LAM 100-150 mg which could be largely contributed to two

outlying studies, both of which were non-RCTs that started treatment very early (pre-pregnancy or in the first trimester) (Appendix Y).[64,72]

Risk of bias across studies

Funnel plots and the Egger's test did not indicate small sample effects in RCTs. In non-RCTs, however, there was evidence of potential small sample effects for the efficacy of each of the treatment types (Appendix AA).

GRADE assessment

The GRADE evidence quality for the primary endpoint, based on RCTs, was high for TDF and moderate for LAM and LdT (due to high/unclear risk of bias in most studies). Although GRADE was lower for non-RCTs, these studies' results were consistent with RCTs. For some safety outcomes evaluated by RCTs, including fetal death, neonatal death, and congenital abnormalities, GRADE was ranked as moderate for TDF and low for LAM and LdT. In contrast, GRADE for postpartum hemorrhage and postpartum flare were low or very low for all types of antivirals (Appendix AB). It was not possible to do GRADE evidence quality analysis for antiviral resistance.

## Discussion

This systematic review and meta-analysis found evidence to support the efficacy and safety of PAP using three different types of nucleos(t)ide analogues; namely, TDF, LAM, and LdT. Meta-analysis of RCTs showed that these antivirals were associated with large and similar reductions

in the likelihood of MTCT. For safety outcomes, there was no evidence for an increased risk associated with any of the antivirals examined, though some findings were based on small number of events. However, this systematic review confirmed the low barrier to resistance of early generation nucleos(t)ide analogues (LAM and LdT).[12,177] Consequently, WHO recommends TDF for HBV-infected women with high viral load to prevent MTCT.

An important strength of this systematic review is its comprehensive search, which covered both English- and Chinese-language databases, leading to the inclusion of more than twice the number of studies compared to previous systematic reviews on this topic.[178-184] The large number of studies included enabled us to perform subgroup analyses for efficacy, and safety evaluations of rarer outcomes. In addition, efforts were employed to exclude articles evaluating the same patient group, in order to avoid doublecounting and overweighting of the same study samples; the inclusion of overlapping patient populations in other systematic reviews has been criticized.[185] We also excluded poorly conducted non-RCTs with a high risk of bias. Subsequently, there was no evidence of heterogeneity in efficacy estimates between English- versus Chinese-language studies, nor between studies with smaller versus larger sample sizes.

The optimal timing to start and stop PAP has not been well established. Different guidelines recommend varying schedules, ranging from starting at 24-28 to 28-32 weeks of gestation, and from stopping at childbirth to 12 weeks postpartum.[186,187] Our *post hoc* analyses suggest that starting in the second trimester might be more efficacious than in the third trimester, and that this may be linked to increased viral load reduction in women treated earlier. However, this finding should be cautiously interpreted as it is based on a small number of studies (4),[37,87,94,139] and events (23 total). Moreover, only two of the included studies in this *post hoc* analysis

administered TDF. More research is needed on this topic prior to making any conclusions. WHO recommends starting PAP from the 28th week of pregnancy, pending additional evidence to support earlier administration.

No difference was observed in the efficacy of PAP when cessation was at the time of childbirth versus at 4-8 weeks postpartum, suggesting that PAP could be stopped immediately after delivery. Another concern, however, is postpartum hepatitis flare. In HBV-infected pregnant women without concurrent antiviral therapy, rapid changes in maternal immunity being suppressed during pregnancy followed by its reconstitution after childbirth could trigger postpartum flare. Early studies have reported that initiating antivirals during pregnancy and its withdrawal at delivery might further increase the risk of postpartum flare.[188] Our meta-analysis did not observe any difference in the risk of postpartum flare between the treated group following discontinuation of PAP and controls; however, none of these comparative studies stopped PAP at the time of child delivery. In four included studies where all women were HBeAg-positive, and which reported on flare only in the treated group, the range of flare risk for women stopping treatment at childbirth was 3.5-19.2% (Appendix V).[67,84,109,145] This range overlaps with that previously reported for non-treated HBeAg-positive women (14.2-40.0%).[189,190] Few studies were included in the safety meta-analysis for postpartum flare and the GRADE evidence quality was low or very low for all treatment types for this outcome. There was also important heterogeneity in all meta-analyses for all treatments that evaluated flare, this is likely explained by the minimal number of eligible studies, as well as important differences in both the safety outcome definitions used and the treatment regimen timing across these studies. The vast majority of all flares described in the studies were mild and self-limiting; only a few required antiviral therapy, and none developed hepatic decompensation.

Our review had potential limitations. Only 6% (2/33) of the RCTs were assessed as having an overall low risk of bias (Appendix F). Very few (18%, 6/33) of the included RCTs presented adequate details of loss-to-follow-up,[13,14,,26,89,103,106] which limited our ability to perform intention-to-treat meta-analysis. 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, indicating multiple methodological limitations (Appendix G). Many of the included studies had small sample sizes (≤30 infants) in either the treated or control group, although sensitivity analysis showed no difference in efficacy estimates between smaller and larger studies for any treatment type (Appendix Q). Some subgroup meta-analyses had few (i.e. <5) eligible studies, such as those examining differences in efficacy by mean maternal viral load at baseline (Appendix L), and therefore, these results should be interpreted cautiously. This is a meta-analysis of aggregate data, and some topics were limited in examining, such as differences in efficacy by maternal viral load, may be better evaluated using a meta-analysis of individual participant data. Importantly, the vast majority of included studies were conducted in Asia, particularly in China. Of the seven studies conducted outside of China, only one from each of Thailand and Taiwan had >30 participants in both treated and control groups. Therefore, there is very limited representation of diverse populations in this meta-analysis and the applicability of our study findings to other regions is uncertain. For example, in sub-Saharan Africa, another area with a high HBV prevalence, the major HBV genotypes, the natural history of CHB, and the current standard of care, all differ from Asia.[191,192] Many African countries have limited coverage of HepB-BD, and are without access to either HBIG or HBV DNA testing. No studies evaluated the efficacy of PAP without HBIG (i.e. with HepB-BD alone), indicating an important research

gap. A field evaluation is ongoing to assess the efficacy of HepB-BD plus PAP versus HepB-BD alone.[193]

Based on the evidence provided by this study as well as a companion systematic review that addressed HBV DNA thresholds for identifying pregnant women at risk of MTCT (*Boucheron P et al.*), the WHO recommends administering TDF to HBV-infected pregnant women with high viral load (≥5.3 log10 IU/mL (≥200,000 IU/mL)) from the 28$^{th}$ week of pregnancy until at least childbirth to prevent MTCT, in addition to three doses of hepatitis B vaccination including HepB-BD. In order to accelerate global HBV elimination by 2030, it is essential to promote the uptake of PAP into routine healthcare, particularly in LMICs that bear the highest HBV disease burden.

## Contributors

AF, JVH, RC, MB, and YS formulated the research questions. AF and YS developed the study protocol, analysed the data, and wrote the manuscript. AF and YL developed the search strategy. AF, YL, KY, TZ, and PB performed the systematic review. All authors reviewed the manuscript and approved the final version.

## Declaration of interests

RC received personal fees from the WHO. The rest of the authors declare no competing interests.

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## References


1 World Health Organization. Global Hepatitis Report 2017. Available at: https://apps.who.int/iris/rest/bitstreams/1082592/retrieve. Last accessed on March 13th 2019.

2 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Available at: https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/ Last accessed on March 6th 2020.

3 Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. *Proc. R. Soc. Lond. B* 1993; **253**:197-201

4 Chang MH. Natural History and clinical management of chronic hepatitis B virus infection in children. *Hepatol Int* 2008; **2:** S28-S36.

5 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.

6 World Health Organization. Hepatitis B vaccines: WHO position paper - July 2017. *Wkly Epidemiol Rec* 2017; **27(92**): 369–392

7 Chen HL, Lin LH, Hu FC, et al. Effects of Maternal Screening and Universal Immunization to Prevent Mother-to-Infant Transmission of HBV. *Gastroenterology* 2012; **142**: 773-781.

8 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

9 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.

10 Wen WH, Chang MH, Zhao LL, 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.

11 Nayagam S, Thursz M, Sicuri E, et al. Requirements for global elimination of hepatitis B: a modelling study. *Lancet Infect Dis* 2016; **16(12)**: 1399-408.

12 World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Available at: http://apps.who.int/medicinedocs/documents/s21813en/s21813en.pdf. Last accessed on March 13th 2019.

13 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

14 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**: 911-23

15 Salvadori N, Fan B, Teeyasoontranon W, 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; **69(1)**: 144-146

16 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

17 World Health Organization. Prevention of mother-to-child transmission of hepatitis B virus (HBV): Guidelines on antiviral prophylaxis in pregnancy. Geneva, Switzerland, 2020.

18 Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; **6(7):** e1000097.

19 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 13th 2019.

20 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).

21 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

22 The GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328:**1490–4.

23 Jourdain G, Ngo Giang Huong N, Cressey TR, Hua L, Harrison L, Tiemey C et al. Prevention of mother-to-child transmission of hepatitis B virus: a phase III, placebo-controlled, double-blind, randomized clinical trial to assess the efficacy and safety of a short course of tenoovir disoproxil fumarate in women with hepatitis B virus e-antigen. *BMC Infect Dis* 2016; 16: 393

24 Lin Y, Liu Y, Ding G, Touqui L, Wang W, Xu N et al. Efficacy of tenofovir in preventing perinatal transmission of HBV infection in pregnant women with high viral loads. *Nature Sci Reports* 2018**; 8:**15514

25 Liu J, Wang J, Qi C, Cao F, Tian Z, Guo D et al. Baseline Hepatitis B Virus Titer Predicts Initial Postpartum Hepatic Flare. *J Clin Gastroenterol* 2018; **51(10):** 902-907

26 Liu MH, 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

27 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

28 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; **19 (48):** 9377-9382

29 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* 2015; **62 (2)**: 375-386

30 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

31 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

32 Greenup AJ, Tan PK, Nguyen V, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of Hepatitis B Virus. *J Hepatol* 2014; **61(3)**: 502-7.

33 Greenup AJ, Tan PK, Nguyen V, et al. Corrigendum to "Efficacy and safety of tenofovir disoproxil fumarate (TDF) in pregnancy to prevent perinatal transmission of hepatitis B virus." *J Hepatol* 2015; **63**: 1054

34 Nguyen V, Tan PK, Greenup AJ, et al. Anti-viral therapy for prevention of perinatal HBV

transmission: extending therapy beyond birth does not protect against post-partum flare. *Aliment Pharmacol Ther* 2014; **39**: 1225-1234

35 Thilakanathan C, Wark G, Maley M, et al. Mother-to-child transmission of hepatitis B: Examining viral cut-offs, maternal HB sAg serology and infant testing. *Liver Int* 2018; **38(7):** 1212-9.

36 He LL, 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

37 Hu MF, Zhuang L, Wang J, 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

38 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

39 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* 2018; **44 (3):** 566–569

40 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

41 Wang HB, 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

42 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

43 Zhang BF, Cheng M, Zhang Q, 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

44 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

45 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

46 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

47 Guo Y, 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

48 Guo YZ, Li SX, Ge SL, Wang JH. The efficacy of lamivudine combined with passive-active immunoprophylaxis to prevent mother-to-child transmission of hepatitis B virus.

*Clinical Focus 2008*; **23 (23):** 1730-1731.

49 Guo YZ, Li SX, Wang JH. The clinical research on lamivudine combined with passive-active immunoprophylaxis to interrupt mother-to-child transmission of HBV. *Community Medicine Journal* 2008; **6 (22):** 27-28.

50 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

51 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

52 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

53 Xu WM, Cui YT, Wang L, 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

54 Yang S, Liu M, Wang L. Effect of high viral hepatitis B virus DNA loads on vertical transmission of hepatitis B virus in late-pregnant women. *Chin J Obstet Gynecol* 2008; **43 (5)**: 329-331.

55 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

56 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

57 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

58 Feng HF, Zhang S. Effect on interruption of hepatitis B virus vertical transmission by lamivudine. *J Appl Clin Pediatr* 2007; **22 (13):** 1019-1020

59 Foaud HM, Maklad S, Gmal El Din A, Mahmoud F. Lamivudine use in pregnant HBsAg-females effectively reduces maternal viremia. *Arab J Gastroenterol* 2019; **20(1):** 8-13.

60 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

61 Ayres A, Yuen L, Jackson KM, et al. Short duration of lamivudine for the prevention of hepatitis B virus transmission in pregnancy: lack of potency and selection of resistance mutations. *J Viral Hepat* 2014; **21**: 809-817

62 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

63 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

64 He T, Bai Y, Cai H, et al. Safety and efficacy of lamivudine or telbivudine started in early pregnancy for mothers with active chronic hepatitis B. *Hepatol Int.* 2018; **12(2):** 118-125. doi: 10.1007/s12072-017-9839-5.

65 Fu D, Ma XY, Liu M, Yi W, Cai HD. Clinical analysis on 89 chronic hepatitis B pregnant women with abnormal liver function during pregnancy. *Chin J Exp Clin Infect Dis* 2014; **8 (4):** 556-560.

66 Fu D, Li ZH, Liu M, Cai HD. Influence of antiviral therapy on pregnancy outcome in active hepatitis B patients during pregnancy. *ADRJ* 2012; **14 (3):** 149-153.

67 Jackson V, Ferguson W, Kelleher TB, et al. Lamivudine treatment and outcome in pregnant women with high hepatitis B viral loads. *Eur J Clin Microbiol Infect Dis* 2015; **34(3):** 619-23.

68 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

69 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

70 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

71 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

72 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

73 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; **24(3):** 246-252.

74 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

75 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

76 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

77 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

78 Tang X. Clinical observation on lamivudine preventing mother-to-child transmission of hepatitis B virus. *Jiangxi Medical Journal* 2009; **44 (3):** 250-251

79 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

80 Wang EJ. Comparison of efficacy and safety between lamivudine and telbivudine in blocking vertical transmission of hepatitis B virus in late stage of pregnancy. *Chinese General Practice* 2012; **15 (11):** 3628-3630

81 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

82 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

83 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

84 Zeng YM, 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

85 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

86 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* 2010a; **26 (5):** 367-368

87 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

88 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

89 Bai HL, Shang H, Li Z. Clinical investigation on telbivudine preventing intrauterine hepatitis B virus infection during late pregnancy. *China Medical Engineerin*g 2013; **21 (6):** 53-54

90 Fu PX. The efficacy and safety of telbivudine to prevent mother-to-child transmission of HBV during late pregnancy. *Psychologist* 2016; **22 (16)**: 109-110

91 Guan ZF, 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

92 Chen LR, Wu Q, Guo L, Ma HP, Xu S. The impact of telbivudine on blocking effect of

passive dual immunity on mother-to-child HBV transmission. *Modern Immunology* 2017; **37 (1):** 38-43.

93 Guo HJ, 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

94 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

95 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

96 Lu QY. 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

97 Peng ML, 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

98 Shi QW. 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

99 Wang HY, 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

100 Xie PY. Nursing management of pregnant women receiving antiviral therapy during pregnancy to interrupt intrauterine transmission of hepatitis B virus. *Psychologist* 2016; **22 (12):** 151-152

101 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

102 Yang HW. 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

103 Zhang LJ, Wang L. Blocking intrauterine infection by telbivudine in pregnant chronic hepatitis B patients. *Chin J Hepatol* 2009; 17 (8): 561-563

104 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

105 Zhao DB, 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

106 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

107 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

108 Zhu LP. The efficacy and safety of telbivudine to prevent intrauterine hepatitis B virus infection. *Chin J Mod Drug Appl* 2014; **8 (9):** 142-143

109 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

110 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

111 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; **75(2):** 146-154.

112 Gu GF, Qin G, Yao W, Cheng L, Zhong JX, Zhang YQ, et al. Clinical study of telbivudine anti-virus treatment during middle to late pregnancy of the pregnant women with hepatitis

B. *Journal of Nantong University (Medical Science)* 2018; **38 (3):** 177-180.

113 Gu GF, Qin G, Zhang LH, Cai MZ, Yao W, Yao Y, et al. The comparison of efficacy of telbivudine and hepatitis B immunoglobulin given during late pregnancy to prevent mother-to-child transmission. *Acta Universitatis Medicinalis Nanjing (Natural Science)* 2018; **38 (6):** 816-819.

114 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

115 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

116 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

117 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

118 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

119 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

120 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; **22(9):** 754-62.

121 Han GR, Cao MK, Zhao W, Jiang HX, Wang CM, Bai SF et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. *J Hepatol* 2011; **55:** 1215-1221

122 Han GR, Jiang HX, Wang GJ, Yue X, Wang CM, Kan NY, et al. Efficacy and safety of telbivudine in pregnant women to prevent perinatal transmission of hepatitis B virus. *Chin J Hepatol* 2012; **20 (3):** 201-205.

123 Pan CQ, Han GR, Jiang HX, Zhao W, Cao MK, Wang CM et al. Telbivudine Prevents Vertical Transmission From HBeAg-Positive Women With Chronic Hepatitis B. *Journal* 2012; **10***:* 520-526.

124 Wang GJ, Han GR, Jiang HX, Wang CM, Ding H. The effect of telbivudine treatment during pregnancy on interruption of mother-to-child transmission and its influence on peripheral T cell subset and complement. *Acta Universitatis Medicinalis Nanjing (Natural Science)* 2017; **37 (11):** 1507-1509.

125 Yu MM, Jiang Q, Ji Y, Wu KH, Ju LL, Tang X et al. Comparison of telbivudine versus lamivudine in interrupting perinatal transmission of hepatitis B virus. *J Clin Virol* 2014; **61:** 55-60

126 Yi W, Li MH, Xie Y, Hu YH, Zhang D, Zhang Y et al. Prospective cohort study on the

efficacy and safety of telbivudine used throughout pregnancy in blocking mother-to-child transmission of hepatitis B virus. *J Viral Hepat* 2017; **24(Suppl. 1):** 49-56

127 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

128 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

129 Cao MK, Hu LQ, Zhao L. Effect of telbivudine in late pregnancy for the prevention of perinatal transmission of hepatitis B virus to the infants. *Modern Medical Journal* 2016; **44 (3):** 292-295.

130 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

131 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

132 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

133 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

134 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

135 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

136 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

137 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

138 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

139 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

140 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

141 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

142 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

143 Qiu B, Zhu L, Chen Y, 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

144 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

145 Sheng QJ, Ding Y, Li B, 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* 2018a; **15(8):** 796-801

146 Sheng QJ, Ding Y, Li BJ, et al. Telbivudine for prevention of perinatal transmission in pregnant women infected with hepatitis B virus in immune-tolerant phase: a study of efficacy and safety of drug withdrawal. *Chin J Hepatol* 2016; **24 (4):** 258-264

147 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* 2018b; **97**:22

148 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

149 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

150 Sun WH, Chu LL, Liu WL, Hao AH, Ma L, Wan Q, et al. Efficacy and safety of telbivudine in preventing mother-to-infant transmission of HBV in pregnant women with high HBV DNA load. *J Clin Hepatol* 2013; **29 (8):** 596-599.

151 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

152 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

153 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

154 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

155 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

156 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

157 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

158 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

159 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

160 Wu QX, Huang H, Sun X, 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

161 Wu QX, Deng GH, Li JN, et al. Effects of telbivudine on transmission of HBsAg and HBeAg through placenta in HBV infected pregnant women in second or third trimester. *J Third Mil Med Univ* 2013; **35 (7):** 665-668.

162 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

163 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

164 Chen XQ, Yao ZC, Wu LP, Chen MC, Zhang YP, Wu Y. Clinical study on telbivudine in preventing mother-to-infant HBV transmission during the late pregnancy. *J Clin Hepatol* 2011; **27 (12):** 1282-1284.

165 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

166 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

167 Zhang GH. To evaluate the efficacy and safety of telbivudine in preventing mother to

child transmission of hepatitis B. *World Latest Medicine Information (Electronic Version*) 2015; **15 (79**): 28, 73.

168 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

169 Zhang YF, Hu Y. Efficacy and safety of telbivudine in preventing mother-to-infant HBV transmission. *ADRJ* 2010b; **12 (3):** 157-159

170 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

171 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

172 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

173 Zhou YJ, Zheng JL, Pan HJ, Jiang S. Efficacy and safety of telbivudine in pregnant chronic hepatitis B patients. *Chin J Hepatol* 2011; **19 (11):** 861-862.

174 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

175 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

176 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

177 Wang J, Liu J, Qi C, Yan T, Cao F, Jin L, He Y, Yang Y, Zhang S, Chen T, Zhao Y. Efficacy of tenofovir disoproxil fumarate to prevent vertical transmission in mothers with lamivudine-resistant HBV. *Antivir Ther.* 2015; **20(7):** 681-7.

178 Brown RS, McMahon BJ, Lok ASF, et al., Antiviral therapy in Chronic Hepatitis B Viral Infection during Pregnancy: A Systematic Review and Meta-analysis. *Hepatology* 2016; **63(1):** 319-33.

179 Hyun MH, Lee YS, Kim JH, et al., Systematic review with meta-analysis: the efficacy and safety of tenofovir to prevent mother-to-child transmission of hepatitis B virus. *Aliment Pharmacol Ther.* 2017; 1–13

180 Njei B, Gupta N, Ewelukwa O, et al., Comparative efficacy of antiviral therapy in preventing vertical transmission of hepatitis B: a network meta-analysis. *Liver Int.* 2016; **36:** 634–641.

181 Sali S, Darvishi M, GhasemiAdl M, Akhlaghdoust M, Mirzazadeh A, Behjati SE, Sheikh-Zeinolabedini H, Shokouhi S, Tavakolpour S. Comparing the Efficacy and Safety of Treating Chronic Hepatitis B Infection during Pregnancy with Lamivudine, Telbivudine,

and Tenofovir: A Meta-analysis. *Journal of Clinical and Translational Hepatology*. 2019; **7(3):** 197.

182 Siemieniuk RA, Foroutan F, Mirza R, et al., Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis. *BMJ Open* 2017; **7:** e019022.

183 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. *J Viral Hepatitis* 2019; **26**: 397–406

184 Tavakolpour S, Darvishi M, Mirsafaei HS, Ghasemiadl. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B infection during pregnancy: a systematic review. *Infect Dis* 2018; **50 (2**); 95–106.

185 Zhou YH, Correspondence: Prevention of Mother-to-Child Transmission of Hepatitis B Virus by Treating Mothers With High Viral Loads. *Hepatology* 2016; **64 (5):** 1823-1824.

186 World Health Organization, Regional Office for the Western Pacific. Third Strategic and Technical Advisory Committee (STAC) for Viral Hepatitis, Manila, Philippines, 17-20 September 2018: meeting report. https://iris.wpro.who.int/handle/10665.1/14317. Last accessed April 20th, 2020.

187 Zhou YH. Issues Meriting Further Study in Preventing Mother-to-Infant Transmission of Hepatitis B by Antiviral Therapy During Pregnancy. *Maternal-Fetal Medicine* 2019; **1**:1

188 Ter Borg MJ, Leemans WF, De Man RA, Janssen HL. Exacerbation of chronic hepatitis B

infection after delivery. *J Viral Hepatitis* 2008; **15(1):** 37-41.

189 Giles M, Visvanathan K, Lewin S, Bowden S, Locarnini S, Spelman T, Sasadeusz J. Clinical and virological predictors of hepatic flares in pregnant women with chronic hepatitis B. *Gut* 2015; **64(11):** 1810-5.

190 Yi W, Pan CQ, Li MH, et al. The characteristics and predictors of postpartum hepatitis flares in women with chronic hepatitis B. *Am J Gastroenterol* 2018; **113(5):** 686-93.

191 Shimakawa Y, Lemoine M, Njai HF, et al. Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia. *Gut* 2016; **65(12):** 2007-16.

192 Spearman CW, Afihene M, Ally R, Apica B, Awuku Y, Cunha L, Dusheiko G, Gogela N, Kassianides C, Kew M, Lam P. Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets. *Lancet Gastroenterol Hepatol* 2017; **2(12):** 900-9.

193 Jourdain G. Clinical Trial Protocol. Antiviral Prophylaxis and Infant Vaccination to Prevent Perinatal Hepatitis B Infection. Available at: https://clinicaltrials.gov/ct2/show/NCT03343431?term=NCT03343431&draw=2&rank=1. Last accessed on March 6th, 2020.

**Table 1. Efficacy of peripartum antiviral prophylaxis (PAP) in the prevention of MTCT*, by subgroups**

| Subgroup | | TDF 300 mg (n=19) | | | LAM 100-150 mg (n=40) | | | LdT 600 mg (n=83) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of studies | OR (95% CI) | P | No. of studies | OR (95% CI) | P | No. of studies | OR (95% CI) | P |
| **Study design** | **RCTs** | 5 | 0.10 (0.03-0.35) | 0.47 | 8 | 0.16 (0.10-0.26) | 0.80 | 21 | 0.14 (0.09-0.21) | 0.08 |
| | **Non-RCTs** | 14 | 0.17 (0.10-0.29) | | 32 | 0.17 (0.12-0.24) | | 62 | 0.09 (0.06-0.12) | |
| **Timing of PAP initiation (median gestational age)** | **<28 weeks** | 10 | 0.10 (0.04-0.25) | 0.15 | 7 | 0.10 (0.04-0.26) | 0.06 † | 24 | 0.08 (0.05-0.13) | 0.20 |
| | **28 weeks** | 7 | 0.25 (0.13-0.48) | | 20 | 0.16 (0.11-0.22) | | 44 | 0.13 (0.10-0.18) | |
| | **>28 weeks** | 5 | 0.10 (0.03-0.29) | | 11 | 0.31 (0.16-0.57) | | 13 | 0.09 (0.04-0.20) | |
| **Timing of PAP discontinuation (postpartum)** | **At delivery** | 5 | 0.11 (0.04-0.28) | 0.96 | 13 | 0.15 (0.10-0.23) | 0.19 | 16 | 0.10 (0.06-0.16) | 0.49 |
| | **4-8 weeks** | 7 | 0.12 (0.04-0.34) | | 21 | 0.23 (0.15-0.34) | | 33 | 0.13 (0.09-0.19) | |
| | **12 weeks** | 2 | N/A | | 2 | N/A | | 8 | 0.06 (0.02-0.16) | |
| | **24 weeks** | 0 | N/A | | 0 | N/A | | 6 | 0.11 (0.04-0.29) | |
| **Mean maternal viral load at baseline (log IU/mL)** | **5.0-5.9** | 0 | N/A | 0.96 | 0 | N/A | N/A | 1 | N/A | 0.14 |
| | **6.0-6.9** | 0 | N/A | | 4 | 0.15 (0.06-0.37) | | 10 | 0.13 (0.07-0.23) | |
| | **7.0-7.9** | 3 | 0.10 (0.03-0.41) | | 1 | N/A | | 13 | 0.06 (0.03-0.13) | |
| | **8.0-8.9** | 3 | 0.11 (0.02-0.51) | | 2 | N/A | | 1 | N/A | |
| **Maternal HBeAg at baseline** | **Positive** | 11 | 0.09 (0.04-0.21) | N/A | 30 | 0.16 (0.12-0.23) | 0.45 | 52 | 0.11 (0.08-0.14) | 0.65 |
| | **Negative** | 0 | N/A | | 0 | N/A | | 1 | N/A | |
| | **Mixed** | 1 | N/A | | 4 | 0.26 (0.08-0.82) | | 6 | 0.09 (0.04-0.21) | |
| **Infant immuno-prophylaxis regimen** | **Timely HepB-BD & HBIG** | 14 | 0.15 (0.09-0.27) | 0.89 | 31 | 0.18 (0.13-0.24) | 0.38 | 64 | 0.10 (0.08-0.14) | 0.83 |
| | **No or unclear timely HepB-BD/HBIG** | 5 | 0.16 (0.06-0.43) | | 9 | 0.13 (0.06-0.25) | | 18 | 0.10 (0.06-0.16) | |

* MTCT is defined as HBsAg positivity in infants aged 6-12 months.

† Non-important heterogeneity ($I^2$ = 7.7%) in the subgroup of >28 weeks may or may not render the p-value non-valid.

**Table 2. Safety of peripartum antiviral prophylaxis**

| Safety measure | TDF 300 mg (N=19) | | | | LAM 100-150 mg (N=40) | | | | LdT 600 mg (N=83) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of studies | Events/ Participants | | RD (95% CI) | No. of studies | Events/ Participants | | RD (95% CI) | No. of studies | Events/ Participants | | RD (95% CI) |
| | | Treated | Control | | | Treated | Control | | | Treated | Control | |
| **Maternal safety** | | | | | | | | | | | | |
| **Fetal death** | 19 | 3/1097 | 1/881 | 0.003 (-0.006-0.012) | 39 | 1/2003 | 9/2087 | 0.000 (-0.006-0.005) | 81 | 3/5645 | 20/5823 | -0.001 (-0.003-0.002) |
| **Postpartum hemorrhage** | 6 | 9/365 | 7/256 | -0.001 (-0.024-0.022) | 8 | 98/611 | 61/752 | 0.008 (-0.012-0.028) | 19 | 125/1729 | 116/ 2020 | -0.001 (-0.010-0.008) |
| **Postpartum hepatitis flare** | 4 | 28/356 | 20/327 | -0.020 (-0.082-0.041)* | 6 | 59/447 | 34/568 | -0.020 (-0.071-0.030)* | 3 | 27/431 | 26/565 | 0.022 (-0.064-0.109)† |
| **Infant safety** | | | | | | | | | | | | |
| **Neonatal death** | 19 | 2/1079 | 1/858 | 0.000 (-0.009-0.009) | 39 | 1/2010 | 1/2093 | 0.000 (-0.006-0.006) | 82 | 2/5752 | 0/5863 | 0.000 (-0.002-0.003) |
| **Preterm birth** | 9 | 19/622 | 22/479 | -0.003 (-0.024-0.019) | 10 | 14/609 | 11/399 | 0.000 (-0.025-0.025)* | 24 | 105/2427 | 120/ 2191 | -0.001 (-0.010-0.008) |
| **Congenital abnormalities** | 14 | 4/802 | 5/687 | -0.002 (-0.013-0.009) | 16 | 8/845 | 5/953 | 0.003 (-0.007-0.014) | 40 | 11/3585 | 9/2983 | 0.000 (-0.004-0.004) |

Abbreviations: n, number of studies that reported on this safety outcome in a way that could be combined in the meta-analysis; RD, weighted risk difference.

* Moderate to substantial heterogeneity in estimate ($I^2 \geq 30\%$ & $< 75\%$)

† Considerable heterogeneity ($I^2 \geq 75\%$)

**Figure 1: Flowchart of study selection**

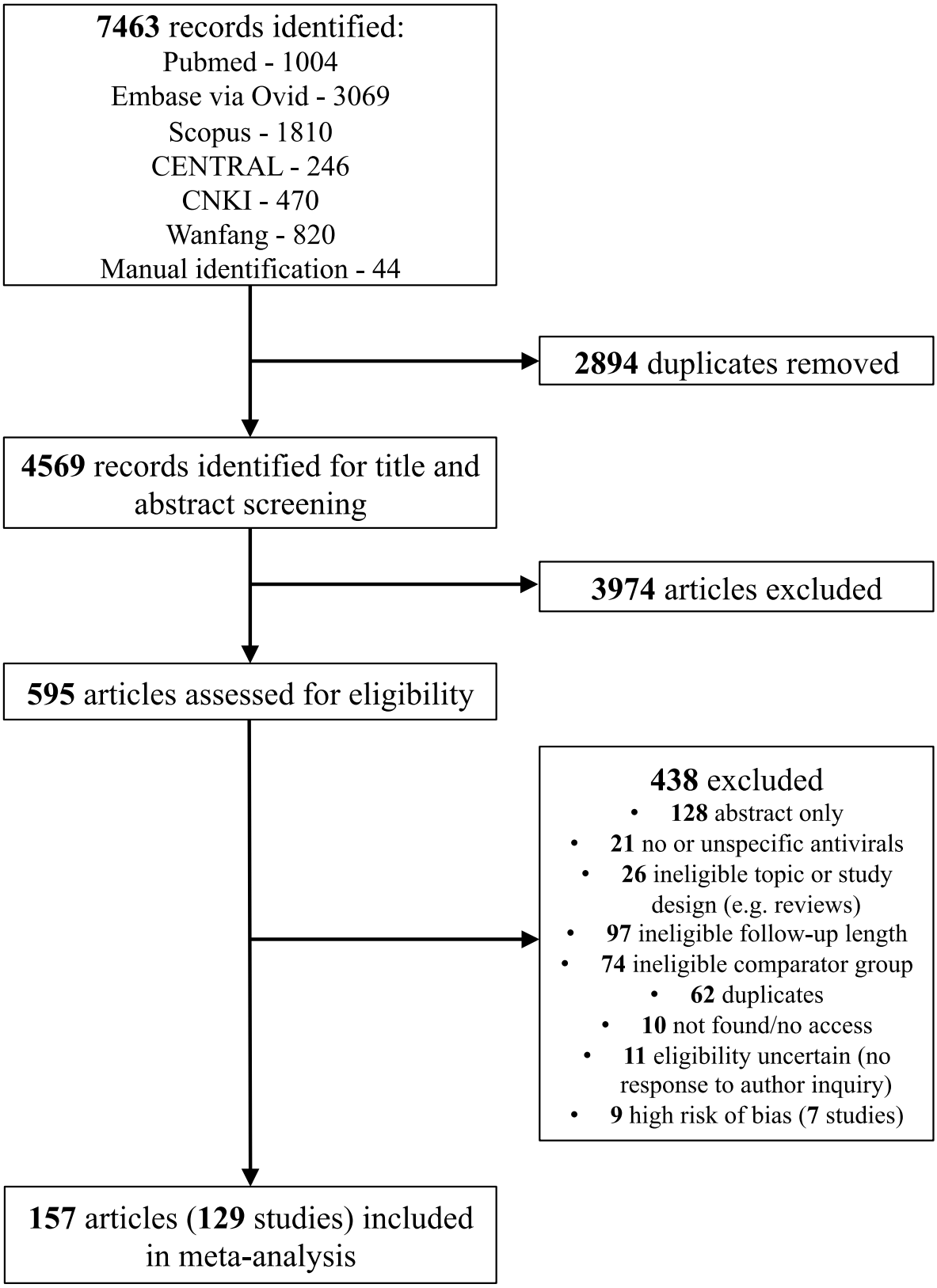
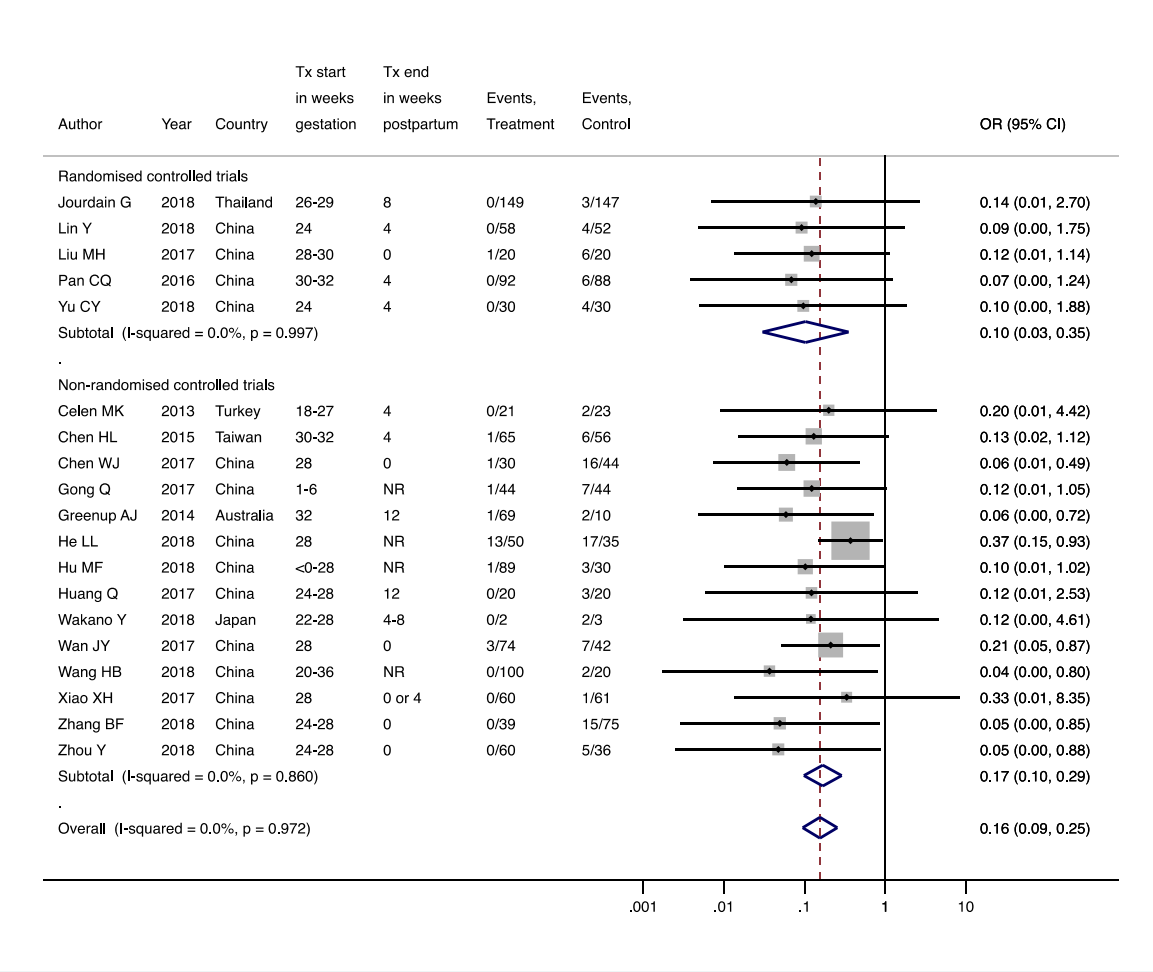


**Figure 2. Efficacy of peripartum antiviral prophylaxis in the prevention of MTCT***

Figure 2A. Efficacy of tenofovir disoproxil fumarate (TDF) 300 mg, by study design




* MTCT is defined as HBsAg positivity in infants aged 6-12 months.

Figure 2B. Efficacy of lamivudine (LAM) 100-150 mg, by study design

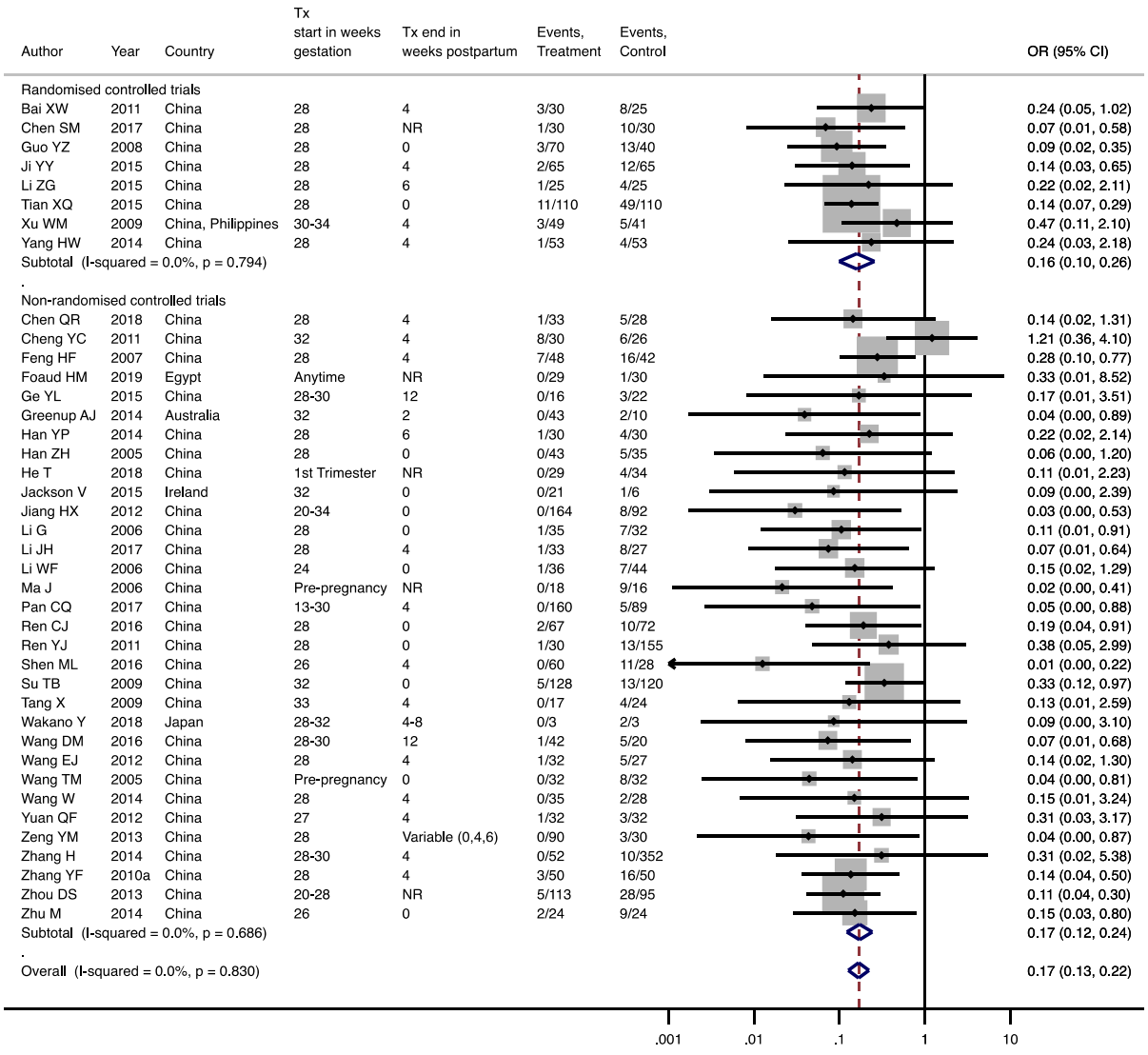


Figure 2C. Efficacy of telbivudine (LdT) 600 mg, by study design

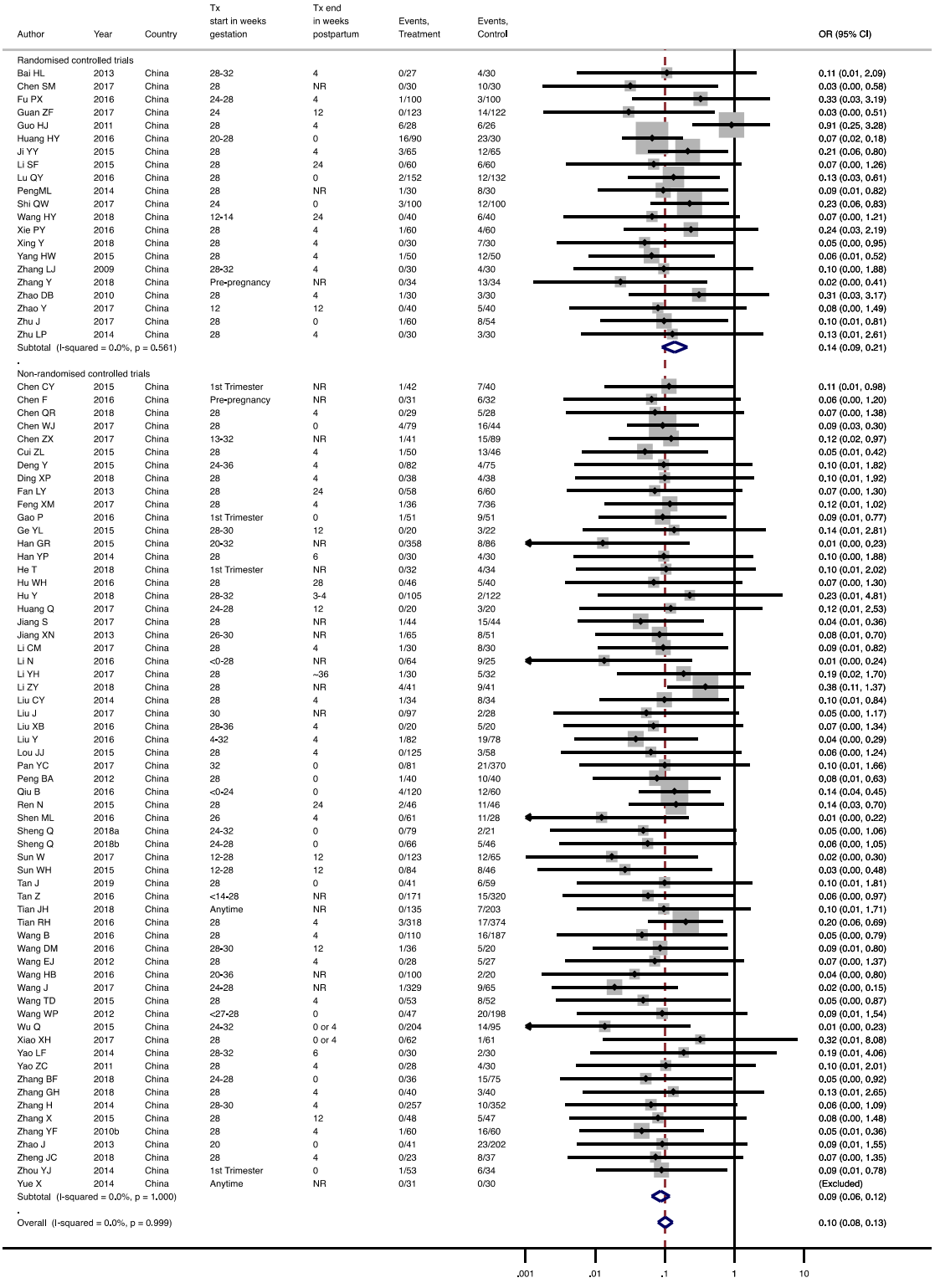
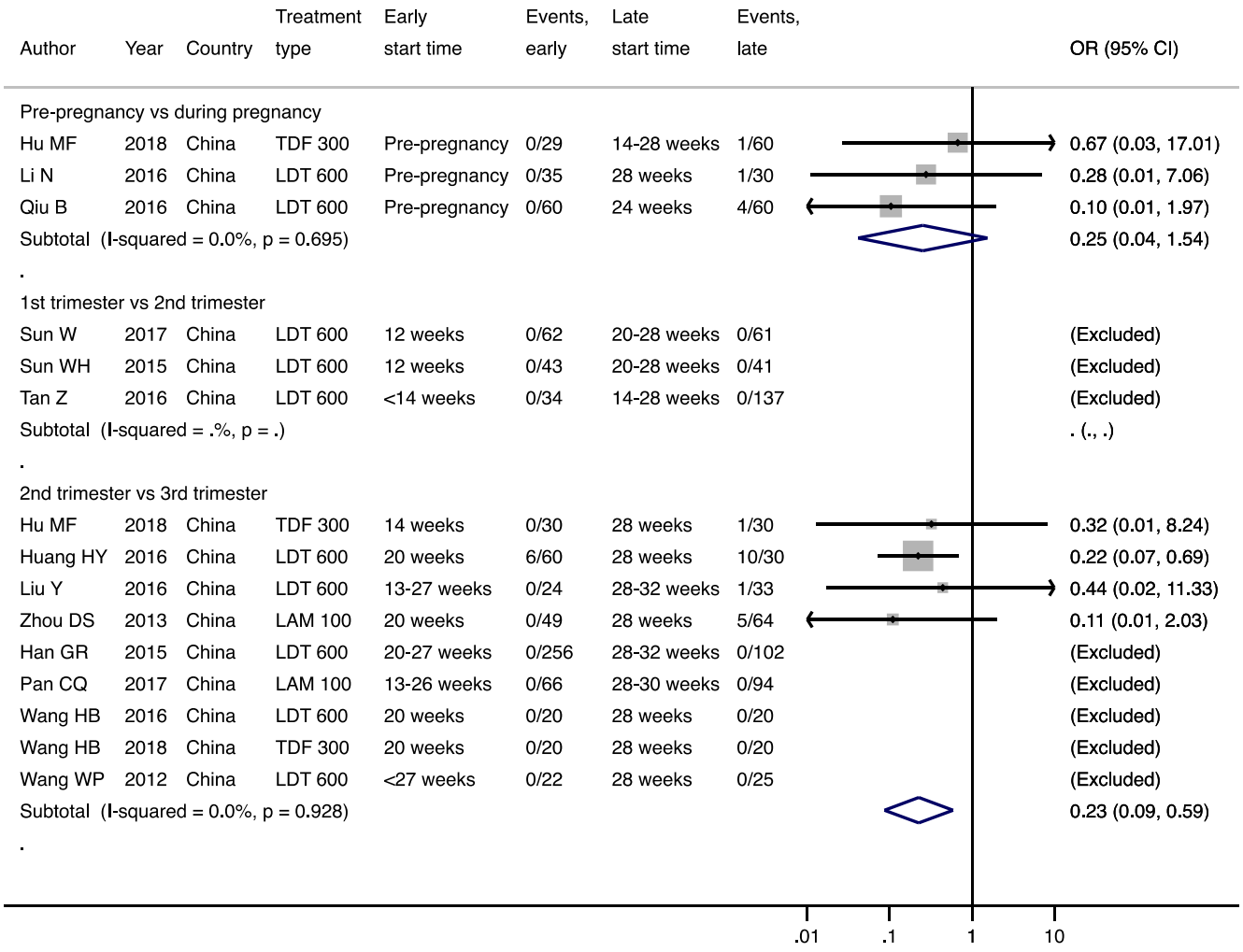


**Figure 3. Efficacy of earlier versus later initiation of peripartum antiviral prophylaxis in the prevention of MTCT***




* MTCT is defined as HBsAg positivity in infants aged 6-12 months.

# Supplementary Appendix

Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis

Anna L. Funk, Ying Lu, Kyoko Yoshida, Tianshuo Zhao, Pauline Boucheron, Judith van Holten, Roger Chou, Marc Bulterys, Yusuke Shimakawa

## Table of Contents

## Appendix A: Search strategies

Database: PubMed

Date searched: March 28th, 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 | 1 793 242 |

| | | |
|---|---|---|
| | 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] | |
| 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: March 28th 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 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. | 2 268 793 |
| 9 | 7 OR 8 | 2 274 006 |
| 10 | 3 AND 6 AND 9 | 3 069 |

Database: Scopus

Date searched: March 28th 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 | 1 810 |

Database: CENTRAL Database (The Cochrane Library)

Date searched: March 28th 2019

Search Strategy:

| Item | Search words | # Trials and Reviews |
|---|---|---|
| 1 | hepatitis b [MeSH, exp] OR hepatitis b virus [MeSH, exp] | 2 462 |
| 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” | 7 692 |
| 3 | 1 OR 2 | 7 692 |
| 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 | 74 080 |

| | | |
|---|---|---|
| | foetal* OR fetus OR foetus OR offspring* OR MTCT OR TME | |
| 9 | 7 OR 8 | 74 912 |
| 10 | 3 AND 6 AND 9 | 246 |

Database: CNKI

Date searched: March 28th, 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: March 28th, 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: List of variables present on data extraction tool

1. **Publication details**
   - First author
   - Year
   - Journal
   - Language
2. **Methods**
   - Country
   - Study design
   - Purpose of study
   - 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. Non-birth dose vaccination (dose, manufacturer)
   - Infant treatment 3. Non-birth dose vaccination (schedule)
   - Infant treatment 4. 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 Treatment arm**
   - Treatment arm: No. of women assigned to treatment (or included if non-randomized)
   - Treatment arm: No. of women with baseline characteristics reported
   - 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: Mean or median HBV DNA

- 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: No. of women with baseline characteristics reported
- 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: Mean or median HBV DNA
- 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 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)
- Treatment arm: No. of infants eventually assessed for all MTCT/ adverse event outcomes

**7. Infant outcomes at birth in 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)
- Control arm: No. of infants eventually assessed for all MTCT/ adverse event outcomes

**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 treatment arm**

- Intention-to-treat or modified intention-to-treat definition used

- Denominator for intention-to-treat analysis: mothers assigned to intervention + twin/triplet
- No. of infants completed MTCT evaluation at 6-12 month timepoint
- 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 treatment arm**

- Denominator for per-protocol analysis: mother-infant pairs completed the intervention treatment & completed MTCT evaluation at 6-12 months timepoint
- No. of infants with HBsAg at 6-12 months in mother-infant pairs completed the intervention treatment & completed MTCT evaluation at 6-12 months timepoint (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 & completed MTCT evaluation at 6-12 months timepoint (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 control arm**

- Denominator for intention-to-treat analysis: mothers assigned to control + twin/triplet
- No. of infants completed MTCT evaluation at 6-12 month timepoint
- 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 control arm**

- Denominator for per-protocol analysis: mother-infant pairs completed the control treatment & completed MTCT evaluation at 6-12 months timepoint
- No. of infants with HBsAg at 6-12 months in mother-infant pairs completed the control treatment & completed MTCT evaluation at 6-12 months timepoint (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 & completed MTCT evaluation at 6-12 months timepoint (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 treatment arm (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)**

- Treatment arm: Foetal 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: Sub-optimal bone density (give definition and the age at evaluation)
- Treatment arm: Any other event

**14. No. of infant adverse events in control arm (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)**

- Control arm: Foetal 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: Sub-optimal bone density (give definition and the age at evaluation)
- Control arm: Any other event

**15. Hepatitis flare**

- Definition of hepatitis flare used

**16. No. of maternal adverse events in treatment arm (list by maternal HBeAg, HBV DNA, HDV, HIV, status where possible)**

- Treatment arm: No. of women considered for adverse events
- Treatment arm: Foetal death or stillbirth
- Treatment arm: Hepatitis flare after treatment discontinuation
- Treatment arm: Postpartum hemorrhage
- Treatment arm: Antiviral resistance
- Treatment arm: Any other event

**17. No. of maternal adverse events in control arm (list by maternal HBeAg, HBV DNA, HDV, HIV, status where possible)**

- Control arm: No. of women considered for adverse events
- Control arm: Foetal death or stillbirth
- Control arm: Hepatitis flare after during a matched period
- Control arm: Postpartum hemorrhage
- Control arm: Antiviral resistance
- Control arm: Any other event

**18. Other**

- Summary of study conclusions
- Funding by industry

## Appendix C: Risk of bias assessment tools

### 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 judgment *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 pre-specified 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 judgment 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 in 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 judgment as a review author, indicate 'low risk' of bias, and 'high risk' of bias. If insufficient information is provided, then the judgment 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 judgment.

Guidance - Newcastle - Ottawa Quality Assessment Scale for Cohort Studies

***(Adapted to the systematic review questions)***

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

**SELECTION**

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

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

- Women identified to carry HBsAg at a general antenatal care clinic or general practitioner with or without subsequently 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

- eg. 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) <u>Selection of the non-exposed cohort (0 or 1 star)</u>**

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) <u>Ascertainment of exposure (exposure = treatment) (0 or 1 star)</u>**

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 antiviral 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 sero-status (within 10 % points)✷
- The same threshold for HBV DNA level AND same HbeAg sero-status should be used for inclusion of treated and controls and/or the reported mean/median HBV DNA level and HbeAg sero-prevalence 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</u> <u>(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 ‘LFU’ then we should assume that LFU was not well reported, and this should not be given a star.

## Appendix D: Descriptions of other antiviral therapies included (<3 studies per regimen)

### Telbivudine (LdT) 100 mg

Three studies were eligible for this meta-analysis that used telbivudine (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 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 performed 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 4 of 25 control infants at the same timepoint (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 performed 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 timepoint (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 (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 life, a vaccination was given at '0 months', and two further vaccinations were performed at 1 and 6 months of life. Of 258 mothers treated during pregnancy, 254 infants were evaluated for MTCT, 6 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 hemorrhage, whereas this was 10.1% (95%CI: 6.7-14.4) in the control group.

### Adefovir (ADV) 10 mg

One non-RCT, specifically, a prospective cohort study, was performed that examined use 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 performed 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 5 of 52 control infants at the same timepoint (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.

## Appendix E: Characteristics of the included studies by treatment type

Aggregate study characteristics

| **Treatment** | **# Studies** | **Study countries** (*% studies*) | **Study design** (*% studies*) | **Time period** | **# Pregnant women included** (treated/not treated) | **HBeAg** # studies/ total studies | **Range of mean viral load at baseline** (# studies reporting) | **Range of treatment start times** | **Range of treatment discontin-uation times** | **# Infants assessed** (of mothers treated/ untreated) | **Infants prophylaxis** # studies/ total studies |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **TDF 300 mg** | 19 | Australia (*5.3*) China (*73.7*) Japan (*5.3*) Taiwan (*5.3*) Thailand (*5.3*) Turkey (*5.3*) | **RCT**= 5 (*26.3*) **non-RCT**= 14 (*73.7*) | 2010-2018 | 1974 (1092/882) | All positive: 11/19 All negative: 0/19 Mixed: 1/19 NR: 7/19 | 3.6 - 8.3 log10 IU/mL (n=16) | Pre-pregnancy to 36 weeks gestation | 0 to 12 weeks post partum | 1908 (1072/836) | HBIG, Hep-B-BD, infant vaccines: 16/19 |
| **LAM 100-150 mg** | 40 | Australia (*2.5*) China[b] (*88.8*) Egypt (*2.5*) Ireland (*2.5*) Japan | **RCT**= 8 (*20.0*) **non-RCT**= 32 | 2001-2016 | 4200 (2080/2120) | All positive: 30/40 All negative: 0/40 Mixed: 4/40 NR: 6/40 | 6.0 - 8.7 log10 IU/mL (n=26) | Pre-pregnancy to 34 weeks gestation[c] | 0 to 12 weeks post partum[e] | 4051 (2007/2044) | HBIG, Hep-B-BD, infant vaccines: 34/40 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | (*2.5*) Phillipines[b] (*1.3*) | (*80.0)* | | | | | | | | |
| **LdT 600 mg** | 83 | China (*100.0*) | **RCT**= 21 (*25.3*) **non-RCT**= 62 (*74.7)* | 2001-2016 | 12104 (6036/6068) | All positive: 52/83 All negative: 1/83 Mixed: 6/83 NR: 24/83 | 2.0- 8.3 log10 IU/mL (n=73) | Pre-pregnancy to 36 weeks gestation[d] | 0 to 36 weeks post partum | 11768 (5971/5797) | HBIG, Hep-B-BD, infant vaccines: 78/83 |

**Note:** All percentages use as a denominator the total number of women/infants included/assessed studies with details reported. [a]In order to be considered as having 'full' prophylaxis, the study report needed to have mentioned clearly that infants were given all of HBIG at birth, HepB-BD, and subsequent HBV vaccinations in infancy. [b]One study took place in China and the Philippines – each have been counted as half for each country in this cell. [c]One study administered treatment 'anytime' which may have extended past 34 weeks gestation. [d]Two studies administered treatment 'anytime' which may have extended past 36 weeks gestation. [e]One study 'continued' treatment past 12 weeks for various and possibly indefinite periods for study participants.

## Individual study characteristics

| General study details and design | | | | Treated pregnant women (tx) | | | | | | Untreated pregnant women (control) | | | | | Infant immunoprophylaxis (all infants) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Author, year** | **Country** | **Recruit-ment period** | **Criteria for maternal HBV DNA (log IU/mL)** | **#** | **Treatment start (gestation weeks) / Treatment discontinuation (postpartum weeks)** | **Mean/ median age (years)** | **HBeAg (%)** | **Mean/ median HBV DNA at baseline (log IU/mL)** | **# Infants assessed for MTCT** | **#** | **Mean/ median age (years)** | **HBeAg (%)** | **Mean/ median HBV DNA at baseline (log IU/mL)** | **# Infants assessed for MTCT** | **HBIG at birth, *timing*** | **HepB-BD, *timing*** | **Infant vaccine, *dose 1 /dose 2… in months*** |
| **TDF 300 mg** | | | | | | | | | | | | | | | | | |
| ***Randomized controlled trials (RCT)*** | | | | | | | | | | | | | | | | | |
| **Jourdain G, 2018[14, 15, 23]** | Thailand | 2013-2015 | None | 168 | 26-29 | 8 | 25.5 [18.3- 42.2] | 100 | 7.6 | 149 | 163 | 26.7 [18.4- 40.9] | 100 | 7.3 | 147 | Yes, <3hr | Yes, <3hr | Yes, 1/2/4/6 |
| **Lin Y, 2018[24,25]** | China | 2013-2016 | ≥6.3 | 60 | 24 | 4 | 28.3 ±3.6 | 100 | 7.4 | 58 | 60 | 28.1 ±3.4 | 100 | 7.7 | 52 | Yes, <24hr | Yes, 12hr | Yes, 1/6 |
| **Liu MH, 2017[26]** | China | 2014-2016 | ≥5.3 | 20 | 28-30 | 0 | 30 [22-38] | 100 | 6.5 | 20 | 20 | 29 [21-38] | 100 | 6.5 | 20 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Pan CQ, 2016[13]** | China | 2012-2013 | ≥5.3 | 100 | 30-32 | 4 | 27.4 ±3.0 | 100 | 8.2 | 92 | 100 | 26.8 ±3.0 | 100 | 8.0 | 88 | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| **Yu CY, 2018[27]** | China | 2017 | ≥6.0 | 30 | 24 | 4 | 26.8 ±4.2 | NR | NR | 30 | 30 | 27.6 ±3.6 | NR | NR | 30 | Yes, <24hr | Yes, <24hr | NR |
| ***Non-randomized controlled trials (Non-RCT)*** | | | | | | | | | | | | | | | | | |
| **Celen MK, 2013[28]** | Turkey | 2010-2012 | ≥6.3 | 21 | 18-27 | 4 | 28.2 ±4.1 | 100 | 8.3 | 21 | 24 | 26.9 ±2.9 | 100 | 8.3 | 23 | Yes, <24hr | No | Yes, 1/2/6 |
| **Chen HL, 2015[29]** | China (Taiwan) | 2011-2013 | ≥7.5 | 62 | 30-32 | 4 | 32.4 ±3.1 | 100 | 8.3 | 65 | 56 | 32.5 ±3.2 | 100 | 8.2 | 56 | Yes, <24hr | Yes, NR | Yes, 1/6 |
| **Chen WJ, 2017[30]** | China | 2014-2015 | ≥6.0 | 30 | 28 | 0 | 28.7 ±5.7 | 100 | 7.5 | 30 | 44 | 29.9 ±5.1 | 100 | 7.5 | 44 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| **Gong Q, 2017[31]** | China | 2015-2016 | NR | 44 | 1-6 | NR | 29.1 ±1.0 | NR | NR | 44 | 44 | 29.1 ±1.2 | NR | NR | 44 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Greenup AJ, 2014[32-35]** | Australia | 2007-2013 | ≥7.0±0.5 | 62 | 32 | 12 | 30 ±8.5 | 94.8 | 7.9 | 69 | 20 | 28±5 | 100 | 8.0 | 10 | Yes, NR | Yes, At birth | Yes, 2/4/6 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **He LL, 2018**[36] | China | 2013-2016 | NR | 50 | 28 | NR | 27.7 ±3.2 | NR | 3.6 | 50 | 35 | 26.3 ±3.0 | NR | 3.7 | 35 | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| **Hu MF, 2018**[37] | China | 2016-2018 | ≥6.0 | 30 | Pre-pregnancy | Various post-pregnancy | 28.4 ±1.4 | NR | 7.4 | 29 | 30 | 26.3 ±2.1 | NR | 7.5 | 30 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| | | | | 30 | 14 | Various post-pregnancy | 23.2 ±3.3 | NR | 7.5 | 30 | | | | | | | | |
| | | | | 30 | 28 | Various post-pregnancy | 24.4 ±3.1 | NR | 7.4 | 30 | | | | | | | | |
| **Huang Q, 2017**[38] | China | 2015 | ≥6.0 | 20 | 24-28 | 12 | 27.1 ±2.4 | 100 | NR | 20 | 20 | 27.0 ±2.3 | 100 | NR | 20 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| **Wakano Y, 2018**[39] | Japan | 2011-2015 | N/A | 2 | 22 or 28 | 4-8 | [28-37] All groups | 100 | 8.3 | 2 | 3 | [28-37] All groups | 100 | 8.3 | 3 | Yes, <12 or <48hr | Yes (some), <12hr | Yes, 2/3/5 or 1/6 |
| **Wan JY, 2017**[40] | China | 2012-2015 | ≥5.3 | 74 | 28 | 0 | 28.5 ±4.2 | NR | 7.7 | 74 | 42 | 27.9 ±4.0 | NR | 7.6 | 42 | NR | NR | NR |
| **Wang HB, 2018**[41] | China | 2013-2016 | NR | 20 | 20 | NR | NR | NR | 7.0 | 20 | 20 | NR | NR | 7.2 | 20 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| | | | | 20 | 24 | NR | NR | NR | 7.1 | 20 | | | | | | | | |
| | | | | 20 | 28 | NR | NR | NR | 7.2 | 20 | | | | | | | | |
| | | | | 20 | 32 | NR | NR | NR | 7.2 | 20 | | | | | | | | |
| | | | | 20 | 36 | NR | NR | NR | 6.7 | 20 | | | | | | | | |
| **Xiao XH, 2017**[42] | China | 2014-2015 | ≥6.0 | 60 | 28 | 0-4 | 27.6 ±3.2 | NR | 7.6 | 60 | 60 | 28.5 ±3.6 | NR | 7.5 | 61 | Yes, NR | Yes, NR | Yes, NR |
| **Zhang BF, 2018**[43] | China | 2016-2017 | ≥6.0 *(tx group)* | 39 | 24-28 | 0 | NR | 100 | 4.8 | 39 | 75 | NR | 100 | 6.0 | 75 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Zhou Y, 2018**[44] | China | 2015-2017 | ≥6.0 | 60 | 24-28 | 0 | 28 [21-38] | 100 | 7.6 | 60 | 36 | 28 [23-39] | 100 | 7.6 | 36 | Yes, <6hr | Yes, <24hr | Yes, 1/6 |

| LAM 100-150 mg | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Randomized controlled trials (RCT)*** | | | | | | | | | | | | | | | | | | |
| **Bai XW, 2011**[45] | China | 2006-2010 | NR | 30 | 28 | 4 | NR | NR | NR | 30 | 25 | NR | NR | NR | 25 | Yes, <24hr (trt group) | Yes, <24 | Yes, 1/6 |
| **Chen SM, 2017**[46] | China | 2013-2014 | ≥4.3 | 30 | 28 | NR | 27.9 ±3.6 | 100 | 7.5 | 30 | 30 | 27.5 ±3.9 | 100 | 8.0 | 30 | Yes, NR | Yes, NR | Yes, NR |
| **Guo YZ, 2008**[47-49] | China | 2003-2006 | NR | 70 | 28 | 0 | NR | 100 | NR | 70 | 40 | NR | 100 | NR | 40 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Ji YY, 2015**[50] | China | 2010-2013 | ≥5.3 | 65 | 28 | 4 | 26.2 ±3.1 | 100 | 7.6 | 65 | 65 | 27.5 ±4.1 | 100 | 7.7 | 65 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Li ZG, 2015**[51] | China | 2013-2014 | ≥4.3 | 25 | 28 | 6 | NR | 100 | NR | 25 | 25 | NR | 100 | NR | 25 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Tian XQ, 2015**[52] | China | 2010-2014 | ≥5.3 | 110 | 28 | 0 | 29±3 | 100 | 7.9 | 110 | 110 | 28±4 | 100 | 8.1 | 110 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Xu WM, 2009**[53,54] | China & Philippines | NR | ≥8.3 | 93 | 30-34 | 4 | 26 [19-32] | 99 | 8.6 | 49 | 62 | 25 [20-36] | 100 | 8.7 | 41 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Yang HW, 2014**[55] | China | 2010-2013 | ≥5.3 | 53 | 28 | 4 | 29±4 | 100 | 7.3 | 53 | 53 | 28±4 | 100 | 7.3 | 53 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| ***Non-randomized controlled trials (Non-RCT)*** | | | | | | | | | | | | | | | | | | |
| **Chen QR, 2018**[56] | China | 2014-2016 | NR | 33 | 28 | 4 | 25.0 ±3.9 | 100 | 7.6 | 33 | 28 | 24.1 ±4.7 | 100 | 7.7 | 28 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Cheng YC, 2011**[57] | China | 2007-2009 | ≥6.3 | 30 | 32 | 4 | 27±4 | 100 | 8.2 | 30 | 26 | 25±5 | 100 | 7.5 | 26 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Feng HF, 2007**[58] | China | 2004-2006 | ≥5.3 | 48 | 28 | 4 | NR | 100 | 7.6 | 48 | 42 | NR | 100 | 7.5 | 42 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Foaud HM, 2019**[59] | Egypt | 2012-2015 | NR | 34 | Anytime | NR | 27.0 ±2.9 (tx in last trimester) 27.7 ±4.0 (tx | 44 | NR | 29 | 39 | 27.4 ±4.6 (low HBV DNA group) 25.7 ±4.3 (diagnosed | 13 | NR | 30 | Yes, At birth | Yes, At birth | Yes, 2/4/6 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | throughout pregnancy) | | | | | too late for tx) | | | | | | |
| **Ge YL, 2015**[60] | China | NR | ≥5.3 | 16 | 28-30 | 12 | 27.9 ±3.6 | 100 | 7.2 | 16 | 22 | 26.5 ±4.2 | 100 | 6.9 | 22 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Greenup AJ, 2014**[32-35,61] | Australia | 2007-2013 | ≥7.0 | 48 | 32 | 2 | 28±5 | 96 | 7.7 | 43 | 20 | 28±5 | 100 | 8.0 | 10 | Yes, NR | Yes, At birth | Yes, 2/4/6 |
| **Han YP, 2014**[62] | China | 2010-2012 | ≥4.3 | 30 | 28 | 6 | 26±4 | 100 | 7.6 | 30 | 30 | 26±4 | 100 | 7.7 | 30 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Han ZH, 2005**[63] | China | 2001-2003 | ≥4.9 | 43 | 28 | 0 | NR | 100 | 6.4 | 43 | 35 | NR | 100 | NR | 35 | Yes, <4hr | No | Yes, 2/3/6 |
| **He T, 2018**[64-66] | China | 2008-2016 | NR | 27 | 1st trimester | Contin-ued | 29.2 ±2.9 | 74 | 6.3 | 29 | 35 | 29.0 ±3.6 | 80 | 6.3 | 34 | Yes, <6hr | Yes, <12hr | Yes, 1/6 |
| **Jackson V, 2015**[67] | Ireland | 2007-2012 | ≥7.2 | 36 | 32 | 0 | 26 [16-40] | 100 | 8.1 | 21 | 9 | NR | 100 | NR | 6 | Yes, <3hr | Yes, <3hr | Yes, 2/4/6 |
| **Jiang HX, 2012**[68] | China | 2007-2010 | ≥5.3 | 164 | 20-34 | 0 | 27.3 ±4.4 | 100 | 7.1 | 164 | 92 | 26.4 ±3.2 | 100 | 7.2 | 92 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Li G, 2006**[69] | China | 2005-2006 | NR | 40 | 28 | 0 | 24±3 | 100 | NR | 35 | 37 | 24±5 | 100 | NR | 32 | Yes, <24hr | No | Yes, 1/2/7 |
| **Li JH, 2017**[70] | China | 2012-2016 | NR | 33 | 28 | 4 | 28.2 ±6.3 | NR | 8.0 | 33 | 27 | 29.4 ±5.7 | NR | 7.7 | 27 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Li WF, 2006**[71] | China | 2001-2003 | ≥4.3 | 36 | 34 | 0 | NR | 100 | 6.1 | 36 | 44 | NR | 100 | NR | 44 | Yes, <6hr | No | Yes, 2/3/7 |
| **Ma J, 2006**[72] | China | NR | NR | 18 | Pre-pregnancy | NR | NR | 100 | NR | 18 | 22 | NR | 100 | NR | 16 | Yes, At birth | Yes, At birth | NR |
| **Pan CQ, 2017**[73] | China | 2008-2015 | ≥5.3 | 66 | 13-26 | 4 | 27.7 ±4.1 | 100 | 6.5 | 66 | 89 | 27.1 ±4.2 | 100 | 6.6 | 89 | Yes, <6hr | Yes, <12hr | Yes, 1/6 |
| | | | | 94 | 28-30 | 4 | 27.4 ±3.5 | 100 | 6.5 | 94 | | | | | | | | |
| **Ren CJ, 2016**[74] | China | 2010-2012 | ≥5.3 | 67 | 28 | 0 | 25.8 ±4.7 | 100 | 6.1 | 67 | 72 | 25.4 ±5.1 | 100 | 6.1 | 72 | Yes, <6hr | Yes, At birth | Yes, 1/6 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ren YJ, 2011**[75] | China | 2008-2009 | NR | 30 | 28 | 0 | NR | 100 | NR | 30 | 155 | NR | 100 | NR | 155 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Shen ML, 2016**[76] | China | 2010-2014 | ≥4.3 | 60 | 26 | 4 | NR | NR | 6.1 | 60 | 28 | NR | NR | 6.0 | 28 | Yes, <24hr | Yes, NR | Yes, NR |
| **Su TB, 2009**[77] | China | 2004-2007 | NR | 128 | 32 | 0 | NR | NR | NR | 128 | 120 | NR | NR | NR | 120 | Yes, <2hr | Yes, 3 days | Yes, 1/6 |
| **Tang X, 2009**[78] | China | 2007-2008 | ≥5.3 | 17 | 33 | 4 | NR | 100 | 6.6 | 17 | 24 | NR | 100 | 6.7 | 24 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Wakano Y, 2018**[39] | Japan | 2011-2015 | NR | 3 | 28-32 | 4-8 | [28-37] All groups | 100 | 8.3 | 3 | 3 | [28-37] All groups | 100 | 8.3 | 3 | Yes, <12 or <48hr | Yes (some), <12hr | Yes, Varied |
| **Wang DM, 2016**[79] | China | 2011-2014 | ≥5.3 | 42 | 28-30 | 12 | 31.4 ±7.3 | 100 | 7.1 | 42 | 20 | 31.7 ±7.0 | 100 | 7.1 | 20 | NR | Yes, <24hr | Yes, 1/6 |
| **Wang EJ, 2012**[80] | China | 2008-2010 | ≥6.3 | 32 | 28 | 4 | 25.0 ±3.8 | 100 | 7.6 | 32 | 27 | 24.0 ±4.7 | 100 | 7.7 | 27 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Wang TM, 2005**[81] | China | 2001-2003 | ≥5.7 | 32 | Pre-pregnancy | 0 | NR | 100 | NR | 32 | 32 | NR | 100 | NR | 32 | NR | Yes, <12hr | Yes, 1/6 |
| **Wang W, 2014**[82] | China | 2011-2012 | NR | 35 | 28 | 4 | 28. 4±3.8 | NR | 7.4 | 35 | 28 | 27.2 ±4.2 | NR | 7.2 | 28 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Yuan QF, 2012**[83] | China | 2010-2011 | NR | 30 | 27 | 4 | 26.5 ±4.5 All groups | 100 | NR | 32 | 30 | 26.5 ±4.5 All groups | 100 | NR | 32 | Yes, <24hr | Yes, <24hr | Yes, 6/12 |
| **Zeng YM, 2013**[84] | China | 2008-2010 | ≥4.3 | 30 | 28 | 0 | NR | 100 | 6.6 | 30 | 30 | NR | 100 | 6.5 | 30 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| | | | | 30 | 28 | 4 | NR | 100 | 6.6 | 30 | | | | | | | | |
| | | | | 30 | 28 | 6 | NR | 100 | 6.5 | 30 | | | | | | | | |
| **Zhang H, 2014**[85] | China | 2009-2011 | ≥6.3 | 55 | 28-30 | 4 | 28.4 ±7.1 | 100 | 6.9 | 52 | 374 | 29.0 ±4.6 | 100 | 6.8 | 352 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| **Zhang YF, 2010a**[86] | China | 2006-2007 | ≥5.3 | 50 | 28 | 4 | NR | 100 | 6.1 | 50 | 50 | NR | 100 | 6.1 | 50 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Zhou DS, 2013**[87] | China | 2009-2012 | ≥5.3 | 49 | 20 | NR | 27.4 ±6.7 | NR | 6.8 | 49 | 95 | 29.2 ±6.1 | NR | 6.9 | 95 | Yes, <12hr | Yes, At birth | Yes, 1/6 |
| | | | | 64 | 28 | NR | 28.1 ±5.3 | NR | 6.7 | 64 | | | | | | | | |
| **Zhu M, 2014**[88] | China | 2012-2013 | NR | 24 | 26 | 0 | NR | 100 | NR | 24 | 25 | NR | 100 | NR | 24 | Yes, <8hr | Yes, <8hr | Yes, 1/6 |
| **LDT 600 mg** | | | | | | | | | | | | | | | | | | |
| ***Randomized controlled trials (RCT)*** | | | | | | | | | | | | | | | | | | |
| **Bai HL, 2013**[89] | China | 2009-2011 | ≥6.3 | 30 | 28-32 | 4 | NR | NR | 6.5 | 27 | 30 | NR | NR | 6.6 | 30 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Chen SM, 2017**[46] | China | 2013-2014 | ≥4.3 | 30 | 28 | NR | 27.4 ±3.5 | 100 | 7.8 | 30 | 30 | 27.5 ±3.9 | 100 | 8.0 | 30 | Yes, NR | Yes, NR | Yes, NR |
| **Fu PX, 2016**[90] | China | 2014-2015 | NR | 100 | 24-28 | 4 | 31.5 ±1.5 | NR | NR | 100 | 100 | 31.7 ±1.6 | NR | NR | 100 | Yes, At birth | Yes, At birth | Yes, NR |
| **Guan ZF, 2017**[91,92] | China | 2005-2015 | ≥6.3 | 12 | 24 | 12 | 26.5 ±9.5 | 100 | 7.1 | 123 | 120 | 27.2 ±9.4 | 100 | 7.1 | 122 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Guo HJ, 2011**[93] | China | 2008-2010 | ≥6.3 | 25 | 28 | 4 | 28 ±3 | 100 | 7.0 | 28 | 25 | 27±4 | 100 | 7.2 | 26 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Huang HY, 2016**[94] | China | 2012–2013 | ≥5.3 | 30 | 20 | 0 | 28.2 ±3.5 | 100 | 7.3 | 30 | 30 | 28.9 ±3.5 | 100 | 7.2 | 30 | NR | NR | NR |
| | | | | 30 | 24 | 0 | 28.6 ±3.4 | 100 | 7.3 | 30 | | | | | | | | |
| | | | | 30 | 28 | 0 | 28.4± 3.2 | 100 | 7.3 | 30 | | | | | | | | |
| **Ji YY, 2015**[50] | China | 2010-2013 | ≥5.3 | 65 | 28 | 4 | 27.2 ±3.6 | 100 | 7.7 | 65 | 65 | 27.5 ±4.1 | 100 | 7.7 | 65 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Li SF, 2015**[95] | China | 2012-2014 | ≥6.3 | 60 | 28 | 24 | NR | NR | 6.9 | 60 | 60 | NR | NR | 6.7 | 60 | Yes, At birth | No | Yes, 1/6 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Lu QY, 2016**[96] | China | 2013-2014 | NR | 152 | 28 | 0 | [29-36] | 47 | NR | 152 | 132 | [29-36] | 41 | NR | 132 | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| **Peng ML, 2014**[97] | China | 2011-2012 | NR | 30 | 28 | NR | 25.9 ±4.2 | 100 | 6.1 | 30 | 30 | 26.4 ±4.4 | 100 | 6.1 | 30 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Shi QW, 2017**[98] | China | NR | ≥5.3 | 100 | 24 | 0 | [23-40] | NR | 7.1 | 100 | 100 | [23-40] | NR | 6.9 | 100 | Yes, <2hr | Yes, At birth | Yes, 1/6 |
| **Wang HY, 2018**[99] | China | 2015-2017 | ≥5.3 | 40 | 12-14 | 24 | NR | 100 | 6.8 | 40 | 40 | NR | 100 | 6.9 | 40 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| **Xie PY, 2016**[100] | China | 2015-2015 | NR | 60 | 28 | 4 | 26.6 ±12.5 | NR | NR | 60 | 60 | 26.1 ±11.6 | NR | NR | 60 | Yes, NR | Yes, NR | Yes, NR |
| **Xing Y, 2018**[101] | China | 2013-2015 | NR | 30 | 28 | 4 | 29.0 ±6.0 | NR | 6.5 | 30 | 30 | 29.5 ±5.3 | NR | 6.5 | 30 | Yes, <6hr | Yes, <6hr | Yes, 1 |
| **Yang HW, 2015**[102] | China | 2012-2014 | ≥5.3 | 50 | 28 | 4 | NR | 100 | 6.1 | 50 | 50 | NR | 100 | 6.1 | 50 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Zhang LJ, 2009**[103] | China | 2007-2008 | ≥6.3 | 31 | 28-32 | 4 | NR | NR | 6.6 | 30 | 30 | NR | NR | 6.7 | 30 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Zhang Y, 2018**[104] | China | 2015-2017 | ≥6.3 | 34 | Pre-pregnancy | NR | 28.4 ±3.1 | NR | 6.6 | 34 | 34 | 28.0 ±3.1 | NR | 6.9 | 34 | Yes, NR | Yes, NR | Yes, NR |
| **Zhao DB, 2010**[105] | China | 2006-2008 | NR | 30 | 28 | 4 | NR | 100 | NR | 30 | 30 | NR | 100 | NR | 30 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Zhao Y, 2017**[106] | China | 2013-2016 | ≥6.3 | 40 | 12 | 12 | 28.1 ±4.1 | 100 | 7.3 | 40 | 40 | 27.9 ±3.9 | 100 | 7.2 | 40 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| **Zhu J, 2017**[107] | China | 2012-2015 | NR | 60 | 28 | 0 | NR | NR | 7.4 | 60 | 60 | NR | NR | 6.9 | 54 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Zhu LP, 2014**[108] | China | 2011-2012 | NR | 30 | 28 | 4 | NR | NR | 6.7 | 30 | 30 | NR | NR | 6.6 | 30 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| ***Non-randomized controlled trials (Non-RCT)*** | | | | | | | | | | | | | | | | | | |
| **Chen CY, 2015**[109] | China | 2008-2011 | ≥6.3 | 43 | 1st trimester | NR | 29.7 ±8.9 | 100 | 7.1 | 42 | 41 | 27.5 ±6.6 | 100 | 7.0 | 40 | Yes, NR | Yes, NR | Yes, NR |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Chen F, 2016**[110] | China | 2008-2014 | ≥6.3 | 31 | Pre-pregnancy | NR | 26.5 ±4.0 | 100 | 6.9 | 31 | 33 | 26.0 ±4.4 | 100 | 6.7 | 32 | Yes, NR | Yes, NR | Yes, NR |
| **Chen QR, 2018**[56] | China | 2014-2016 | NR | 29 | 28 | 4 | 26.9 ±4.3 | 100 | 7.8 | 29 | 28 | 24.1 ±4.7 | 100 | 7.7 | 28 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Chen WJ, 2017**[30] | China | 2014-2015 | ≥6.0 | 79 | 28 | 0 | 31.1 ±6.3 | 100 | 8.3 | 79 | 44 | 29.9 ±5.1 | 100 | 7.5 | 44 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Chen ZX, 2017**[111-113] | China | 2001-2015 | ≥5.3 | 43 | 13-32 | NR | 28.1 ±6.7 | 70 | 6.5 | 41 | 89 | 26.2 ±4.5 | 83 | 6.5 | 89 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| **Cui ZL, 2015**[114] | China | 2013-2014 | ≥5.3 | 50 | 28 | 4 | 28.0 ±1.8 | 100 | 7.1 | 50 | 50 | 27.6 ±2.1 | 100 | 6.9 | 46 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Deng Y, 2015**[115] | China | 2011-2014 | ≥6.0 | 82 | 24-36 | 4 | 25.4 ±3.7 | NR | 7.0 | 82 | 75 | 25.7 ±3.6 | NR | 7.0 | 75 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| **Ding XP, 2018**[116] | China | 2013-2017 | ≥6.3 | 38 | 28 | 4 | NR | 100 | 7.3 | 38 | 38 | NR | 100 | 7.2 | 38 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Fan LY, 2013**[117] | China | 2010-2011 | ≥5.3 | 58 | 28 | 24 | 27.8 ±3.0 | 100 | 6.9 | 58 | 60 | 29.0 ±2.9 | 100 | 6.7 | 60 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Feng XM, 2017**[118] | China | 2014-2016 | ≥6.3 | 36 | 28 | 4 | 29.6 ±6.3 | 100 | 6.9 | 36 | 36 | 28.4 ±5.1 | 100 | 6.7 | 36 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Gao P, 2016**[119] | China | 2012-2014 | NR | 51 | 1st trimester | 0 | 28.4 ±3.8 | NR | 7.1 | 51 | 51 | 27.2 ±3.6 | NR | 7.0 | 51 | Yes, NR | Yes, NR | Yes, NR |
| **Ge YL, 2015**[60] | China | NR | ≥5.3 | 20 | 28-30 | 12 | 28.6 ±3.5 | 100 | 7.1 | 20 | 22 | 26.5 ±4.2 | 100 | 6.9 | 22 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Han GR, 2015**[120-125] | China | 2008-2010 | ≥5.3 | 257 | 20-27 | Variable | 27 [20-35] | 100 | 7.9 | 256 | 92 | 26 [20-35] | 100 | 7.9 | 86 | Yes, <3hr | Yes, <12hr | Yes, 1/6 |
| | | | | 105 | 28-32 | Variable | 28 [20-38] | 100 | 7.8 | 102 | | | | | | | | |
| **Han YP, 2014**[62] | China | 2010-2012 | ≥4.3 | 30 | 28 | 6 | 26±4 | 100 | 7.7 | 30 | 30 | 26±4 | 100 | 7.7 | 30 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **He T, 2018**[64,126] | China | 2008-2016 | NR | 32 | 1st trimester | Contin-ued | 29.2 ±2.9 | 84 | 6.6 | 32 | 35 | 29.0 ±3.6 | 80 | 6.2 | 34 | Yes, <6hr | Yes, <12hr | Yes, 1/6 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hu WH, 2016**[127] | China | 2013-2015 | NR | 46 | 28 | 28 | 28.9 ±3.3 | NR | 6.7 | 46 | 40 | 29.2 ±3.4 | NR | 6.6 | 40 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Hu Y, 2018**[128,129] | China | 2012-2014 | NR | 149 | 28-32 | 3-4 | 25.9 ±3.7 | 100 | 7.4 | 105 | 179 | 26.4 ±3.4 | 100 | 7.3 | 122 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Huang Q, 2017**[38] | China | 2015-2015 | ≥6.0 | 20 | 24-28 | 12 | 26.8 ±2.5 | 100 | NR | 20 | 20 | 27.0 ±2.3 | 100 | NR | 20 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| **Jiang S, 2017**[130] | China | 2015-2016 | NR | 44 | 28 | NR | 28.3 ±3.4 | NR | 6.1 | 44 | 44 | NR | NR | 6.1 | 44 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| **Jiang XN, 2013**[131] | China | 2010-2011 | ≥4.3 | 65 | 26-30 | NR | NR | 100 | 6.0 | 65 | 51 | NR | 100 | 5.9 | 51 | Yes, NR | Yes, At birth | Yes, 1/6 |
| **Li CM, 2017**[132] | China | 2013-2015 | ≥2.3 | 30 | 28 | 4 | 43.2 ±1.3 | NR | 6.1 | 30 | 30 | 43.2 ±1.3 | NR | 6.1 | 30 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Li N, 2016**[133] | China | 2012-2015 | ≥4.3 | 35 | Pre-pregnancy | NR | NR | NR | 5.1 | 35 | 25 | NR | NR | 5.0 | 25 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| | | | | 30 | 28 | NR | NR | NR | 5.1 | 30 | | | | | | | | |
| **Li YH, 2017**[134] | China | 2015-2017 | ≥6.3 | 30 | 28 | ~36 | 29.5 ±2.7 | 100 | 3.2 | 30 | 31 | 28.8 ±3.5 | 100 | 3.2 | 32 | Yes, <24hr | Yes, NR | Yes, NR |
| **Li ZY, 2018**[135] | China | 2015-2016 | ≥5.3 | 41 | 28 | NR | 26.2 ±4.4 | 100 | 6.1 | 41 | 41 | 26.3 ±4.2 | 100 | 6.1 | 41 | Yes, <24hr | No | Yes, 1/6 |
| **Liu CY, 2014**[136] | China | 2011-2011 | ≥5.3 | 34 | 28 | 4 | 27.2 ±3.6 | 100 | 7.1 | 34 | 34 | 26.9 ±4.1 | 100 | 7.4 | 34 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Liu J, 2017**[137] | China | 2013-2015 | ≥6.0 | 102 | 30 | NR | 27.8 ±4.1 | 100 | 8.1 | 97 | 28 | 26.7 ±3.9 | 100 | 8.1 | 28 | NR | Yes, <12hr | Yes, 1/6 |
| **Liu XB, 2016**[138] | China | 2014-2015 | ≥6.0 | 20 | 28-36 | 4 | 25.4 ±3.7 | 100 | 7.0 | 20 | 20 | 25.4 ±3.6 | 100 | 7.0 | 20 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| **Liu Y, 2016**[139] | China | 2010-2012 | ≥6.0 | 50 | 4-27 | 4 | 27.9 ±3.7 | 94 | 7.7 | 50 | 78 | 27.5 ±3.5 | 97 | 7.5 | 78 | Yes, NR | Yes, At birth | Yes, 1/6 |
| | | | | 32 | 28-32 | 4 | 28.3 ±3.8 | 97 | 7.5 | 32 | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Lou JJ, 2015**[140] | China | 2012-2013 | ≥4.6 | 127 | 28 | 4 | 30 ±6 | 100 | 6.8 | 125 | 58 | 31±6 | 100 | 6.7 | 58 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Pan YC, 2017**[141] | China | 2012-2015 | ≥6.3 | 81 | 32 | 0 | 28.8 ±3.3 | 100 | 8.3 | 81 | 453 | 27.6 ±3.8 | 100 | 8.1 | 370 | Yes, <2hr | Yes, <2hr | Yes, 1/6 |
| **Peng BA, 2012**[142] | China | 2008-2009 | ≥5.3 | 40 | 28 | 0 | NR | 100 | 6.0 | 40 | 40 | NR | 100 | 6.1 | 40 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| **Qiu B, 2016**[143] | China | 2009-2014 | ≥5.3 | 60 | Pre-pregnancy | 0 | NR | NR | 6.9l | 60 | 60 | NR | NR | 6.8 | 60 | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| | | | | 60 | 24 | 0 | NR | NR | 6.9 | 60 | | | | | | | | |
| **Ren N, 2015**[144] | China | 2011-2014 | ≥5.3 | 46 | 28 | 24 | NR | 100 | 7.2 | 46 | 46 | NR | 100 | 7.5 | 46 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Shen ML, 2016**[76] | China | 2010-2014 | ≥4.3 | 60 | 26 | 4 | NR | NR | 5.9 | 61 | 28 | NR | NR | 6.0 | 28 | Yes, <24hr | Yes, NR | Yes, NR |
| **Sheng Q, 2018a**[145,146] | China | 2013-2015 | ≥5.0 | 91 | 24-32 | 0[a] | 27.8 ±4.2 | 100 | 8.1 | 79 | 21 | 26.8 ±3.7 | 100 | 8.0 | 21 | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| **Sheng Q, 2018b**[147] | China | 2016-2016 | ≥6.3 | 66 | 24-28 | 0 | 31.3 ±4.4 | 89 | 8.1 | 66 | 46 | 30.4 ±4.2 | 89 | 7.9 | 46 | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| **Sun W, 2017**[148] | China | 2013-2015 | ≥6.3 | 62 | 12 | 12 | 28.9 ±11.8 | 100 | 7.1 | 62 | 65 | 27.5 ±12.9 | 100 | 7.0 | 65 | Yes, <6hr | Yes, <12hr | Yes, 1/6 |
| | | | | 61 | 20-28 | 12 | 29.7 ±9.8 | 100 | 7.1 | 61 | | | | | | | | |
| **Sun WH, 2015**[149,150] | China | 2009-2013 | ≥6.3 | 42 | 12 | 12 | 28.9 ±11.8 | 100 | 7.1 | 43 | 45 | 27.5 ±12.9 | 100 | 7.1 | 46 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| | | | | 41 | 20-28 | 12 | 29.7 ±9.8 | 100 | 7.2 | 41 | | | | | | | | |
| **Tan J, 2019**[151] | China | 2013-2015 | NR | 41 | 28 | 0 | NR | NR | 7.6 | 41 | 59 | NR | NR | 7.5 | 59 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Tan Z, 2016**[152] | China | 2012-2015 | ≥6.0 | 145 | 14-28 | NR | 29 [23-39] | 90 | 7.6 | 137 | 334 | 28 [20-41] | 85 | 7.6 | 320 | Yes, <6hr | Yes, At birth | Yes, 1/6 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | NR | 37 | <14 | NR | 29 [20-38] | 65 | 2.0 | 34 | | | | | | | | |
| **Tian JH, 2018[153]** | China | 2000-2017 | ≥4.6 | 135 | Anytime | NR | NR | 100 | NR | 135 | 203 | NR | 100 | NR | 203 | Yes, <6hr | Yes, <12hr | Yes, 1/6 |
| **Tian RH, 2016[154]** | China | 2013-2013 | ≥6.0 | 318 | 28 | 4 | 27.2 ±3.2 | 100 | 6.5 | 318 | 374 | 27.3 ±3.2 | 100 | 6.6 | 374 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| **Wang B, 2016[155]** | China | 2011-2012 | ≥6.0 | 110 | 28 | 4 | 24±5 | 100 | 7.9 | 110 | 187 | 24±4 | 100 | 7.9 | 187 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| **Wang DM, 2016[79]** | China | 2011-2014 | ≥5.3 | 36 | 28-30 | 12 | 31.4 ±7.3 | 100 | 7.1 | 36 | 20 | 31.7 ±7.0 | 100 | 7.1 | 20 | NR | Yes, <24hr | Yes, 1/6 |
| **Wang EJ, 2012[80]** | China | 2008-2010 | ≥6.3 | 28 | 28 | 4 | 27.0 ±3.4 | 100 | 7.9 | 28 | 27 | 24.0 ±4.7 | 100 | 7.7 | 27 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Wang HB, 2016[156]** | China | 2013-2016 | NR | 20 | 20 | NR | NR | NR | 6.9 | 20 | 20 | NR | NR | 7.2 | 20 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| | | | | 20 | 24 | NR | NR | NR | 7.2 | 20 | | | | | | | | |
| | | | | 20 | 28 | NR | NR | NR | 7.1 | 20 | | | | | | | | |
| | | | | 20 | 32 | NR | NR | NR | 7.2 | 20 | | | | | | | | |
| | | | | 20 | 36 | NR | NR | NR | 6.7 | 20 | | | | | | | | |
| **Wang J, 2017[157]** | China | 2010-2015 | ≥6.0 | 329 | 24-28 | NR | 27.8 ±3.7 | NR | 7.8 | 329 | 65 | 27.6 ±3.5 | NR | 7.8 | 65 | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| **Wang TD, 2015[158]** | China | 2012-2013 | ≥6.3 | 53 | 28 | 4 | 26.3 ±3.1 | 100 | 7.3 | 53 | 52 | 25.8 ±3.9 | 100 | 7.5 | 52 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Wang WP, 2012[159]** | China | 2010-2011 | ≥4.3 | 22 | <27 | 0 | NR | 100 | 6.8 | 22 | 198 | NR | 100 | 6.3 | 198 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| | | | | 25 | 28 | 0 | NR | 100 | 6.7 | 25 | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Wu QX, 2015**[160,161] | China | 2008-2014 | ≥6.0 | 279 | 24-32 | 0 or 4 | 27 [17-38] | 100 | 7.2 | 204 | 171 | 28 [18-40] | 100 | 7.4 | 95 | Yes, At birth | Yes, At birth | Yes, 1/6 |
| **Xiao XH, 2017**[42] | China | 2014-2015 | ≥6.0 | 60 | 28 | 0 or 4 | 28.6 ±3.2 | NR | 7.5 | 62 | 60 | 28.5 ±3.6 | NR | 7.5 | 61 | Yes, NR | Yes NR | Yes, NR |
| **Yao LF, 2014**[162] | China | 2012-2013 | ≥6.0 | 30 | 28-32 | 6 | NR | 100 | 7.3 | 30 | 30 | NR | 100 | 8.2 | 30 | Yes, NR | Yes, NR | Yes, NR |
| **Yao ZC, 2011**[163,164] | China | 2008-2010 | ≥5.3 | 28 | 28 | 4 | NR | NR | 6.8 | 28 | 30 | NR | NR | 6.8 | 30 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Yue X, 2014**[165] | China | 2007-2012 | ≥5.3 | 31 | Any-time | NR | 29.7 ±5.1 | 0 | 5.5 | 31 | 31 | 27.6 ±2.9 | 0 | 5.6 | 30 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Zhang BF, 2018**[43] | China | 2016-2017 | ≥6.0 | 36 | 24-28 | 0 | NR | 100 | 5.0 | 36 | 75 | NR | 100 | NR | 75 | Yes, <6hr | Yes, At birth | Yes, 1/6 |
| **Zhang GH, 2018**[166,167] | China | 2012-2014 | ≥6.3 | 40 | 28 | 4 | NR | 100 | NR | 40 | 40 | NR | 100 | NR | 40 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Zhang H, 2014**[85] | China | 2009-2011 | ≥5.3 | 263 | 28-30 | 4 | 29.8 ±6.3 | 100 | 6.9 | 257 | 374 | 29.0 ±4.6 | 100 | 6.8 | 352 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| **Zhang X, 2015**[168] | China | 2012-2013 | ≥6.3 | 48 | 28 | 12 | NR | 100 | 7.0 | 48 | 47 | NR | 100 | 6.8 | 47 | Yes, <24hr | Yes, At birth | Yes, 1/6 |
| **Zhang YF, 2010b**[169] | China | 2008-2009 | ≥5.3 | 60 | 28 | 4 | NR | 100 | 6.1 | 60 | 60 | NR | 100 | 6.1 | 60 | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| **Zhao J, 2013**[170] | China | 2010-2011 | ≥6.3 | 41 | 20 | 0 | NR | 100 | NR | 41 | 202 | NR | 100 | NR | 202 | Yes, <6hr | Yes, <6hr | Yes, 1/6 |
| **Zheng JC, 2018**[171] | China | 2012-2015 | ≥5.3 | 23 | 28 | 4 | NR | 100 | NR | 23 | 37 | NR | 100 | NR | 37 | Yes, <6hr | Yes, <24hr | Yes, 1/6 |
| **Zhou YJ, 2014**[172,173] | China | 2007-2013 | ≥6.3 | 70 | 1st trimester | 0 | NR | NR | NR | 53 | 39 | NR | NR | NR | 34 | Yes, NR | Yes, At birth | Yes, 1/6 |

[a] 87/91 women stopped therapy at baseline and 4 others continued therapy

## Appendix F: Cochrane Collaboration's Risk of Bias Assessment Tool for RCTs

TDF 300 mg

### A. English language studies

| Study (year), journal, 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 |
| **Pan CQ, (2016), N Engl J Med, 13** | **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), N Engl J Med, 14** | **Low risk** *Quotes:* "participants were randomly assigned in a 1:1 ratio" "Randomization | **Low/Unclear 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, the investigators, and | **Low Risk** *Quotes:* "The participants, the trial staff on site and at the coordination center, the investigators, and the laboratory | **Low Risk** *Comment:* 88 and 90% with full follow-up in treated and control group respectively. | **Low risk** *Comment*: 95 and 98% of infants included in this analysis from treated and control, | **High risk** *Comment:* although >90% women considered until discontinuatio | **Low risk** *Comment:* the protocol is available in a separate publication as well as online |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | was performed with the use of permuted blocks and stratified according to trial site" | center, the investigators, and the laboratory personnel were unaware of the trial-group assignments"<br>*Comment:* no detail provided about sealed envelopes | the laboratory personnel were unaware of the trial-group assignments." "matching placebo (similar to active tablets minus the active pharmaceutical ingredient)" | personnel were unaware of the trial-group assignments." | Numbers of mothers/infants withdrawn or LFU detailed in Figure 1. Similar withdrawal/LFU proportions in each group and 1 fetal/ infant death in each group. | 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' ) | n of the trial regimen, some key adverse events not addressed (e.g. antiviral resistance, postpartum hemorrhage) | at NEJM.org. The current outcomes of interest that this meta-analysis is recording were pre-specified. |
| **Lin Y, (2018), Sci Rep, 24** | **Low risk**<br>*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**<br>*Quotes:* "…sealed envelopes were used for concealment of the random allocation." | **High risk**<br>*Quotes:* "The control individuals did not receive anti-viral treatment." "The participants, care providers … did not know whether the patients had accepted the intervention."<br>*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**<br>*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."<br>*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**<br>*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**<br>*Comment:* same numbers used and therefore comment as for MTCT outcome. | **High risk**<br>*Comment:* same numbers used and therefore comment as for MTCT outcome. | **Low risk**<br>*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), journal, 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), J of Pub Health and Prev med, 27** | **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. hepatitis 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), Chinese** | **Low risk/Unclear** *Quotes:* "participants were randomly | **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 | **Low risk** *Comment*: the protocol is available in the method |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Journal of Woman and Child Health Research, 26** | assigned in a 1:1 ratio"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | | received antiviral treatment with TDF"<br>*Comment*: the study did not address this outcome and no mention of placebo | | | Apgar score, premature labor, congenital abnormality and retarded development reported. Other key adverse events not addressed. | outcome. Women considered until delivery. Only postpartum hemorrhage reported. Other key adverse events not addressed. | 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), journal, 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 |
| **Xu WM (2009), Journal of Viral Hepatitis, 53** | **High risk**<br>*Comment:* Mentions that women were randomly assigned but does not give any indication of method for randomization. | **Low/unclear risk**<br>*Quotes:* "After written informed consent was obtained, participants were randomly assigned in a 1:1 ratio ~"<br>*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**<br>*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"<br>*Comment:* Calls the trial blinded and mentions some extra efforts put in to preserve blinding with study personnel. | **Low risk**<br>*Quotes:* "To preserve study blinding, the investigators were instructed not to determine serum HBV DNA levels locally while the mother was receiving blinded treatment"<br>*Comment:* Calls the trial blinded and mentions some extra efforts put in to preserve blinding with study personnel (specifically lab personnel) | **Unclear risk**<br>*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**<br>*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**<br>*Comment:* Though >90% women were included in this analysis, some key adverse events, were not addressed (e.g. antiviral resistance, postpartum hemorrhage) | **Unclear risk**<br>*Comment:* Both reviewers were unable to find the trial protocol online. |

**B. Chinese language studies**

| Study (year), journal, 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), Journal of China Prescription Drug, 46** | **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), Chin J Postgrad** | **Low risk** *Quotes:* "Referring to random number table, the patients were divided into | **Unclear** *Comment:* the method of concealment not described | **High risk** *Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral | **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 | **High risk** *Comment:* the protocol is available in the method section of the |

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| **Med, 50** | telbivudine group, lamivudine group and control group, with 65 cases in each group" | | treatment with telbivudine or lamivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | | mentioning clearly that there were no cases LFU) | | | article. But not all of the study's pre-specified primary outcomes have been reported (e.g. maternal liver function after antiviral treatment). |
| **Li ZG (2015), World Latest Medicine Information, 51** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into lamivudine group,<br>telbivudine group and control group, with 25 cases in each group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment"<br>"The observation group received antiviral treatment with lamivudine or telbivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* the study did not address this outcome | **Low risk**<br>*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), Shanxi Med J, 52** | **Low risk**<br>*Quotes:*<br>"Referring to random number table, the patients were divided into the observation group and the | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received HBIG"<br>"The observation group received lamivudine on the basis of HBIG for the control group"<br>*Comment*: the study did | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there | **High risk**<br>*Comment:*<br>Though all the infants were included in this analysis, some key adverse | **High risk**<br>*Comment:*<br>Though all women were included in this analysis, the adverse | **High risk**<br>*Comment*: the protocol is available in the method section of the article. But one or more |

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| | control group, with 110 cases in each group" | | not address this outcome and no mention of placebo | | were no cases LFU) | events including Apgar and bone density were not reported. | events observed, were not addressed | reported primary outcomes were not pre-specified (mainly maternal and infantile adverse reactions) |
| **Yang HW (2014), Hebei Medical Journal, 55** | **Low risk/Unclear**<br>*Quotes:*<br>"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"<br>*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 | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The experimental II group received HBIG" "The experimental I group received lamivudine on the basis of HBIG"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **High risk**<br>*Comment:*<br>Though all the infants were included in this analysis, some key adverse events including Apgar and bone density were not reported. | **High risk**<br>*Comment:*<br>Though all women were included in this analysis, some key adverse events, were not addressed (e.g. antiviral resistance) | **High risk**<br>*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) |

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| | group and that of the control group | | | | | | | |
| **Bai XW (2011), Maternal and Child Health Care of China, 45** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into observation group 1, observation group 2 and control group, with 30, 30 and 25 cases, respectively"<br>*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**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group 1 received HBIG and the observation group 2 antiviral treatment with lamivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* the study did not address this outcome | **Low risk**<br>*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), Chin J of Clinical Rational Drug** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into the observation group and the control group, with 70 cases in the observation group | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with lamivudine"<br>*Comment*: the study did not address this outcome and no | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* the study did not address this outcome | **Low risk**<br>*Comment:* the protocol is available in the method section of the article. The current outcomes of interest that this meta- |

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| **Use , 47** | and 40 cases in the control group" *Comment:* the study did not describe the exact random component in the sequence generation process; importantly, there's a huge disparity between the numbers of cases in observation and control groups | | mention of placebo | | | | | analysis is recording were pre-specified in that protocol. |

LDT 600 mg

## A. English language studies

None

## B. Chinese language studies

| Study (year), journal, 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), Contemporary Medicine, 99** | **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, sub-optimal 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 |

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| | | | | | | | | age and congenital abnormality) |
| **Xing Y (2018), Clinical Research, 101** | **Low risk**<br>*Quotes:*<br>"Referring to random number table, the patients were divided into the observation group and the control group, with 30 cases in each group" | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*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"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **High risk**<br>*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, sub-optimal bone density) | **Unclear**<br>*Comment:* the study did not address this outcome | **Low risk**<br>*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), Chinese Journal of Woman and Child Health Research, 104** | **Low risk**<br>*Quotes:*<br>"Referring to random number table, the patients were divided into the observation group and the control group, with 34 cases in each group" | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*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"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Only congenital abnormality and Apgar score reported. Other key adverse events not addressed. | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Only CK reported. Key adverse events not addressed. | **High risk**<br>*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**<br>*Quotes:* | **Unclear**<br>*Comment:* the method of | **High risk**<br>*Quotes:* "The control group received no | **Unclear**<br>*Comment:* the study did not | **Unclear**<br>*Comment:* No statement about | **Unclear**<br>*Comment:* the study did not | **Unclear**<br>*Comment:* the study did not | **Low risk**<br>*Comment*: the protocol is |

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| **Journal of China Prescription Drug, 46** | "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"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | concealment not described | antiviral treatment" "The observation groups received antiviral treatment with lamivudine or telbivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | address this outcome | LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | address this outcome | address this outcome | 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. |
| **Guan ZF (2017), Acta Med Univ Sci Technol Huazhong, 91** | **Low risk**<br>*Quotes:*<br>"Referring to random number table, the patients were divided into the observation group and the control group, with 120 cases in each group" | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received liver protecting treatment with compound glycyrrhizin" "The observation group received antiviral treatment with telbivudine"<br>*Comment*: the study did not address this outcome and no use of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Only Apgar score reported. Other key adverse events not addressed. | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Women considered until delivery. Only postpartum hemorrhage reported. Other key adverse events not addressed. | **High risk**<br>*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**<br>*Quotes:* | **Unclear**<br>*Comment:* the method of | **High risk**<br>*Quotes:* "The control group received HBIG" | **Unclear**<br>*Comment:* the study did not | **Unclear**<br>*Comment:* No statement about | **High risk**<br>*Comment:* | **High risk**<br>*Comment:* | **High risk**<br>*Comment*: the protocol is |

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| **Mod Diagn Treat, 98** | "200 cases of pregnant women with chronic hepatitis B were randomly divided into experimental group and control group, 100 cases in each group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | concealment not described | "The observation group received telbivudine on the basis of HBIG for the control group"<br>*Comment*: the study did not address this outcome and no mention of placebo | address this outcome | LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | Though all the infants were included in this analysis, some key adverse events including neonatal death and bone density were not reported. | Though all women were included in this analysis, some key adverse events, were not addressed (e.g. antiviral resistance, postpartum hemorrhage) | available in the method section of the article. But one or more reported primary outcomes were not pre-specified (mainly maternal adverse reactions) |
| **Zhao Y (2017), J Prac Hepatol, 106** | **Low risk**<br>*Quotes:*<br>"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**<br>*Quotes:* "…sealed and opaque envelopes were used for concealment of the random allocation." | **High risk**<br>*Quotes:* "The control group received compound glycyrrhizin" "The observation group received antiviral treatment with telbivudine on the basis of compound glycyrrhizin"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Low risk**<br>*Comment:* 100% follow-up in both treated and control group | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Only Apgar score reported. Other key adverse events not addressed. | **High risk**<br>*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**<br>*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), Maternal and Child Health** | **Low risk**<br>*Quotes:*<br>"Referring to random number table, the patients were divided into the observation group and the | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine" | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Only Apgar score and neonatal asphyxia reported. Other | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Women considered | **Low risk**<br>*Comment*: the protocol is available in the method section of the article. The current |

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| **Care of China, 107** | control group, with 60 cases in each group" | | *Comment*: the study did not address this outcome and no mention of placebo | | were no cases LFU); 6 cases of foetal death in control group | key adverse events not addressed. | until delivery. Only foetal death and postpartum hemorrhage reported. Other key adverse events not addressed | outcomes of interest that this meta-analysis is recording were pre-specified in that protocol. |
| **Fu PX (2016), Psychologist, 90** | **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), Chinese** | **Low risk** *Quotes:* "Referring to random number table, the patients were divided into the observation | **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 | **Unclear** *Comment:* the study did not address this outcome | **Unclear** *Comment:* No statement about LFU (not reporting any LFU, and also not mentioning | **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 |

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| **Journal of Eugenics and Genetics, 94** | group 1, 2, 3 and the control group, with 30 cases in each group" | | telbivudine at 20, 24 and 28 weeks, respectively"<br>*Comment*: the study did not address this outcome and no mention of placebo | | clearly that there were no cases LFU) | | | current outcomes of interest that this meta-analysis is recording were pre-specified in that protocol. |
| **Xie PY (2016), Psychologist, 100** | **Low risk**<br>*Quotes:*<br>"Referring to random number table, the patients were divided into the observation group and the control group, with 60 cases in each group" | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* the study did not address this outcome | **Low risk**<br>*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), Henan J Prev Med, 96** | **Low risk/Unclear**<br>*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"<br>*Comment:* the study did not describe the exact | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received HBIG" "The observation group received telbivudine on the basis of HBIG for the control group"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **High risk**<br>*Comment:* Though all the infants were included in this analysis, some key adverse events including Apgar and bone density were not reported. | **High risk**<br>*Comment:* Though all women were included in this analysis, some key adverse events, were not addressed (e.g. antiviral resistance, postpartum hemorrhage) | **High risk**<br>*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 |

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| | random component in the sequence generation process; and importantly, there's a huge disparity between the number of cases in the observation group and that of the control group | | | | | | | adverse reactions) |
| **Ji YY (2015), Chin J Postgrad Med, 50** | **Low risk**<br>*Quotes:*<br>"Referring to random number table, the patients were divided into telbivudine group, lamivudine group and control group, with 65 cases in each group" | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine or lamivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* the study did not address this outcome | **High risk**<br>*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), World of Mother and** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into the observation group and the control | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine" | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Only Apgar score reported. Other key adverse | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Women considered | **High risk**<br>*Comment:* the protocol is available in the method section of the article. But one or more |

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| **Infant, 95** | group, with 60 cases in each group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | | *Comment*: the study did not address this outcome and no mention of placebo | | were no cases LFU) | events not addressed. | until 6 months after delivery. Only adverse reactions, abnormal pregnancy, and CK elevation reported. Other key adverse events not addressed | reported primary outcomes 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), Journal of Hainan Medical University, 102** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into the intervention group and the control group, with 50 cases in each group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Comment:* the study did not address this outcome | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Women considered until delivery. Only adverse reactions reported. Other key adverse events not addressed. | **High risk**<br>*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) |

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| **Peng ML (2014), Chin J Nosocomiol, 97** | **Low risk/Unclear**<br>*Quotes:*<br>"60 cases of pregnant women with chronic hepatitis B were randomly divided into experimental group and control group, 30 cases in each group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received HBIG" "The observation group received telbivudine on the basis of HBIG for the control group"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* the study did not address this outcome | **Low risk**<br>*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 LP (2014), Chin J Mod Drug Appl, 108** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into the observation group and the control group, with 30 cases in each group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Comment:* the study did not address this outcome | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Women considered until delivery. Only adverse reactions, renal function despair, and CK elevation reported. Other key adverse events not addressed. | **High risk**<br>*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) |

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| **Bai HL (2013), China Medical Engineering, 89** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into the observation group and the control group, with 30 cases in each group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Low risk**<br>*Comment:* 100% follow-up in both treated and control group | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Only CK elevation reported. Other key adverse events not addressed. | **High risk**<br>*Comment:* same numbers used as for MTCT outcome. Women considered until delivery. Only adverse reactions, renal function despair, and CK elevation reported. Other key adverse events not addressed. | **High risk**<br>*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 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 hemorrhage) |
| **Guo HJ (2011), Journal of Changzhi Medical College,** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into the observation group and the control group, with 25 cases in each | **Unclear**<br>*Comment:* the method of concealment not described | **Unclear**<br>*Quotes:* "The control group received placebo provided by the manufacturer" "The observation group received antiviral treatment with telbivudine"<br>*Comment*: the study did | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* the study did not address this outcome | **High risk**<br>*Comment:* the protocol is available in the method section of the article. But one or more reported primary |

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| **93** | group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | | not address this outcome, though mention of placebo | | | | | outcomes were not pre-specified (e.g. maternal liver function, total bilirubin, and HBV DNA). |
| **Zhao DB (2010), Chin J Mod Drug Appl, 105** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into the observation group and the control group, with 30 cases in each group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Unclear**<br>*Comment:* No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU) | **Unclear**<br>*Quotes:* "no adverse reactions found in two groups of mothers and infants"<br>*Comment:* insufficient reporting | **Unclear**<br>*Quotes:* "no adverse reactions found in two groups of mothers and infants"<br>*Comment:* insufficient reporting | **High risk**<br>*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).<br>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). |

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| **Zhang LJ (2009), Chin J Hepatol, 103** | **Low risk/Unclear**<br>*Quotes:* "The patients were randomly divided into the observation group and the control group, with 31 cases in the observation group and 30 cases in the control group"<br>*Comment:* the study did not describe the exact random component in the sequence generation process | **Unclear**<br>*Comment:* the method of concealment not described | **High risk**<br>*Quotes:* "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine"<br>*Comment*: the study did not address this outcome and no mention of placebo | **Unclear**<br>*Comment:* the study did not address this outcome | **Low risk**<br>*Comment:* 96.8% and 100.0% with full follow-up in treated and control group respectively. Similar follow-up proportions in each group. | **High risk**<br>*Comment:* all infants included in this analysis from both treated and control groups. Only CK elevation reported. Other key adverse events not addressed. | **High risk**<br>*Comment:* All women considered until delivery. Only adverse reactions, renal function despair, and CK elevation reported. Other key adverse events not addressed. | **High risk**<br>*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 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 hemorrhage). |

## Appendix G: Newcastle-Ottawa Risk of Bias Assessment Tool for non-RCTs

TDF 300 mg

### A. English Language Observational Studies

| Study (year), journal, No. | Representa tive-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 occur | Adequacy of follow up of cohorts | Total number of stars (risk of bias)[a] |
|---|---|---|---|---|---|---|---|---|---|
| Celen MK, (2013), World J Gastroenterol, 28 | ☆ At least somewhat representative of the average HBV infected pregnant woman | ☆ Drawn from the same community (same inclusion and exclusion criteria also) | Do 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), J Hepatol, 32 | ☆ 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) |

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| Chen HL, (2015), Hepatology, 29 | ✯ 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)[1] | ✯ At least somewhat representative of the average HBV infected pregnant woman | Not same population, the untreated did not have high viremia or pre-existing liver disease, whereas the treated did. | Adherence is mentioned but was ascertained in 16/23 women (<70%), and only 2/3rds 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), J Obstet Gynaecol Res, 39 | Not representative of the general population (women who've 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 amongst the groups of treated and | Laboratory assays not well described. | ✯ Yes | ✯ 100% retention | 6 (high) |

[1] Kochaksaraei GS, Castillo E, Osman M, et al. Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant participants in a low hepatitis B virus endemic region. *J Viral Hepat* 2016; **23(1)**:15-22.

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| | | | | | 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), journal, No. | 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 occur | Adequacy of follow up of cohorts | Total number of stars (risk of bias)[a] |
|---|---|---|---|---|---|---|---|---|---|
| He LL, (2018), Maternal and Child Health Care of China, 36 | ☆ 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 sero-status 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 of LFU | 7 (low) |
| Hu MF, (2018), Chin J Drug Depend, 37 | ☆ 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 sero-status 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 of LFU | 7 (low) |

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| Wang HB, (2018), Chin J Exp Clin Infect Dis, 41 | ✯ 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 sero-status 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 of LFU | 7 (low) |
| Zhang BF, (2018), Chin J Hepatol, 43 | ✯ 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 but different thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth | No description | ✯ Yes | No statement of LFU | 6 (high) |
| Zhou Y, (2018), New Medical Science, 44 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory | ✯ Yes | No statement of LFU | 8 (low) |

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| | | | | | | and/or record linkage. | | | |
| Chen WJ, (2017), Shandong Medicine, 30 | ✯ 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 | ✯Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Gong Q, (2017), China Continuing Medical Education, 31 | ✯ 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 | ✯ Both HBeAg sero-status and threshold for HBV DNA level not described. Same regimen for infant immunoprophylaxis at birth | No description | ✯ Yes | No statement of LFU | 6 (high) |
| Huang Q, (2017), Qinghai Medical Journal, 38 | ✯ 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 sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis | No description | ✯ Yes | No statement of LFU | 7 (low) |

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| | | | subsequent to the treatment) | | at birth | | | | |
| Wan JY, (2017), China Tropical Medicine, 40 | ✯ 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 sero-status not described. Regimen for infant immunoprophylaxis at birth not described | ✯Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 6 (high) |
| Xiao XH, (2017), Maternal and Child Health Care of China, 42 | ✯ 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 sero-status not described. 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 | There is a description of LFU for the exposed but not for the control group | 6 (high) |

[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) | Representa tive-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 occur | Adequacy of follow up of cohorts | Total number of stars (risk of bias)[a] |
|---|---|---|---|---|---|---|---|---|---|
| Greenup AJ (2014), J Hepatol, 32 | ☆ 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), Hepatology, 85 | ☆ 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), Eur | ☆ At least | ☆ Drawn from the | ☆ Mentions good | ☆ Always the case | HBV DNA level and HBeAg not described in control group. Mentions | ☆ Laboratory | ☆ Yes | <80% retention in both treated and control groups | 6 (high) |

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| J Clin Microbiol Infect Dis, 67 | somewhat representative of the average HBV infected pregnant woman | same community (same inclusion and exclusion criteria also) | 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). | | 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. | assays described, with indication of record linkage (results viewed retrospectively in medical records) | | | |
| Liu CP (2015)[2] | ✯ 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 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 timepoint (this is therefore misclassified as a cohort study, and | 5 (high) |

[2] Liu CP, Zeng YL, Zhou M, et al. Factors Associated with Mother-to-child Transmission of Hepatitis B Virus Despite Immunoprophylaxis. *Intern Med* 2015; **54(7)**: 711-716.

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| | | | | | | | | has a high risk of bias for loss to follow-up) | |
| Pan CQ (2017), J Viral Hepat, 73 | ✯ 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), Hepatol Int, 64 | ✯ At least somewhat representative of the average HBV infected pregnant woman | ✯ Drawn from the same community with same inclusion and exclusion criteria. | ✯ Detailed information on reduction of viral load given, including specific data for each women (every one had a -6 to -8 log | ✯ 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) |

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|---|---|---|---|---|---|---|---|---|---|
| | | | reduction) | | | | | | |
| Wakano Y (2018), J Obstet Gynaecol Res, 39 | Not representative of the general population (women who've 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 amongst the groups of treated and non-treated. | Laboratory assays not well described. | ☆ Yes | ☆ 100% retention | 6 (high) |
| Foaud HM (2019), Arab J Gastroenterol, 59 | ☆ Truly representative of the average HBV infected pregnant woman | Control group was comprised of women who were not a candidate 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 timepoint. (Note: at later timepoint, that study defined, there was >80% followup) | 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), journal, No. | 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 occur | Adequacy of follow up of cohorts | Total number of stars (risk of bias)[a] |
|---|---|---|---|---|---|---|---|---|---|
| Chen QR (2018), Maternal and Child Health Care of China, 56 | ☆ 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 sero-status and comparable HBV DNA levels at baseline. Same regimen for infant immunoprophylaxis at birth | No description | ☆ Yes | No statement of LFU | 6 (high) |
| Li JH (2017), Chinese General Practice, 70 | ☆ 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 sero-status 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), J Med Theor & Prac, 74 | ☆ 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 sero-status and same thresholds for HBV DNA level. Same | ☆ Laboratory methods described in | ☆ Yes | No statement of LFU | 8 (low) |

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| | 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 laboaratory and/or record linkage. | | | |
| Shen ML (2016), WCJD, 76 | ✰ 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 sero-status not described. 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 | 6 (high) |
| Wang DM (2016), Chinese Hepatology, 79 | ✰ 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 | ✰ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✰ Yes | No statement of LFU | 8 (low) |

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|---|---|---|---|---|---|---|---|---|---|
| Ge YL (2015), Chin J Clin Pharmacol, 60 | ☆ 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 of LFU | 7 (low) |
| Han YP (2014), Hebei Medical Journal, 62 | ☆ 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 of LFU | 7 (low) |
| Wang W (2014), Hebei Medical Journal, 82 | ☆ 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 sero-status 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 | ☆ Yes | No statement of LFU | 7 (low) |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | linkage. | | | |
| Zhu M (2014), Hebei Medicine, 88 | ✯ 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 sero-status but HBV DNA levels not described. Same regimen for infant immunoprophylaxis. | ✯ Laboratory assays described | ✯ Yes (always the case) | No statement of LFU | 6 (high) |
| Zeng YM (2013), J Med Res, 84 | ✯ 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 described clearly | ✯ 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) |
| Zhou DS (2013), Hainan Med J, 87 | ✯ 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 thresholds for HBV DNA level but HBeAg sero-status not described. Same regimen for infant immunoprophylaxis | ✯ Laboratory methods described in detail (which assay used), indicating use | ✯ Yes | No statement of LFU | 6 (high) |

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| | | | | | at birth | of a central laboaratory and/or record linkage. | | | |
| Jiang HX (2012), Chin J Hepatol, 68 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Wang EJ (2012), Chinese General Practice, 80 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Yuan QF (2012), | ✯ At least | ✯ Drawn from | Adherence/compliance not mentioned and no | ✯ Always the case | ✯ Comparable for HBeAg sero-status | ✯ Indication of | ✯ Yes (always | No statement of LFU | 6 (high) |

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|---|---|---|---|---|---|---|---|---|---|
| Chinese Manipulation & Rehabilitation Medicine, 83 | somewhat representative of the average HBV infected pregnant woman | the same community (same inclusion and exclusion criteria also) | data presented on decrease in HBV DNA levels | | but HBV DNA level not described. Same regimen for infant immunoprophylaxis. | record linkage | the case) | | |
| Cheng YC (2011), Zhejiang Practical Medicine, 57 | ☆ 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 | ☆ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ☆ Yes | No statement of LFU | 8 (low) |
| Ren YJ (2011), Hebei Medical Journal, 75 | ☆ 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 sero-status but not for HBV DNA level. Same regimen for infant immunoprophylaxis. | ☆ Laboratory assays described | ☆ Yes (always the case) | No statement of LFU | 7 (low) |
| Zhang YF (2010a), | ☆ At least somewhat | ☆ Drawn from the same | ☆ Valid method was used to | ☆ Always the case | ☆☆ Same HBeAg sero-status and same | No description | ☆ Yes | No statement of LFU | 7 (low) |

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| Journal of Practical Obstetrics and Gynecology, 86 | representative of the average HBV infected pregnant woman | community (same inclusion and exclusion criteria also) | ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment) | | thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth | | | | |
| Su TB (2009), Chinese Journal of Coal Industry Medicine, 77 | ☆ At least somewhat representative of the average HBV infected pregnant woman | ☆ Drawn from the same community (same inclusion and exclusion criteria also) | Do not provide any details on adherence. | ☆ Always the case | ☆ Both HBeAg sero-status and HBV DNA not described. Same regimen for infant immunoprophylaxis. | ☆ Testing done centrally in the hospital that study staffs worked in. | ☆ Yes (always the case) | No statement of LFU | 6 (high) |
| Tang X (2009), Jiangxi Medical Journal, 78 | ☆ 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 | ☆ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ☆ Yes | No statement of LFU | 8 (low) |
| Feng HF (2007), J Appl Clin Pediatr, | ☆ At least somewhat representative of | ☆ Drawn from the same community | ☆ Valid method was used to ascertain | ☆ Always the case | ☆☆ Same HBeAg sero-status and same thresholds for HBV | ☆ Laboratory methods | ☆ Yes | No statement of LFU | 8 (low) |

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| 58 | 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 | described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | | | |
| Li G (2006), Journal of Wenzhou Medical College, 69 | ☆ 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 sero-status 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), Chinese Hepatology, 71 | ☆ 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 | ☆Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ☆ Yes | No statement of LFU | 8 (low) |

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| Ma J (2006), China Practical Medical, 72 | ☆ 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 sero-status but HBV DNA levels not described. Regimen for infant immunoprophylaxis not described | ☆ Laboratory assays described | ☆ Yes (always the case) | No statement of LFU | 6 (high) |
| Han ZH (2005), Chin J Intern Med, 63 | ☆ 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 | ☆Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ☆ Yes | No statement of LFU | 8 (low) |
| Wang TM (2005), Chinese Journal of Eugenics and Genetics, 81 | ☆ 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 but HBV DNA level not described. Same regimen for infant immunoprophylaxis at birth | No description | ☆ Yes | No statement of 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), journal, No. | Representa tive-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 occur | Adequacy of follow up of cohorts | Total number of stars (risk of bias)[a] |
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| Zhang H, (2014), Hepatology, 85 | ☆ 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), J Viral Hepat, 120 | ☆ 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 | ☆ Yes | ☆ LFU reported and <20% LFU in all treatment and control groups | 9 (low) |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | linkage to results) | | | |
| Liu CP, (2015)[3] | ☆ 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 timepoint (this is therefore misclassified as a cohort study, and has a high risk of bias for loss to follow-up) | 5 (high) |
| Wu QX, (2015), Clinical Gastroenterology and Hepatology, 160 | ☆ 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 | ☆ 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) |

[3] Liu CP, Zeng YL, Zhou M, et al. Factors Associated with Mother-to-child Transmission of Hepatitis B Virus Despite Immunoprophylaxis. *Intern Med* 2015; **54(7)**: 711-716.

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| | | | controls. | | | | | | |
| Liu Y, (2016), Hepatology Research, 139 | ☆ At least somewhat representative of the average HBV infected pregnant woman | ☆ Drawn from the same community (same inclusion and exclusion criteria also) | 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 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 | 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. | 6 (high) |
| Tan Z, (2016), Medicine, 152 | ☆ 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), J | ☆ At least | ☆ Drawn from the | Adherence/compliance not mentioned and no | ☆ Always the case | ☆ Comparable for HBV | ☆ Lab testing done | ☆ Yes | Loss to follow-up not mentioned and flow-chart of | 6 (high) |

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| infect, 111 | somewhat representative of the average HBV infected pregnant woman | same community (same inclusion and exclusion criteria also) | data presented on decrease in HBV DNA levels | | DNA level but more than 10% points different for HBeAg positive. Same regimen for infant immunoprophylaxis | centrally as part of the study, laboratory assays for defining infant outcome described. | | 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. | |
| Sun W, (2017), BMC Gastroenterology, 148 | ✯ 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 detai. ~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), Hepatol Int, 64 | ✯ At least somewhat representative of the average HBV infected pregnant woman | ✯ Drawn from the same community with same inclusion and exclusion criteria. | ✯ Detailed information on reduction of viral load given, including specific data for each women (every one had a -6 to -8 log | ✯ 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) |

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| | | | reduction) | | | | | | |
| Hu Y, (2018), J Viral Hepat, 128 | ✯ 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 to 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), Int J med Sci, 145 | ✯ 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 group | 9 (low) |
| Sheng QJ, (2018b), Medicine, 147 | ✯ At least somewhat representative of the average HBV infected pregnant woman | ✯ 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 decrease in HBV | ✯ Always the case | ✯ Comparable for HBV DNA level. HBeAg comparability not clear as they only give the proportion overall of women who were HBeAg positive. Same | ✯ Lab testing done centrally as part of the study, laboratory assays for defining infant outcome described. | ✯ Yes | No description of any loss to follow-up or confirmation that there was no loss-to-follow-up. | 7 (low) |

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| | | | DNA level for treated cohort. | | regimen for infant immunoprophylaxis | | | | |

[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), journal, No. | 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 occur | Adequacy of follow up of cohorts | Total number of stars (risk of bias)[a] |
|---|---|---|---|---|---|---|---|---|---|
| Tan J, (2019), J Prac Hepatol, 151 | ☆ 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 sero-status 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 of LFU | 7 (low) |
| Chen QR, (2018), Maternal and Child Health Care of China, 56 | ☆ 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 sero-status and comparable HBV DNA levels at baseline. Same regimen for infant immunoprophylaxis at birth | No description | ☆ Yes | No statement of LFU | 6 (high) |
| Ding XP, (2018), Health Research, 116 | ☆ At least somewhat | ☆ Drawn from the same | ☆ Valid method was used to | ☆ Always the case | ☆☆ Same HBeAg sero-status | No description | ☆ Yes | No statement of LFU | 7 (low) |

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| | representative of the average HBV infected pregnant woman | community (same inclusion and exclusion criteria also) | ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment) | | and comparable HBV DNA levels at baseline. Same regimen for infant immunoprophylaxis at birth | | | | |
| Li ZY, (2018), Drug Evaluation Research, 135 | ☆ 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 sero-status 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), China & Foreign Medical Treatment, 153 | ☆ 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 sero-status used. 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 of LFU | 7 (low) |
| Zhang BF, | ☆ At least | ☆ Drawn | ☆ Valid method | ☆ Always the | ☆ Same HBeAg | No description | ☆ Yes | No statement | 6 (high) |

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| (2018), Chin J Hepatol, 43 | somewhat representative of the average HBV infected pregnant woman | from the same community (same inclusion and exclusion criteria also) | was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment) | case | sero-status but different thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth | | | of LFU | |
| Zhang GH, (2018), China Health Care & Nutrition, 166 | ✰ 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 of LFU | 7 (low) |
| Zheng JC, (2018), China Rural Medicine, 171 | ✰ 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 sero-status 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 of LFU | 7 (low) |

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| Chen WJ, (2017), Shandong Medicine, 30 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Feng XM, (2017), Clinical Research and Practice, 118 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Huang Q, (2017), Qinghai Medical Journal, 38 | ✯ 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 sero-status and same thresholds for HBV DNA level. Same regimen for infant | No description | ✯ Yes | No statement of LFU | 7 (low) |

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| | | | load levels subsequent to the treatment) | | immunoprophylaxis at birth | | | | |
| Jiang S, (2017), Diet Health, 130 | ✯ 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 sero-status not described. Same regimen for infant immunoprophylaxis at birth | No description a | ✯ Yes | No statement of LFU | 6 (high) |
| Li CM, (2017), Northern Pharmacy, 132 | ✯ 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 sero-status not described. Same regimen for infant immunoprophylaxis. | Laboratory assays used not well described | ✯ Yes (always the case) | No statement of LFU | 6 (high) |
| Li YH, (2017), Northern Pharmacy, 134 | ✯ 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 sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis | ✯ Laboratory methods described in detail (which assay used), indicating use | ✯ Yes | No statement of LFU | 8 (low) |

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| | | | subsequent to the treatment) | | at birth | of a central laboaratory and/or record linkage. | | | |
| Liu J, (2017), Maternal and Child Health Care of China, 137 | ✯ 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 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)[4] | ✯ 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 sero-status not described. Regimen for infant immunoprophylaxis at birth not clearly described | No description | ✯ Yes | No statement of LFU | 5 (high) |
| Pan YC, (2017), J Clin Hepatol, 141 | ✯ At least somewhat representative of | ✯ Drawn from the same community | No description | ✯ Always the case | ✯✯ Same HBeAg sero-status and same thresholds | ✯ Laboratory methods | ✯ Yes | ✯ Subjects lost to | 8 (low) |

[4] Luo D, He K. A study on the effect of telbivudine to interrupt mother-to-child transmission of hepatitis B virus and nursing intervention. *Chin J Woman Child Health Res* 2017; **28 (2)**: 626.

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| | the average HBV infected pregnant woman | (same inclusion and exclusion criteria also) | | | for HBV DNA level. Same regimen for infant immunoprophylaxis at birth | described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | | follow up unlikely to introduce bias, small number lost | |
| Wang J, (2017), Chinese Journal of Woman and Child Health Research, 157 | ✯ 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 sero-status not described. Same regimen for infant immunoprophylaxis at birth | No description | ✯ Yes | No statement of LFU | 6 (high) |
| Xiao XH, (2017), Maternal and Child Health Care of China, 42 | ✯ 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 sero-status not described. 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 | There is a description of LFU for the exposed but not for the control group | 6 (high) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Chen F, (2016), Journal of Practical Medicine, 110 | ✯ 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), J Medical Forum, 119 | ✯ 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 sero-status not described. 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 | 6 (high) |
| Hu WH, (2016), Journal of Qiqihar University of Medicine, 127 | ✯ 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 | ✯ Comparable for HBV DNA levels but HBeAg sero-status not described. Same regimen for infant | ✯ Laboratory methods described in detail (which assay used), | ✯ Yes | No statement of LFU | 7 (low) |

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|---|---|---|---|---|---|---|---|---|---|
| | | | load levels subsequent to the treatment) | | immunoprophylaxis at birth | indicating use of a central laboaratory and/or record linkage. | | | |
| Li N, (2016), Medical Innovation of China, 133 | ✯ 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 sero-status not described. Same regimen for infant immunoprophylaxis at birth | No description | ✯ Yes | No statement of LFU | 6 (high) |
| Liu XB, (2016), Journal of Contemporary Clinical Medicine, 138 | ✯ 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 of LFU | 7 (low) |
| Qiu B, (2016), J Prac Hepatol, 143 | ✯ At least somewhat representative of the average HBV infected pregnant | ✯ Drawn from the same community (same inclusion and exclusion | ✯ Valid method was used to ascertain adherence to the antiviral therapy | ✯ Always the case | ✯ Same thresholds for HBV DNA level but HBeAg sero-status not described. Same regimen for | ✯ Laboratory methods described in detail (which | ✯ Yes | No statement of LFU | 7 (low) |

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|---|---|---|---|---|---|---|---|---|---|
| | woman | criteria also) | (decrease in viral load levels subsequent to the treatment) | | infant immunoprophylaxis at birth | assay used), indicating use of a central laboaratory and/or record linkage. | | | |
| Shen ML, (2016), WCJD, 76 | ✯ 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 sero-status not described. 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 | 6 (high) |
| Tian RH, (2016), Chinese Journal of Clinical Research, 154 | ✯ 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 sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth | No description | ✯ Yes | No statement of LFU | 6 (high) |
| Wang B, (2016), Chinese Remedies & | ✯ At least somewhat representative of | ✯ Drawn from the same community | ✯ Valid method was used to ascertain adherence to the | ✯ Always the case | ✯✯ Comparable for HBeAg sero-status and HBV DNA level. Same | ✯ Laboratory assays described | ✯ Yes (always the case) | No statement of LFU | 8 (low) |

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|---|---|---|---|---|---|---|---|---|---|
| Clinics, 155 | the average HBV infected pregnant woman | (same inclusion and exclusion criteria also) | antiviral therapy (decrease in viral load levels subsequent to the treatment) | | regimen for infant immunoprophylaxis. | | | | |
| Wang DM, (2016), Chinese Hepatology, 79 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Wang HB, (2016), Journal of Practical Medicine, 156 | ✯ 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 sero-status not described. Same regimen for infant immunoprophylaxis at birth | No description | ✯ Yes | No statement of LFU | 6 (high) |

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|---|---|---|---|---|---|---|---|---|---|
| Zhang R, (2016)[5] | ✯ 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 sero-status and threshold for HBV DNA level not described. Regimen for infant immunoprophylaxis at birth not clearly described | No description | ✯ Yes | No statement of LFU | 4 (high) |
| Chen CY, (2015), Chin J Hepatol, 109 | ✯ 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) |
| Cui ZL, (2015), IMHGN, 114 | ✯ 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 sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth | ✯ Laboratory methods described in detail (which assay used), indicating use | ✯ Yes | No statement of LFU | 8 (low) |

[5] 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.

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|---|---|---|---|---|---|---|---|---|---|
| | | | subsequent to the treatment) | | | of a central laboaratory and/or record linkage. | | | |
| Deng Y, (2015), Chin J Hepatol, 115 | ✯ 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 sero-status not described. Same regimen for infant immunoprophylaxis at birth | No description | ✯ Yes | No statement of LFU | 6 (high) |
| Ge YL, (2015), Chin J Clin Pharmacol, 60 | ✯ 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 of LFU | 7 (low) |
| Lou JJ, (2015), Chinese Journal of Microecology, 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 | ✯ Always the case | ✯✯ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis | ✯ Laboratory methods described in detail (which assay used), | ✯ Yes | No statement of LFU | 8 (low) |

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| | | | load levels subsequent to the treatment) | | at birth | indicating use of a central laboaratory and/or record linkage. | | | |
| Ren N, (2015), China Medicine and Pharmacy, 144 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Sun WH, (2015), Chin J Hepatol, 149 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Wang TD, | ✯ At least | ✯ Drawn | ✯ Valid method | ✯ Always the | ✯✯ Same HBeAg | ✯ | ✯ Yes | No statement | 8 (low) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (2015), China Pharmaceuticals, 158 | somewhat representative of the average HBV infected pregnant woman | from the same community (same inclusion and exclusion criteria also) | was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment) | case | sero-status 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. | | of LFU | |
| Zhang X, (2015), J Prac Hepatol, 168 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Chen YL, (2014)[6] | 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 | ✯ Always the case | ✯ Comparable for HBV DNA levels but HBeAg sero-status not described. Same regimen for | No description | ✯ Yes | No statement of LFU | 4 (high) |

[6] Chen Y, Gao X, Li J. Telbivudine combined with hepatitis B vaccine to interrupt hepatitis B virus intrauterine infection. *Acta Universitatis Medicinalis Nanjing (Natural Science)* 2014; **34 (1)**: 67-68.

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| | | | (decrease in viral load levels subsequent to the treatment) | | infant immunoprophylaxis at birth | | | | |
| Han YP, (2014), Hebei Medical Journal, 62 | ✯ 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 of LFU | 7 (low) |
| Liu CY, (2014), Journal of Yanan University, 136 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Yao LF, (2014), Chin J Obstet Gynecol | ✯ 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 sero-status and same thresholds for HBV DNA level. | ✯ Laboratory methods described in | ✯ Yes | No statement of LFU | 7 (low) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pediatr, 162 | infected pregnant woman | and exclusion criteria also) | antiviral therapy (decrease in viral load levels subsequent to the treatment) | | Regimen for infant immunoprophylaxis at birth not clearly described | detail (which assay used), indicating use of a central laboaratory and/or record linkage. | | | |
| Yue X, (2014), Chin J Infect Dis, 165 | ✯ 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 | ✯ Complete follow-up | 8 (low) |
| Zhou YJ, (2014), Chin J Hepatol, 172 | ✯ 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 sero-status 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 laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 6 (high) |
| Fan LY, | ✯ At least | ✯ Drawn | ✯ Valid method | ✯ Always the | ✯✯ Same HBeAg | No description | ✯ Yes | No statement | 7 (low) |

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|---|---|---|---|---|---|---|---|---|---|
| (2013), J Med Res, 117 | somewhat representative of the average HBV infected pregnant woman | from the same community (same inclusion and exclusion criteria also) | was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment) | case | sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth | | | of LFU | |
| Jiang XN, (2013), J Clin Hepatol, 131 | ✰ 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 described clearly | No description | ✰ Yes | ✰ Complete follow-up | 7 (low) |
| Zhao J, (2013), China Clinician, 170 | ✰ 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 sero-status 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 of LFU | 7 (low) |

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|---|---|---|---|---|---|---|---|---|---|
| Peng BA, (2012), Chin Pharm J, 142 | ✯ 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 of LFU | 7 (low) |
| Wang EJ, (2012), Chinese General Practice, 80 | ✯ 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 | ✯ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage. | ✯ Yes | No statement of LFU | 8 (low) |
| Wang WP, (2012), Prog Obstet Gynecol, 159 | ✯ 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 | ✯ Always the case | ✯✯ Same HBeAg sero-status 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 of LFU | 8 (low) |

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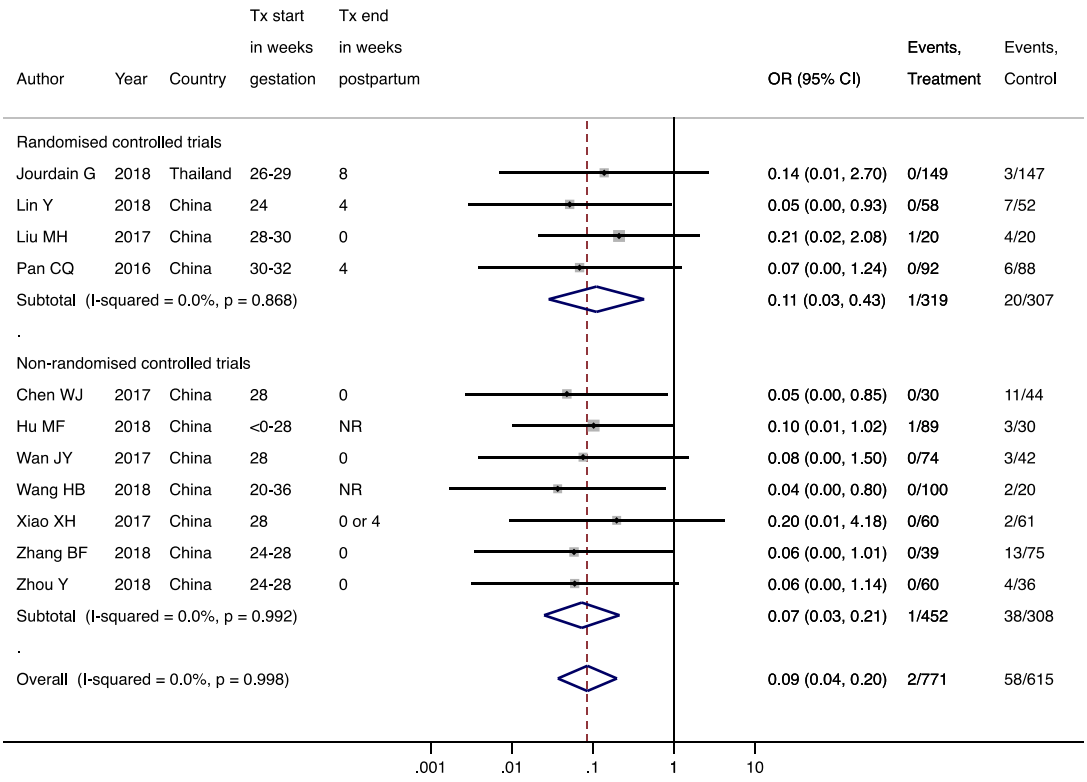
|---|---|---|---|---|---|---|---|---|---|
| | | | treatment) | | | laboaratory and/or record linkage. | | | |
| Yao ZC, (2011), J Clin Hepatol, 163 | ✯ At least somewhat representative of the average HBV infected pregnant woman | ✯ Drawn from the same community (same inclusion and exclusion criteria 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 sero-status 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 of LFU | 7 (low) |
| Zhang YF, (2010b), ADRJ, 169 | ✯ 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 of LFU | 7 (low) |

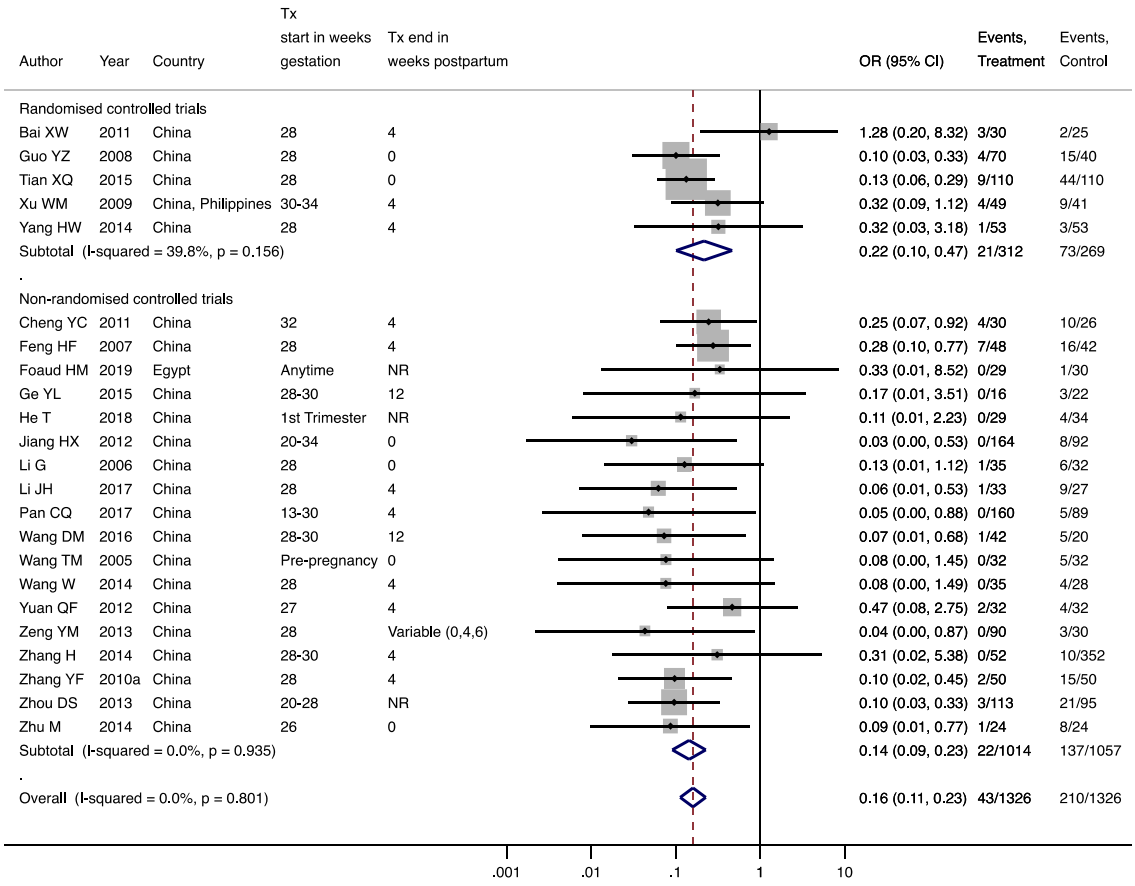
[a]Risk of bias assessments should be classified as being either low (≥ 7) or high (< 7) by the Newcastle-Ottawa scale

## Appendix H: Efficacy on the infants' HBV DNA positivity

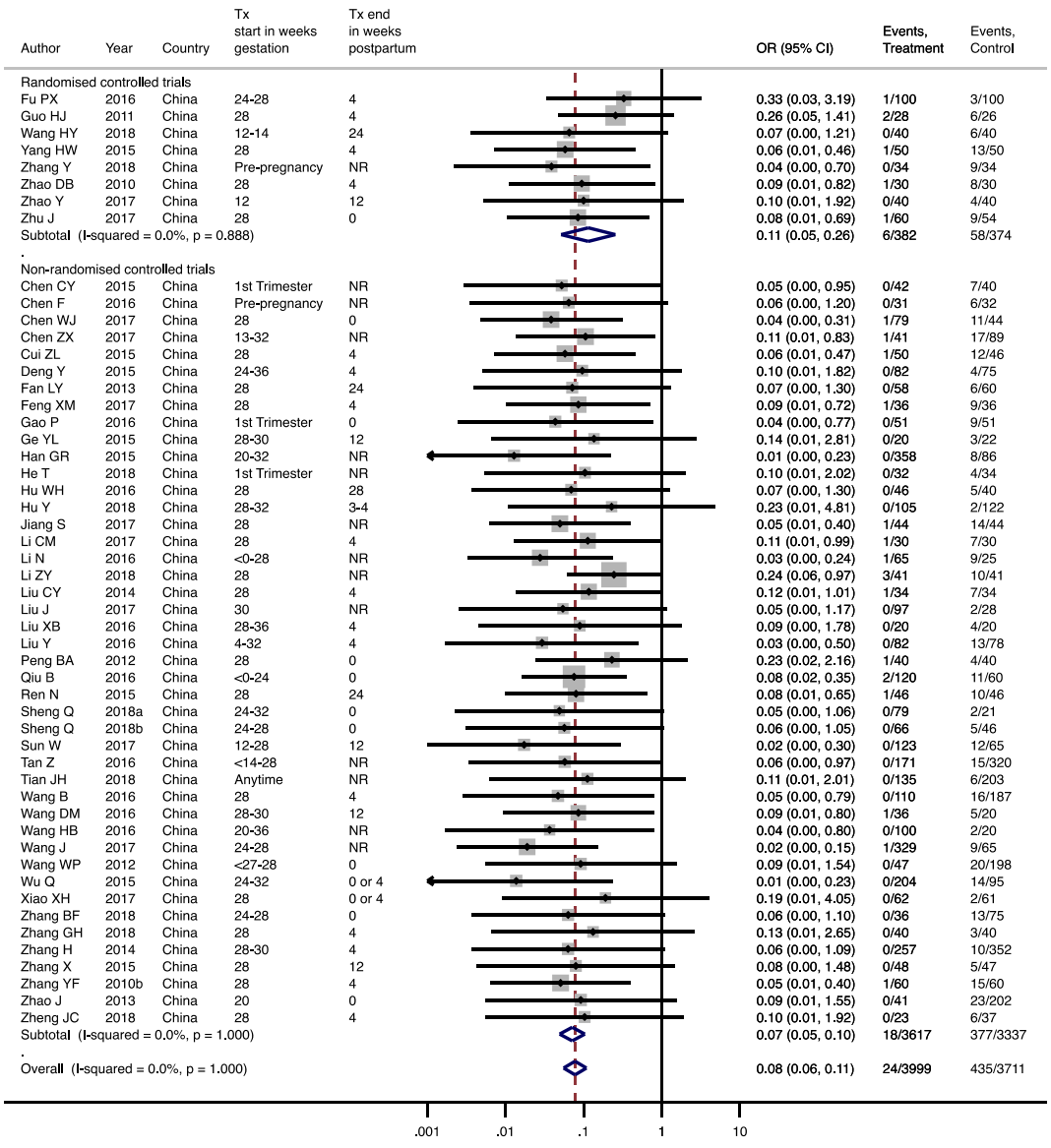
- **TDF 300 mg (infants' HBV DNA positivity)**
  - Overall pooled OR= 0.09 (95%CI: 0.04-0.20), p<0.001, $I^2$=0%
- RCTs only (n=4): pooled OR=0.11 (95%CI: 0.03-0.43), p=0.001, $I^2$=0%
- Non-RCTs only (n=7): pooled OR=0.07 (95%CI: 0.03-0.21), p<0.001, $I^2$=0%
- The p-value for heterogeneity between RCTs and non-RCTs was 0.64



- **LAM 100-150 mg (infants' HBV DNA positivity)**
  - 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%
- The p-value for heterogeneity between RCTs and non-RCTs was 0.47



- **LdT 600 mg (infants' HBV DNA positivity)**
  - Overall pooled OR= 0.08 (95%CI: 0.06-0.11), p<0.001, $I^2$=0.0%
- RCTs only: pooled OR= 0.11 (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



## Appendix I: Characteristics of infants with MTCT despite maternal TDF 300 mg prophylaxis

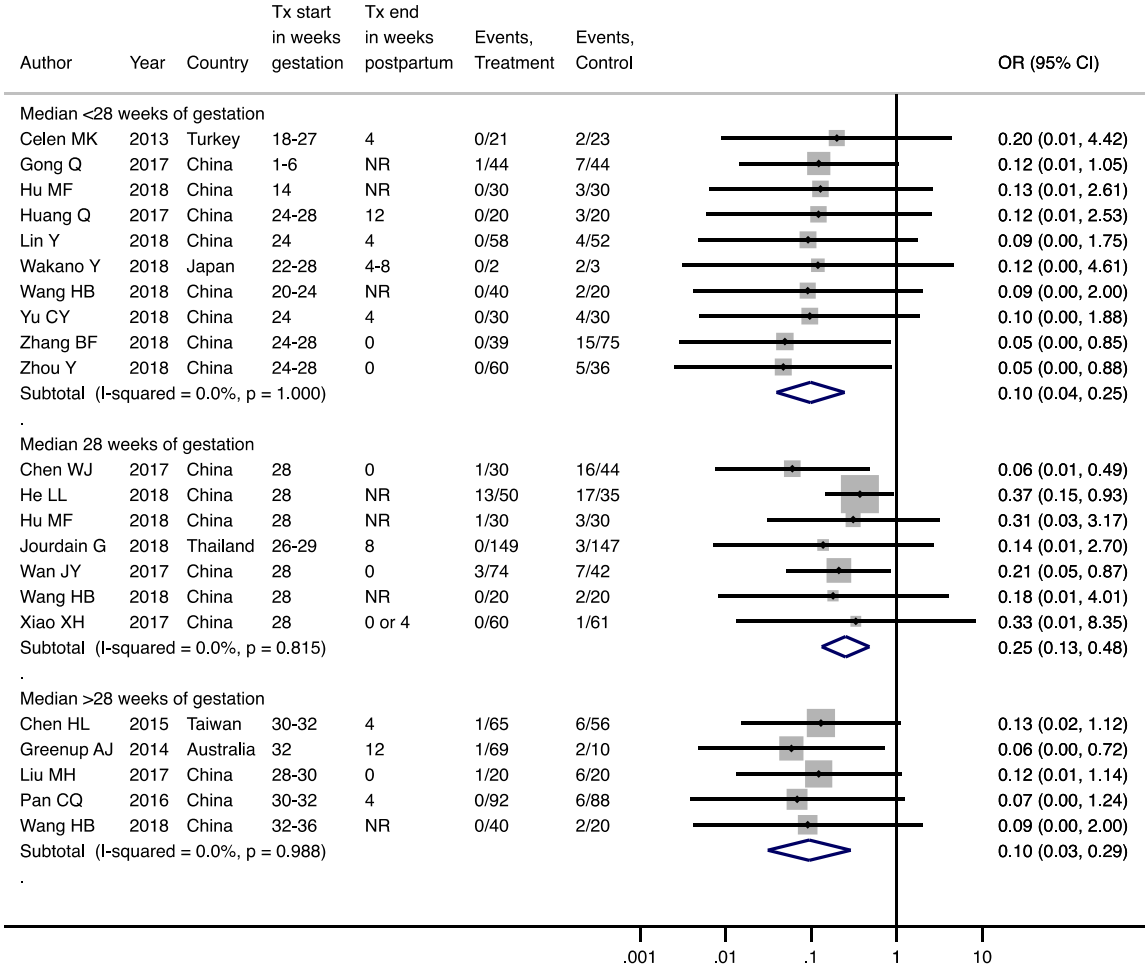
| ID | Author, year | Country | Characteristics of mothers | | | | | Peripartum antiviral prophylaxis | | Characteristics of infants | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Age at baseline | HBV DNA at baseline (log IU/mL) | HBeAg at baseline | Other (e.g. HIV, HDV, etc) | HBV DNA at delivery (log IU/mL) | Treatment start | Treatment discontinuation | Mode of delivery | HepB-BD | HBIG | Infant vaccines (HepB3) |
| 1 | Liu MH, 2017 | China | Between 20-40 years | ≥5.3 | Positive | No HCV/HIV | >6.0 | Between weeks 28 and 30 | At delivery | N/R | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| 2 | Chen HL, 2015 | Taiwan | N/R | 8.2 | Positive | No HCV/HIV | 4.2 | Between weeks 30 and 32 | 1 month postpartum | N/R | Yes, NR | Yes, <24hr | Yes, 1/6 |
| 3 | Chen WJ, 2017 | China | N/R | ⩾6.0 | Positive | No HCV/HIV | N/R | 28 | At delivery | N/R | Yes, At birth | Yes, At birth | Yes, 1/6 |
| 4 | Gong Q, 2017 | China | Between 22-36 years | N/R | N/R | N/R | N/R | Between weeks 1 and 6 | N/R | N/R | Yes, <24hr | Yes, <24hr | Yes, 1/6 |
| 5 | Greenup AJ, 2014 | Australia | N/R | N/R | Positive | N/R | 4.4 | 32 | 12 weeks postpartum | Vaginal | Yes, At birth | Yes, NR | Yes, 2/4/6 |
| 6 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 7 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 8 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 9 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 10 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 11 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 12 | He LL, | China | Between | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, | Yes, | Yes, |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2018 | | 22-36 years | | | | | | | | <12hr | <12hr | 1/6 |
| 13 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 14 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 15 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 16 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 17 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 18 | He LL, 2018 | China | Between 22-36 years | N/R | N/R | N/R | N/R | 28 | N/R | N/R | Yes, <12hr | Yes, <12hr | Yes, 1/6 |
| 19 | Wan JY, 2017 | China | N/R | ≥5.3 | N/R | No HCV/HIV | N/R | 28 | At delivery | N/R | N/R | N/R | N/R |
| 20 | Wan JY, 2017 | China | N/R | ≥5.3 | N/R | No HCV/HIV | N/R | 28 | At delivery | N/R | N/R | N/R | N/R |
| 21 | Wan JY, 2017 | China | N/R | ≥5.3 | N/R | No HCV/HIV | N/R | 28 | At delivery | N/R | N/R | N/R | N/R |
| 22 | Hu MF, 2018 | China | N/R | ≥6.0 | N/R | No HCV/HIV | N/R | 28 | N/R | N/R | Yes, At birth | Yes, At birth | Yes, 1/6 |

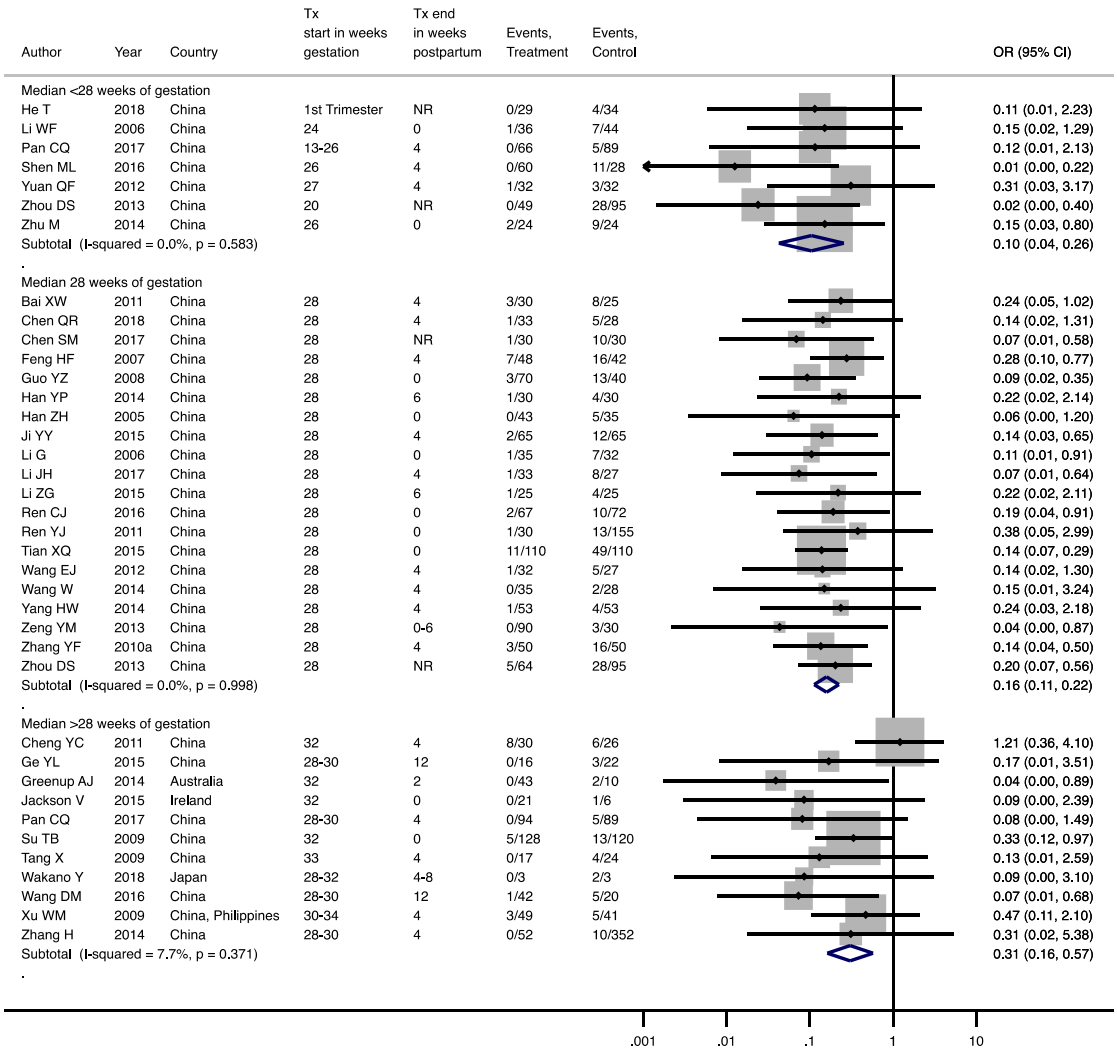
Abbreviations: N/R, not reported
Sex of infant was not reported in any of the MTCT cases.

## Appendix J: Efficacy by timing of PAP initiation

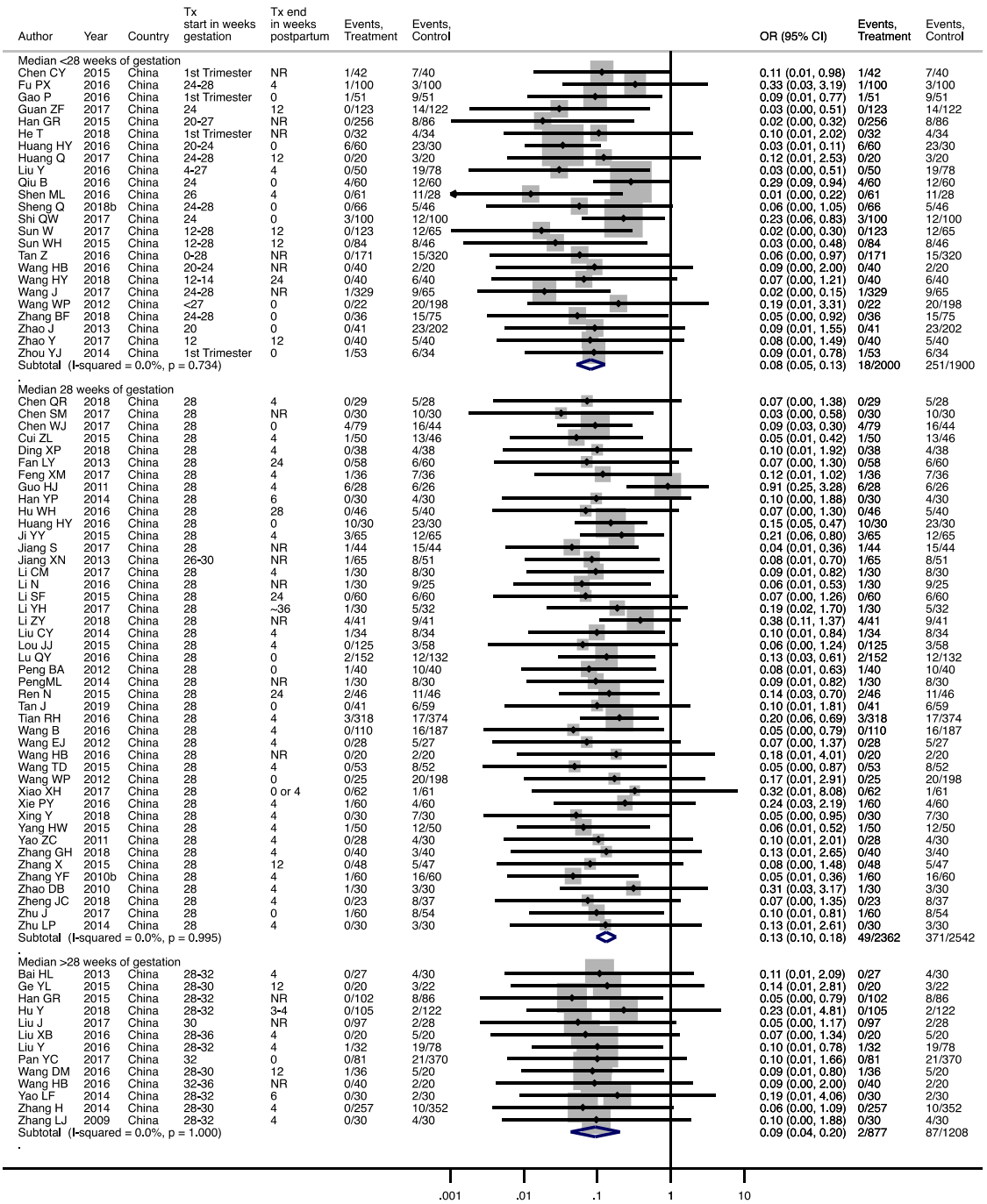
- **TDF 300 mg by timing of PAP initiation**
  - <28 weeks gestation (n=10): pooled OR= 0.10 (95%CI: 0.04-0.25), p<0.001, $I^2$=0%
  - 28 weeks gestation (n=7): pooled OR=0.25 (95%CI: 0.13-0.48), p<0.001, $I^2$=0%
  - >28 weeks gestation (n=5): pooled OR=0.10 (95%CI: 0.03-0.29), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.15



- **LAM 100-150 mg by timing of PAP initiation**
  - <28 weeks gestation (n=7): pooled OR= 0.10 (95%CI: 0.04-0.26), p<0.001, $I^2$=0%
  - 28 weeks gestation (n=20): pooled OR=0.16 (95%CI: 0.11-0.22), p<0.001, $I^2$=0%
  - >28 weeks gestation (n=11): pooled OR=0.31 (95%CI: 0.16-0.57), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.06



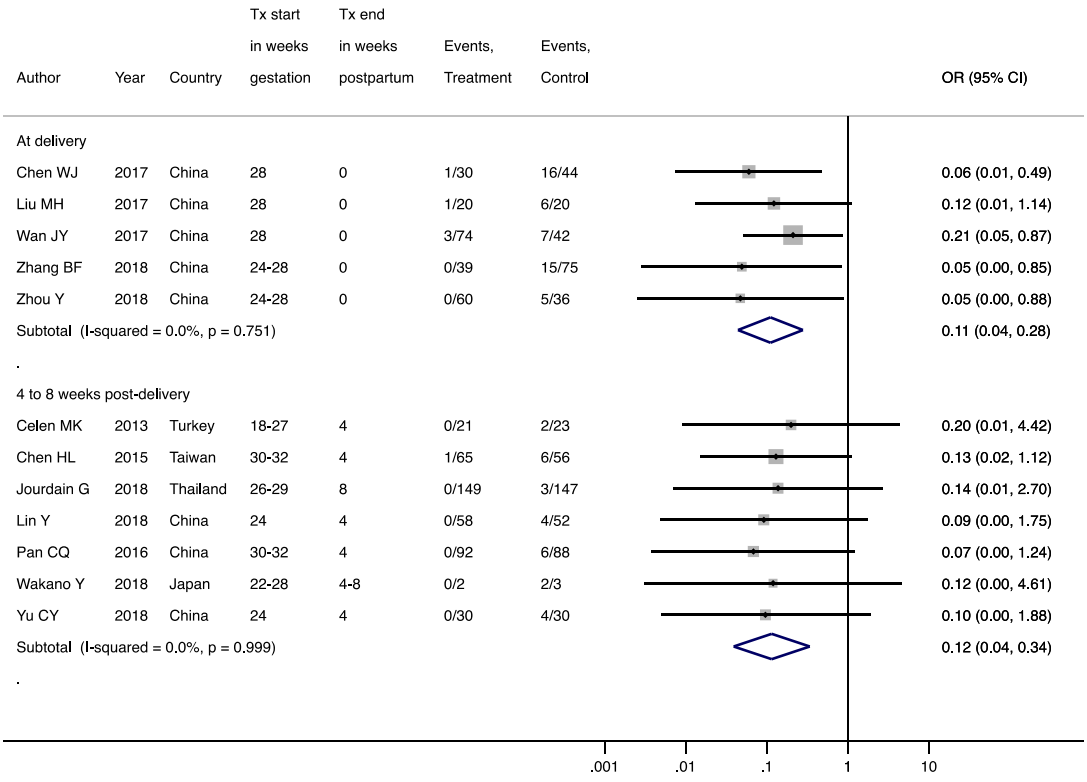
- **LdT 600 mg by timing of PAP initiation**
  - <28 weeks gestation (n=24): pooled OR=0.08 (95%CI: 0.05-0.13), p<0.001, $I^2$=0%
  - 28 weeks gestation (n=44): pooled OR=0.13 (95%CI: 0.10-0.18), p<0.001, $I^2$=0%
  - >28 weeks gestation (n=13): pooled OR=0.09 (95%CI: 0.04-0.20), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.20



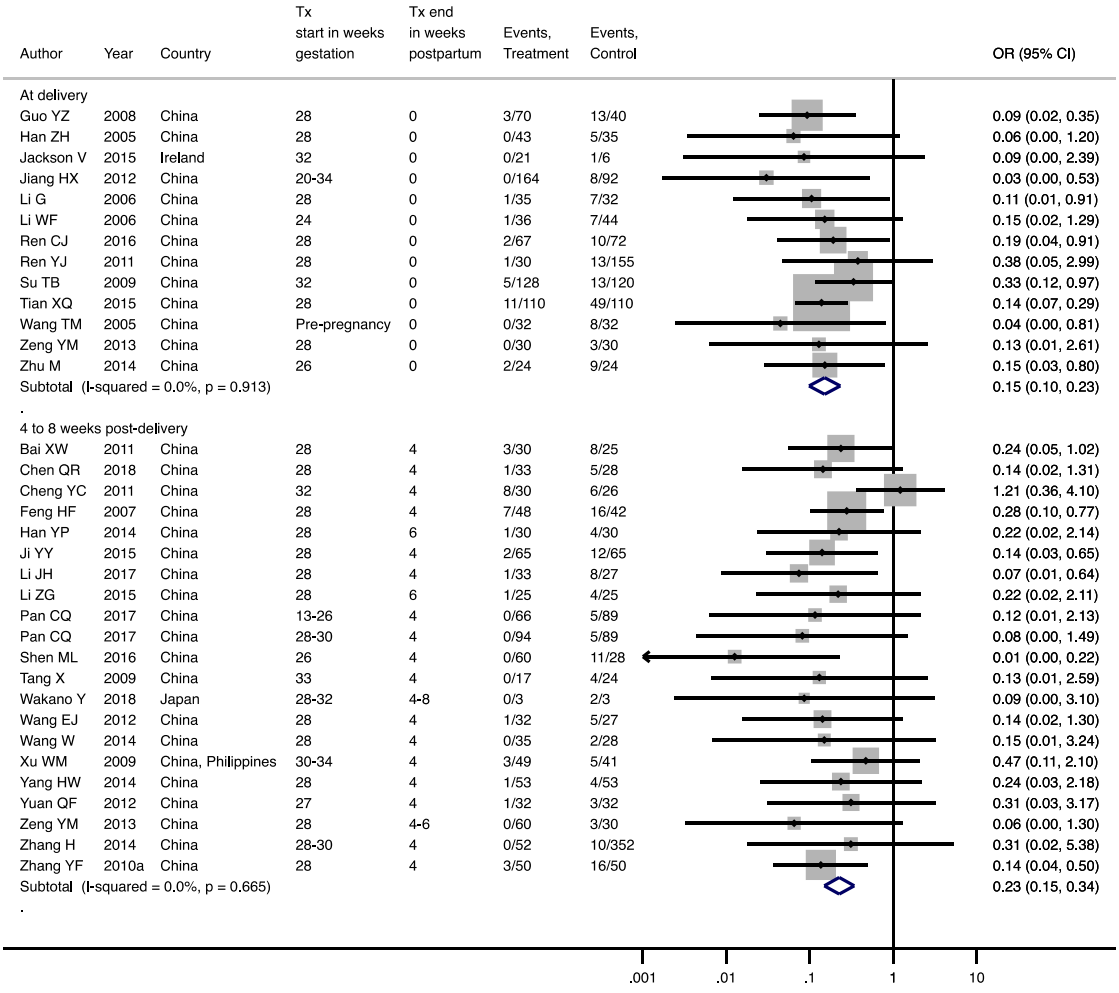
| Author | Year | Country | Tx start in weeks gestation | Tx end in weeks postpartum | Events, Treatment | Events, Control | OR (95% CI) | Events, Treatment | Events, Control |
|---|---|---|---|---|---|---|---|---|---|
| Median <28 weeks of gestation | | | | | | | | | |
| Chen CY | 2015 | China | 1st Trimester | NR | 1/42 | 7/40 | 0.11 (0.01, 0.98) | 1/42 | 7/40 |
| Fu PX | 2016 | China | 24-28 | 4 | 1/100 | 3/100 | 0.33 (0.03, 3.19) | 1/100 | 3/100 |
| Gao P | 2016 | China | 1st Trimester | 0 | 1/51 | 9/51 | 0.09 (0.01, 0.77) | 1/51 | 9/51 |
| Guan ZF | 2017 | China | 24 | 12 | 0/123 | 14/122 | 0.03 (0.00, 0.51) | 0/123 | 14/122 |
| Han GR | 2015 | China | 20-27 | NR | 0/256 | 8/86 | 0.02 (0.00, 0.32) | 0/256 | 8/86 |
| He T | 2018 | China | 1st Trimester | NR | 0/32 | 4/34 | 0.10 (0.01, 2.02) | 0/32 | 4/34 |
| Huang HY | 2016 | China | 20-24 | 0 | 6/60 | 23/30 | 0.03 (0.01, 0.11) | 6/60 | 23/30 |
| Huang Q | 2017 | China | 24-28 | 12 | 0/20 | 3/20 | 0.12 (0.01, 2.53) | 0/20 | 3/20 |
| Liu Y | 2016 | China | 4-27 | 4 | 0/50 | 19/78 | 0.03 (0.00, 0.51) | 0/50 | 19/78 |
| Qiu B | 2016 | China | 24 | 0 | 4/60 | 12/60 | 0.29 (0.09, 0.94) | 4/60 | 12/60 |
| Shen ML | 2016 | China | 26 | 4 | 0/61 | 11/28 | 0.01 (0.00, 0.22) | 0/61 | 11/28 |
| Sheng Q | 2018b | China | 24-28 | 0 | 0/66 | 5/46 | 0.06 (0.00, 1.05) | 0/66 | 5/46 |
| Shi QW | 2017 | China | 24 | 0 | 3/100 | 12/100 | 0.23 (0.06, 0.83) | 3/100 | 12/100 |
| Sun W | 2017 | China | 12-28 | 12 | 0/123 | 12/65 | 0.02 (0.00, 0.30) | 0/123 | 12/65 |
| Sun WH | 2015 | China | 12-28 | 12 | 0/84 | 8/46 | 0.03 (0.00, 0.48) | 0/84 | 8/46 |
| Tan Z | 2016 | China | 0-28 | NR | 0/171 | 15/320 | 0.06 (0.00, 0.97) | 0/171 | 15/320 |
| Wang HB | 2016 | China | 20-24 | NR | 0/40 | 2/20 | 0.09 (0.00, 2.00) | 0/40 | 2/20 |
| Wang HY | 2018 | China | 12-14 | 24 | 0/40 | 6/40 | 0.07 (0.00, 1.21) | 0/40 | 6/40 |
| Wang J | 2017 | China | 24-28 | NR | 1/329 | 9/65 | 0.02 (0.00, 0.15) | 1/329 | 9/65 |
| Wang WP | 2012 | China | <27 | 0 | 0/22 | 20/198 | 0.19 (0.01, 3.31) | 0/22 | 20/198 |
| Zhang BF | 2018 | China | 24-28 | 0 | 0/36 | 15/75 | 0.05 (0.00, 0.92) | 0/36 | 15/75 |
| Zhao J | 2013 | China | 20 | 0 | 0/41 | 23/202 | 0.09 (0.01, 1.55) | 0/41 | 23/202 |
| Zhao Y | 2017 | China | 12 | 12 | 0/40 | 5/40 | 0.08 (0.00, 1.49) | 0/40 | 5/40 |
| Zhou YJ | 2014 | China | 1st Trimester | 0 | 1/53 | 6/34 | 0.09 (0.01, 0.78) | 1/53 | 6/34 |
| Subtotal (I-squared = 0.0%, p = 0.734) | | | | | | | 0.08 (0.05, 0.13) | 18/2000 | 251/1900 |
| Median 28 weeks of gestation | | | | | | | | | |
| Chen QR | 2018 | China | 28 | 4 | 0/29 | 5/28 | 0.07 (0.00, 1.38) | 0/29 | 5/28 |
| Chen SM | 2017 | China | 28 | NR | 0/30 | 10/30 | 0.03 (0.00, 0.58) | 0/30 | 10/30 |
| Chen WJ | 2017 | China | 28 | 0 | 4/79 | 16/44 | 0.09 (0.03, 0.30) | 4/79 | 16/44 |
| Cui ZL | 2015 | China | 28 | 4 | 1/50 | 13/46 | 0.05 (0.01, 0.42) | 1/50 | 13/46 |
| Ding XP | 2018 | China | 28 | 4 | 0/38 | 4/38 | 0.10 (0.01, 1.92) | 0/38 | 4/38 |
| Fan LY | 2013 | China | 28 | 24 | 0/58 | 6/60 | 0.07 (0.00, 1.30) | 0/58 | 6/60 |
| Feng XM | 2017 | China | 28 | 4 | 1/36 | 7/36 | 0.12 (0.01, 1.02) | 1/36 | 7/36 |
| Guo HJ | 2011 | China | 28 | 4 | 6/28 | 6/26 | 0.91 (0.25, 3.28) | 6/28 | 6/26 |
| Han YP | 2014 | China | 28 | 6 | 0/30 | 4/30 | 0.10 (0.00, 1.88) | 0/30 | 4/30 |
| Hu WH | 2016 | China | 28 | 28 | 0/46 | 5/40 | 0.07 (0.00, 1.30) | 0/46 | 5/40 |
| Huang HY | 2016 | China | 28 | 0 | 10/30 | 23/30 | 0.15 (0.05, 0.47) | 10/30 | 23/30 |
| Ji YY | 2015 | China | 28 | 4 | 3/65 | 12/65 | 0.21 (0.06, 0.80) | 3/65 | 12/65 |
| Jiang S | 2017 | China | 28 | NR | 1/44 | 15/44 | 0.04 (0.01, 0.36) | 1/44 | 15/44 |
| Jiang XN | 2013 | China | 26-30 | NR | 1/65 | 8/51 | 0.08 (0.01, 0.70) | 1/65 | 8/51 |
| Li CM | 2017 | China | 28 | 4 | 1/30 | 8/30 | 0.09 (0.01, 0.82) | 1/30 | 8/30 |
| Li N | 2016 | China | 28 | NR | 1/30 | 9/25 | 0.06 (0.01, 0.53) | 1/30 | 9/25 |
| Li SF | 2015 | China | 28 | 24 | 0/60 | 6/60 | 0.07 (0.00, 1.26) | 0/60 | 6/60 |
| Li YH | 2017 | China | 28 | ~36 | 1/30 | 5/32 | 0.19 (0.02, 1.70) | 1/30 | 5/32 |
| Li ZY | 2018 | China | 28 | NR | 4/41 | 9/41 | 0.38 (0.11, 1.37) | 4/41 | 9/41 |
| Liu CY | 2014 | China | 28 | 4 | 1/34 | 8/34 | 0.10 (0.01, 0.84) | 1/34 | 8/34 |
| Lou JJ | 2015 | China | 28 | 4 | 0/125 | 3/58 | 0.06 (0.00, 1.24) | 0/125 | 3/58 |
| Lu QY | 2016 | China | 28 | 0 | 2/152 | 12/132 | 0.13 (0.03, 0.61) | 2/152 | 12/132 |
| Peng BA | 2012 | China | 28 | 0 | 1/40 | 10/40 | 0.08 (0.01, 0.63) | 1/40 | 10/40 |
| PengML | 2014 | China | 28 | NR | 1/30 | 8/30 | 0.09 (0.01, 0.82) | 1/30 | 8/30 |
| Ren N | 2015 | China | 28 | 24 | 2/46 | 11/46 | 0.14 (0.03, 0.70) | 2/46 | 11/46 |
| Tan J | 2019 | China | 28 | 0 | 0/41 | 6/59 | 0.10 (0.01, 1.81) | 0/41 | 6/59 |
| Tian RH | 2016 | China | 28 | 4 | 3/318 | 17/374 | 0.20 (0.06, 0.69) | 3/318 | 17/374 |
| Wang B | 2016 | China | 28 | 4 | 0/110 | 16/187 | 0.05 (0.00, 0.79) | 0/110 | 16/187 |
| Wang EJ | 2012 | China | 28 | 4 | 0/28 | 5/27 | 0.07 (0.00, 1.37) | 0/28 | 5/27 |
| Wang HB | 2016 | China | 28 | NR | 0/20 | 2/20 | 0.18 (0.01, 4.01) | 0/20 | 2/20 |
| Wang TD | 2015 | China | 28 | 4 | 0/53 | 8/52 | 0.05 (0.00, 0.87) | 0/53 | 8/52 |
| Wang WP | 2012 | China | 28 | 0 | 0/25 | 20/198 | 0.17 (0.01, 2.91) | 0/25 | 20/198 |
| Xiao XH | 2017 | China | 28 | 0 or 4 | 0/62 | 1/61 | 0.32 (0.01, 8.08) | 0/62 | 1/61 |
| Xie PY | 2016 | China | 28 | 4 | 1/60 | 4/60 | 0.24 (0.03, 2.19) | 1/60 | 4/60 |
| Xing Y | 2018 | China | 28 | 4 | 0/30 | 7/30 | 0.05 (0.00, 0.95) | 0/30 | 7/30 |
| Yang HW | 2015 | China | 28 | 4 | 1/50 | 12/50 | 0.06 (0.01, 0.52) | 1/50 | 12/50 |
| Yao ZC | 2011 | China | 28 | 4 | 0/28 | 4/30 | 0.10 (0.01, 2.01) | 0/28 | 4/30 |
| Zhang GH | 2018 | China | 28 | 4 | 0/40 | 3/40 | 0.13 (0.01, 2.65) | 0/40 | 3/40 |
| Zhang X | 2015 | China | 28 | 12 | 0/48 | 5/47 | 0.08 (0.00, 1.48) | 0/48 | 5/47 |
| Zhang YF | 2010b | China | 28 | 4 | 1/60 | 16/60 | 0.05 (0.01, 0.36) | 1/60 | 16/60 |
| Zhao DB | 2010 | China | 28 | 4 | 1/30 | 3/30 | 0.31 (0.03, 3.17) | 1/30 | 3/30 |
| Zheng JC | 2018 | China | 28 | 4 | 0/23 | 8/37 | 0.07 (0.00, 1.35) | 0/23 | 8/37 |
| Zhu J | 2017 | China | 28 | 0 | 1/60 | 8/54 | 0.10 (0.01, 0.81) | 1/60 | 8/54 |
| Zhu LP | 2014 | China | 28 | 4 | 0/30 | 3/30 | 0.13 (0.01, 2.61) | 0/30 | 3/30 |
| Subtotal (I-squared = 0.0%, p = 0.995) | | | | | | | 0.13 (0.10, 0.18) | 49/2362 | 371/2542 |
| Median >28 weeks of gestation | | | | | | | | | |
| Bai HL | 2013 | China | 28-32 | 4 | 0/27 | 4/30 | 0.11 (0.01, 2.09) | 0/27 | 4/30 |
| Ge YL | 2015 | China | 28-30 | 12 | 0/20 | 3/22 | 0.14 (0.01, 2.81) | 0/20 | 3/22 |
| Han GR | 2015 | China | 28-32 | NR | 0/102 | 8/86 | 0.05 (0.00, 0.79) | 0/102 | 8/86 |
| Hu Y | 2018 | China | 28-32 | 3-4 | 0/105 | 2/122 | 0.23 (0.01, 4.81) | 0/105 | 2/122 |
| Liu J | 2017 | China | 30 | NR | 0/97 | 2/28 | 0.05 (0.00, 1.17) | 0/97 | 2/28 |
| Liu XB | 2016 | China | 28-36 | 4 | 0/20 | 5/20 | 0.07 (0.00, 1.34) | 0/20 | 5/20 |
| Liu Y | 2016 | China | 28-32 | 4 | 1/32 | 19/78 | 0.10 (0.01, 0.78) | 1/32 | 19/78 |
| Pan YC | 2017 | China | 32 | 0 | 0/81 | 21/370 | 0.10 (0.01, 1.66) | 0/81 | 21/370 |
| Wang DM | 2016 | China | 28-30 | 12 | 1/36 | 5/20 | 0.09 (0.01, 0.80) | 1/36 | 5/20 |
| Wang HB | 2016 | China | 32-36 | NR | 0/40 | 2/20 | 0.09 (0.00, 2.00) | 0/40 | 2/20 |
| Yao LF | 2014 | China | 28-32 | 6 | 0/30 | 2/30 | 0.19 (0.01, 4.06) | 0/30 | 2/30 |
| Zhang H | 2014 | China | 28-30 | 4 | 0/257 | 10/352 | 0.06 (0.00, 1.09) | 0/257 | 10/352 |
| Zhang LJ | 2009 | China | 28-32 | 4 | 0/30 | 4/30 | 0.10 (0.00, 1.88) | 0/30 | 4/30 |
| Subtotal (I-squared = 0.0%, p = 1.000) | | | | | | | 0.09 (0.04, 0.20) | 2/877 | 87/1208 |

## Appendix K: Efficacy by timing of PAP discontinuation

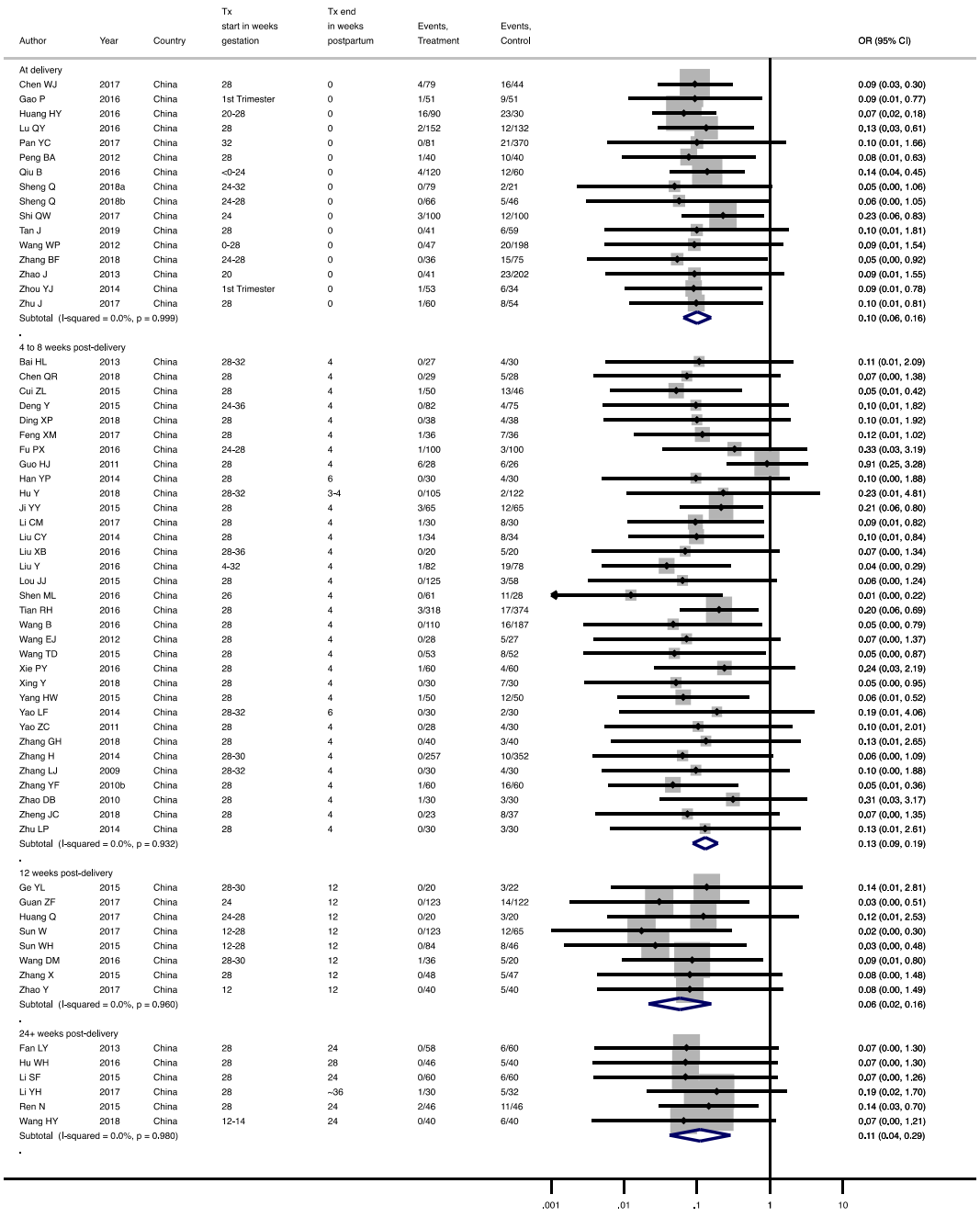
- **TDF 300 mg by timing of PAP discontinuation**
  - At delivery (n=5): pooled OR= 0.11 (95%CI: 0.04-0.28), p<0.001, $I^2$=0%
  - 4-8 weeks after delivery (n=7): pooled OR=0.12 (95%CI: 0.04-0.34), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.96



- **LAM 100-150 mg by timing of PAP discontinuation**
  - At delivery (n=13): pooled OR= 0.15 (95%CI: 0.10-0.23), p<0.001, $I^2$=0%
  - 4-8 weeks after delivery (n=21): pooled OR=0.23 (95%CI: 0.15-0.34), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.19

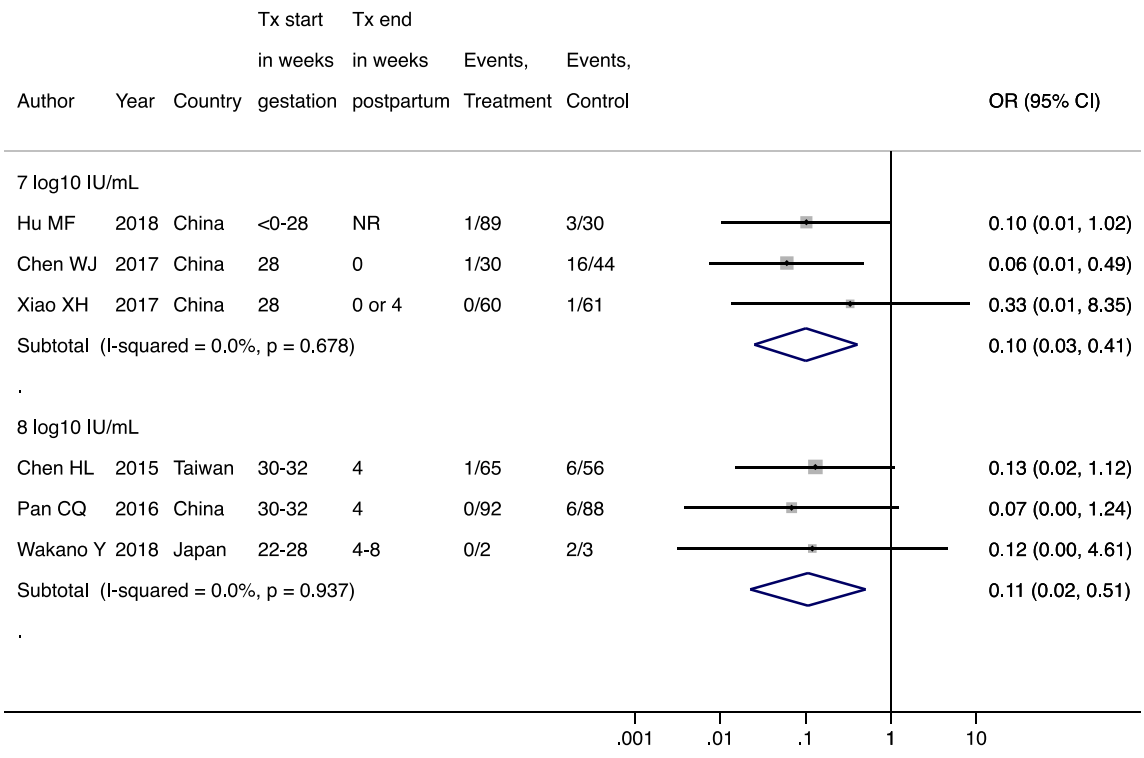


- **LdT 600 mg by timing of PAP discontinuation**
  - At delivery (n=16): pooled OR=0.10 (95%CI: 0.06-0.16), p<0.001, $I^2$=0%
  - 4-8 weeks after delivery (n=33): pooled OR=0.13 (95%CI: 0.09-0.19), p<0.001, $I^2$=0%
  - 12 weeks after delivery (n=8): pooled OR=0.06 (95%CI: 0.02-0.16), p<0.001, $I^2$=0%
  - 24+ weeks after delivery (n=6): pooled OR=0.11 (95%CI: 0.04-0.29), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.49

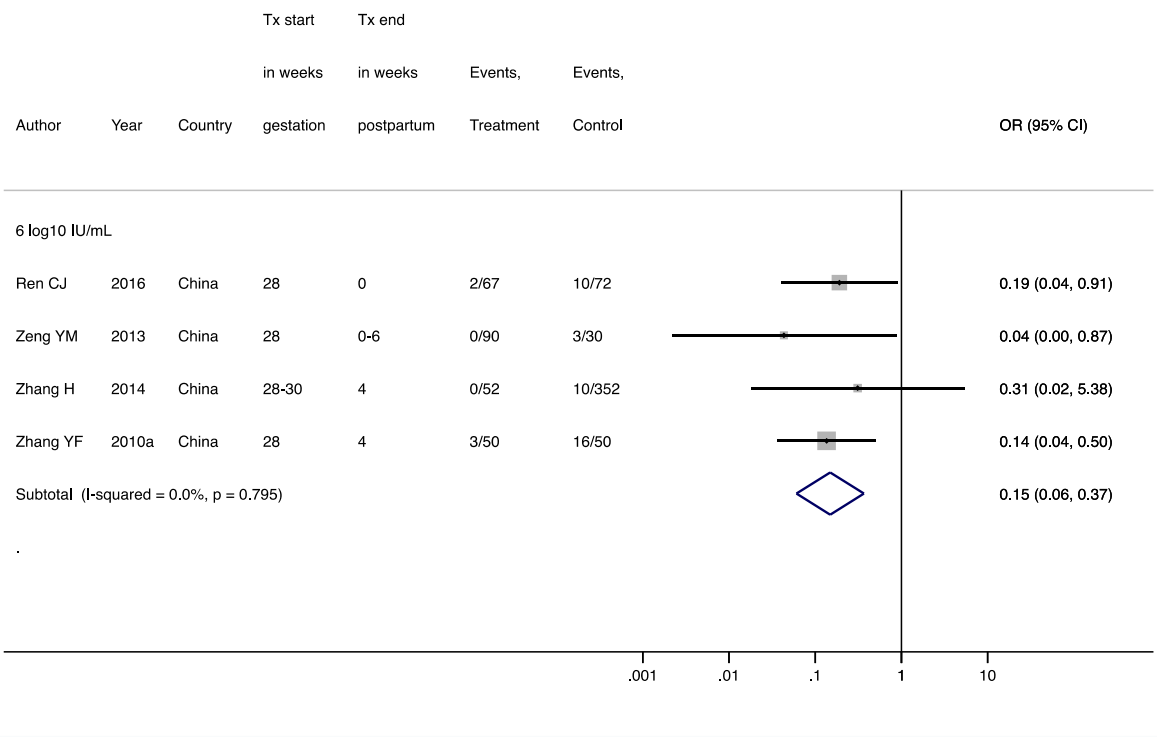


## Appendix L: Efficacy by mean maternal viral load at baseline

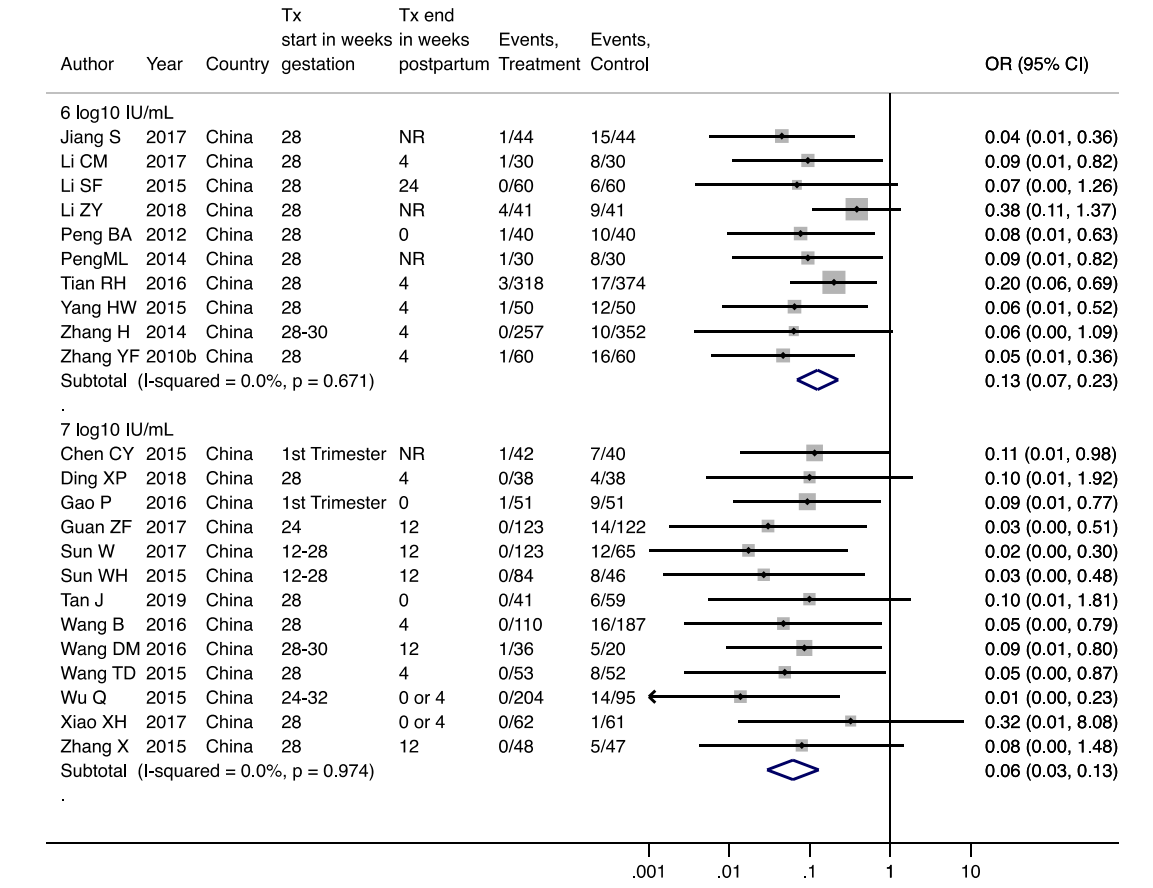
- **TDF 300 mg by mean maternal viral load at baseline**
  - 7.0-7.9 log10 IU/mL (n=3): pooled OR= 0.10 (95%CI: 0.03-0.41), p=0.001, $I^2$=0%
  - 8.0-8.9 log10 IU/mL (n=3): pooled OR= 0.11 (95%CI: 0.02-0.51), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.96
  - Note: Studies were only included in this analysis if the standard deviation for the mean viral load at baseline was less than or equal to 1



- **LAM 100-150 mg by mean maternal viral load at baseline**
  - 6.0-6.9 log10 IU/mL (n=4): pooled OR= 0.15 (95%CI: 0.06-0.37), p=0.001, $I^2$=0%

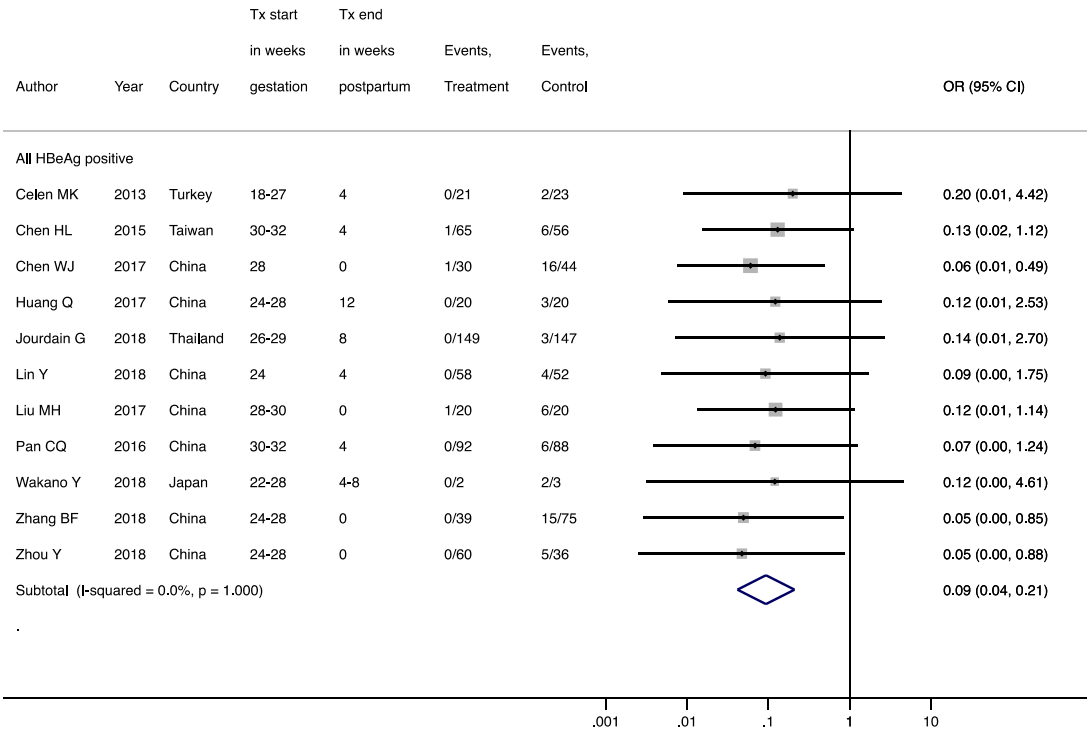


- **LdT 600 mg by mean maternal viral load at baseline**
  - 6.0-6.9 log10 IU/mL (n=10): pooled OR= 0.13 (95%CI: 0.07-0.23), p<0.001, $I^2$=0%
  - 7.0-7.9 log10 IU/mL (n=13): pooled OR= 0.06 (95%CI: 0.03-0.13), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.14

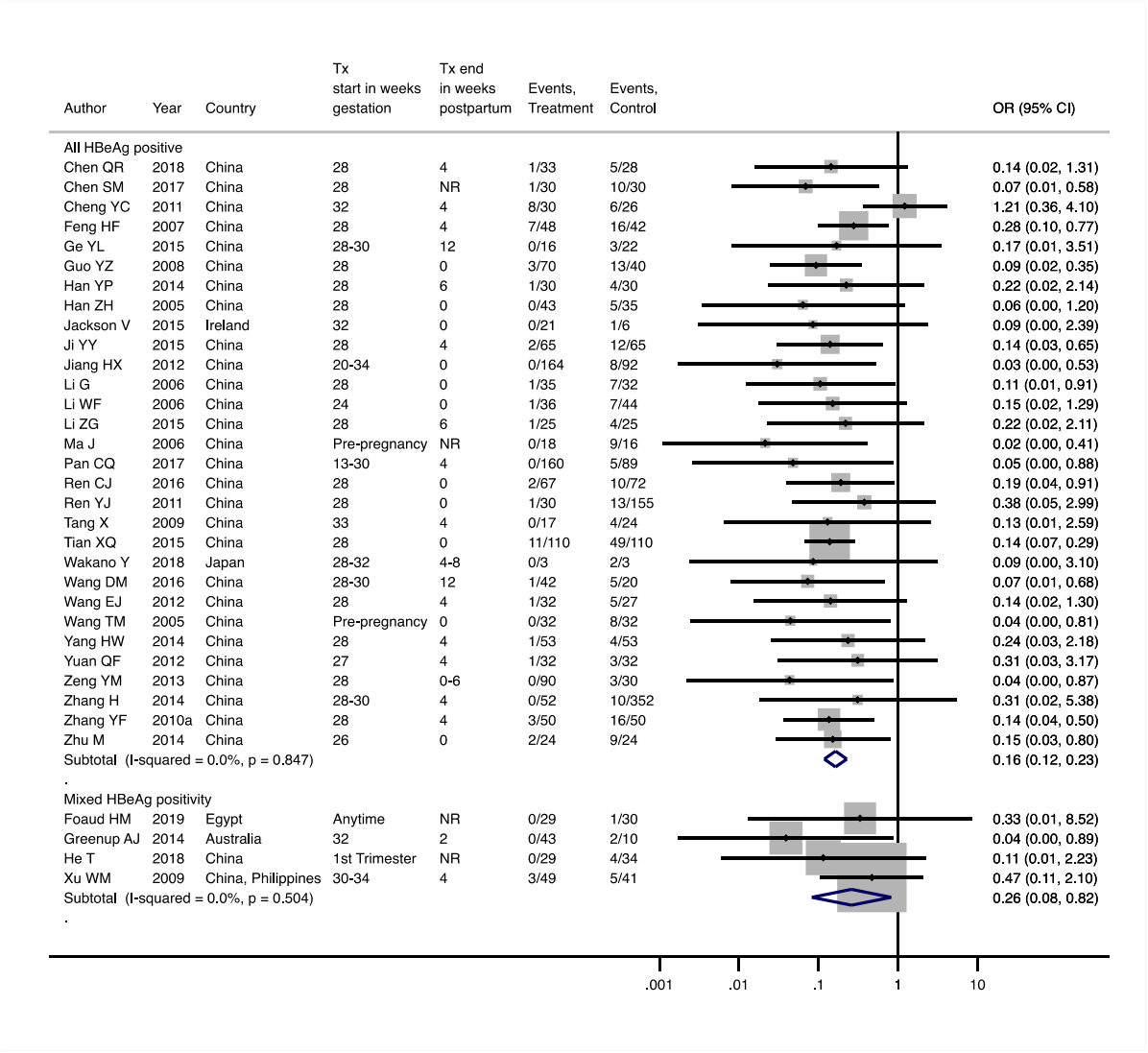


## Appendix M: Efficacy by maternal HBeAg status at baseline

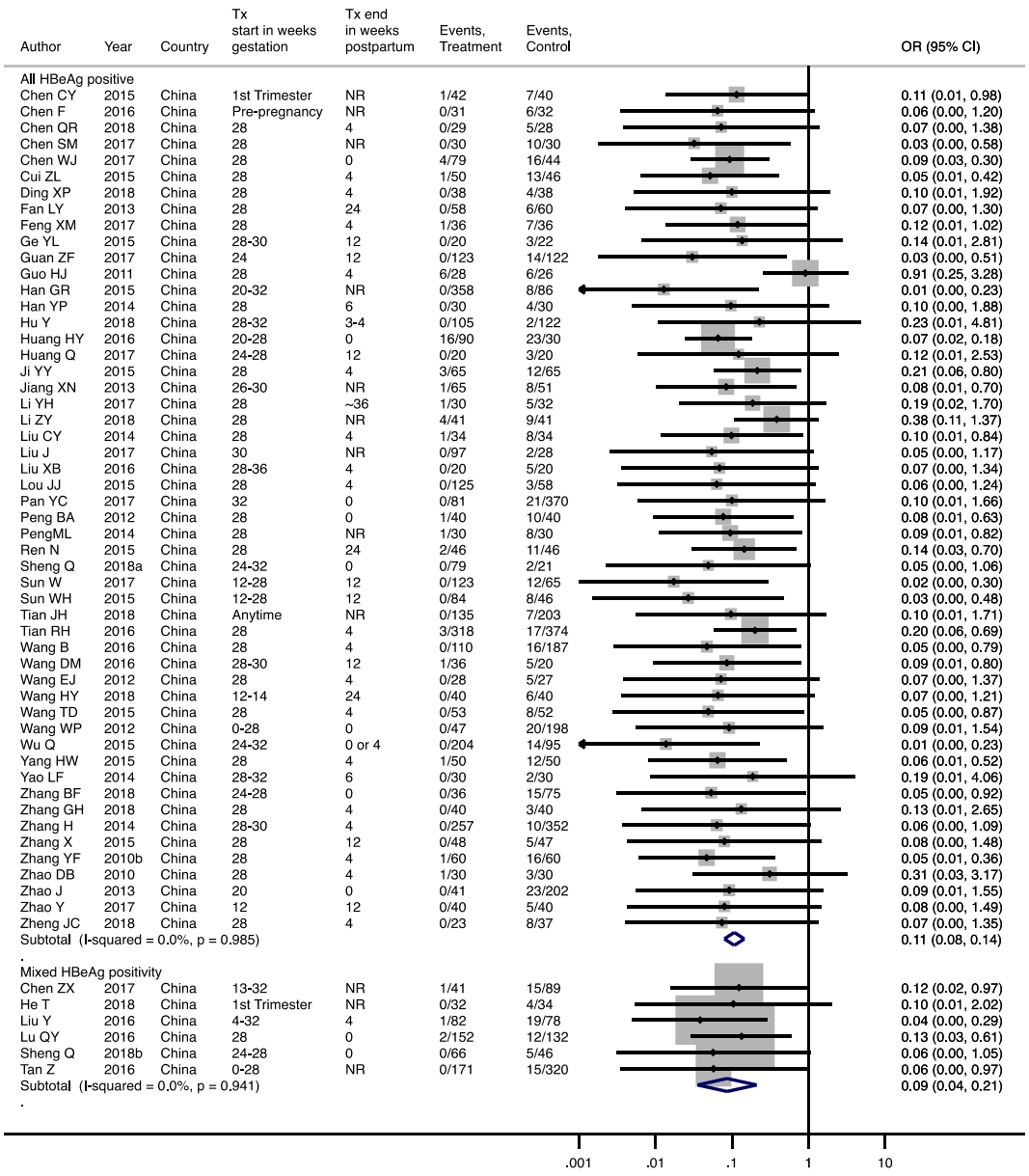
- **TDF 300 mg by maternal HBeAg status at baseline**
  - HBeAg positive only (n=11): pooled OR= 0.09 (95%CI: 0.04-0.21), p<0.001, $I^2$=0%



- **LAM 100-150 mg by maternal HBeAg status at baseline**
  - HBeAg positive only (n=30): pooled OR= 0.16 (95%CI: 0.12-0.23), p<0.001, $I^2$=0%
  - Mixed HBeAg positivity (n=4): pooled OR=0.26 (95%CI: 0.08-0.82), p=0.022, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.45

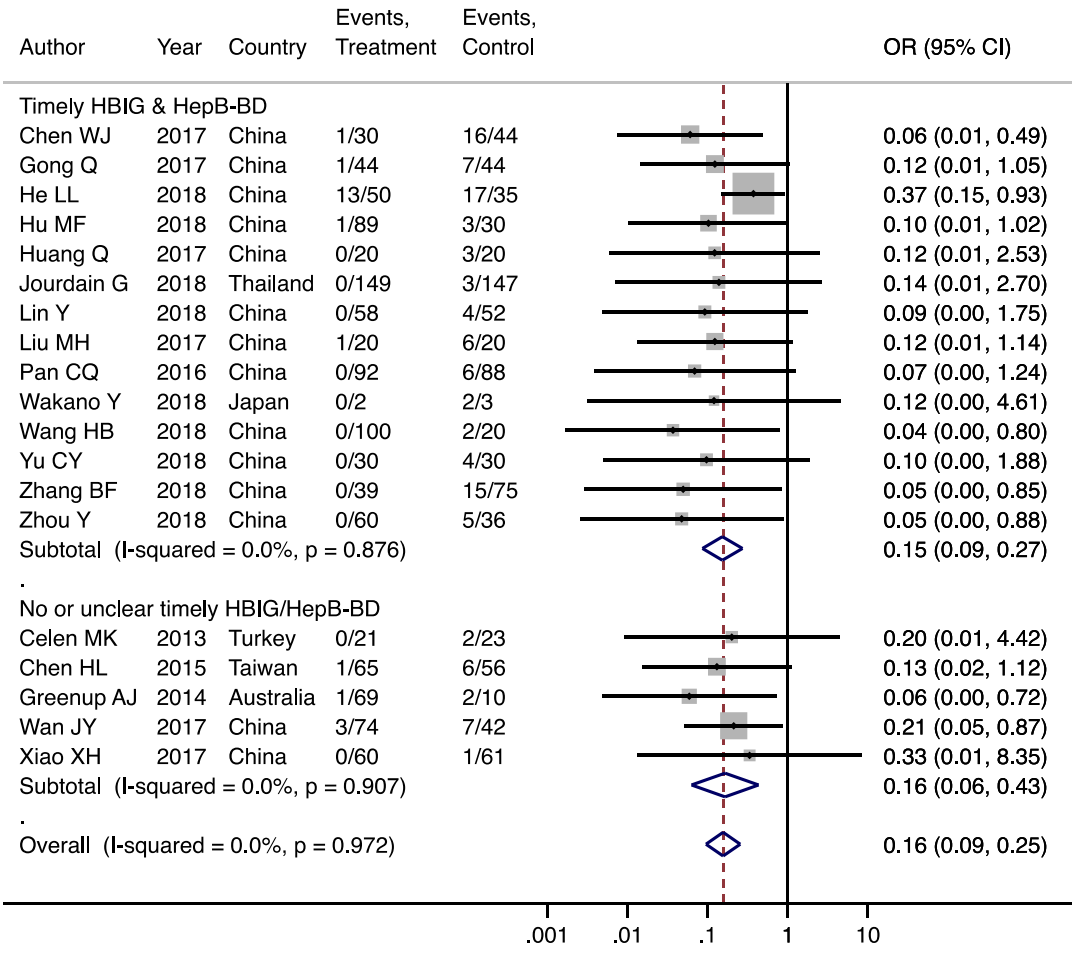


- **LdT 600 mg by maternal HBeAg status at baseline**
  - HBeAg positive only (n=52): pooled OR= 0.11 (95%CI: 0.08-0.14), p<0.001, $I^2$=0%
  - Mixed HBeAg positivity (n=6): pooled OR=0.09 (95%CI: 0.04-0.21), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.65

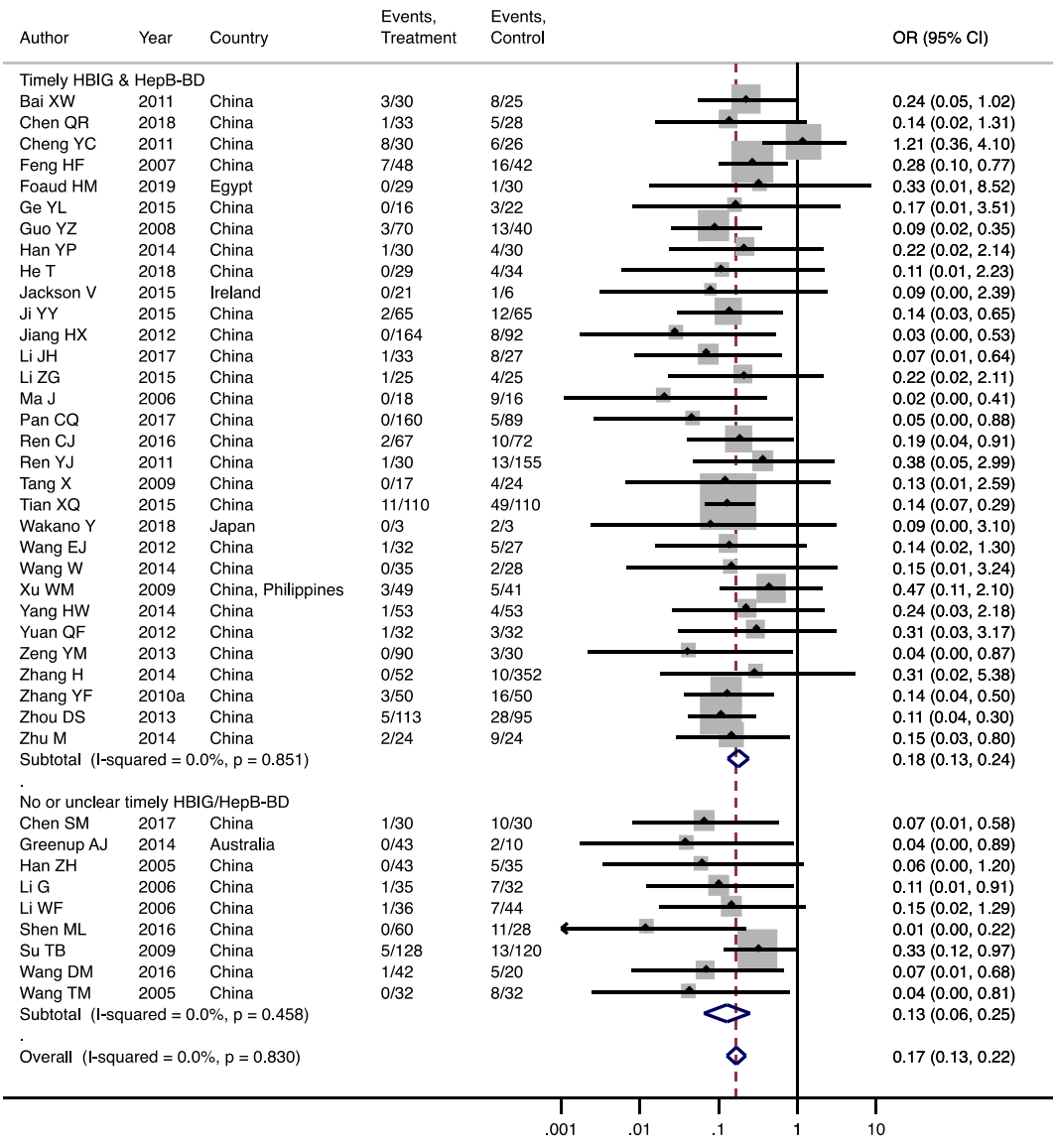


## Appendix N: Efficacy by infant immunoprophylaxis regimen

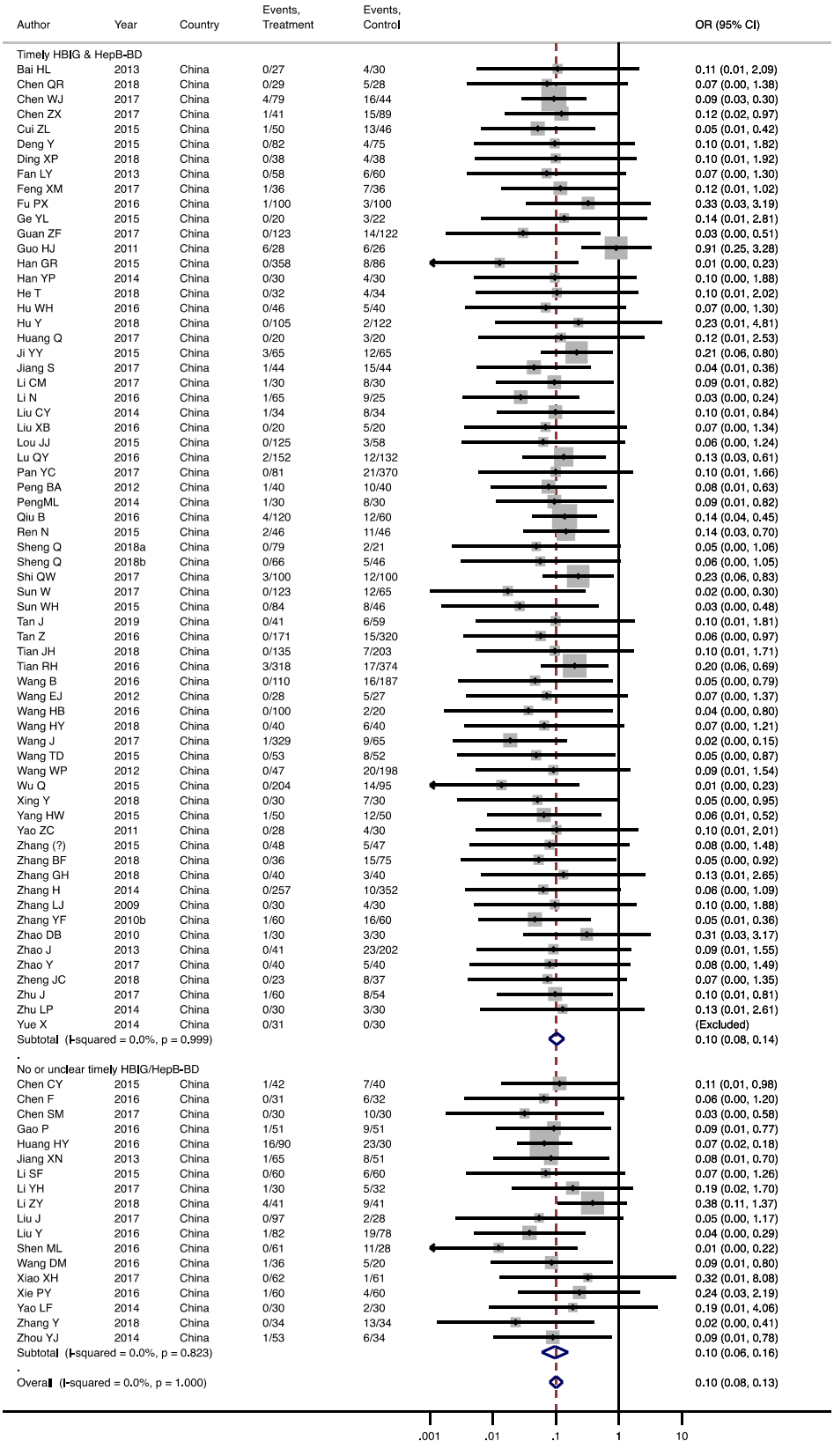
- **TDF 300 mg by infant immunoprophylaxis regimens**
  - Timely HepB-BD & HBIG (n=14): pooled OR= 0.15 (95%CI: 0.09-0.27), p<0.001, $I^2$=0%
  - No or unclear timely HepB-BD/HBIG (n=5): pooled OR=0.16 (95%CI: 0.06-0.43), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.89



- **LAM 100-150 mg by infant immunoprophylaxis regimens**
  - Timely HepB-BD & HBIG (n=31): pooled OR= 0.18 (95%CI: 0.13-0.24), p<0.001, $I^2$=0%
  - No or unclear timely HepB-BD/HBIG (n=9): pooled OR=0.13 (95%CI: 0.06-0.25), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.38

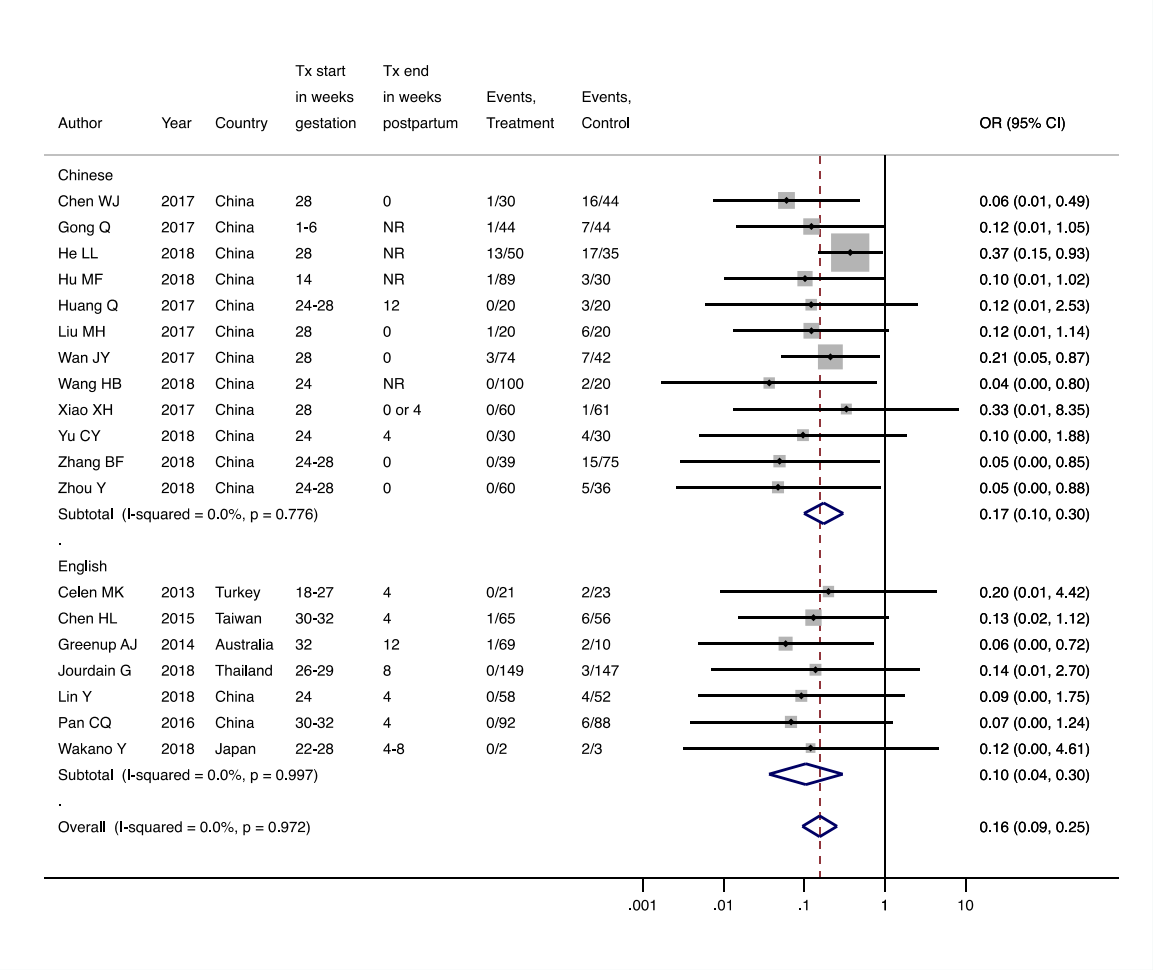


- **LdT 100-150 mg by infant immunoprophylaxis regimens**
  - Timely HepB-BD & HBIG (n=64): pooled OR= 0.10 (95%CI: 0.08-0.14), p<0.001, $I^2$=0%
  - No or unclear timely HepB-BD/HBIG (n=18): pooled OR=0.10 (95%CI: 0.06-0.16), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.83

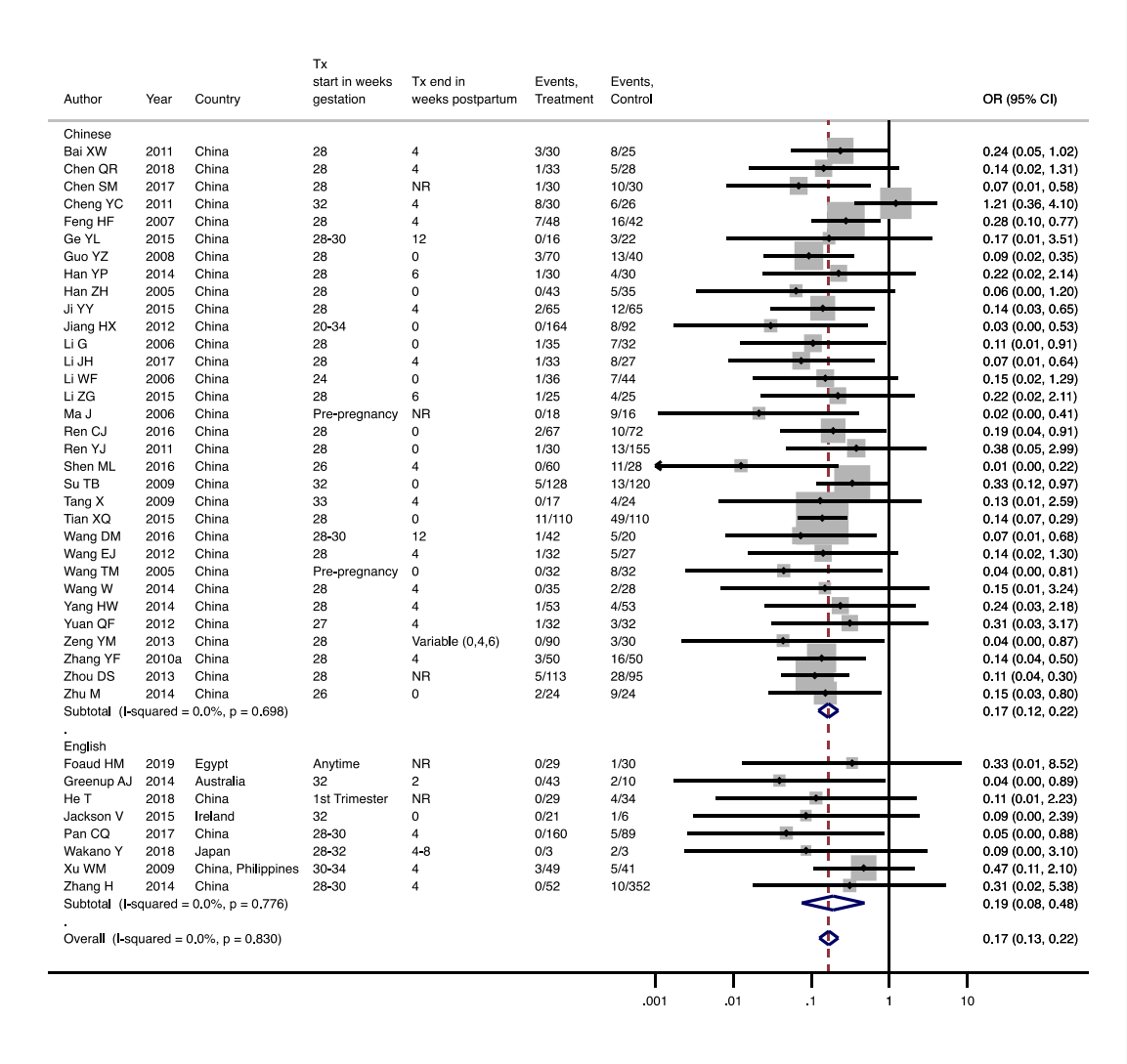


## Appendix O: Efficacy by language used for reporting (Chinese versus English)

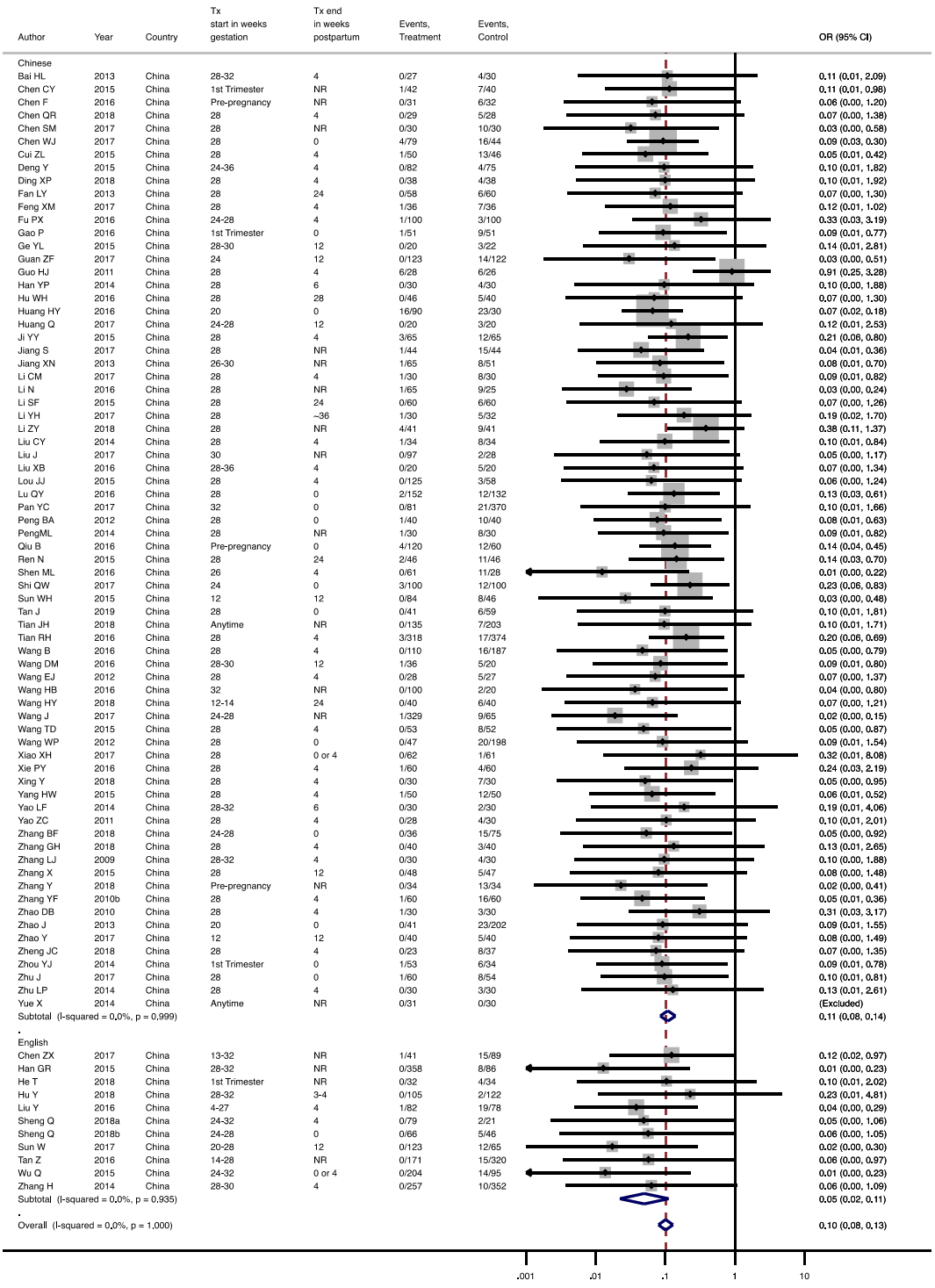
- **TDF 300 mg by language used for reporting (Chinese versus English)**
  - Chinese language (n=12): pooled OR= 0.17 (95%CI: 0.10-0.30), p<0.001, $I^2$=0%
  - English language (n=7): pooled OR=0.10 (95%CI: 0.04-0.30), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.40



- **LAM 100-150 mg by language used for reporting (Chinese versus English)**
  - Chinese language (n=32): pooled OR= 0.17 (95%CI: 0.12-0.22), p<0.001, $I^2$=0%
  - English language (n=8): pooled OR=0.19 (95%CI: 0.08-0.48), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.78

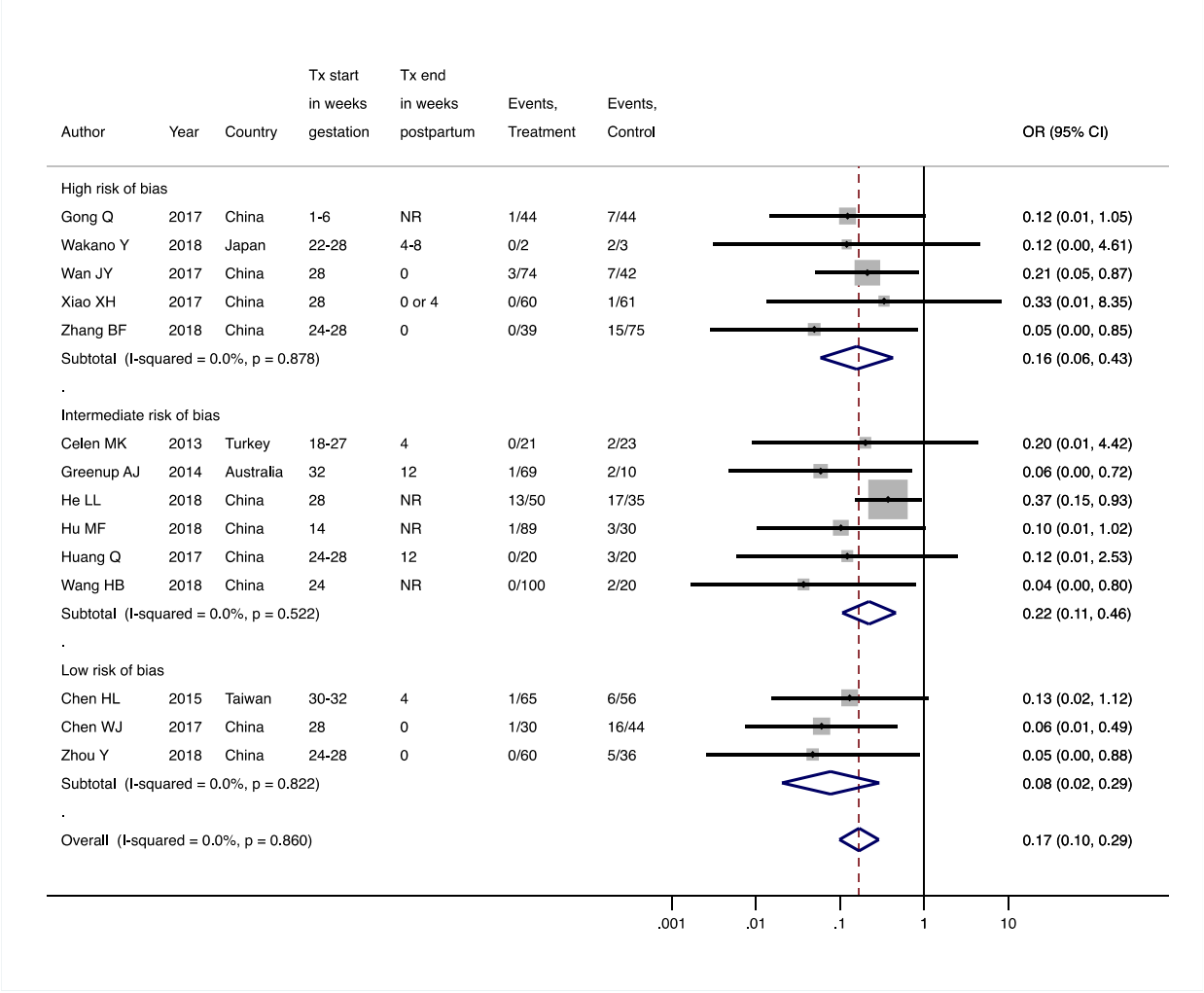


- **LdT 600 mg by language used for reporting (Chinese versus English)**
  - Chinese language (n=72): pooled OR= 0.11 (95%CI: 0.08-0.14), p<0.001, $I^2$=0%
  - English language (n=11): pooled OR=0.05 (95%CI: 0.02-0.11), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.07

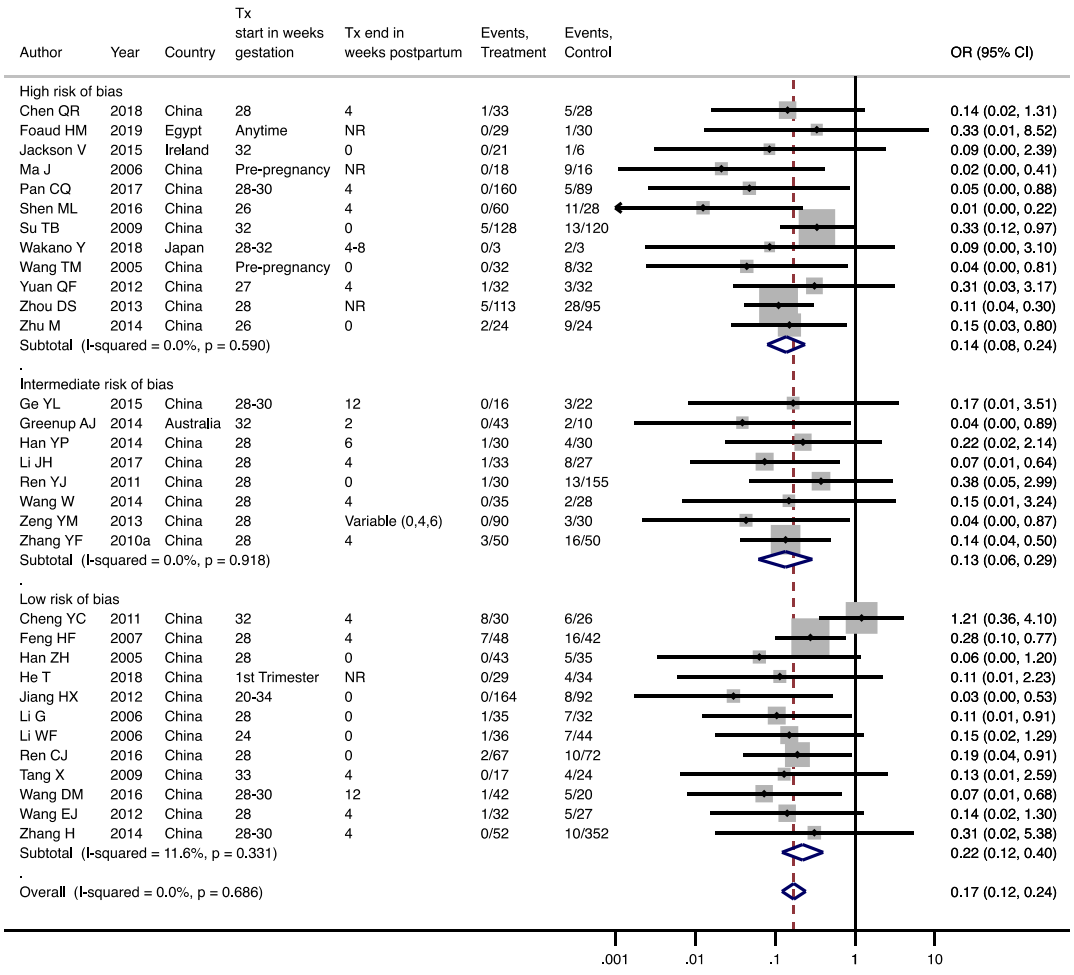


## Appendix P: Efficacy by risk of bias score for non-RCTs

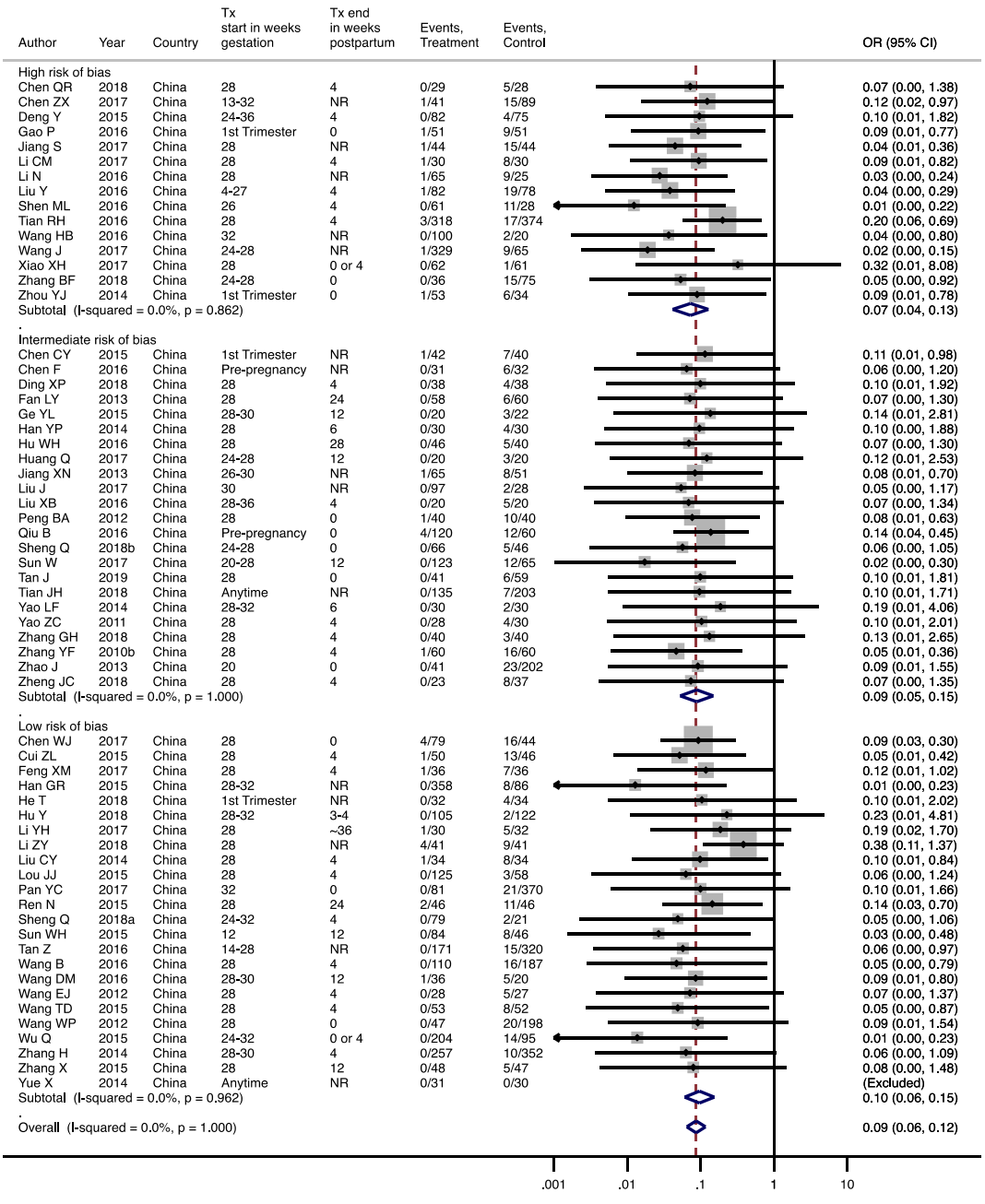
- **TDF 300 mg by risk of bias score for non-RCTs**
  - High risk (score of 6) (n=5): pooled OR= 0.16 (95%CI: 0.06-0.43), p<0.001, $I^2$=0%
  - Intermediate risk (score of 7) (n=6): pooled OR=0.22 (95%CI: 0.11-0.46), p<0.001, $I^2$=0%
  - Low risk (score of 8-9) (n=3): pooled OR=0.08 (95%CI: 0.02-0.29), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.39



- **LAM 100-150 mg by risk of bias for non-RCTs**
  - High risk (score of 6) (n=12): pooled OR= 0.14 (95%CI: 0.08-0.24), p<0.001, $I^2$=0%
  - Intermediate risk (score of 8) (n=8): pooled OR=0.13 (95%CI: 0.06-0.29), p<0.001, $I^2$=0%
  - Low risk (score of 8-9) (n=12): pooled OR=0.22 (95%CI: 0.12-0.40), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.29

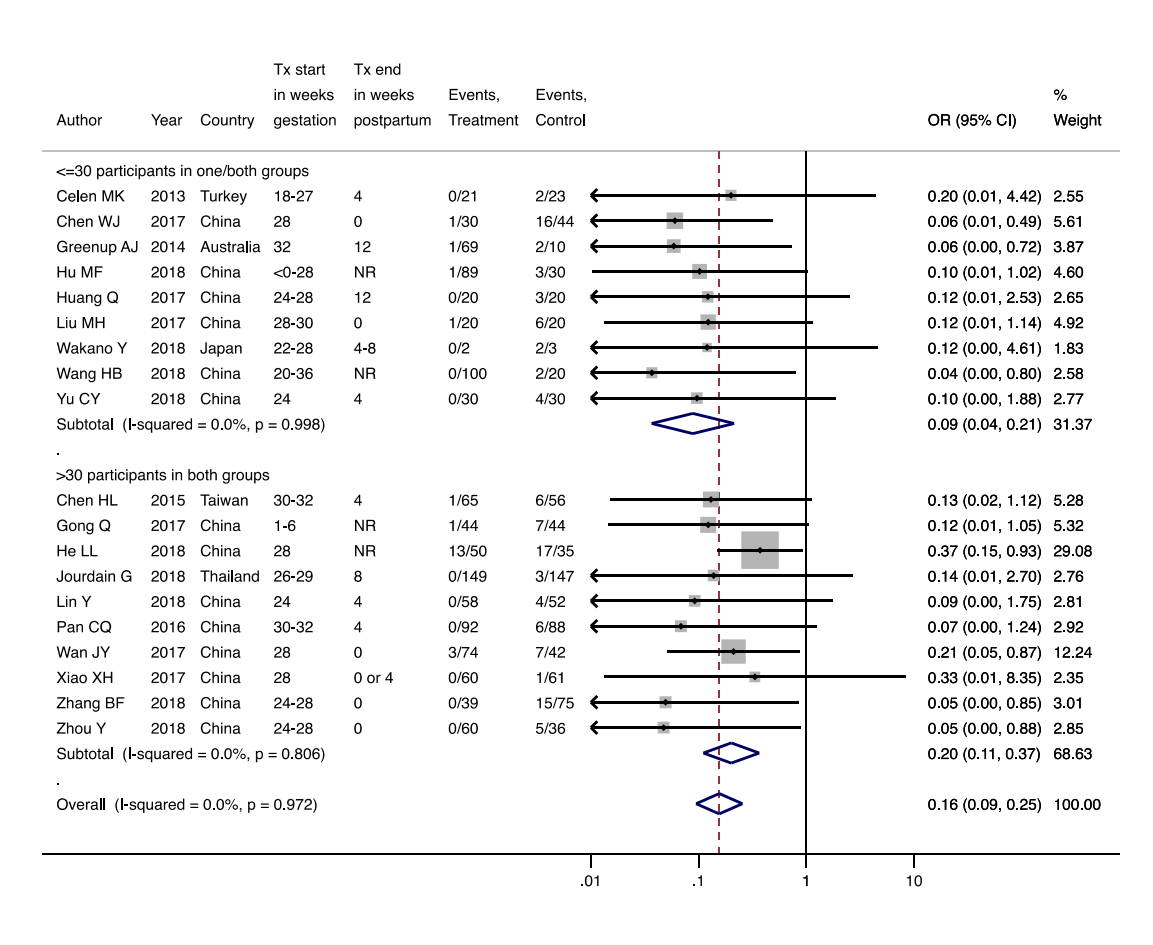


- **LdT 600 mg by risk of bias for non-RCTs**
  - High risk (score of 6) (n=15): pooled OR= 0.07 (95%CI: 0.04-0.13), p<0.001, $I^2$=0%
  - Intermediate risk (score of 8) (n=23): pooled OR=0.09 (95%CI: 0.05-0.15), p<0.001, $I^2$=0%
  - Low risk (score of 8-9) (n=24): pooled OR=0.10 (95%CI: 0.06-0.15), p<0.001, $I^2$=0%
  - The p-value for heterogeneity between subgroups was 0.75

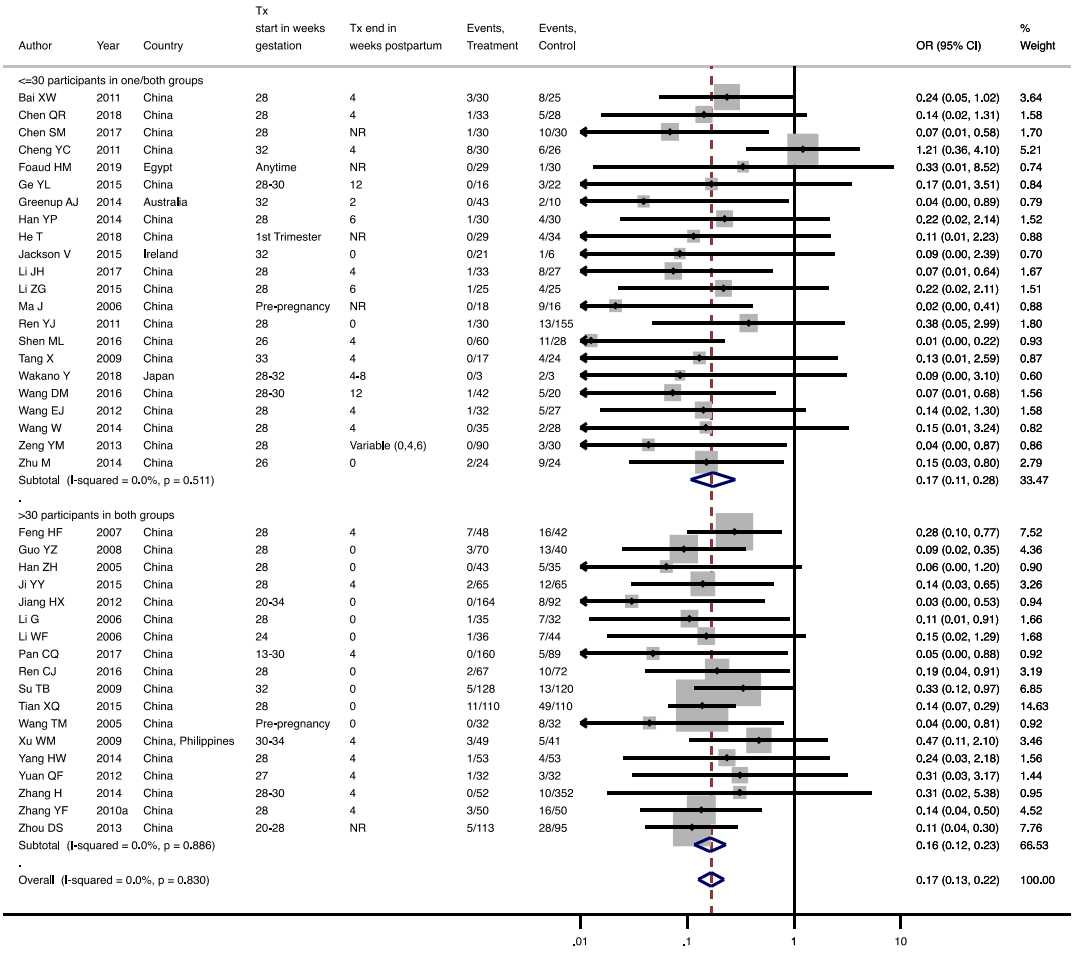


## Appendix Q: Efficacy by study sample size

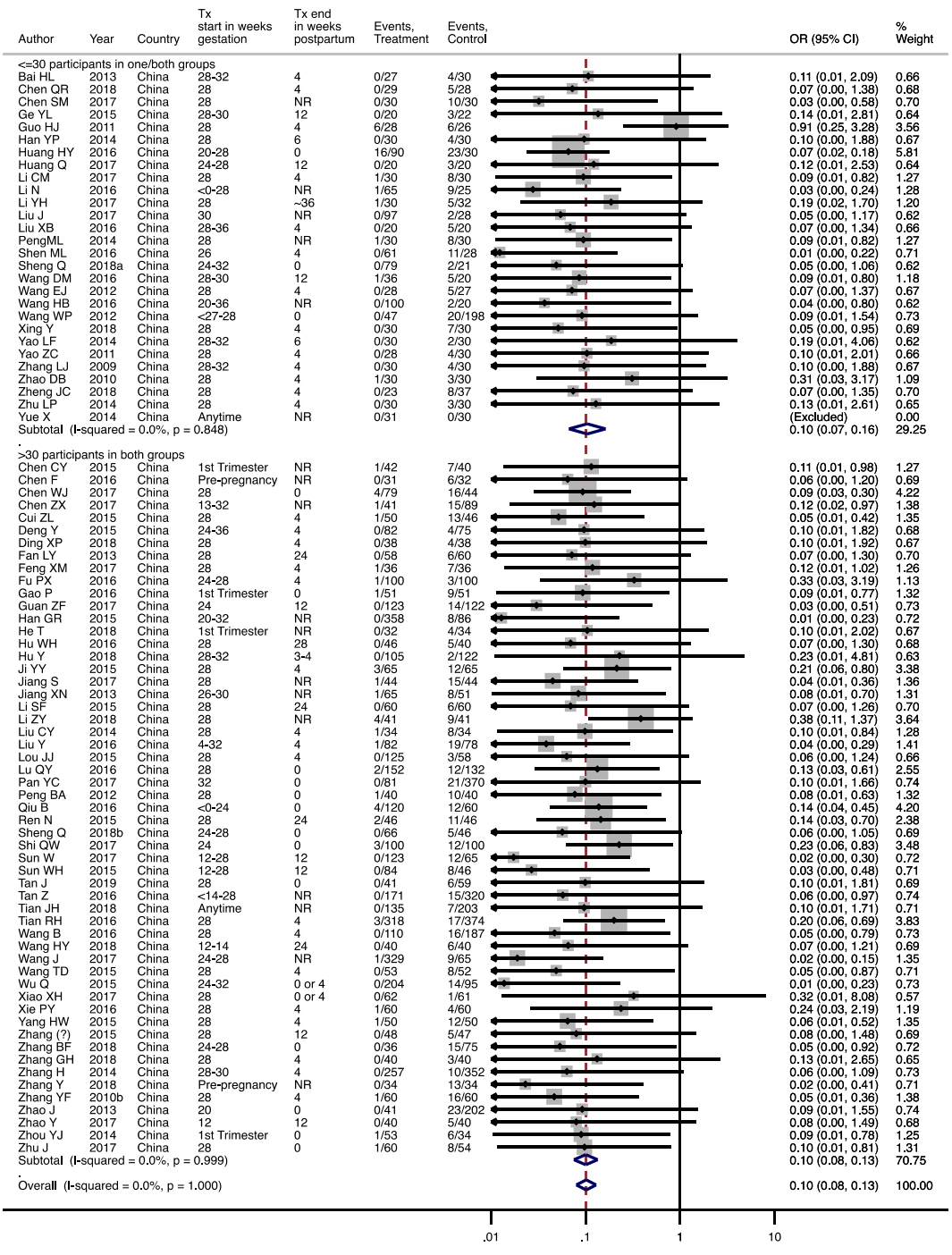
- **TDF 300 mg by study sample size (<=30 participants in either group versus >30 participants in both groups)**
  - The p-value for heterogeneity between subgroups was 0.131



- **LAM 100-150 mg by study sample size (<=30 participants in either group versus >30 participants in both groups)**
  - The p-value for heterogeneity between subgroups was 0.838

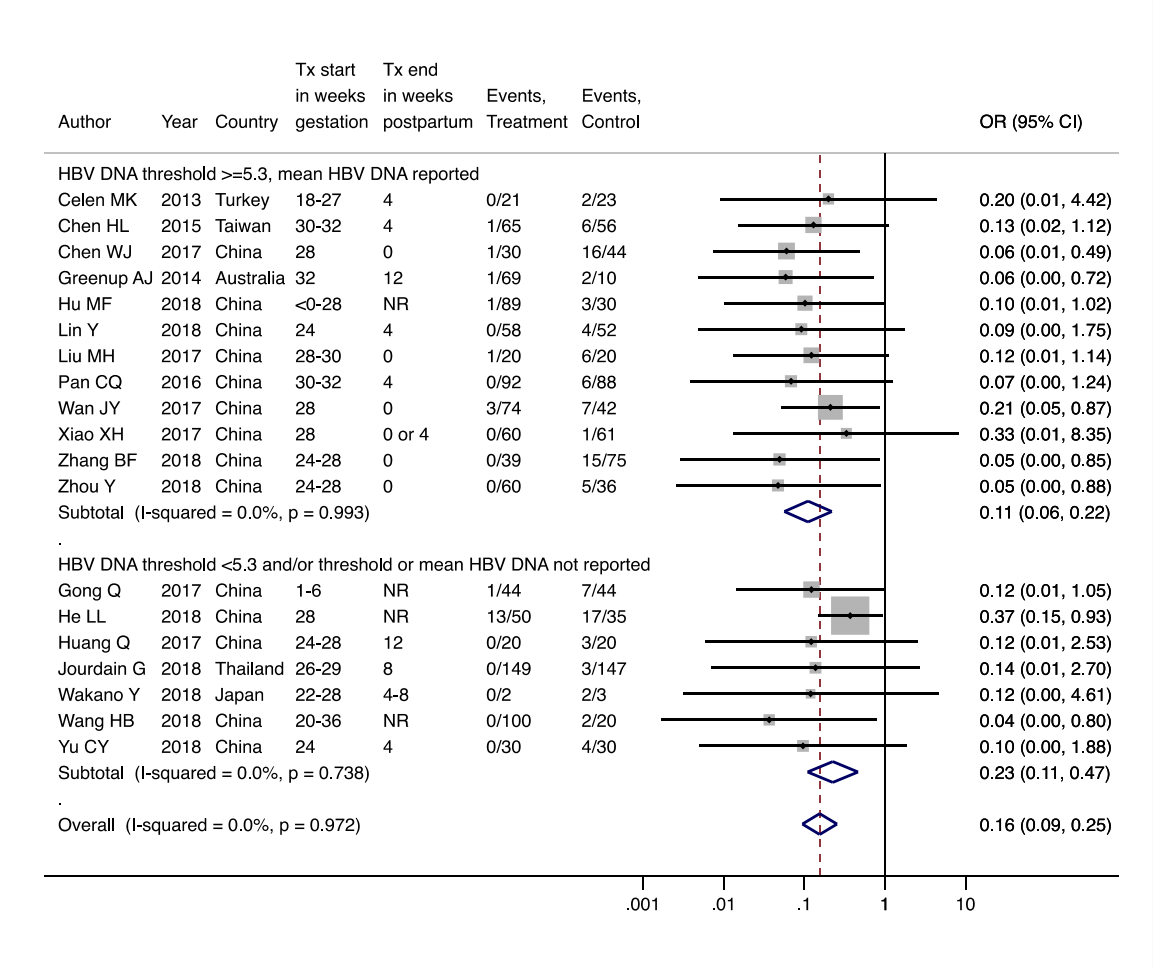


- **LdT 600 mg by study sample size (<=30 participants in either group versus >30 participants in both groups)**
  - The p-value for heterogeneity between subgroups was 0.892

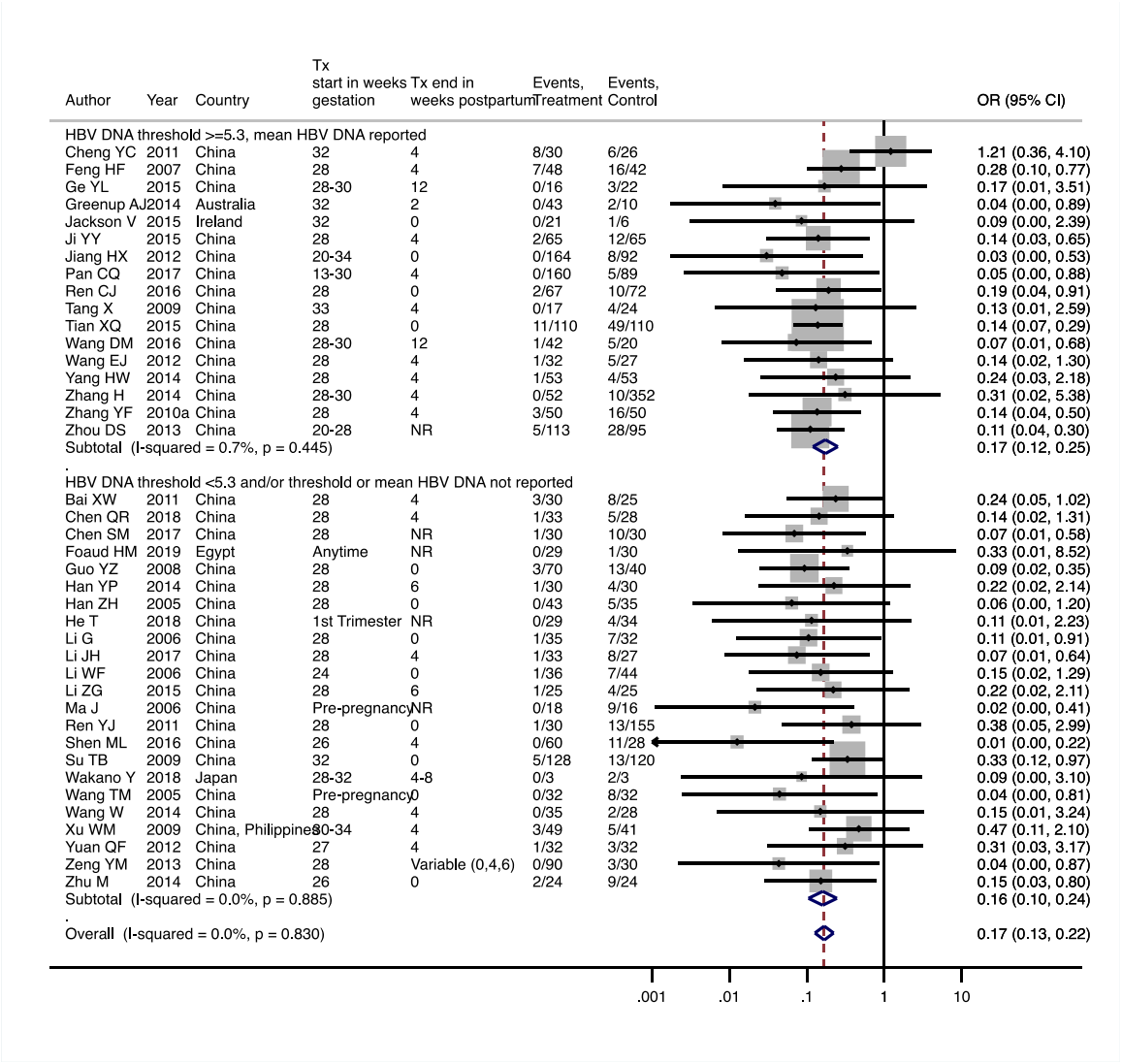


## Appendix R: Efficacy by maternal viral load criteria

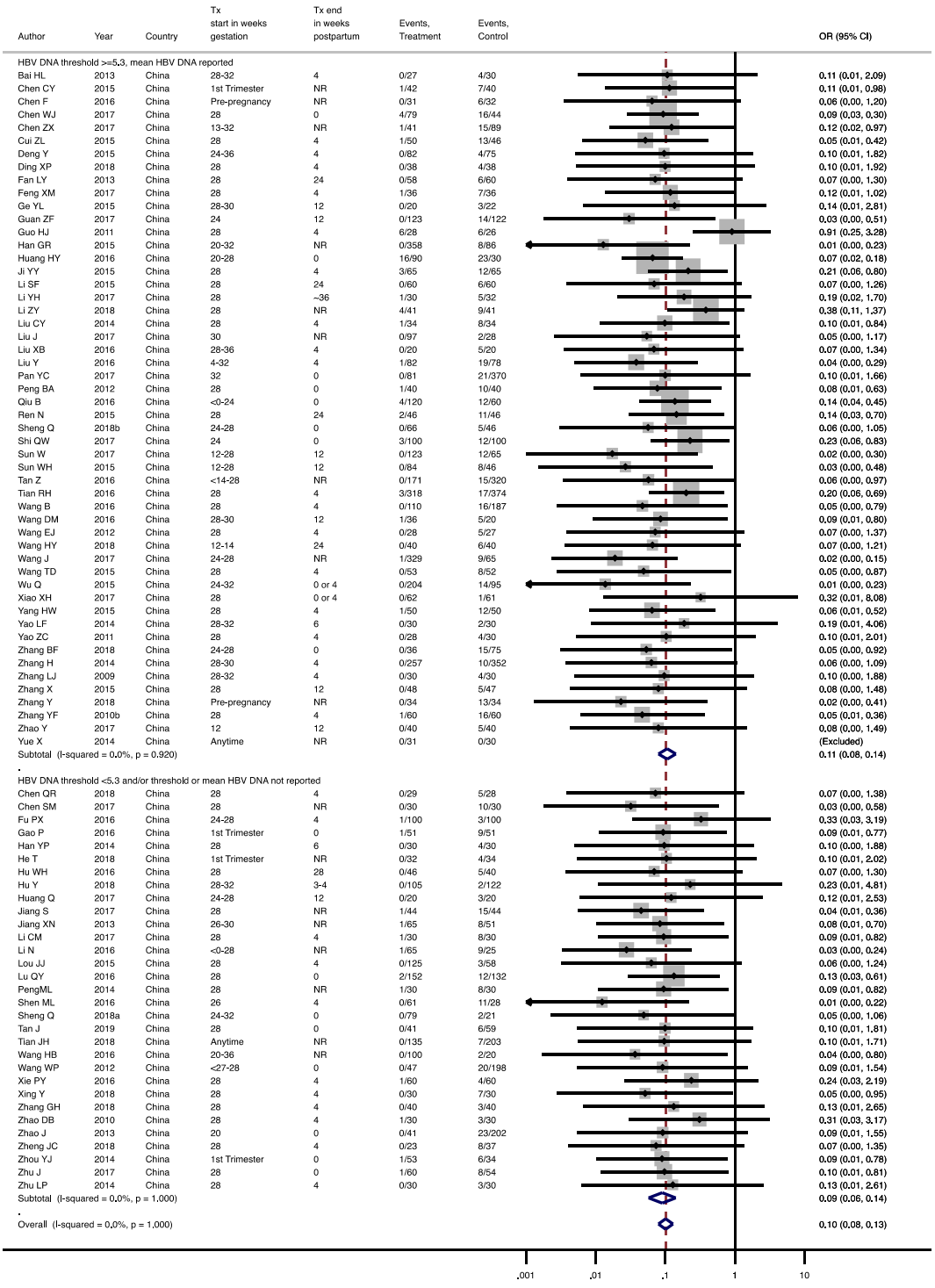
- **TDF 300 mg by maternal viral load criteria (Pre-specified viral load threshold of ≥5.3 log10 IU/mL and mean HBV DNA level reported for participating women *versus* viral load threshold not specified or threshold was low (<5.3 log10 IU/ml) and/or HBV DNA level of participating women not reported)**
  - The p-value for heterogeneity between subgroups was 0.161



- **LAM 100-150 mg by maternal viral load criteria (Pre-specified viral load threshold of ≥5.3 log10 IU/mL and mean HBV DNA level reported for participating women *versus* viral load threshold not specified or threshold was low (<5.3 log10 IU/ml) and/or HBV DNA level of participating women not reported)**
  - The p-value for heterogeneity between subgroups was 0.781

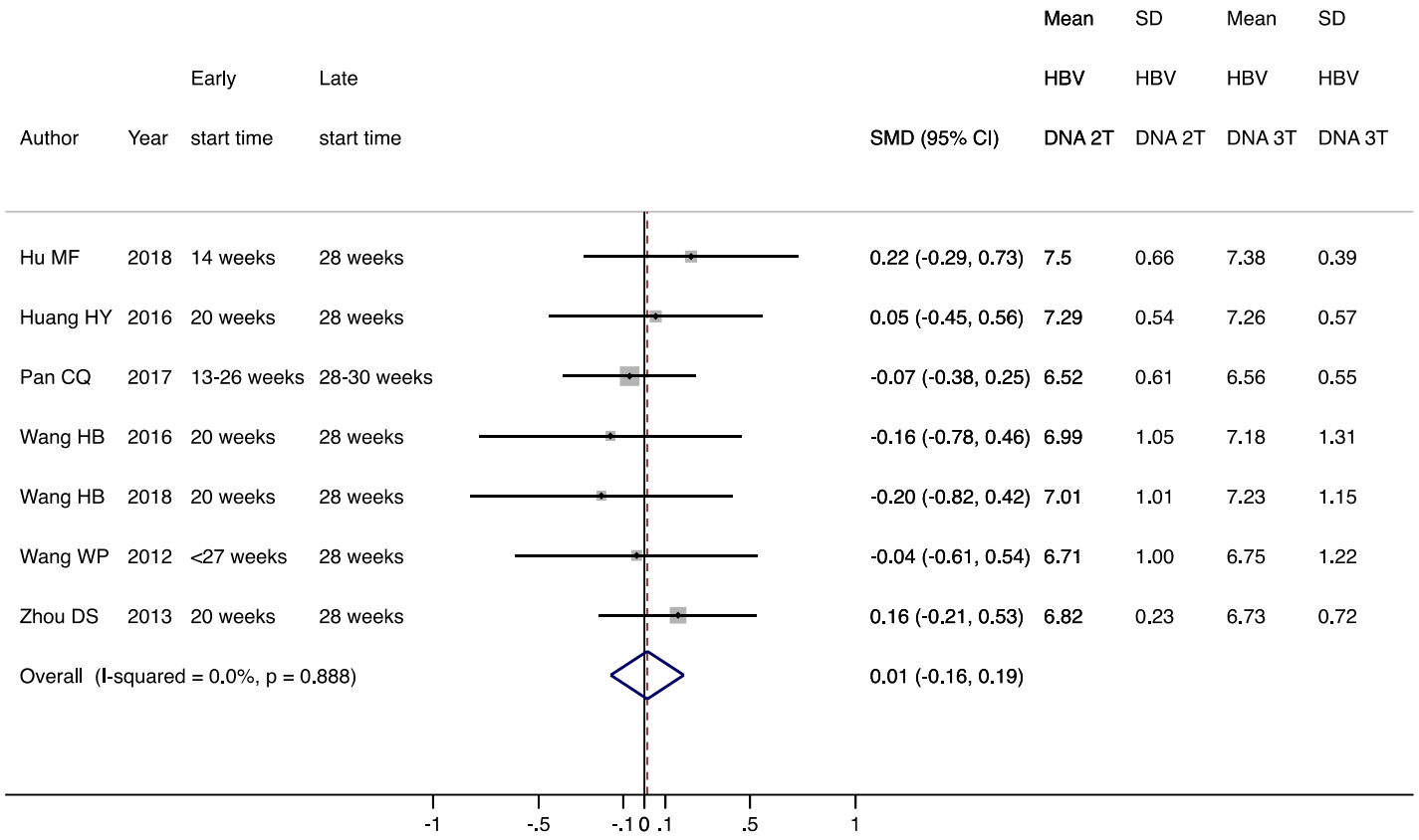


- **LdT 600 mg by maternal viral load criteria (Pre-specified viral load threshold of ≥5.3 log10 IU/mL and mean HBV DNA level reported for participating women *versus* viral load threshold not specified or threshold was low (<5.3 log10 IU/ml) and/or HBV DNA level of participating women not reported)**
  - The p-value for heterogeneity between subgroups was 0.546

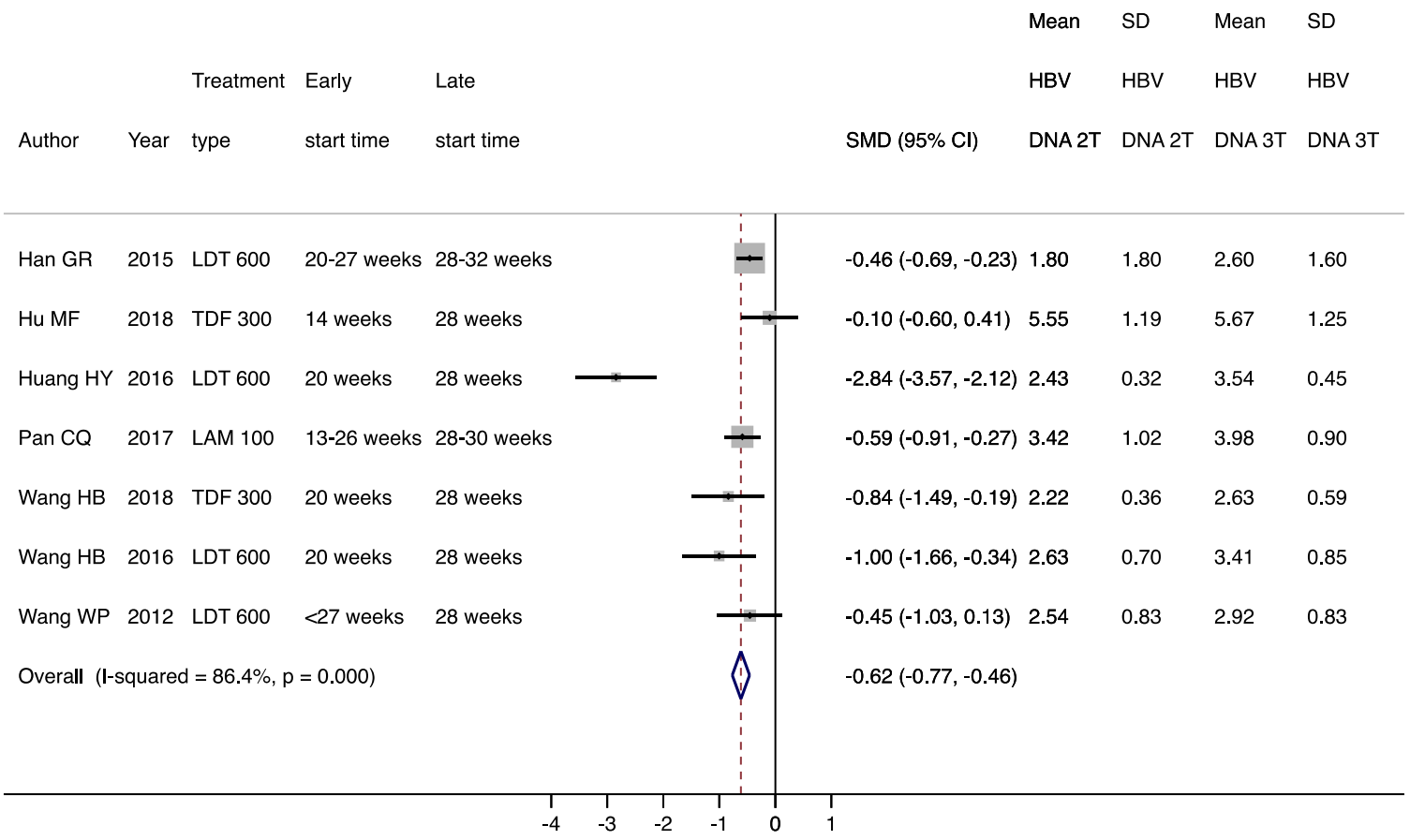

Author
Year
Country
Tx start in weeks gestation
Tx end in weeks postpartum
Events, Treatment
Events, Control
OR (95% CI)
HBV DNA threshold >=5.3, mean HBV DNA reported
Bai HL 2013 China 28-32 4 0/27 4/30 0.11 (0.01, 2.09)
Chen CY 2015 China 1st Trimester NR 1/42 7/40 0.11 (0.01, 0.98)
Chen F 2016 China Pre-pregnancy NR 0/31 6/32 0.06 (0.00, 1.20)
Chen WJ 2017 China 28 0 4/79 16/44 0.09 (0.03, 0.30)
Chen ZX 2017 China 13-32 NR 1/41 15/89 0.12 (0.02, 0.97)
Cui ZL 2015 China 28 4 1/50 13/46 0.05 (0.01, 0.42)
Deng Y 2015 China 24-36 4 0/82 4/75 0.10 (0.01, 1.82)
Ding XP 2018 China 28 4 0/38 4/38 0.10 (0.01, 1.92)
Fan LY 2013 China 28 24 0/58 6/60 0.07 (0.00, 1.30)
Feng XM 2017 China 28 4 1/36 7/36 0.12 (0.01, 1.02)
Ge YL 2015 China 28-30 12 0/20 3/22 0.14 (0.01, 2.81)
Guan ZF 2017 China 24 12 0/123 14/122 0.03 (0.00, 0.51)
Guo HJ 2011 China 28 4 6/28 6/26 0.91 (0.25, 3.28)
Han GR 2015 China 20-32 NR 0/358 8/86 0.01 (0.00, 0.23)
Huang HY 2016 China 20-28 0 16/90 23/30 0.07 (0.02, 0.18)
Ji YY 2015 China 28 4 3/65 12/65 0.21 (0.06, 0.80)
Li SF 2015 China 28 24 0/60 6/60 0.07 (0.00, 1.26)
Li YH 2017 China 28 ~36 1/30 5/32 0.19 (0.02, 1.70)
Li ZY 2018 China 28 NR 4/41 9/41 0.38 (0.11, 1.37)
Liu CY 2014 China 28 4 1/34 8/34 0.10 (0.01, 0.84)
Liu J 2017 China 30 NR 0/97 2/28 0.05 (0.00, 1.17)
Liu XB 2016 China 28-36 4 0/20 5/20 0.07 (0.00, 1.34)
Liu Y 2016 China 4-32 4 1/82 19/78 0.04 (0.00, 0.29)
Pan YC 2017 China 32 0 0/81 21/370 0.10 (0.01, 1.66)
Peng BA 2012 China 28 0 1/40 10/40 0.08 (0.01, 0.63)
Qiu B 2016 China <0-24 0 4/120 12/60 0.14 (0.04, 0.45)
Ren N 2015 China 28 24 2/46 11/46 0.14 (0.03, 0.70)
Sheng Q 2018b China 24-28 0 0/66 5/46 0.06 (0.00, 1.05)
Shi QW 2017 China 24 0 3/100 12/100 0.23 (0.06, 0.83)
Sun W 2017 China 12-28 12 0/123 12/65 0.02 (0.00, 0.30)
Sun WH 2015 China 12-28 12 0/84 8/46 0.03 (0.00, 0.48)
Tan Z 2016 China <14-28 NR 0/171 15/320 0.06 (0.00, 0.97)
Tian RH 2016 China 28 4 3/318 17/374 0.20 (0.06, 0.69)
Wang B 2016 China 28 4 0/110 16/187 0.05 (0.00, 0.79)
Wang DM 2016 China 28-30 12 1/36 5/20 0.09 (0.01, 0.80)
Wang EJ 2012 China 28 4 0/28 5/27 0.07 (0.00, 1.37)
Wang HY 2018 China 12-14 24 0/40 6/40 0.07 (0.00, 1.21)
Wang J 2017 China 24-28 NR 1/329 9/65 0.02 (0.00, 0.15)
Wang TD 2015 China 28 4 0/53 8/52 0.05 (0.00, 0.87)
Wu Q 2015 China 24-32 0 or 4 0/204 14/95 0.01 (0.00, 0.23)
Xiao XH 2017 China 28 0 or 4 0/62 1/61 0.32 (0.01, 8.08)
Yang HW 2015 China 28 4 1/50 12/50 0.06 (0.01, 0.52)
Yao LF 2014 China 28-32 6 0/30 2/30 0.19 (0.01, 4.06)
Yao ZC 2011 China 28 4 0/28 4/30 0.10 (0.01, 2.01)
Zhang BF 2018 China 24-28 0 0/36 15/75 0.05 (0.00, 0.92)
Zhang H 2014 China 28-30 4 0/257 10/352 0.06 (0.00, 1.09)
Zhang LJ 2009 China 28-32 4 0/30 4/30 0.10 (0.00, 1.88)
Zhang X 2015 China 28 12 0/48 5/47 0.08 (0.00, 1.48)
Zhang Y 2018 China Pre-pregnancy NR 0/34 13/34 0.02 (0.00, 0.41)
Zhang YF 2010b China 28 4 1/60 16/60 0.05 (0.01, 0.36)
Zhao Y 2017 China 12 12 0/40 5/40 0.08 (0.00, 1.49)
Yue X 2014 China Anytime NR 0/31 0/30 (Excluded)
Subtotal (I-squared = 0.0%, p = 0.920) 0.11 (0.08, 0.14)
HBV DNA threshold <5.3 and/or threshold or mean HBV DNA not reported
Chen QR 2018 China 28 4 0/29 5/28 0.07 (0.00, 1.38)
Chen SM 2017 China 28 NR 0/30 10/30 0.03 (0.00, 0.58)
Fu PX 2016 China 24-28 4 1/100 3/100 0.33 (0.03, 3.19)
Gao P 2016 China 1st Trimester 0 1/51 9/51 0.09 (0.01, 0.77)
Han YP 2014 China 28 6 0/30 4/30 0.10 (0.00, 1.88)
He T 2018 China 1st Trimester NR 0/32 4/34 0.10 (0.01, 2.02)
Hu WH 2016 China 28 28 0/46 5/40 0.07 (0.00, 1.30)
Hu Y 2018 China 28-32 3-4 0/105 2/122 0.23 (0.01, 4.81)
Huang Q 2017 China 24-28 12 0/20 3/20 0.12 (0.01, 2.53)
Jiang S 2017 China 28 NR 1/44 15/44 0.04 (0.01, 0.36)
Jiang XN 2013 China 26-30 NR 1/65 8/51 0.08 (0.01, 0.70)
Li CM 2017 China 28 4 1/30 8/30 0.09 (0.01, 0.82)
Li N 2016 China <0-28 NR 1/65 9/25 0.03 (0.00, 0.24)
Lou JJ 2015 China 28 4 0/125 3/58 0.06 (0.00, 1.24)
Lu QY 2016 China 28 0 2/152 12/132 0.13 (0.03, 0.61)
PengML 2014 China 28 NR 1/30 8/30 0.09 (0.01, 0.82)
Shen ML 2016 China 26 4 0/61 11/28 0.01 (0.00, 0.22)
Sheng Q 2018a China 24-32 0 0/79 2/21 0.05 (0.00, 1.06)
Tan J 2019 China 28 0 0/41 6/59 0.10 (0.01, 1.81)
Tian JH 2018 China Anytime NR 0/135 7/203 0.10 (0.01, 1.71)
Wang HB 2016 China 20-36 NR 0/100 2/20 0.04 (0.00, 0.80)
Wang WP 2012 China <27-28 0 0/47 20/198 0.09 (0.01, 1.54)
Xie PY 2016 China 28 4 1/60 4/60 0.24 (0.03, 2.19)
Xing Y 2018 China 28 4 0/30 7/30 0.05 (0.00, 0.95)
Zhang GH 2018 China 28 4 0/40 3/40 0.13 (0.01, 2.65)
Zhao DB 2010 China 28 4 1/30 3/30 0.31 (0.03, 3.17)
Zhao J 2013 China 20 0 0/41 23/202 0.09 (0.01, 1.55)
Zheng JC 2018 China 28 4 0/23 8/37 0.07 (0.00, 1.35)
Zhou YJ 2014 China 1st Trimester 0 1/53 6/34 0.09 (0.01, 0.78)
Zhu J 2017 China 28 0 1/60 8/54 0.10 (0.01, 0.81)
Zhu LP 2014 China 28 4 0/30 3/30 0.13 (0.01, 2.61)
Subtotal (I-squared = 0.0%, p = 1.000) 0.09 (0.06, 0.14)
Overall (I-squared = 0.0%, p = 1.000) 0.10 (0.08, 0.13)
.001
.01
.1
1
10

## Appendix S: Viral load prior to treatment and prior to delivery in studies comparing second versus third trimester PAP initiation

- **Standardized mean difference (SMD) of viral load AT START OF TREATMENT comparing participants starting PAP in the second ("experimental/treatment") versus third trimester ("control")**
  - 7/9 studies contributing (appropriate measures not provided by Liu Y, 2016 or Han GR 2015), SMD=0.01 (95%CI: -0.16-0.19) p=0.874

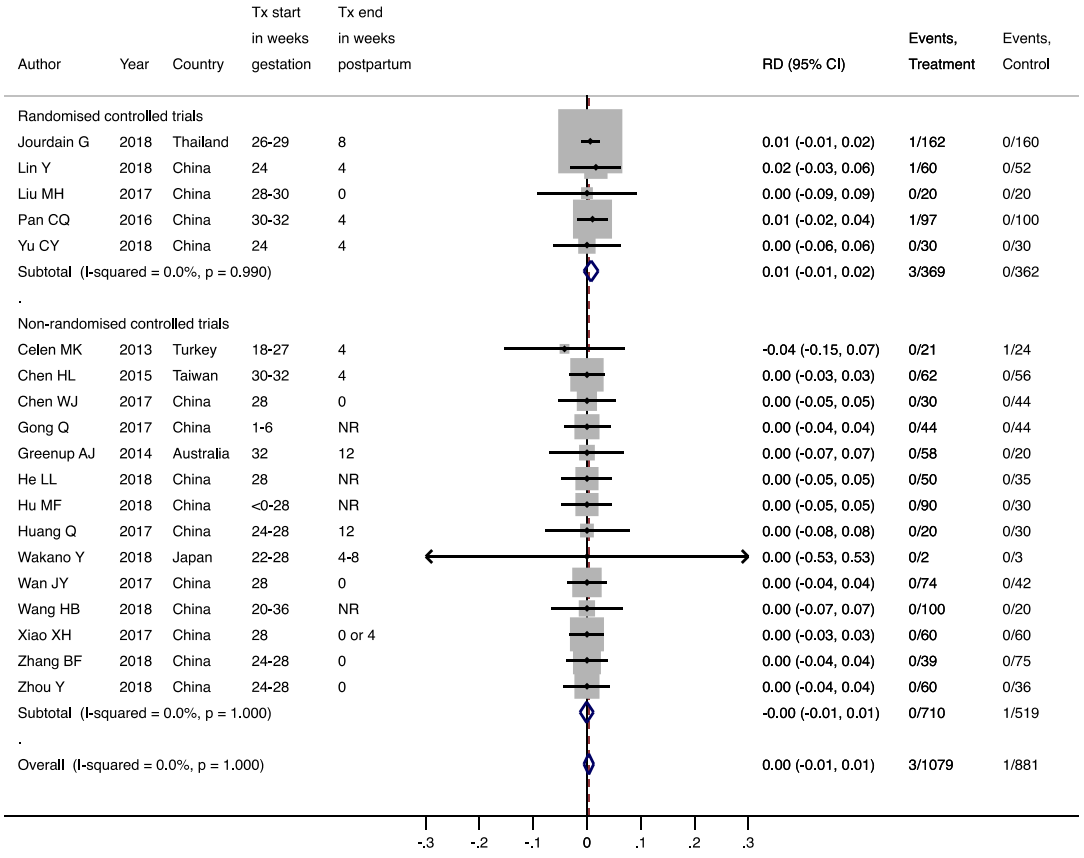


- **Standardized mean difference (SMD) of viral load AT TIME OF DELIVERY comparing participants starting PAP in the second ("experimental/treatment") versus third trimester ("control")**
    - 7/9 studies contributing (not Liu Y, 2016 or Zhou DS 2013), SMD= -0.62 (95%CI: -0.77- -0.46) p<0.001

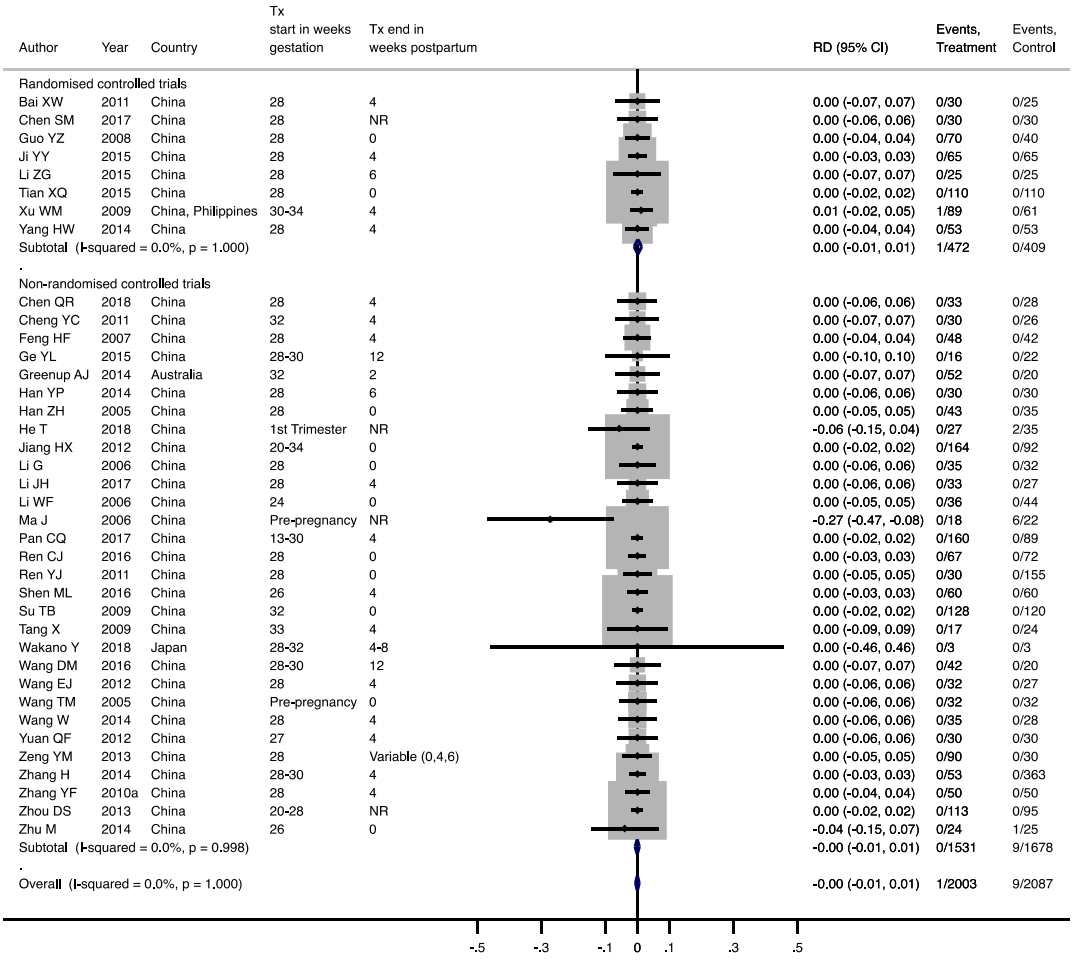


## Appendix T: Maternal safety 1. Fetal deaths

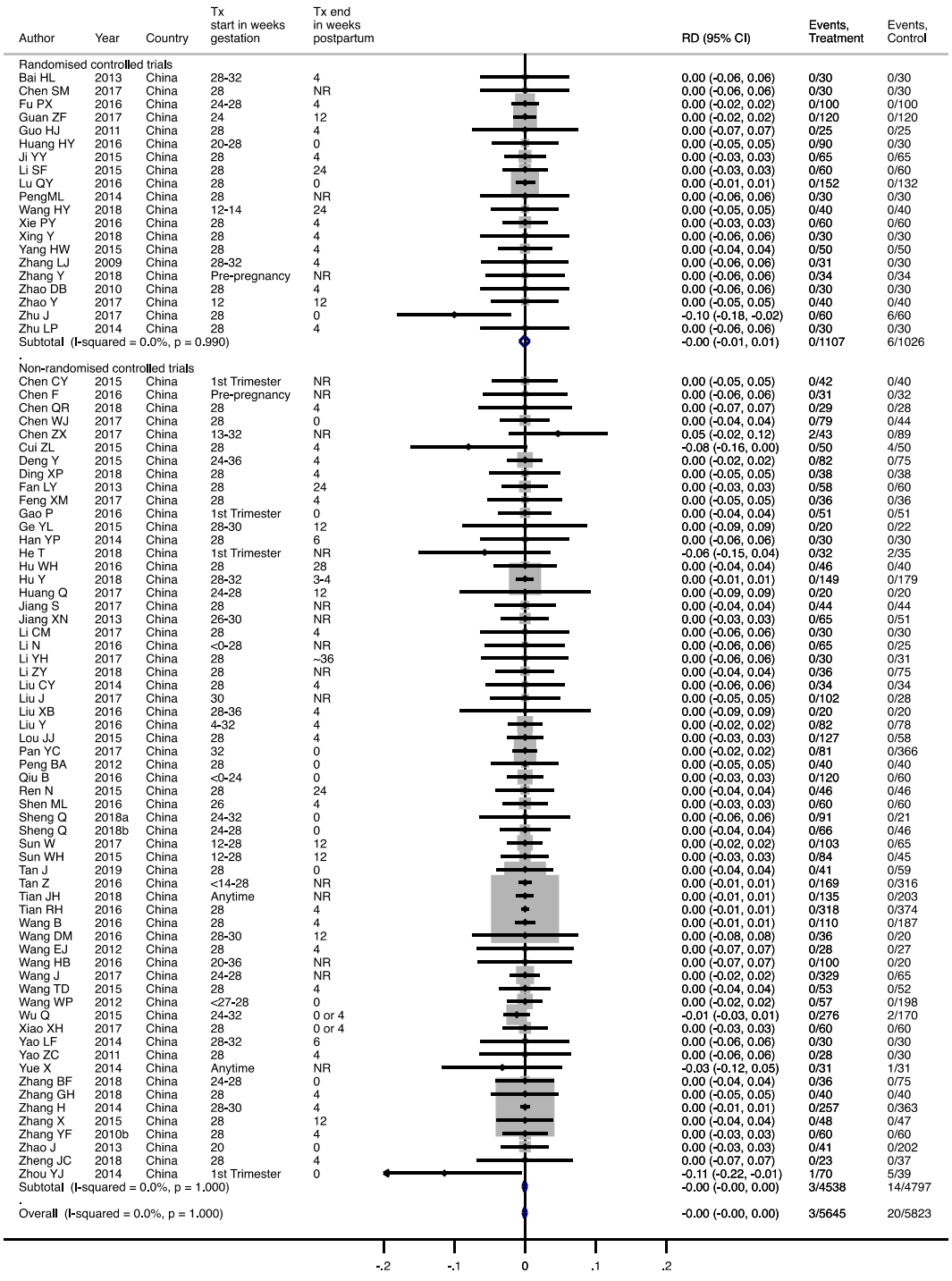
- **TDF 300 mg risk difference for fetal death**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$ statistic overall = 0%
    - $I^2$ statistic RCTs = 0%
    - $I^2$ statistic non-RCTs = 0%



- **LAM 100-150 mg risk difference for fetal death**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%

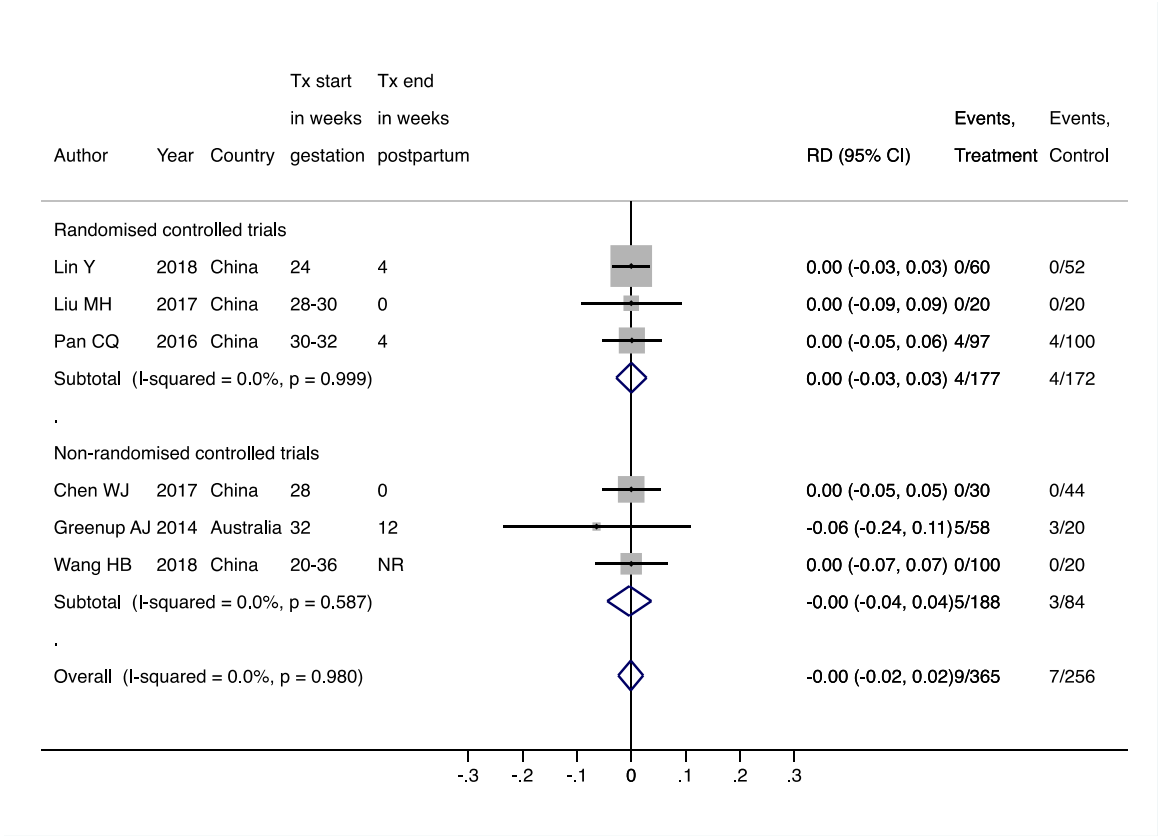


- **LdT 600 mg risk difference for fetal death**
  - Weighted pooled risk difference: 0.00 (95%CI: 0.00 – 0.00).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%

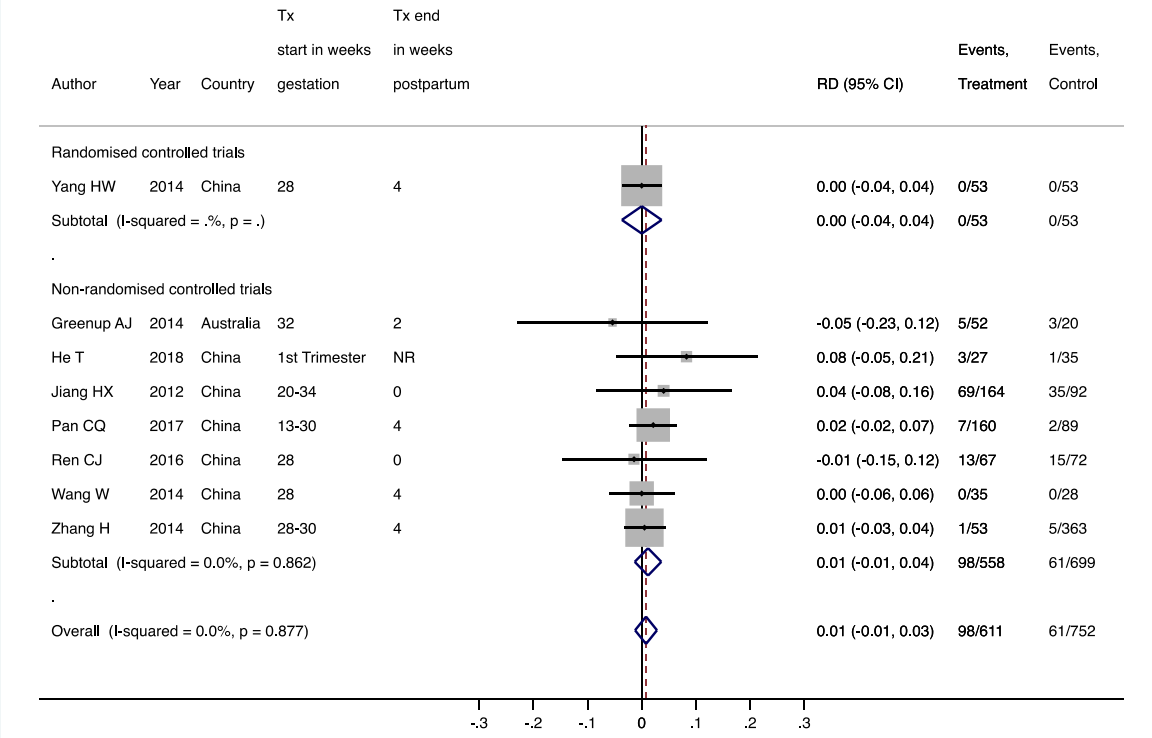


## Appendix U: Maternal safety 2. Postpartum hemorrhage

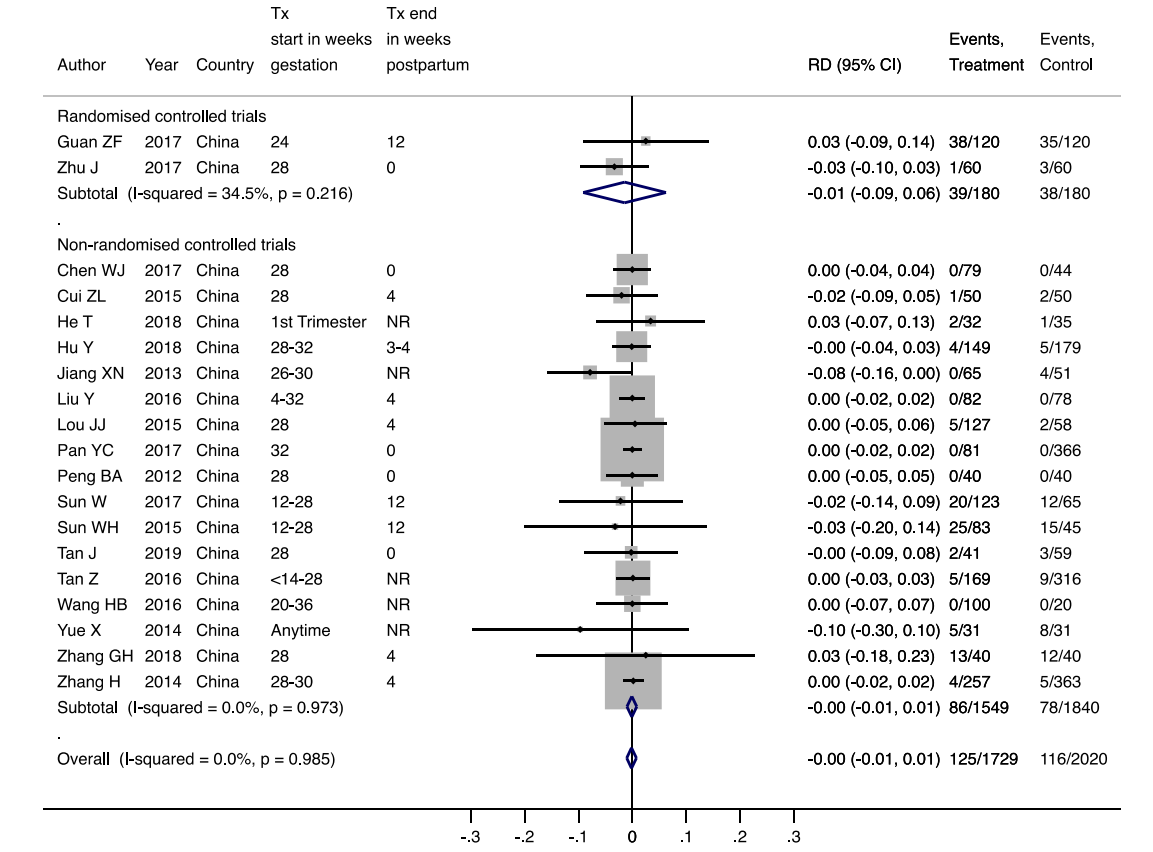
- **TDF 300 mg risk difference for postpartum hemorrhage**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.02 – 0.02).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%



- **LAM 100-150 mg risk difference for postpartum hemorrhage**
  - Weighted pooled risk difference: 0.01 (95%CI: -0.01 – 0.03).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = not enough studies
    - $I^2$ statistic non-RCTs = 0.0%



- **LdT 600 mg risk difference for postpartum hemorrhage**
  - Weighted pooled risk difference: -0.001 (95%CI: -0.01 – 0.01).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = not enough studies
    - $I^2$ statistic non-RCTs = 0.0%



## Appendix V: Maternal safety 3. Postpartum hepatitis flare

- **Table: Summary of postpartum hepatitis flare after discontinuation of PAP in treated group, and during the comparable period for control group**

| Study | Definition of flare | Timing of PAP discontinu-ation in treated group | Results | Included in meta-analysis | Any very severe case (decompen-sation, death)? | Clinical course of flare cases |
|---|---|---|---|---|---|---|
| **TDF** | | | | | | |
| Celen MK, 2013 | None given (until 4 weeks postpartum) | 4 weeks | No hepatic flare was observed in treated group until 4 weeks postpartum. No data reported for control group. | No (no control) | Unknown (not mentioned) | Unknown (not mentioned) |
| Chen HL, 2015 | ALT >5 x ULN (evaluated at 1, 2, 4, and 6 months postpartum) | 4 weeks | At 2 months postpartum (1 month after discontinuation) 1/62 in treated group and 8/56 in control group. | Yes | No case of hepatic decompensation | Unknown (not mentioned) |
| Chen WJ, 2017 | Hepatic insufficiency (no time-point specified) | At delivery | 0/30 in treated, 0/44 in control | No (no time-point specified) | No hepatic insufficiency | N/A |
| Greenup AJ, 2014 (& Nguyen | Moderate: ALT ≥5 x ULN (i.e. ≥95 U/L) (within 24 weeks postpartum). | 12 weeks | In Greenup, vague saying no correlation with flare. In Nguyen (subset n=43) it states 17/43 in treated group | Yes | No case of hepatic decompen-sation | 8/15 in treated and 3/4 in control group spontaneously |

| | | | | | | |
|---|---|---|---|---|---|---|
| V, 2014)* | Severe: ALT ≥20 x ULN (i.e. ≥380 U/L) (within 24 weeks postpartum) | | and 4/14 in control group had post-partum flare. Severe flare was observed 2/17 in treated group and 2/4 in control group. | | | resolved. 6/15 in treated and 1/4 in control group resolved with antiviral therapy. |
| Jourdain G, 2018 | ALT >300 IU/L (after the discontinuation of PAP) | 8 weeks | 9/154 in treated, 5/157 in control | Yes | No symptomatic case | No women started or restarted TDF after flares that occurred within 6 months postpartum. |
| Lin Y, 2018 | ALT >5 x ULN (no time-point specified) | 4 weeks | 2/60 in treated, 0/52 in control | No (no time-point specified) | Unknown (not mentioned) | Unknown (not mentioned) |
| Pan CQ, 2016 | Severe: ALT 5-10 x ULN (no time-point specified). Serious: ALT >10 x ULN (after child delivery until 28 weeks postpartum). | 4 weeks | 5 severe and 1 serious = 6 total (6/97 in treated group); 6 severe and 3 serious = 9 total (9/100 in the control group). It is unclear whether "severe" flare included only those occurred postpartum or throughout the study period. We therefore used "serious flare" in the meta-analysis. | Yes | No case of hepatic decompen-sation | All cases of serious flare (1 in treated and 3 in control group) normalized their ALT levels after restarting/starting antiviral therapy. |
| Wakano Y, 2018 | Elevation of ALT (no time-point specified) | 4-8 weeks | No ALT elevation was observed in treated group. No data reported for control group. | No (no control) | Unknown (not mentioned) | Unknown (not mentioned) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Zhou Y, 2018 | Impairment of liver function (during treatment) | At delivery | 0/60 in treated group. No data reported for control group | No (no control) | No | N/A |
| **LAM** | | | | | | |
| Cheng YC, 2011 | None given (after discontinuation of treatment) | 4 weeks | 7/30 in treated group, 5/26 in control group Note: in these cases there was elevation of ALT levels during treatment, but still <10×ULN | Yes | Unknown (not mentioned) | Resolved after restarting/ starting antiviral therapy. |
| Ge YL, 2015 | Abnormality for liver function (during treatment) | 3 months | 0/16 in treated group. No data reported for control group. | No (no control) | No | N/A |
| Greenup AJ, 2014 (& Nguyen V, 2014)** | Moderate: ALT ≥5 x ULN (i.e. ≥95 U/L) (within 24 weeks postpartum). Severe: ALT ≥20 x ULN (i.e. ≥380 U/L) (within 24 weeks postpartum) | 2 weeks | In the paper from Greenup et al., which had the full cohort, it was stated that there were 'no differences' in flare between the treated and non-treated group. In a subset presented in Nguyen et al., 22/44 in treated group and 4/14 in control group had postpartum flare. | Yes | Unknown (not mentioned) | 15/20 in treated and 3/4 in control group spontaneously resolved. 5/20 in treated and 1/4 in control group resolved with antiviral therapy. |
| He T, 2018 | ALT >2 x baseline (after child delivery) | All women continued treatment after child delivery, stop time not | 0/27 in treated, 6/35 in control. However, all women in treated group continued antiviral therapy after child delivery, so this is not used for the meta-analysis of flare. | No (treatment continued) | Unknown (not mentioned) | All flare cases spontaneously resolved without antiviral therapy. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | mentioned. | | | | |
| Jackson V, 2015 | ALT >3 x ULN (postpartum following discontinuation of PAP) | At delivery | 5/26 in treated.<br>No data reported for control group. | No (no control) | Unknown (not mentioned) | Unknown (not mentioned) |
| Pan CQ, 2017 | ALT >10 x ULN or >5 x baseline (after child delivery) | 4 weeks | 1/147 in treated, 5/89 in control.<br>13 mothers in treated group who continued treatment beyond postpartum week 4 were excluded from this analysis. | Yes | No case of hepatic decompen-sation | One flare case in treated group improved ALT level without antiviral therapy. Five flare cases in control all started antiviral therapy. |
| Ren YJ, 2011 | Impairment of liver function (before and after delivery) | At delivery | 0/30 in treated group.<br>No data reported for control group. | No (no control) | No | N/A |
| Wakano Y, 2018 | Elevation of ALT (no time-point specified) | 4-8 weeks | No ALT elevation was observed in treated group.<br>No data reported for control group. | No (no control) | Unknown (not mentioned) | Unknown (not mentioned) |
| Wang DM, 2016 | None given | 12 weeks | 1/42 in treated group.<br>No data reported for control group.<br>Note: in this one case there was elevation of ALT levels during treatment, but still <5×ULN | No (no control) | Unknown (not mentioned) | Transient, resolved spontaneously |
| Wang | Abnormality for | At delivery | 0/30 in treated, 0/30 in | No (no | No | N/A |

| | | | | | | |
|---|---|---|---|---|---|---|
| TM, 2005 | liver function (no time-point specified) | | control. | time-point specified) | | |
| Wang W, 2014 | Impairment of liver function (no time-point specified) | 4 weeks | 0/35 in treated, 0/28 in control. | No (no time-point specified) | No | N/A |
| Xu WM, 2009 | ALT >3 x ULN (from postpartum week 4 to week 12) | 4 weeks | 16/83 in treated, 15/46 in control | Yes | No case of ALT elevations in association with signs of hepatic insufficiency | Unknown (not mentioned) |
| Yang HW, 2014 | Impairment of liver function (no time-point specified) | 4 weeks | 0/53 in treated, 0/53 in control. | No (no time-point specified) | No | N/A |
| Zeng YM, 2013 | Elevated ALT and AST outside of the normal range (>50 U/L) (after child delivery) | At delivery, 4 weeks and 6 weeks | In treated group:<br>I. discontinuation at delivery: 4/30 (1, 2 and 1 case at 1, 3 and 6 months after discontinuation, respectively);<br>II. discontinuation at 4 weeks: 4/30 (1 and 3 cases at 1 and 3 months after discontinuation, | Yes | No case of ALT elevation with jaundice; No case of severe hepatitis | Unknown (not mentioned) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | respectively);<br>III. discontinuation at 6 weeks: 5/30, (2 and 3 cases at 1 and 3 months after discontinuation, respectively)<br>In control group: 5/30: (2 cases at 3 months after delivery, 3 cases at 6 months after delivery) | | | |
| Zhang H, 2014 | ALT >10 x ULN or >5 x baseline (from postpartum week 4 to week 52) | 4 weeks | 0/53 in treated, 0/363 in control | Yes | No case of hepatic decompen-sation | N/A |
| Zhu M, 2014 | Aggravation of liver function impairment (during pregnancy) | At delivery | 0/24 in treated, 1/25 in control | No (not post-partum) | Unknown (not mentioned) | Unknown (not mentioned) |
| **LdT** | | | | | | |
| Chen CY, 2015 | None given (no time-point specified) | Treatment continued after delivery, unless discontin-uation criteria met. Disaggregated numbers not | 1/41 in control group (severe hepatitis at 28 weeks of gestation). No data reported for treated group. | No (no data for treated group) | Unknown (not mentioned) | Unknown (not mentioned) (receiving treatment thereafter and dropping out) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | available. | | | | |
| Chen WJ, 2017 | Hepatic insufficiency (no time-point specified) | At delivery | 0/79 in treated, 0/44 in control | No (no time-point specified) | No hepatic insufficiency | N/A |
| Chen QR, 2018 | ALT elevation (during pregnancy) | 4 weeks | 1/29 in treated, 1/28 in control | No (not post-partum) | Unknown (not mentioned) | Both cases resolved spontaneously |
| Deng Y, 2015 | Obvious abnormality for liver biochemical indicators (during treatment) | 1 month | 0/82 in treated group. No data reported for control group. | No (no control) | No | N/A |
| Ding XP, 2018 | Impairment of liver function (during intervention) | 1 month | 0/38 in treated, 0/38 in control | No (no time-point specified) | No | N/A |
| Ge YL, 2015 | Obvious abnormality for liver function (during treatment) | 3 months | 0/20 in treated group. No data reported for control group. | No (no control) | No | N/A |
| Fan LY, 2013 | Severe impairment of liver function (after PAP discontinuation) | At least 6 months (9 in 60 pregnant women discontinued treatment 1 month after delivery) | 0/9 pregnant women who discontinued antiviral treatment at 1 month after delivery. No data reported for control group. | No (no control data) | No | N/A |
| Han GR, | Flare: ALT >5 x | Variable | In treated group: 3/236 | No (no | No | 6 of 46 with any |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2015 | ULN (after discontinuation of PAP). Severe: ALT >10 x ULN (after discontinuation of PAP). | (236 stopped at 4 weeks and 126 continued after 4 weeks) | had >5 x ULN, 0/236 with >10 x ULN. 126 mothers in treated group who continued treatment beyond postpartum week 4 were excluded from above. No data reported for control group. | control) | | ALT elevation had clinical therapies to reduce ALT levels and by 7-12 months post-partum, ALT of all mothers had returned to normal. |
| He T, 2018 | ALT > 2 x baseline (after child delivery) | All women continued treatment after child delivery. | 0/32 in treated, 6/35 in control. However, all women in treated group continued antiviral therapy after child delivery, so this is not used for the meta-analysis of flare. | No (treatment continued) | Unknown (not mentioned) | All flare cases spontaneously resolved without antiviral therapy. |
| Hu Y, 2018 | ALT > 40 U/L (by the 7-14 months postpartum) | 3-4 weeks | 22/103 in treated, 25/124 in control | Yes | No case of elevated bilirubin or fulminant hepatitis. | ALT normalized within 2-4 weeks. |
| Jiang S, 2017 | Abnormal liver function (no time-point specified) | None given | 0/44 in treated group. No data reported for control group. | No (no control) | No | N/A |
| Jiang XN, 2013 | Abnormal ALT (7 months after delivery) | All women continued treatment | 0/65 in treated, 4/51 in control. | No (treatment | 3/51 in control group | Unknown (not mentioned) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | after child delivery | | continued ) | progressed to severe hepatitis before delivery; 2/51 in control group developed ascites and liver cirrhosis at 7 months after delivery | |
| Li N, 2016 | None given (no time-point specified) | Not specified/ clarified | 1/35 in treated group a (re-bounce of ALT, breakthrough during treatment, due to antiviral resistance)<br>2/30 in treated group b (in one case, ALT elevated to 416 U/L during treatment and then declined gradually to 102 U/L at delivery; in the other case, ALT elevated to 336 U/L during treatment and then declined to 86 U/L at delivery)<br>No data reported for | No (no control) | Unknown (not mentioned) | Transient for both cases in treated group b (treatment starting from 28 weeks of gestation); Unknown (not mentioned) for the case in treated group a (treatment starting before pregnancy) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | control group. | | | |
| Li YH, 2017 | ALT elevation (no time-point specified) | Approximately 36 weeks postpartum (treatment started at 28 weeks gestation and went for 48 weeks) | 1/30 in treated group. No data reported for control group. Mild elevation of ALT levels at 34 weeks of gestation, ALT<5×ULN | No (no control) | Unknown (not mentioned) | Transient, resolved spontaneously without liver protecting drugs |
| Liu J, 2017 | Elevation in ALT levels (1 month and 6 months postpartum) | Treatment continued after delivery, unless discontinuation criteria met (disaggregated numbers not available) | 2/102 in treated, 1/28 in control at 1 month after delivery. 4/102 in treated, 1/28 in control at 6 months after delivery. | No (some continued treatment) | Unknown (not mentioned) | Unknown (not mentioned) |
| Liu XB, 2016 | Abnormality for liver biochemical indicators (during treatment) | 1 month | 0/20 in treated group. No data reported for control group. | No (no control) | No | N/A |
| Liu Y, 2016 | ALT ≥2 x ULN (from discontinuation of PAP to postpartum | 4 weeks | 5/71 in treated, 1/78 in control. 11 mothers in treated group who continued | Yes | No case of ALT >8 x ULN. | Four flare cases in treated group restarted antiviral (entecavir). |

| | | | | | | |
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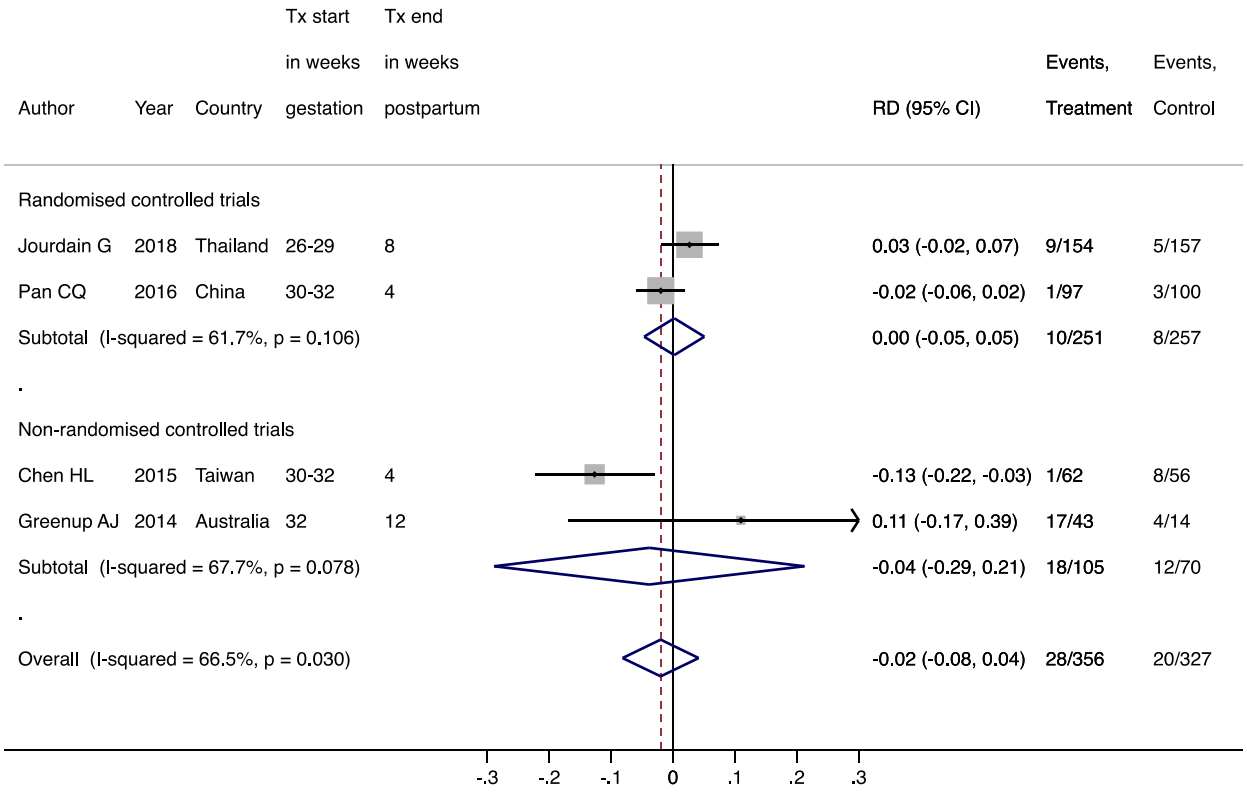
| | week 51) | | treatment beyond postpartum week 4 were excluded from this analysis. | | | |
| Lou JJ, 2015 | ALT between 2×ULN and 5×ULN (no time-point specified) | 30 days | 2/127 in treated group. No data reported for control group. | No (no control) | Unknown (not mentioned) | Active hepatitis, without obvious symptoms, stable after antiviral treatment with NA |
| Lu QY, 2016 | Impairment of liver function (during and after treatment) | At delivery | 0/152 in treated group. No data reported for control group. | No (no control) | No | N/A |
| Pan YC, 2017 | High ALT levels (after child delivery) | At delivery | 3/22 in treated group at 7 months after delivery. No data reported for control group. | No (no control) | Unknown (not mentioned) | All cases resolved spontaneously at 1 year after delivery |
| Peng BA, 2012 | Abnormal liver function (no time-point specified) | At delivery | 0/40 in treated group. No data reported for control group. | No (no control) | No | N/A |
| Qiu B, 2016 | Abnormality for liver function indicators (until 48 weeks after discontinuation) | At delivery | 0/120 in treated group (60 starting treatment before pregnancy and 60 starting treatment at 24 weeks of gestation). No data reported for control group. | No (no control) | No | N/A |
| Sheng Q, 2018a | ALT ≥2 x ULN (after | At delivery | 3/87 in treated. 4 mothers in treated | No (no control) | No case of hepatic | All flare cases in treated group |

| | | | | | | |
|---|---|---|---|---|---|---|
| | discontinuation of PAP) | | group who continued treatment after child delivery were excluded from the analysis. No data reported for control group. | | decompen-sation | restarted antiviral and resolved. |
| Shi QW, 2017 | Elevation in ALT levels (during treatment) | At delivery | 3/100 in treated group. No data reported for control group. | No (no control) | Unknown (not mentioned) | Resolved spontaneously 1-2 weeks after discontinuation |
| Tian JH, 2018 | Unstable liver function (during treatment) | At least 1 month | 0/135 in treated group. No data reported for control group. | No (no control) | No | N/A |
| Wang EJ, 2012 | ALT elevation (no time-point specified) | 4 weeks | 1/28 in treated, 1/27 in control. Mild elevation of ALT levels (ALT<5×ULN) | No (no time-point specified) | Unknown (not mentioned) | Transient, resolved spontaneously without use of liver protecting drugs |
| Wang WP, 2012 | ALT elevation (no time-point specified) | At delivery | 5/47 in treated group. No data reported for control group. | No (no control) | Unknown (not mentioned) | Resolved after liver protecting treatment |
| Yao LF, 2014 | ALT elevation (during pregnancy) | 6 weeks | 7/30 in treated group. No data reported for control group. | No (no control group) | Unknown (not mentioned) | Resolved spontaneously without interventions, back to normal levels before delivery |
| Zhang H, 2014 | Severe: ALT >10 x ULN or 5 x baseline (from postpartum week 4 to week 52) | 4 weeks | 0/257 in treated, 0/363 in control | Yes | No case of hepatic decompen-sation | N/A |

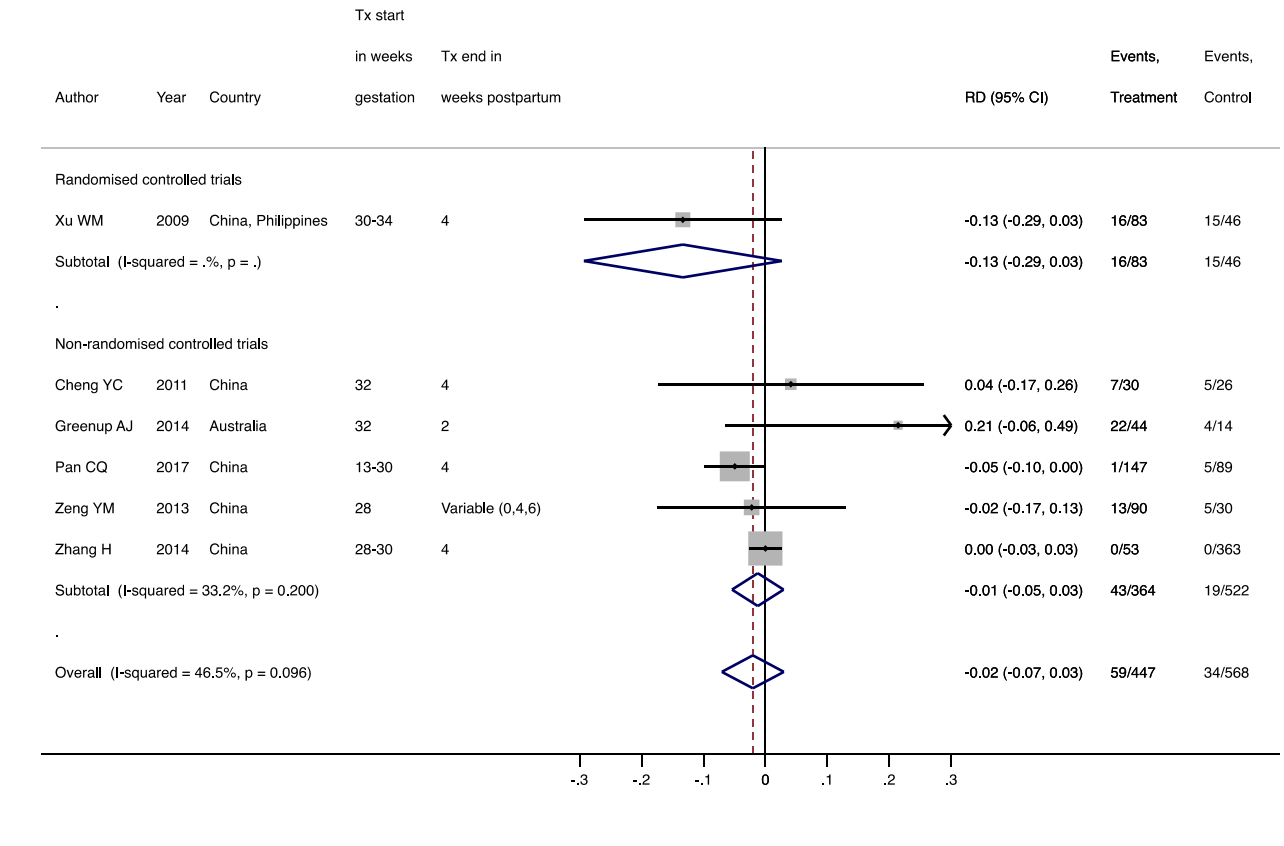
| | | | | | | |
|---|---|---|---|---|---|---|
| Zhou YJ, 2014 | Abnormal liver biochemical indicators (17 weeks of gestation) | Treatment continued after delivery, unless discontinuation criteria met (disaggregated numbers not available) | 5/39 in control group. No data reported for treated group. | No (no data for treated group) | 1 case of death (this woman received treatment from 17 weeks to delivery, she died of large hemorrhage (unspecified type) at delivery) | 4 cases stopped pregnancy; 1 case of death (continuing pregnancy and receiving treatment from 17 weeks to delivery, die of massive hemorrhage at delivery) |

* In Nguyen V, 2014, 12% (5/43) in the intervention group received LAM.
** In Nguyen V, 2014, 18% (8/44) in the intervention group received TDF.

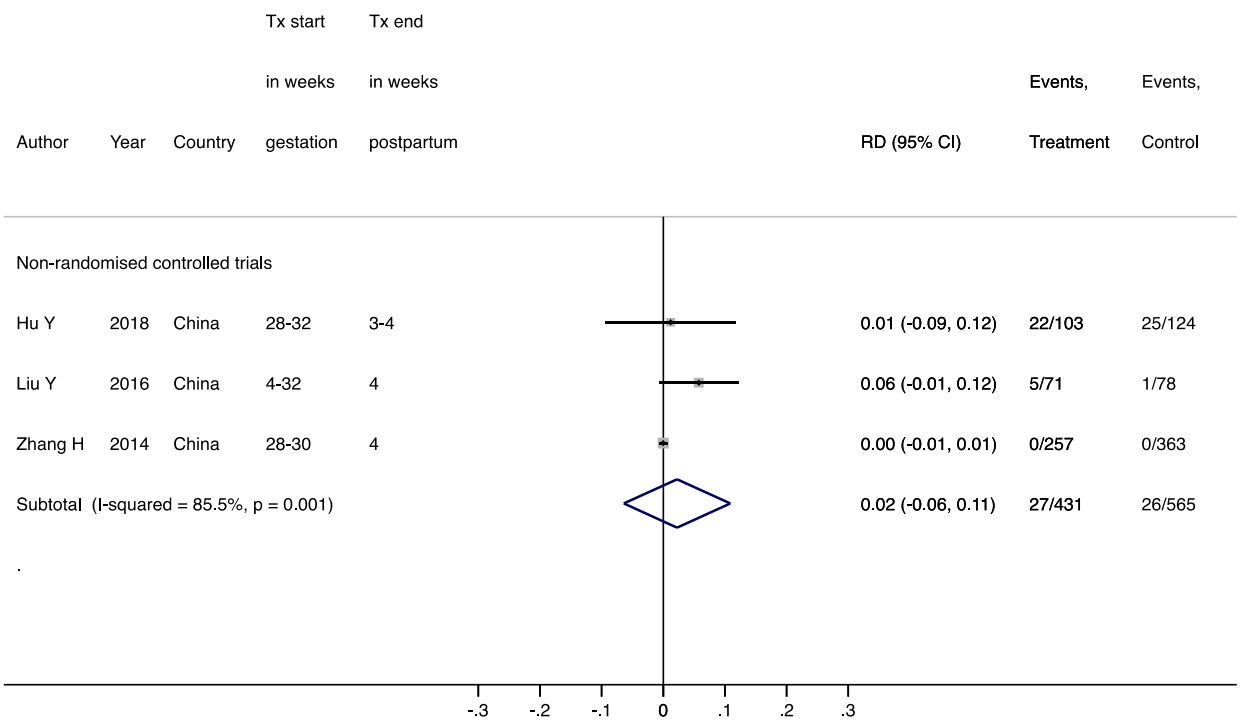
- **Figure: Forest plot for TDF 300 mg weighted risk difference of postpartum hepatitis flare after treatment discontinuation**



- **Figure: Forest plot for LAM 100-150 mg weighted risk difference of postpartum hepatitis flare after treatment discontinuation**

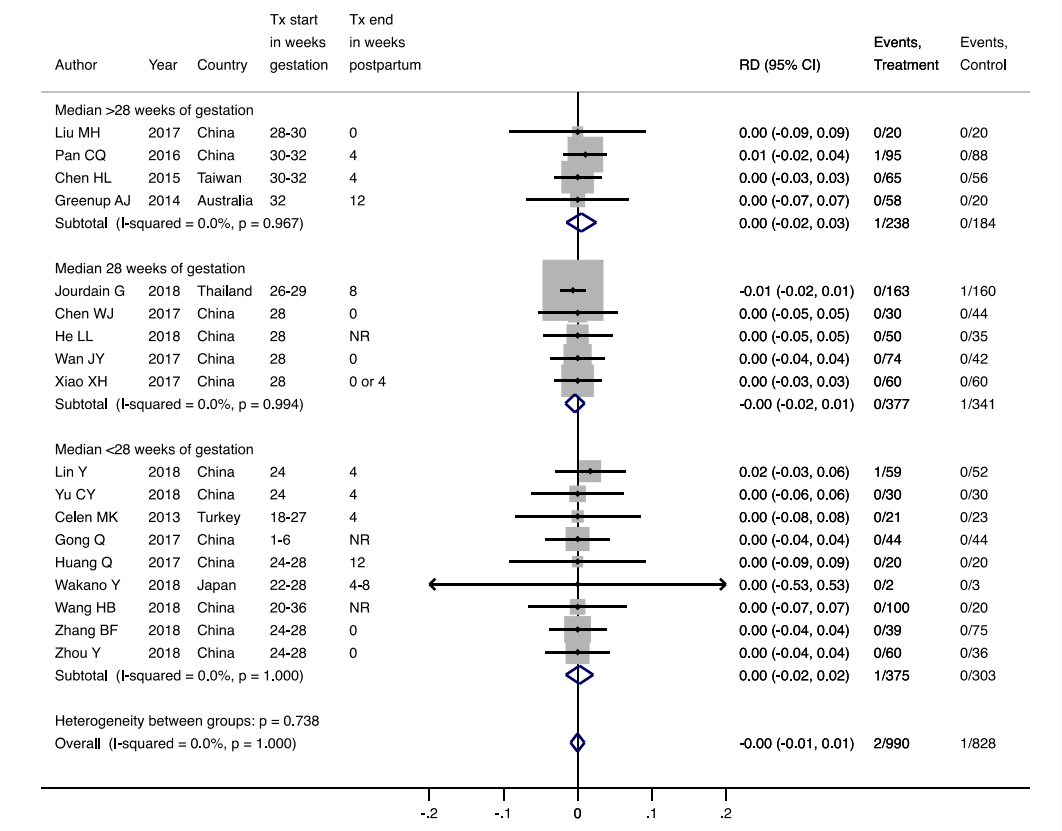


- **Figure: Forest plot for LdT 600 mg weighted risk difference of postpartum hepatitis flare after treatment discontinuation**

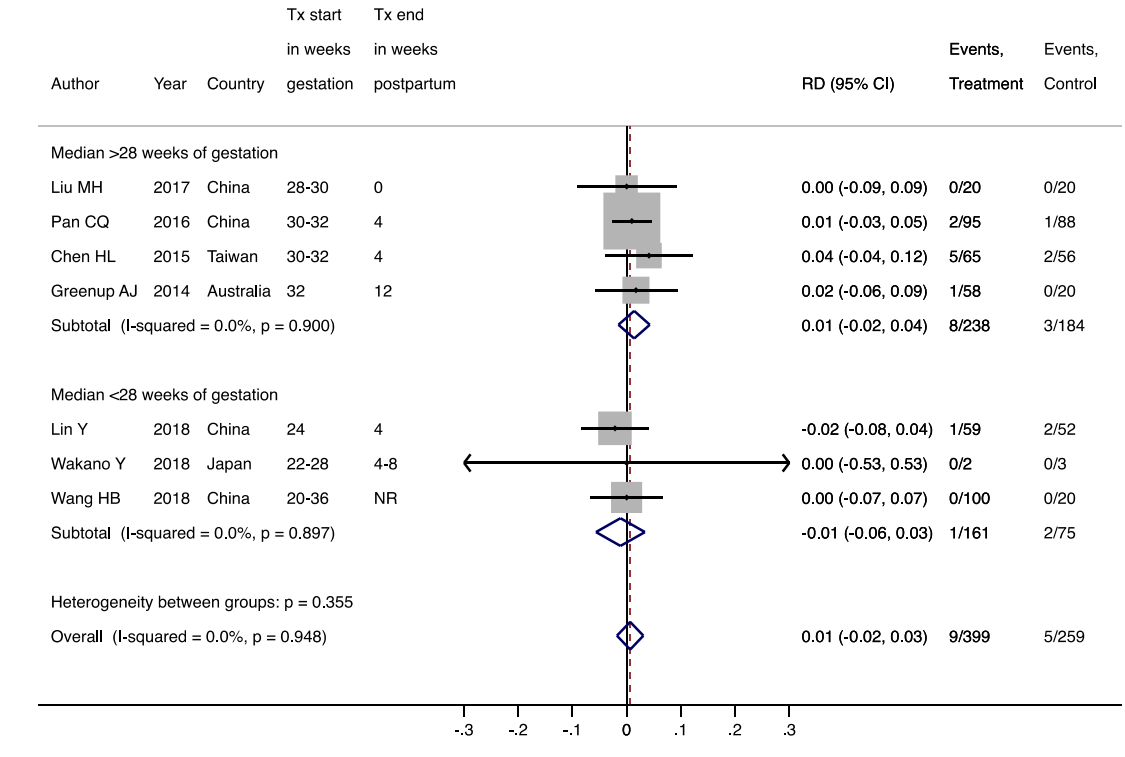


## Appendix W: Maternal and Infant Safety Subgroup Analysis

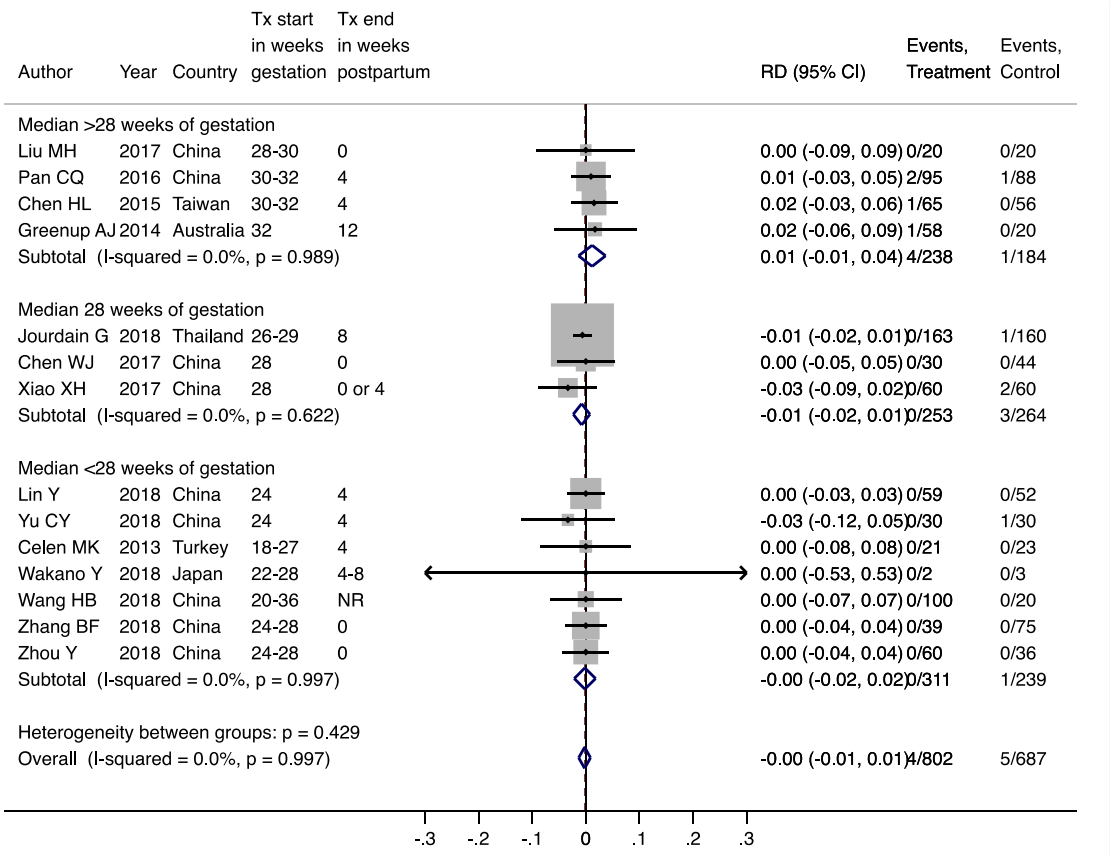
- **TDF 300 mg risk difference of neonatal death by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.738



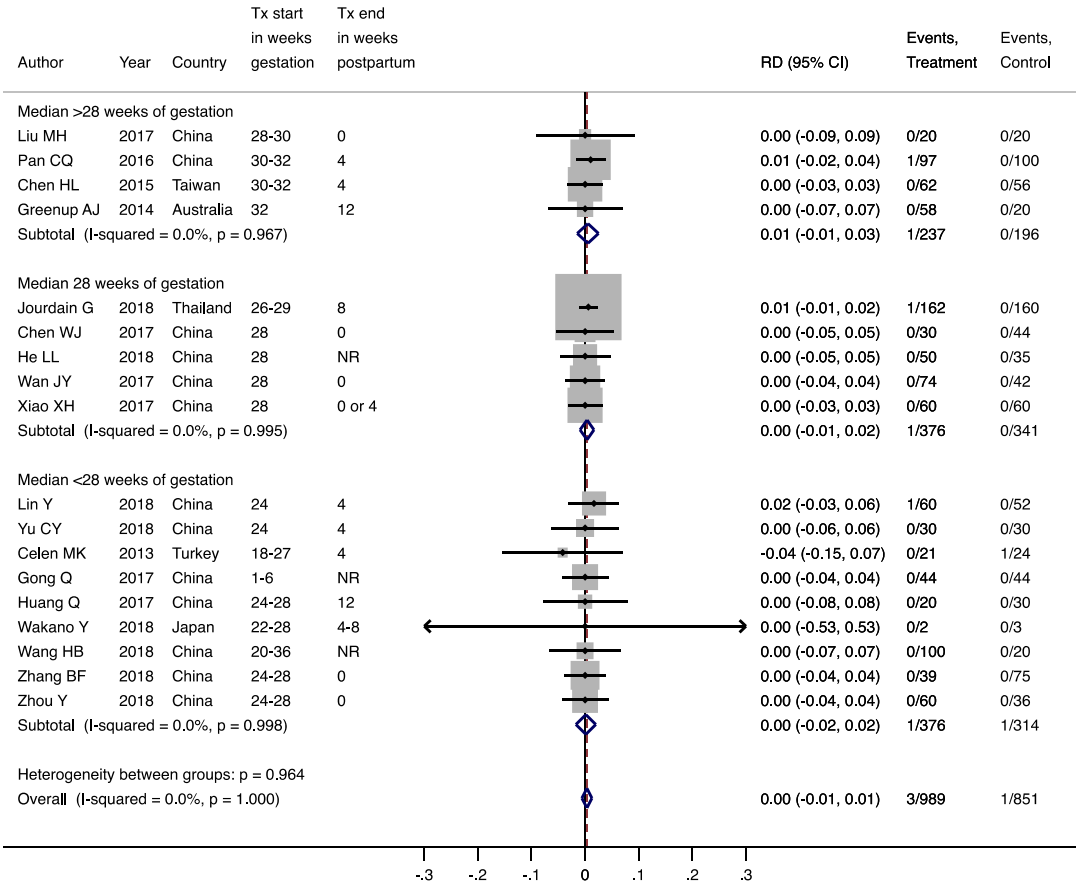
- **TDF 300 mg risk difference of preterm birth by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.355



- **TDF 300 mg risk difference of congenital abnormalities by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.429



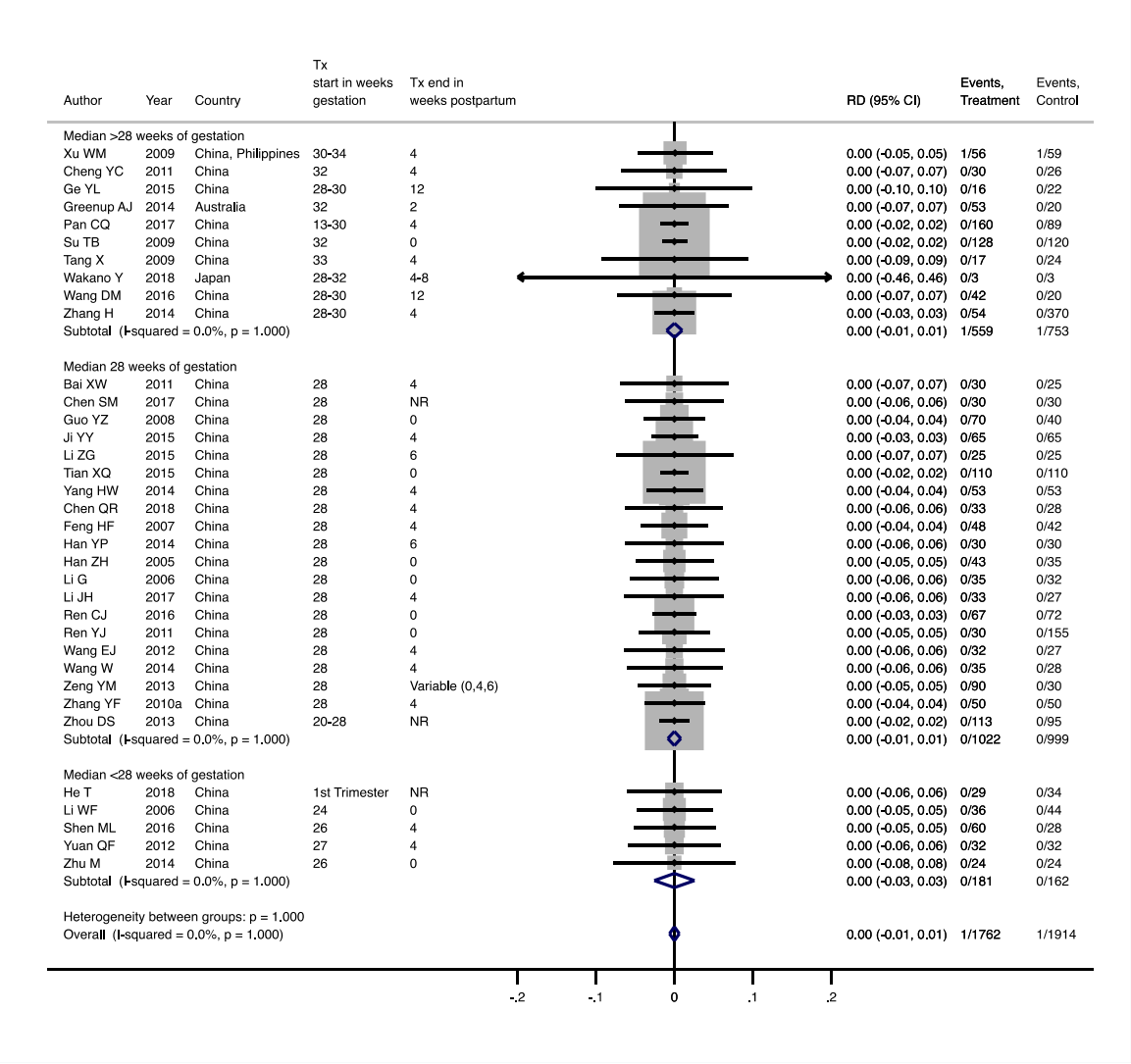
- **TDF 300 mg risk difference of foetal death by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.964



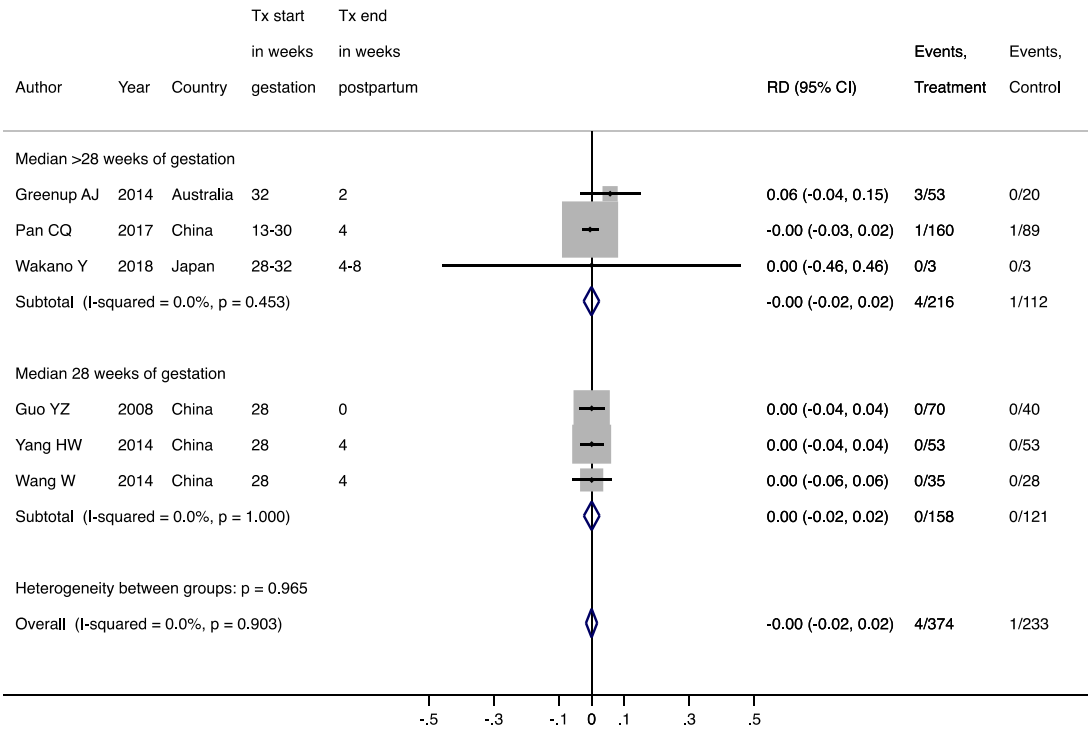

- **TDF 300 mg risk difference of postpartum hemorrhage by timing of treatment initiation**
    - Too few studies for subgroup analysis

- **TDF 300 mg risk difference of postpartum hepatitis flare by timing of treatment initiation**
    - Too few studies for subgroup analysis

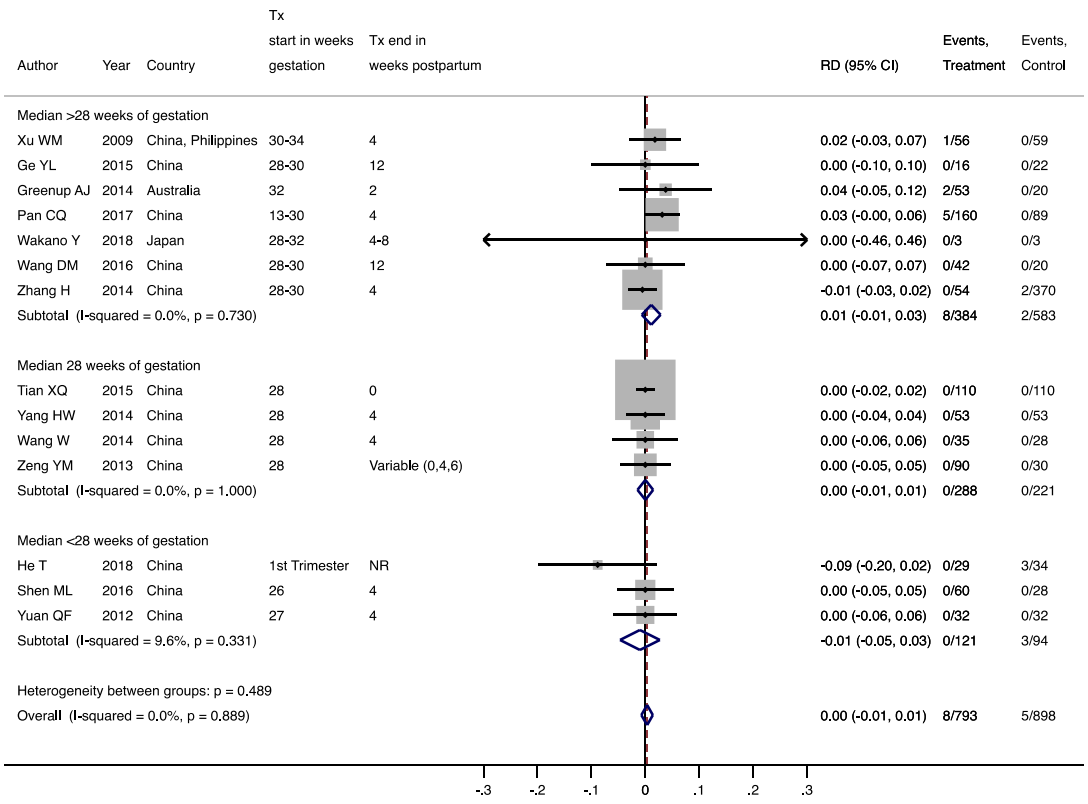
- **LAM 100-150 mg risk difference of neonatal death by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 1.000



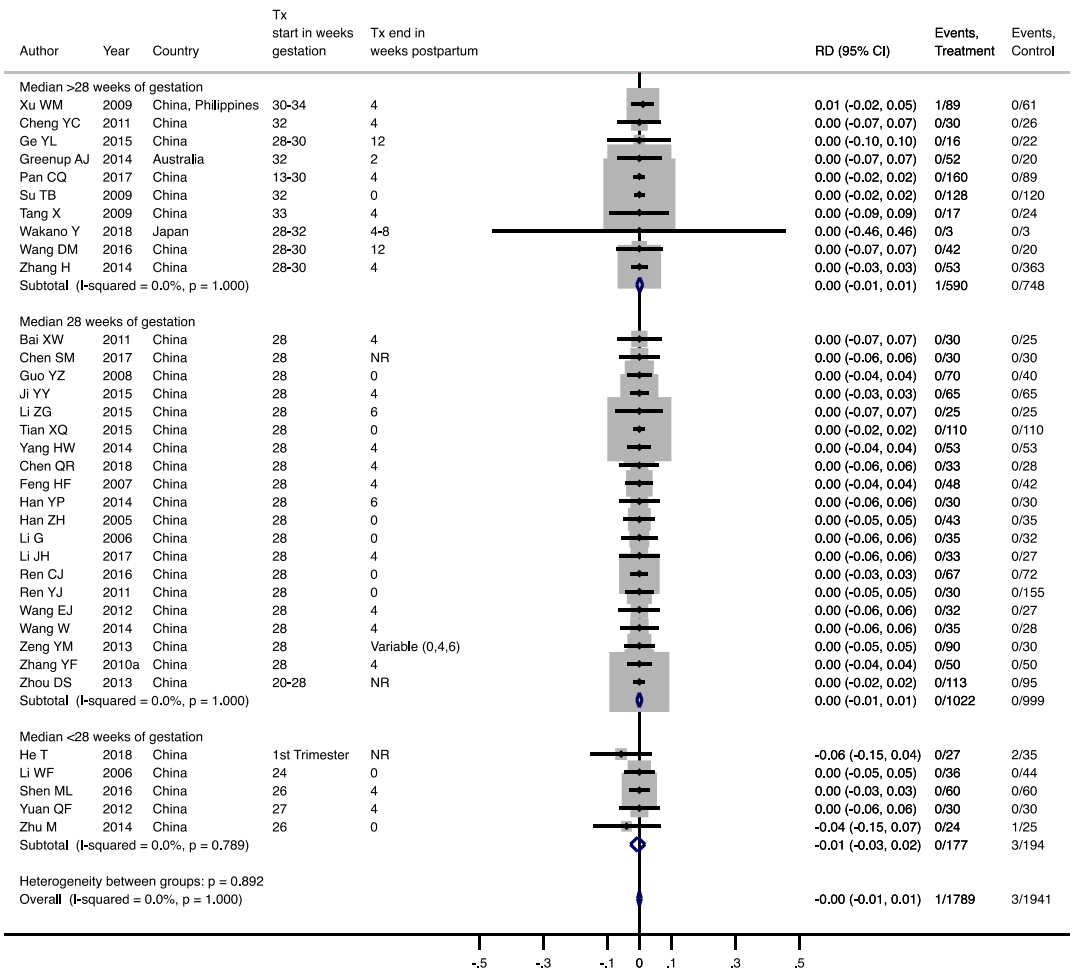
- **LAM 100-150 mg risk difference of preterm birth by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.965



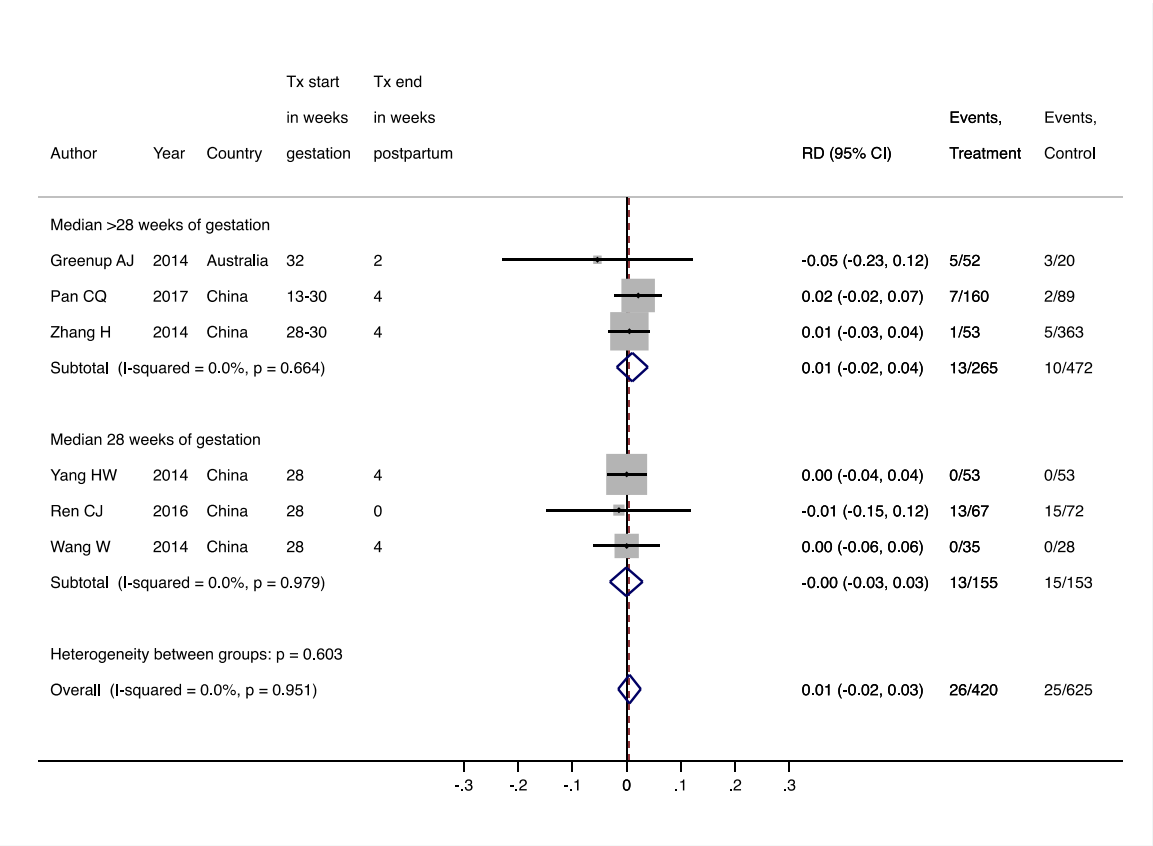
- **LAM 100-150 mg risk difference of congenital abnormalities by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.489



- **LAM 100-150 mg risk difference of foetal death by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.892

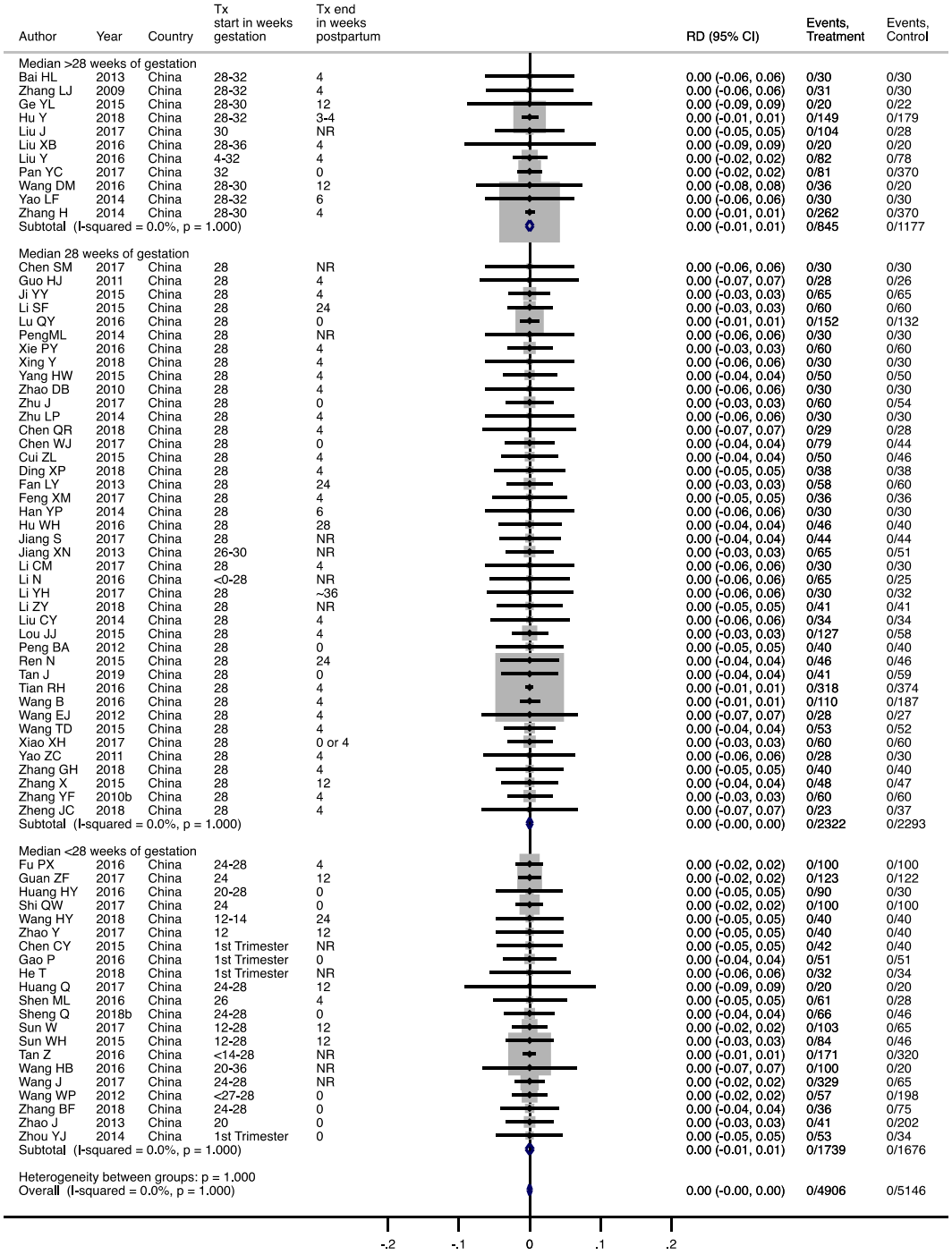


- **LAM 100-150 mg risk difference of postpartum hemorrhage by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.603

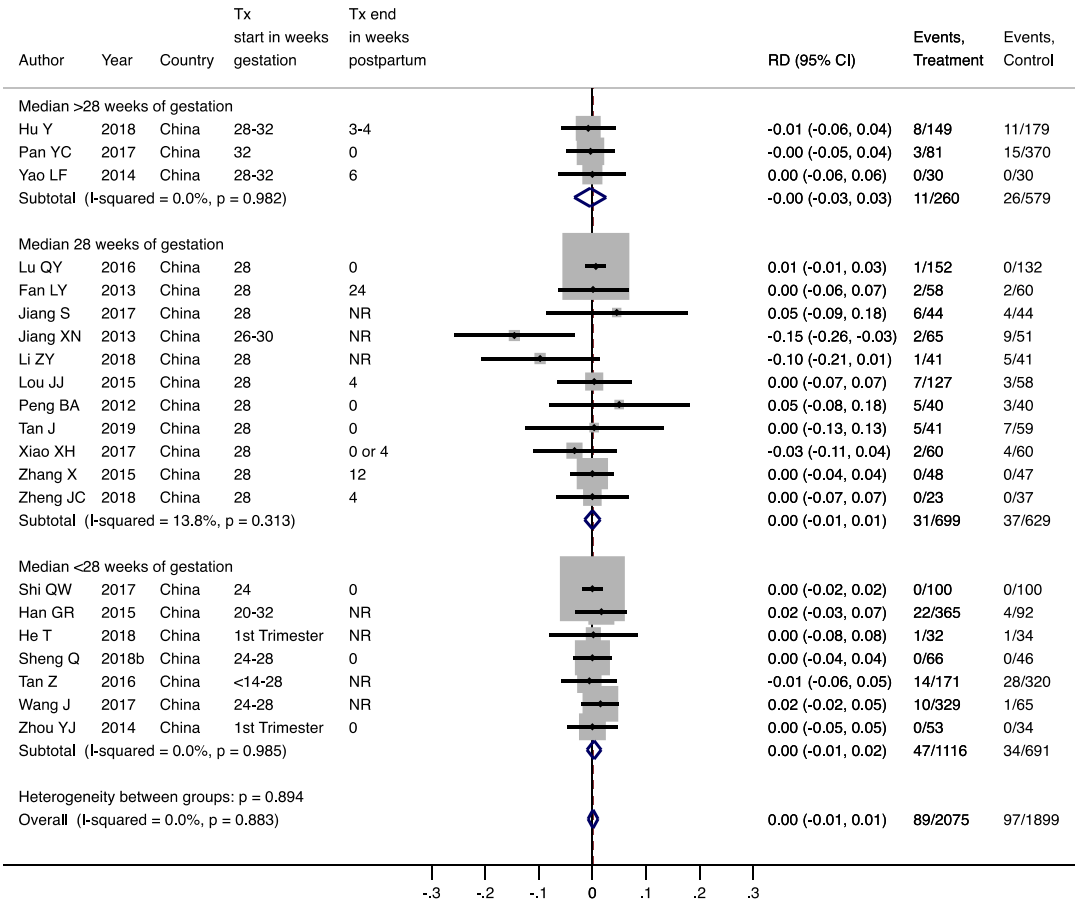



- **LAM 100-150 mg risk difference of postpartum flare by timing of treatment initiation**
    - Too few studies for subgroup analysis

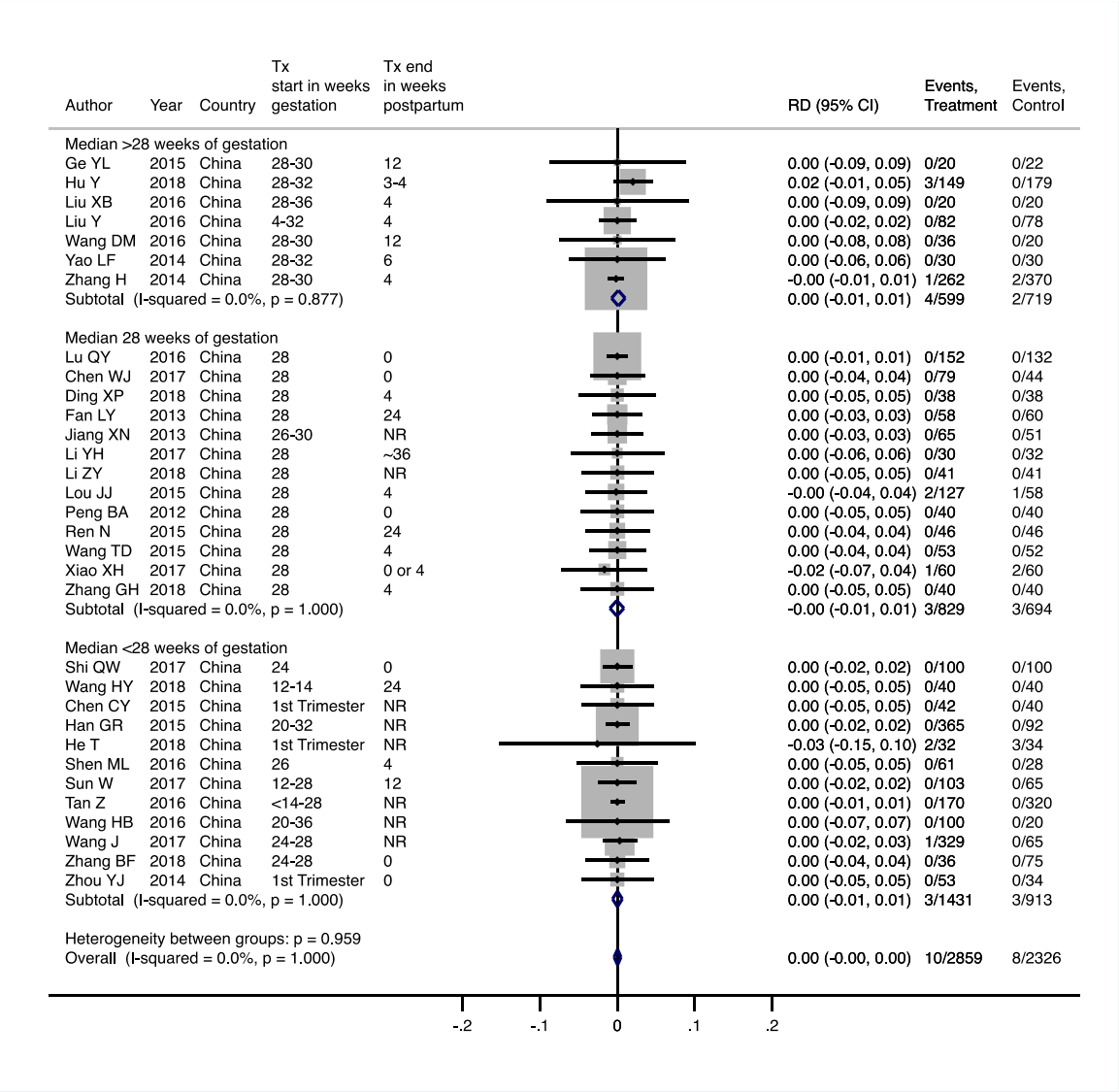
- **LdT 600 mg risk difference of neonatal death by timing of treatment initiation**
  - The p-value for heterogeneity between subgroups was 1.000



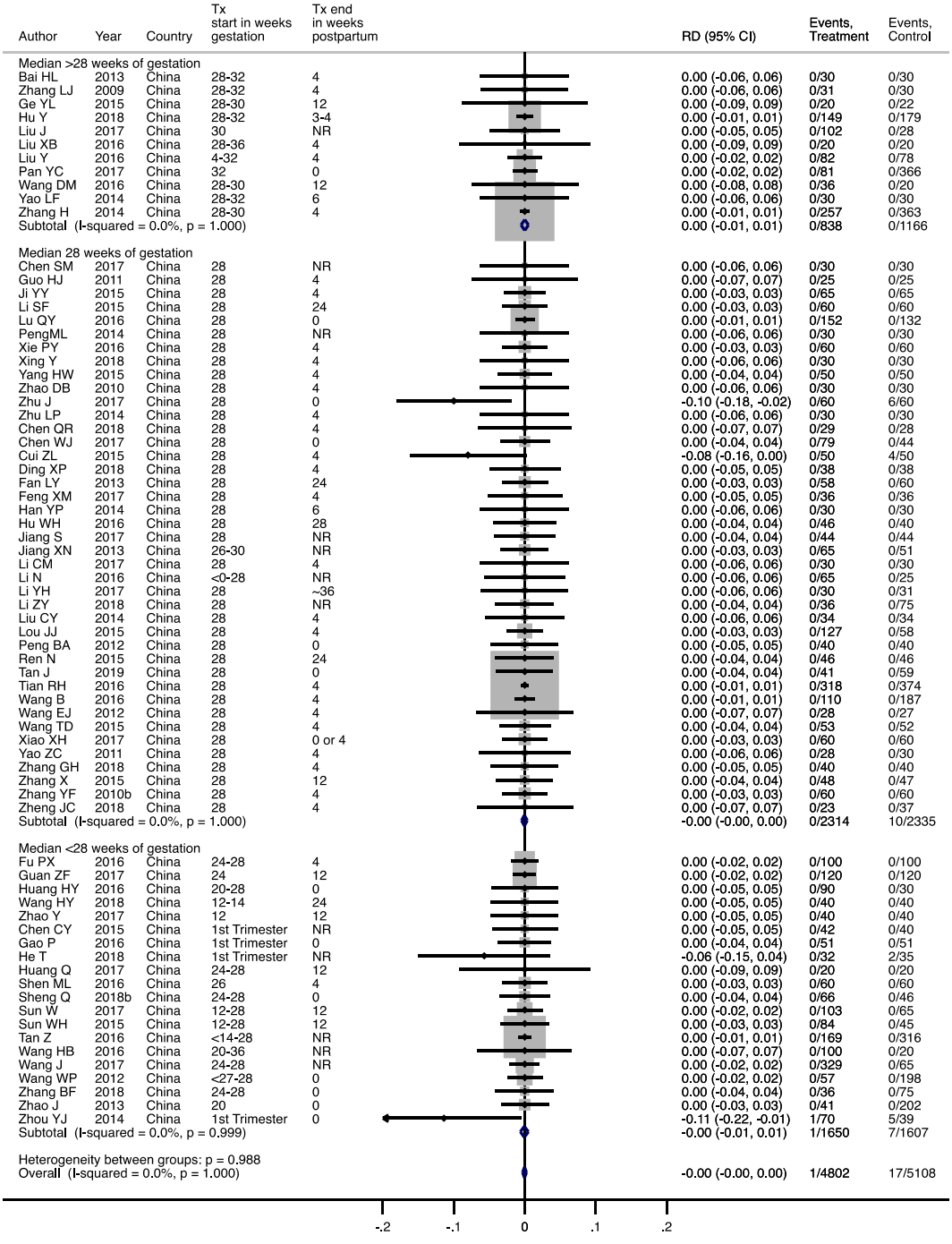
- **LdT 600 mg risk difference of preterm birth by timing of treatment initiation**
  - The p-value for heterogeneity between subgroups was 0.894



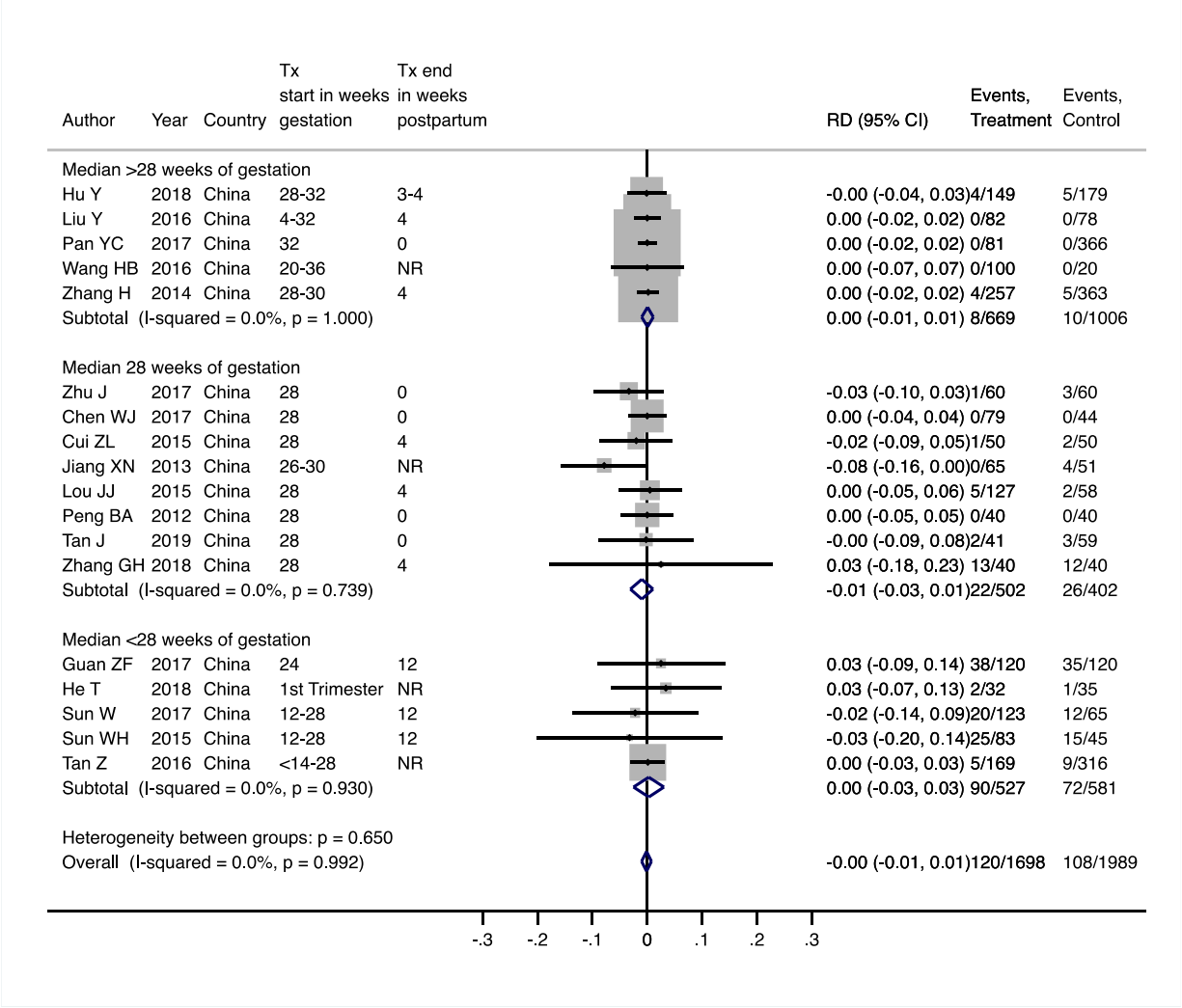
- **LdT 600 mg risk difference of congenital abnormalities by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.959



- **LdT 600 mg risk difference of foetal death by timing of treatment initiation**
  - The p-value for heterogeneity between subgroups was 0.988



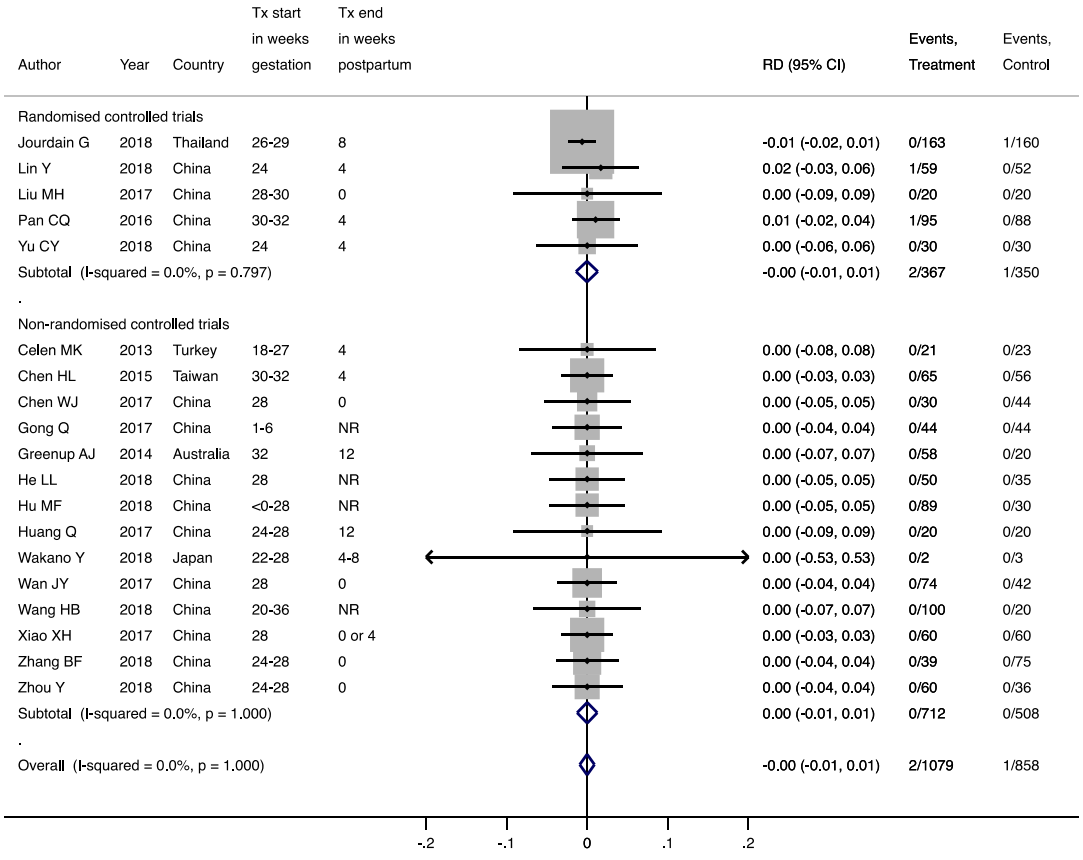
- **LdT 600 mg risk difference of postpartum hemorrhage by timing of treatment initiation**
    - The p-value for heterogeneity between subgroups was 0.650



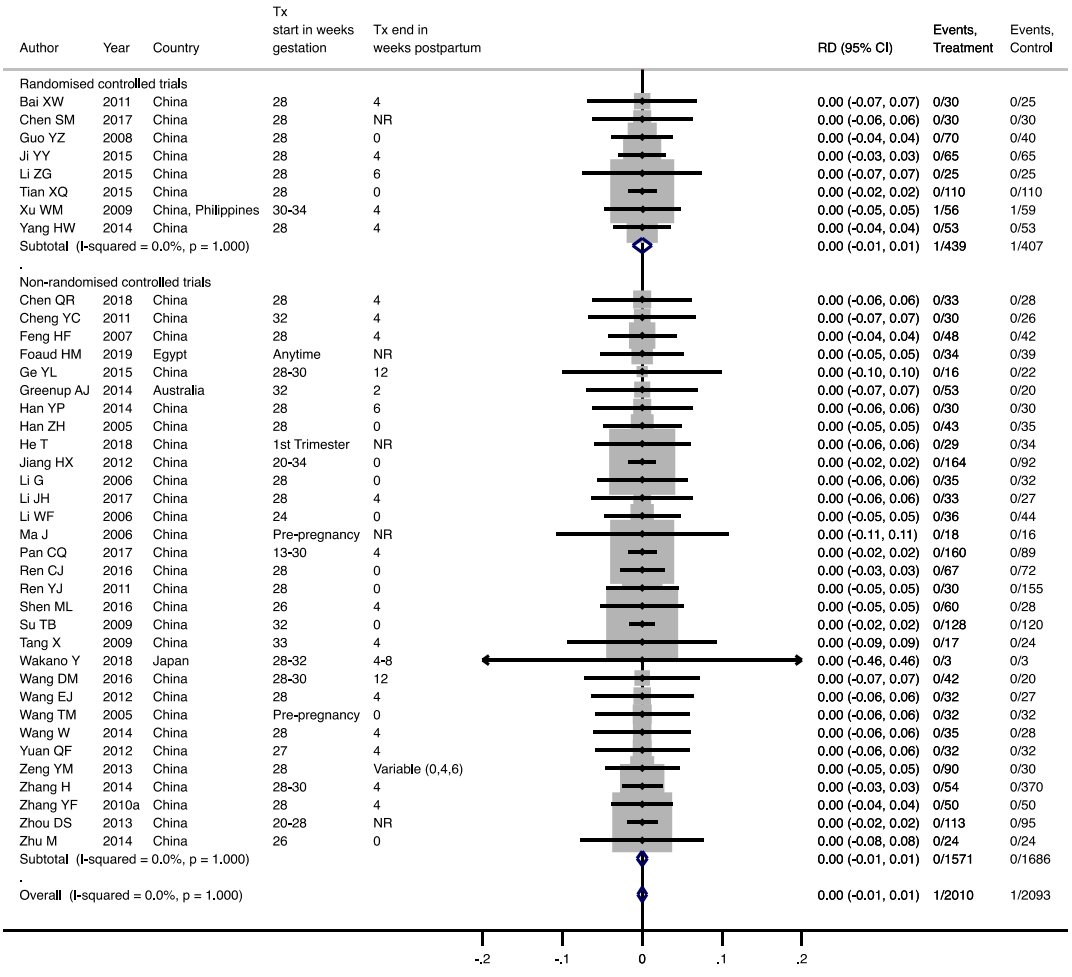

- **LdT 600 mg risk difference of postpartum flare by timing of treatment initiation**
    - Not enough studies for subgroup analysis

## Appendix X: Infant safety 1. Neonatal deaths

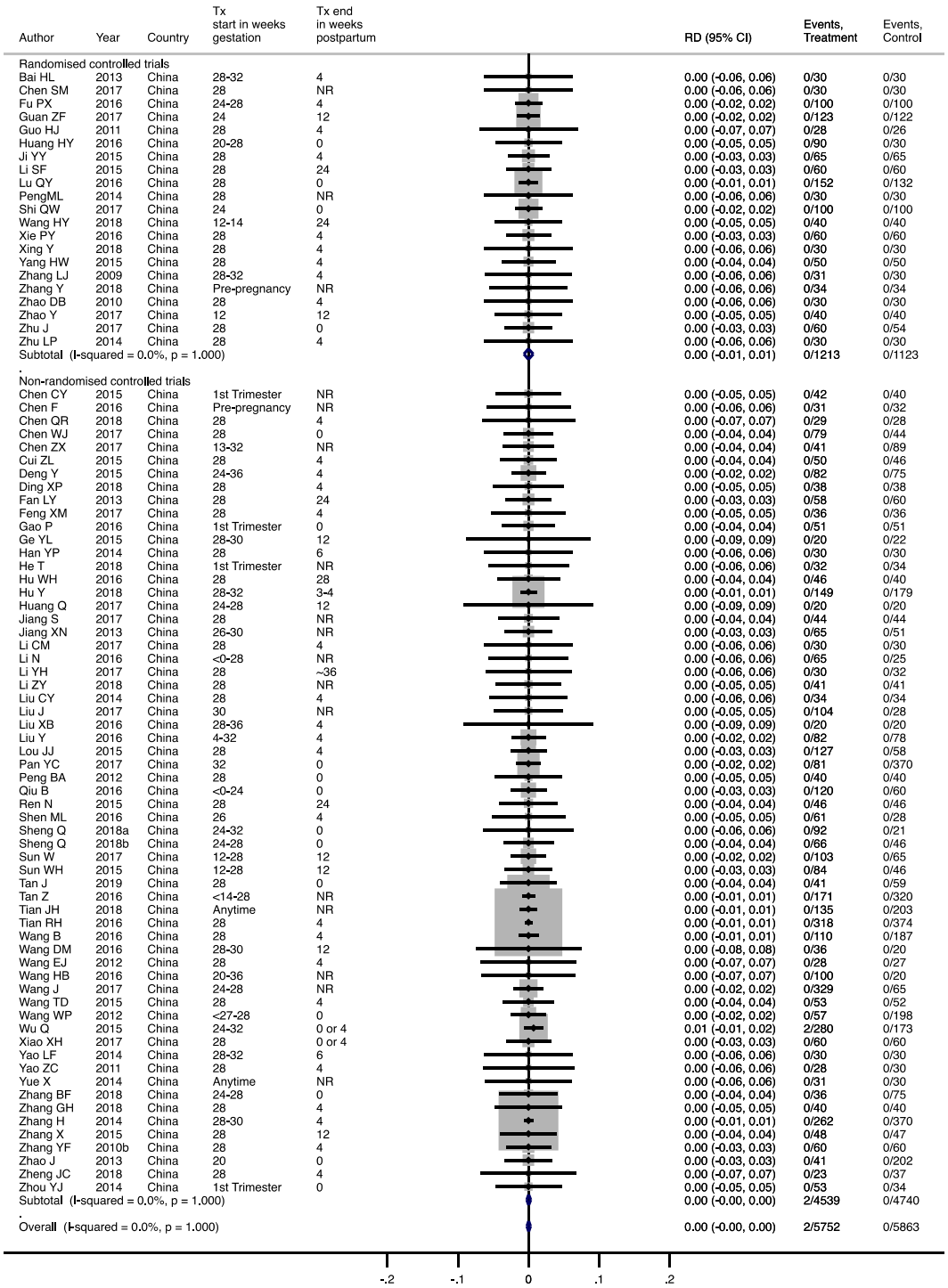
- **TDF 300 mg risk difference for neonatal death**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%



- **LAM 100-150 mg risk difference for neonatal death**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%

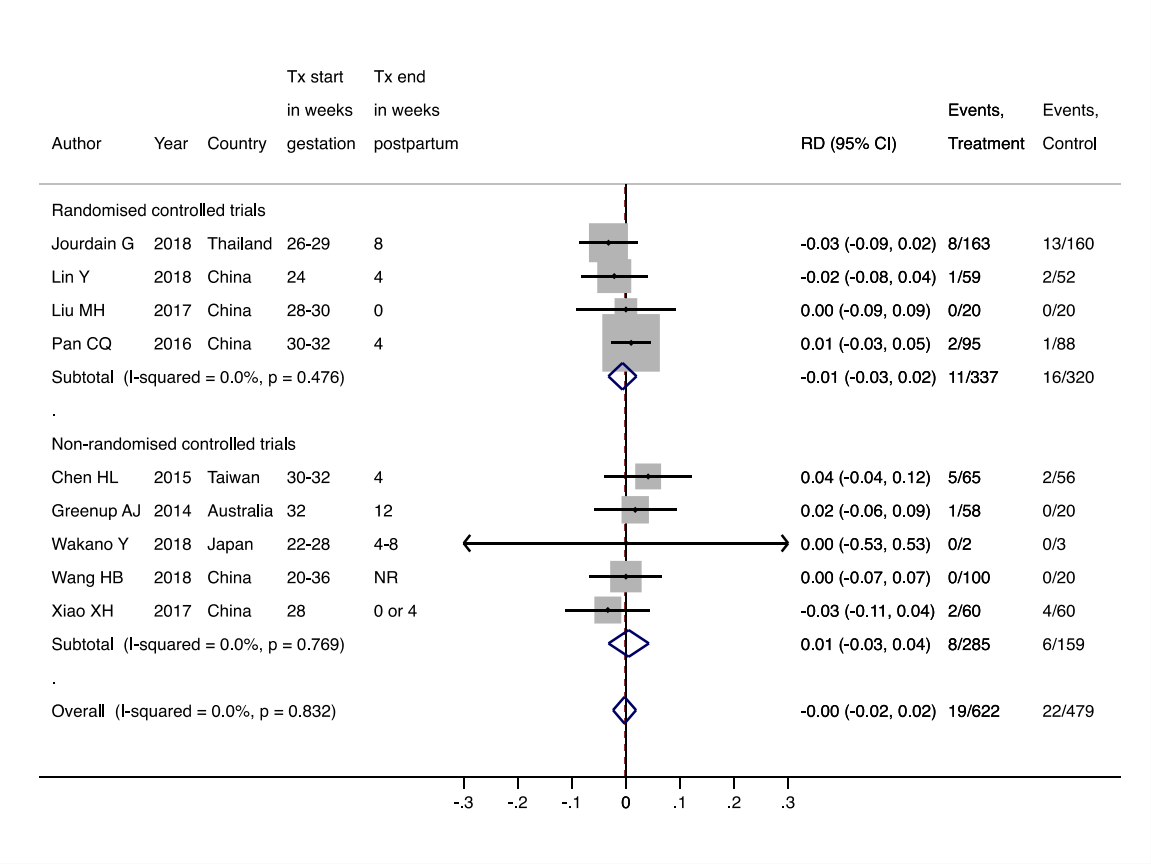


- **LdT 600 mg risk difference for neonatal death**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.00 – 0.00).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%

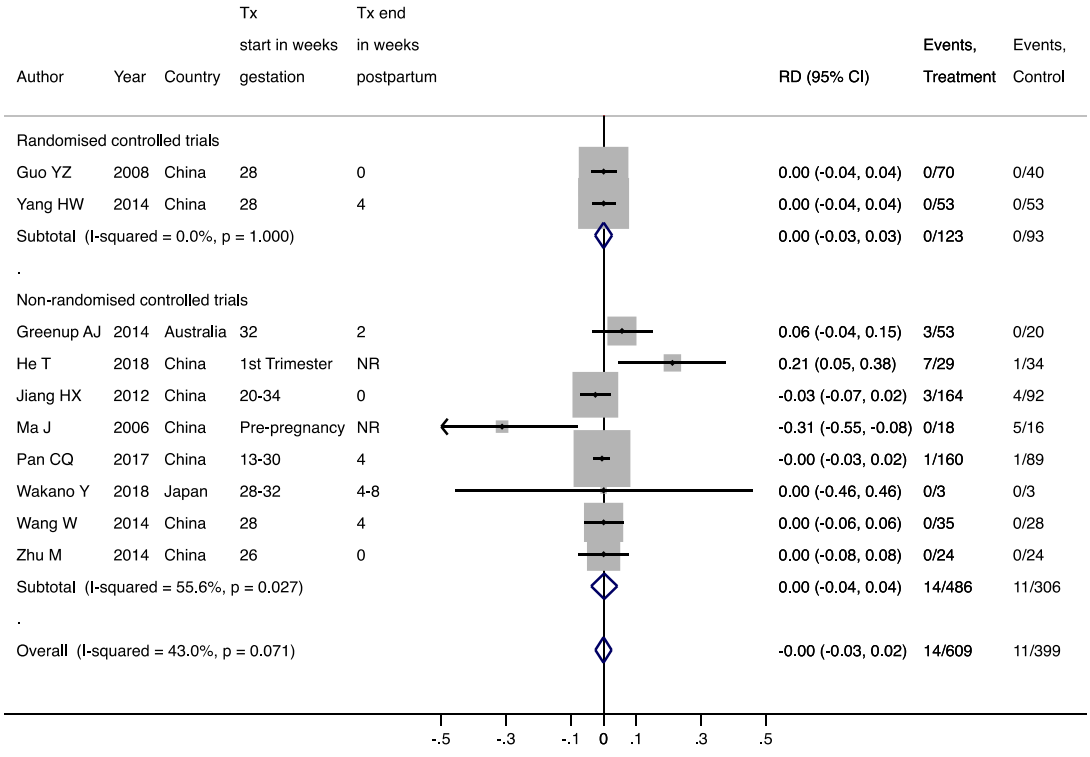


## Appendix Y: Infant safety 2. Preterm birth

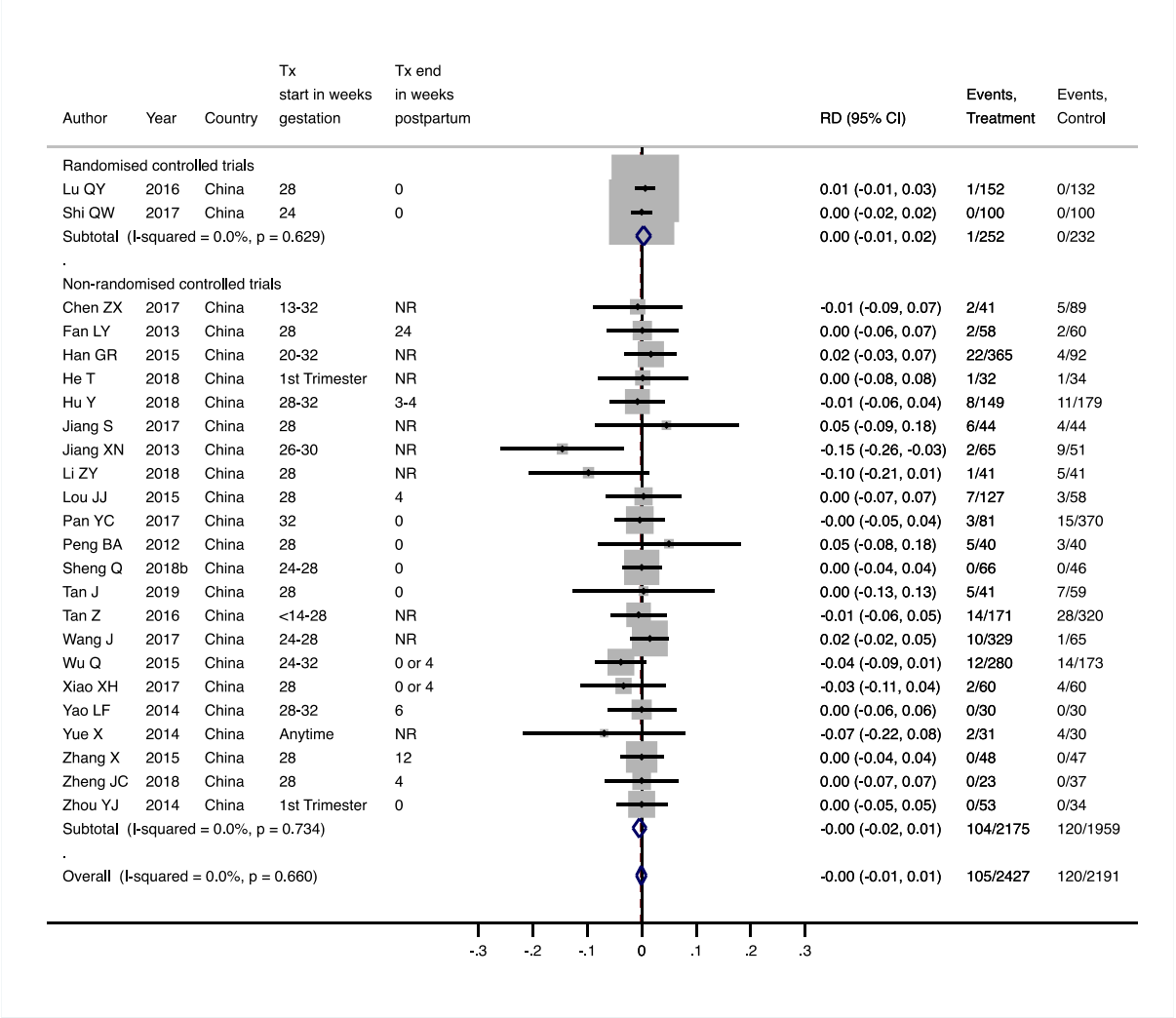
- **TDF 300 mg risk difference for preterm birth**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.02 – 0.02).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%



- **LAM 100-150 mg risk difference for preterm birth**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.03 – 0.02).
  - $I^2$ statistic overall = 43.0%
    - $I^2$ statistic RCTs = not enough studies
    - $I^2$ statistic non-RCTs = 55.6%

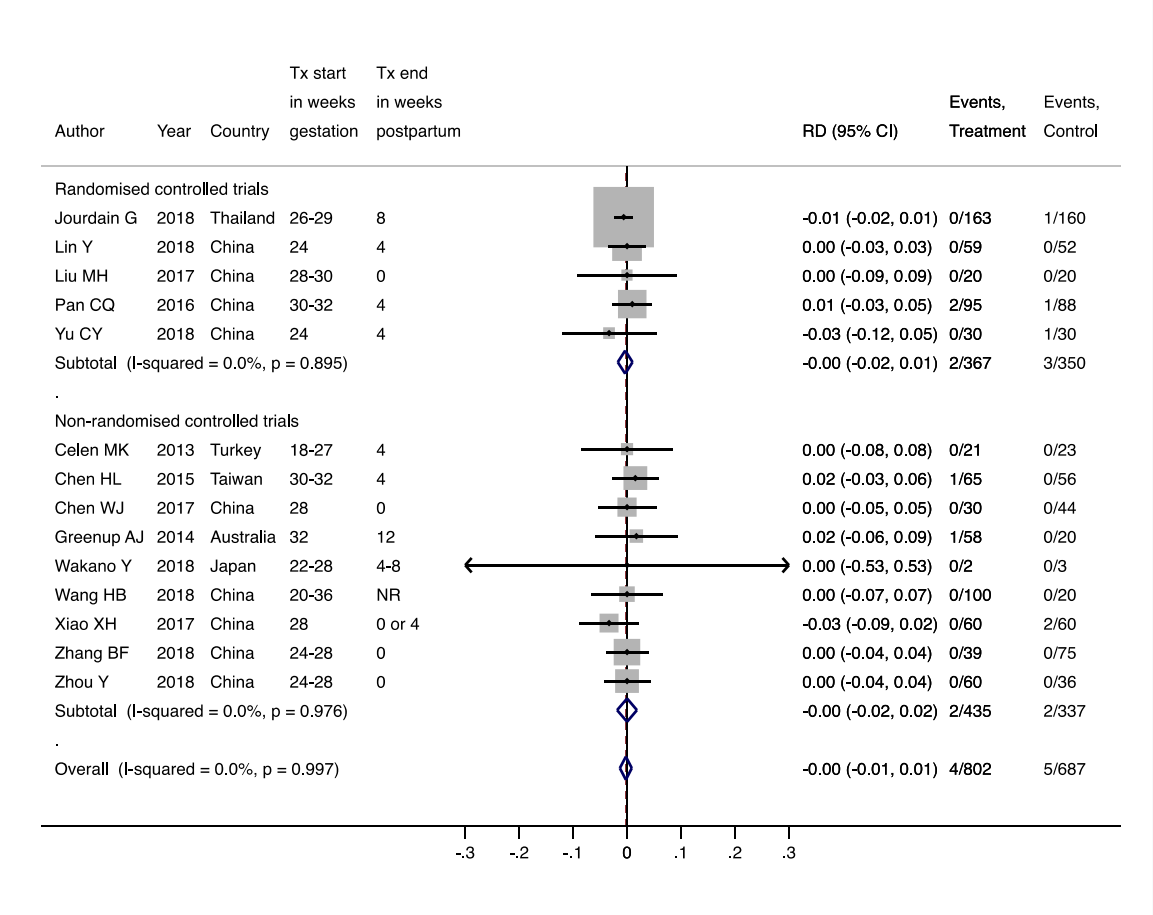


- **LdT 600 mg risk difference for preterm birth**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = not enough studies
    - $I^2$ statistic non-RCTs = 0.0%

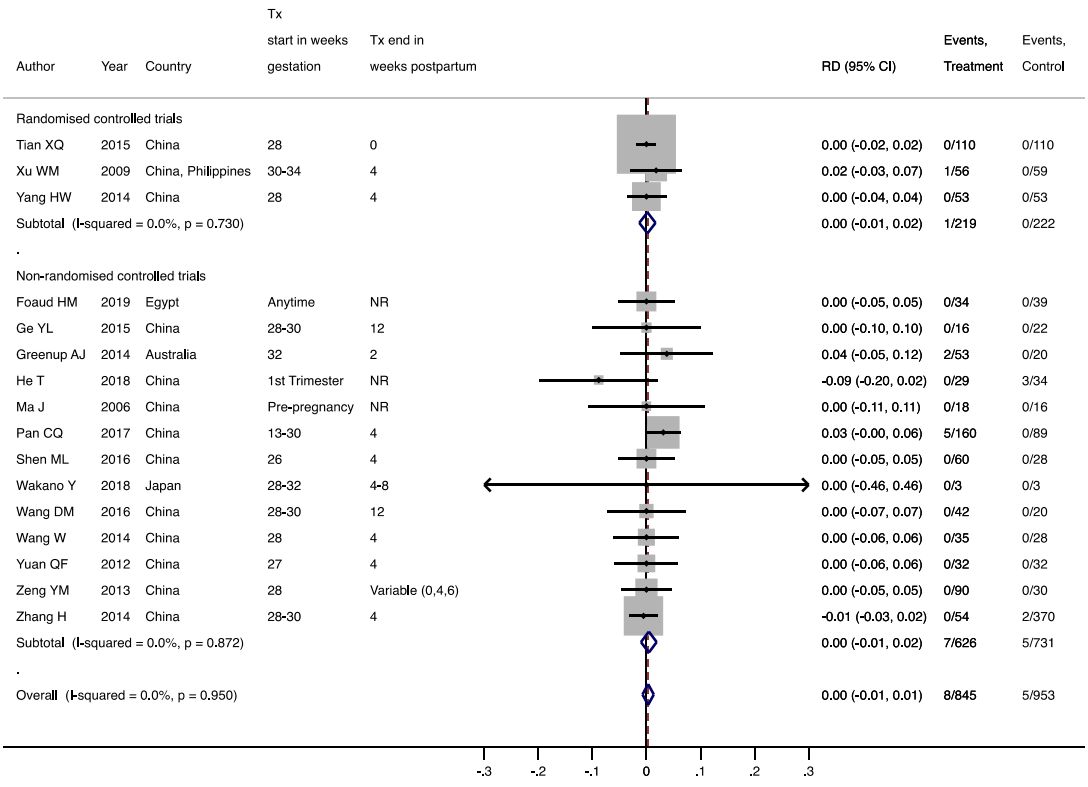


## Appendix Z: Infant safety 3. Congenital abnormalities

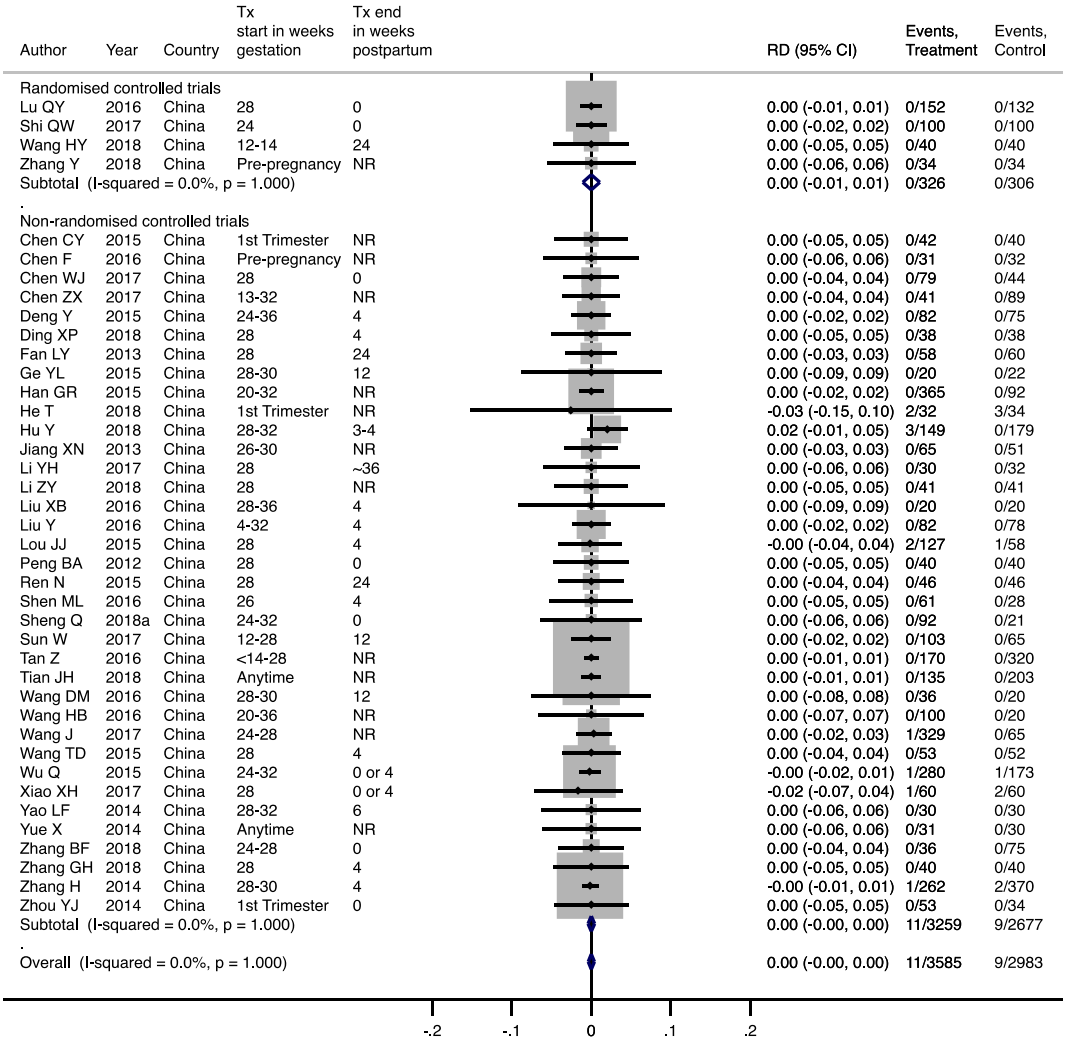
- **TDF 300 mg risk difference for congenital abnormalities**
  - Weighted pooled risk difference: -0.00 (95%CI: -0.01 – 0.01).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%



- **LAM 100-150 mg risk difference for congenital abnormalities**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%



- **LdT 600 mg risk difference of congenital abnormalities**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.00 – 0.00).
  - $I^2$ statistic overall = 0.0%
    - $I^2$ statistic RCTs = 0.0%
    - $I^2$ statistic non-RCTs = 0.0%



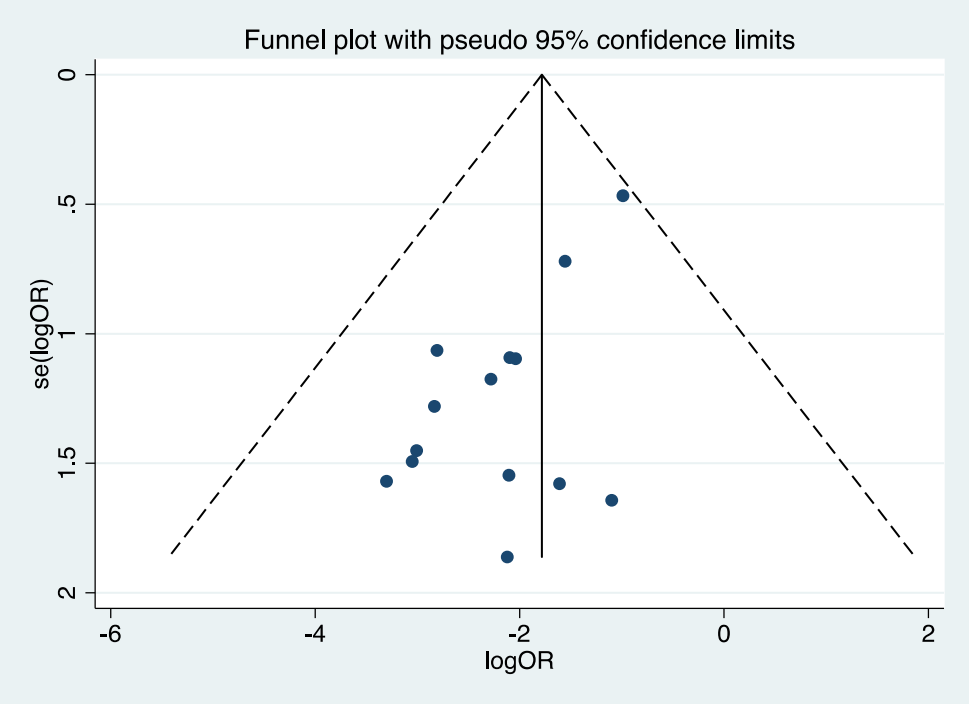
## Appendix AA: Publication Bias Assessment (Funnel Plots)

Efficacy (HBsAg)

TDF 300 mg

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

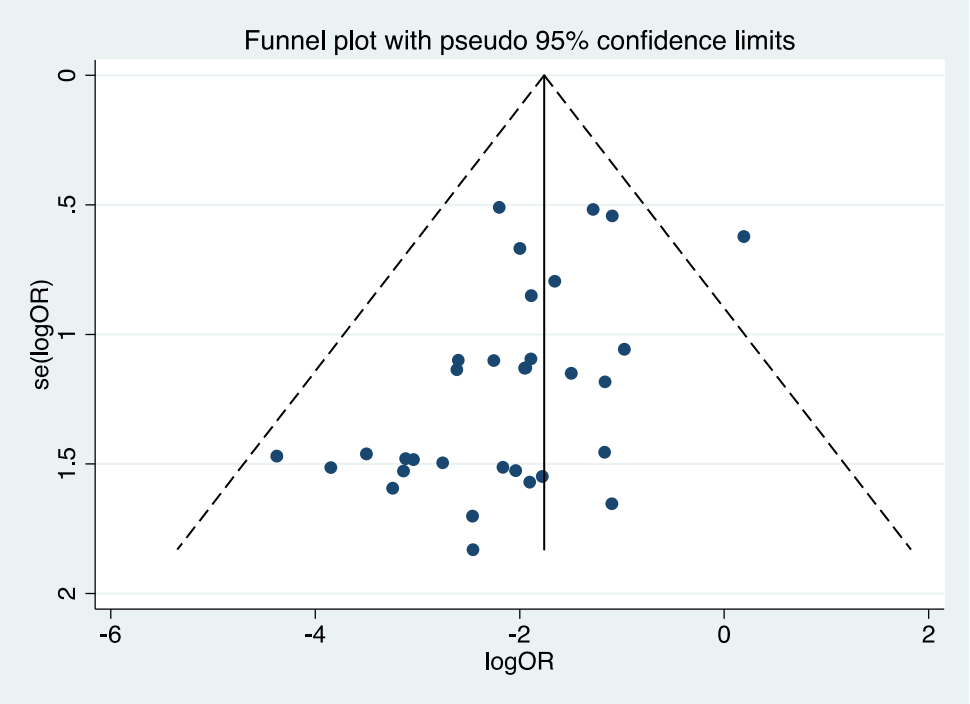
- Possible publication bias/small study effects, Egger's test p-value=0.002



LAM 100-150 mg

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

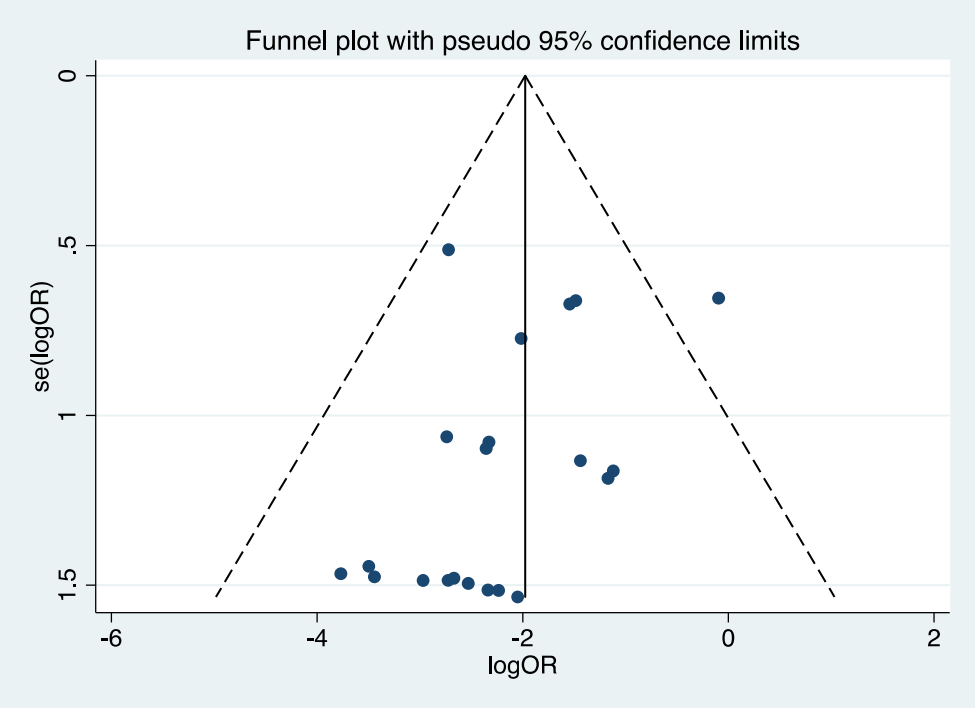
- Possible publication bias/small study effects, Egger's test p-value=0.002



LdT 600 mg

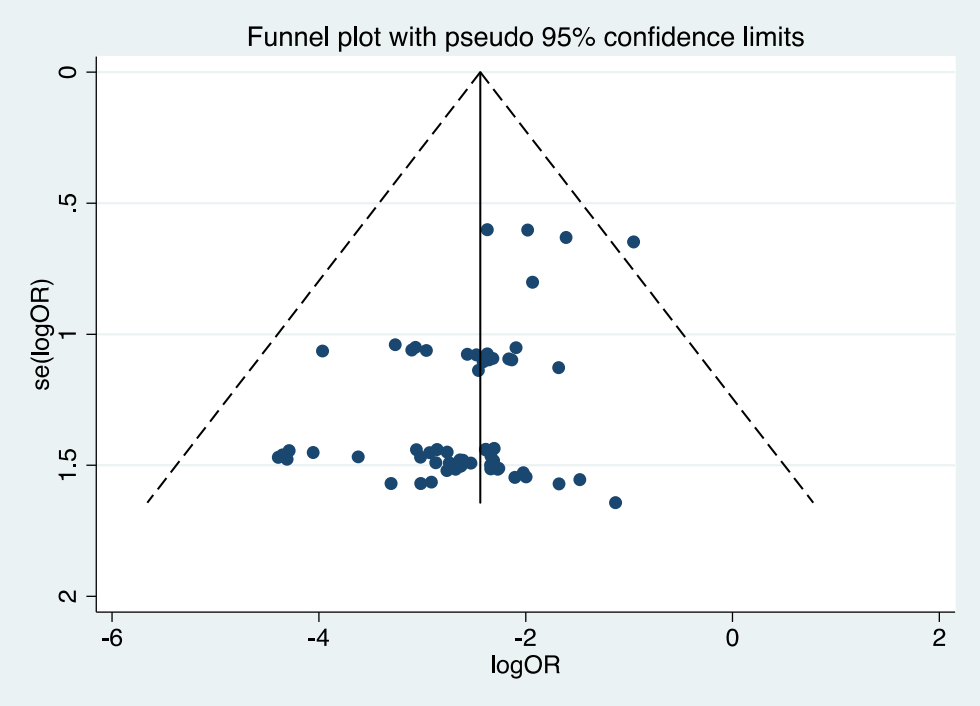
***MTCT indicated by HBsAg positivity at 6-12 months, RCTs***

- No evidence of publication bias, Egger's test p-value=0.119




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

- Possible publication bias/small study effects, Egger's test p-value<0.001

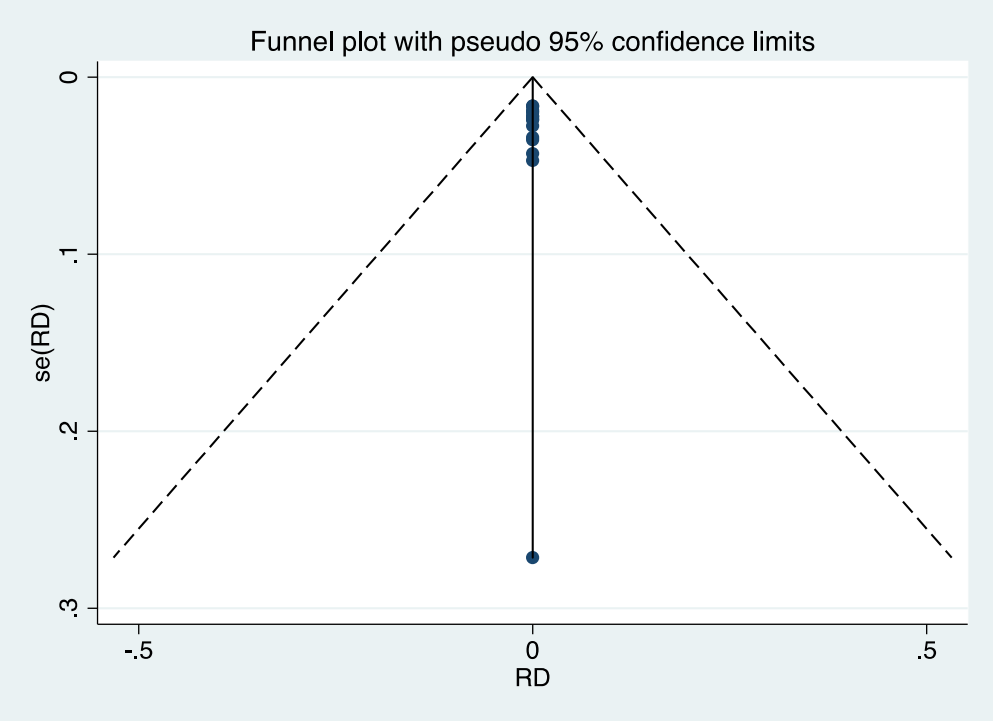


## Safety outcomes

TDF 300 mg

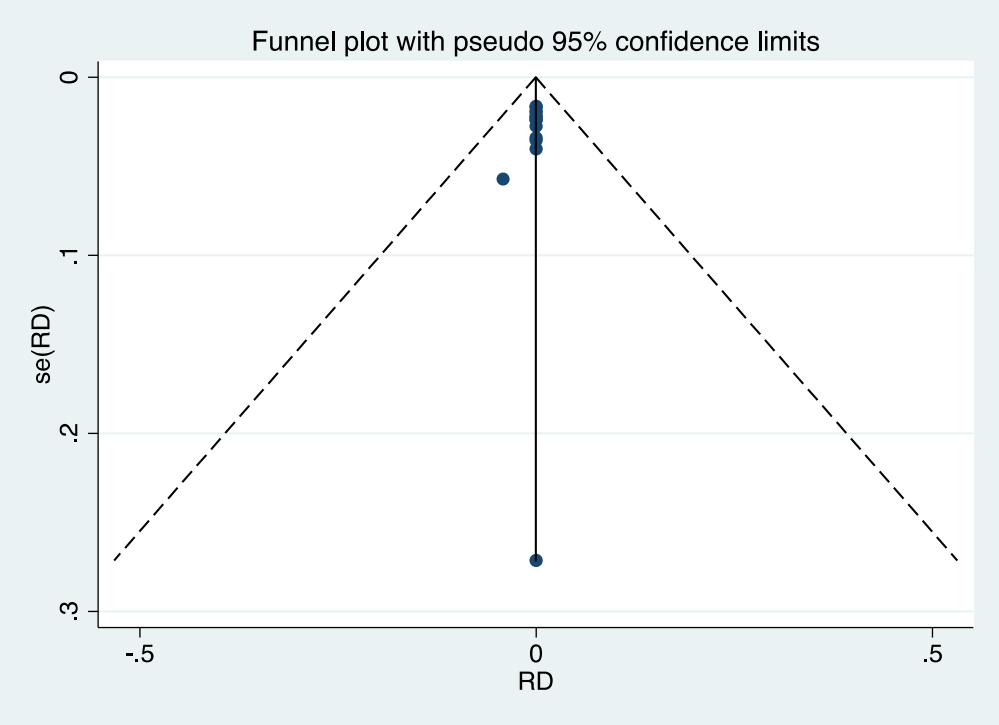
***Neonatal deaths, non-RCTs***

- No evidence of publication bias



***Fetal deaths, non-RCTs***

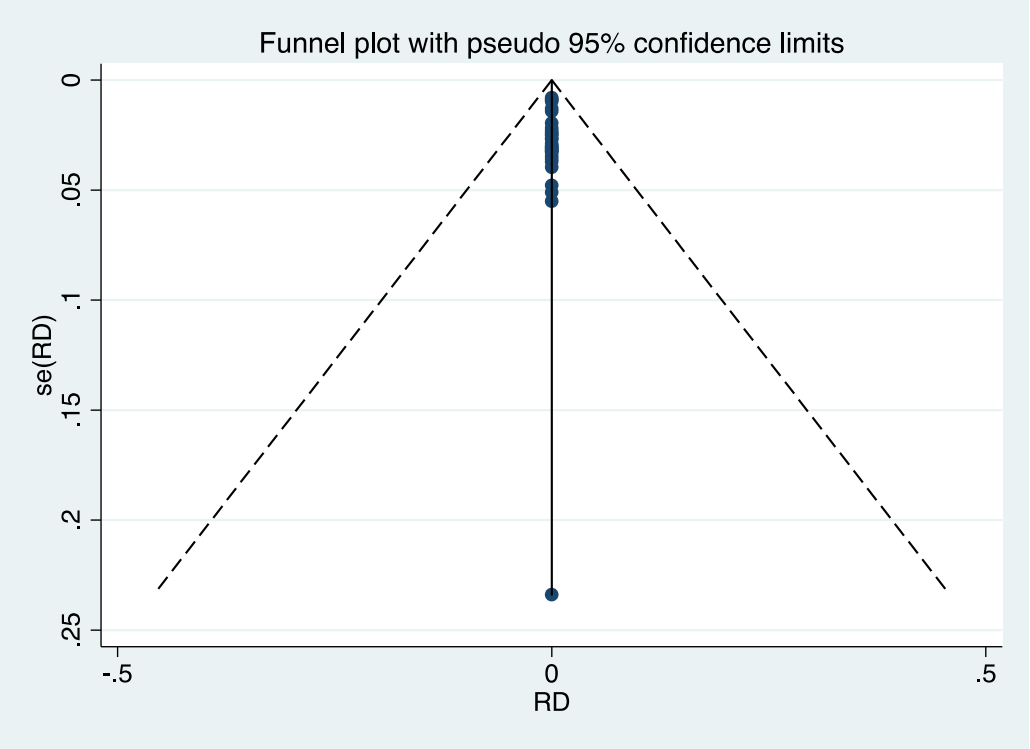
- No evidence of publication bias



LAM 100-150 mg

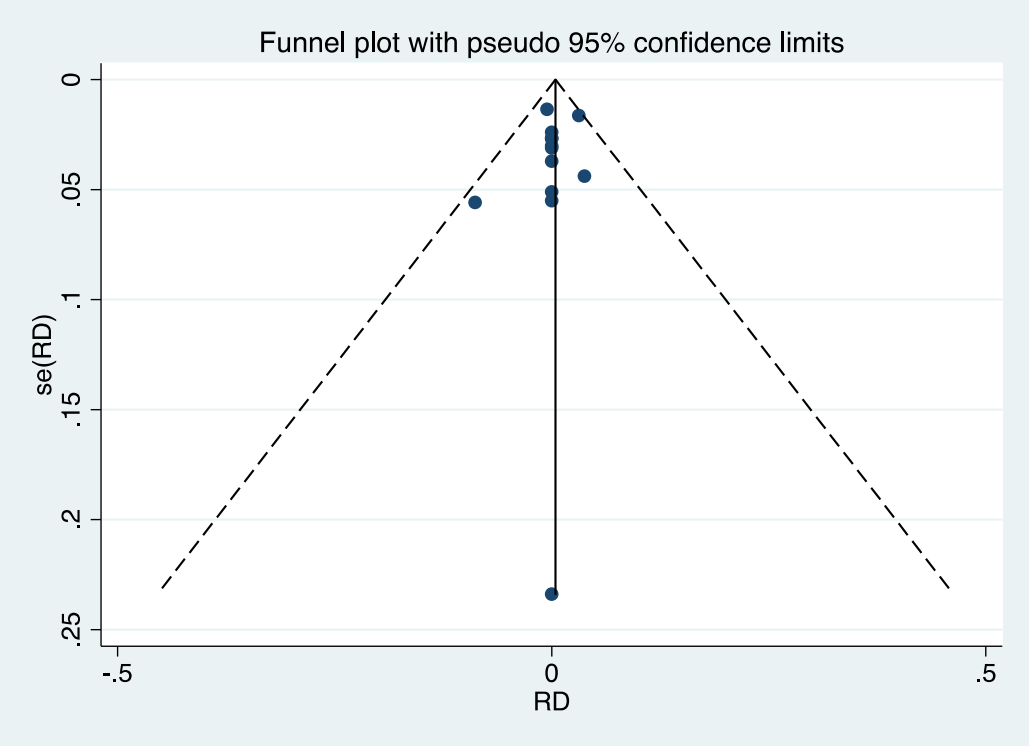
***Neonatal deaths, non-RCTs***

- No evidence of publication bias



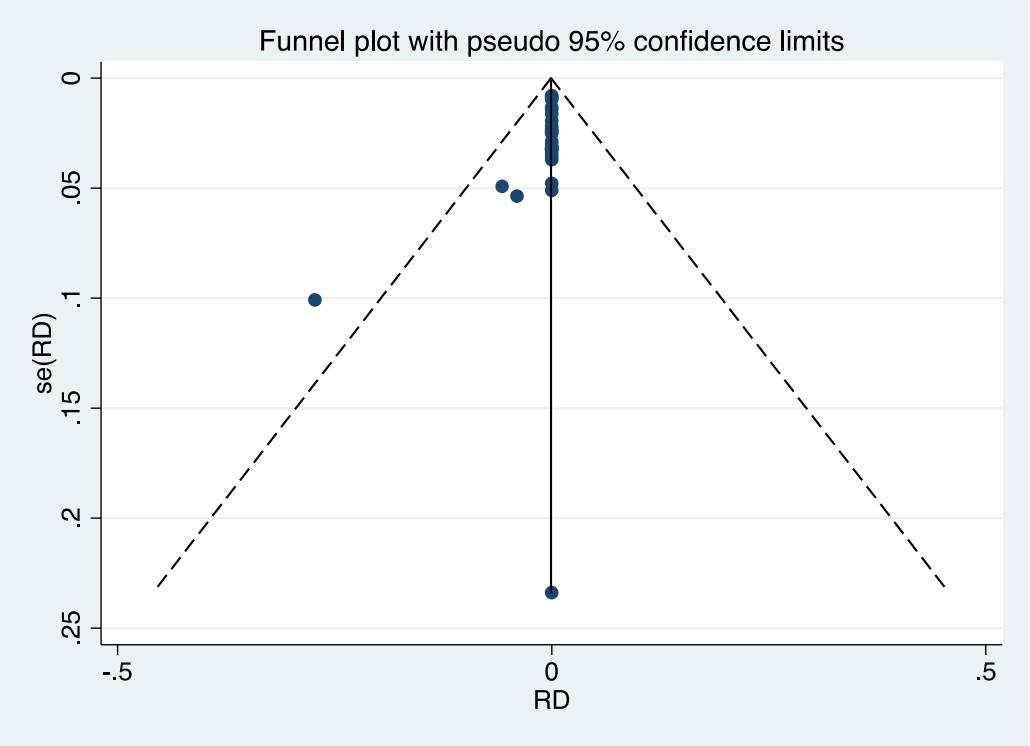
***Congenital abnormalities, non-RCTs***

- No evidence of publication bias




***Fetal deaths, non-RCTs***

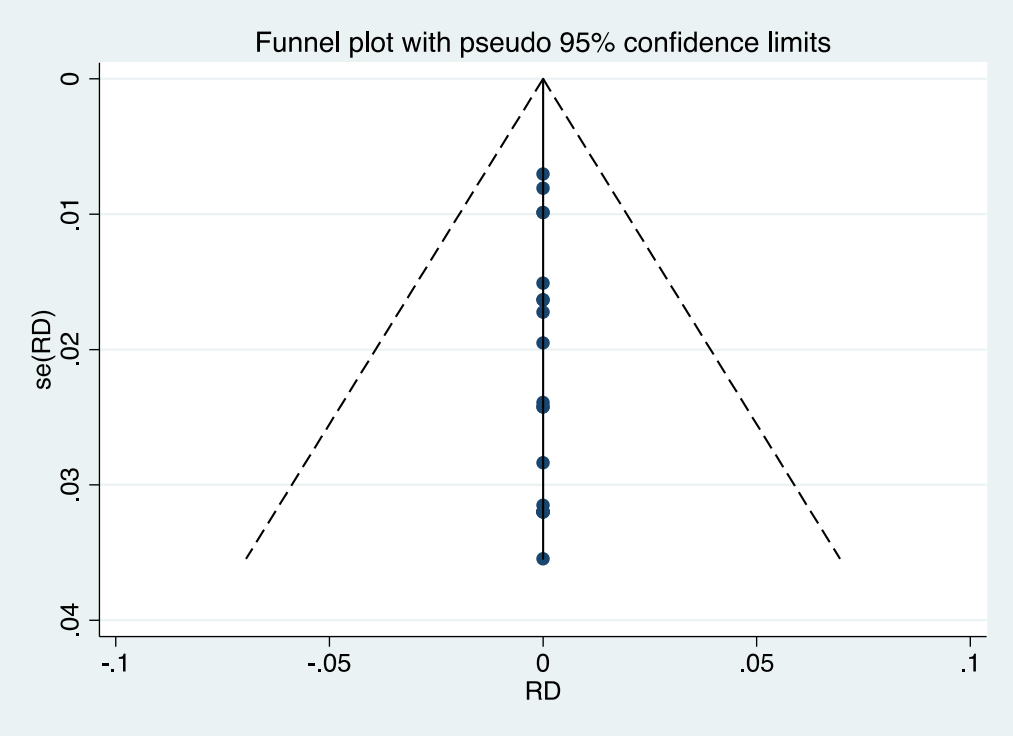
- No evidence of publication bias



LdT 600 mg

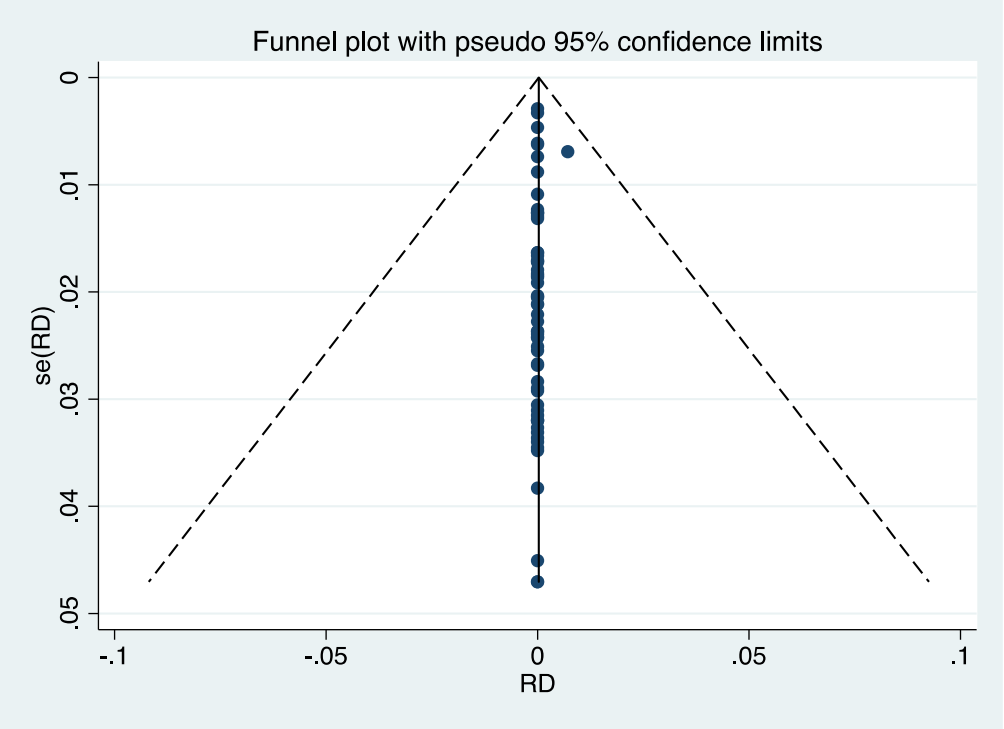
***Neonatal deaths, RCTs***

- No evidence of publication bias



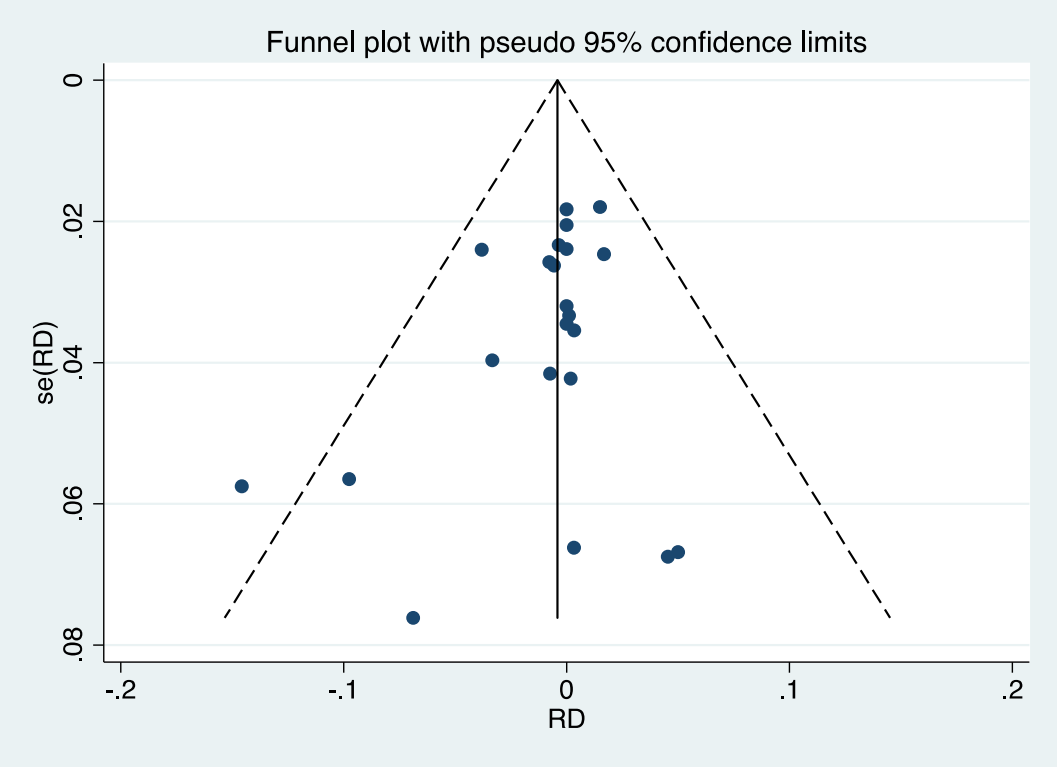
***Neonatal deaths, non-RCTs***

- No evidence of publication bias



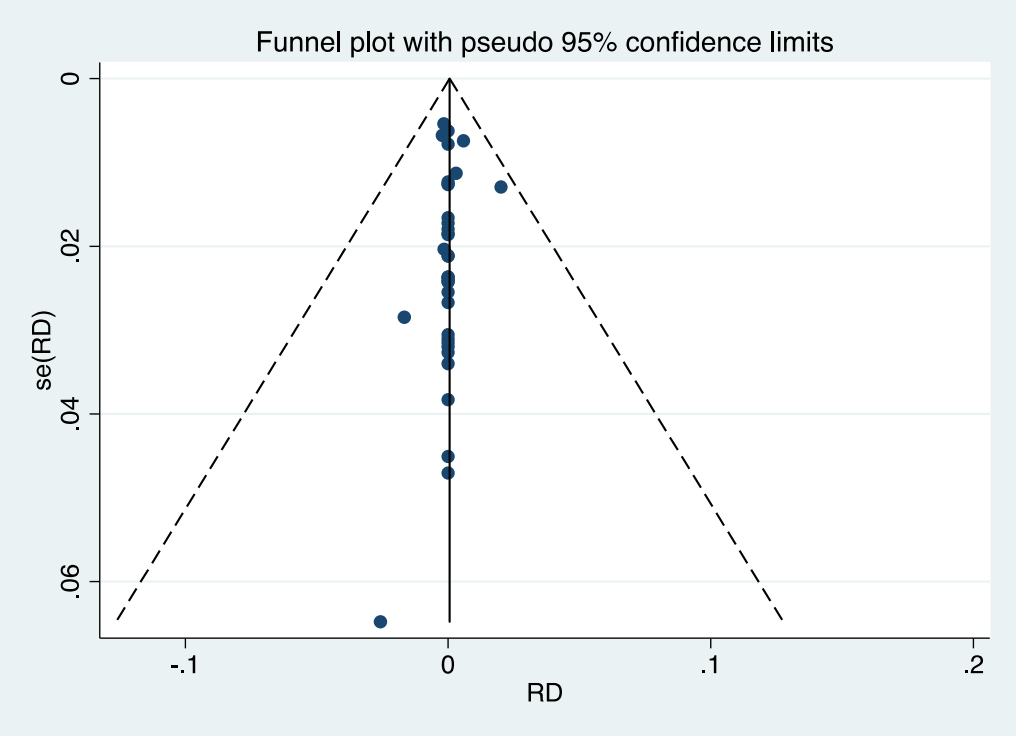

***Prematurity, non-RCTs***

- Unclear/no evidence of publication bias



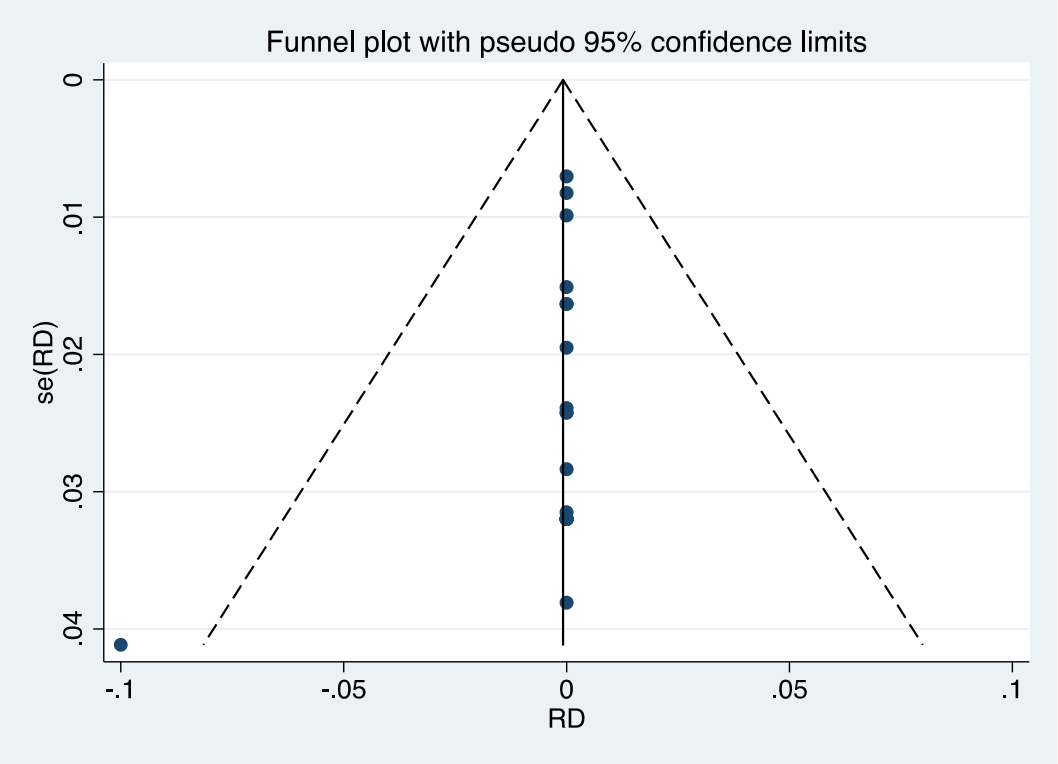
***Congenital abnormalities, non-RCTs***

- No evidence of publication bias



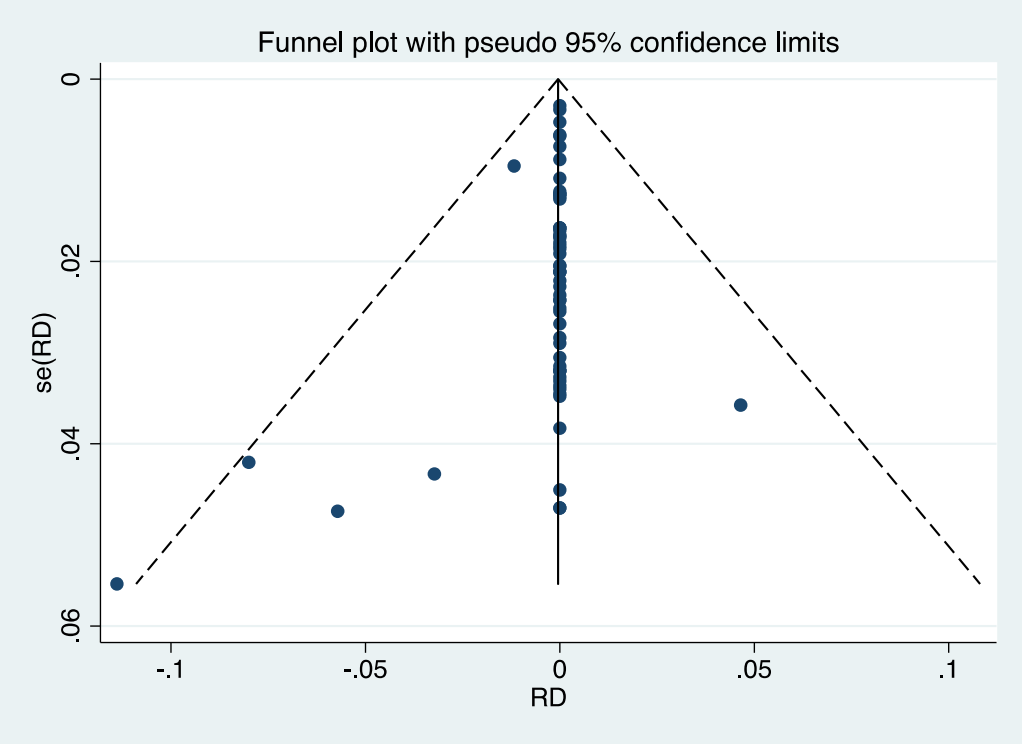

***Fetal deaths, RCTs***

- No evidence of publication bias



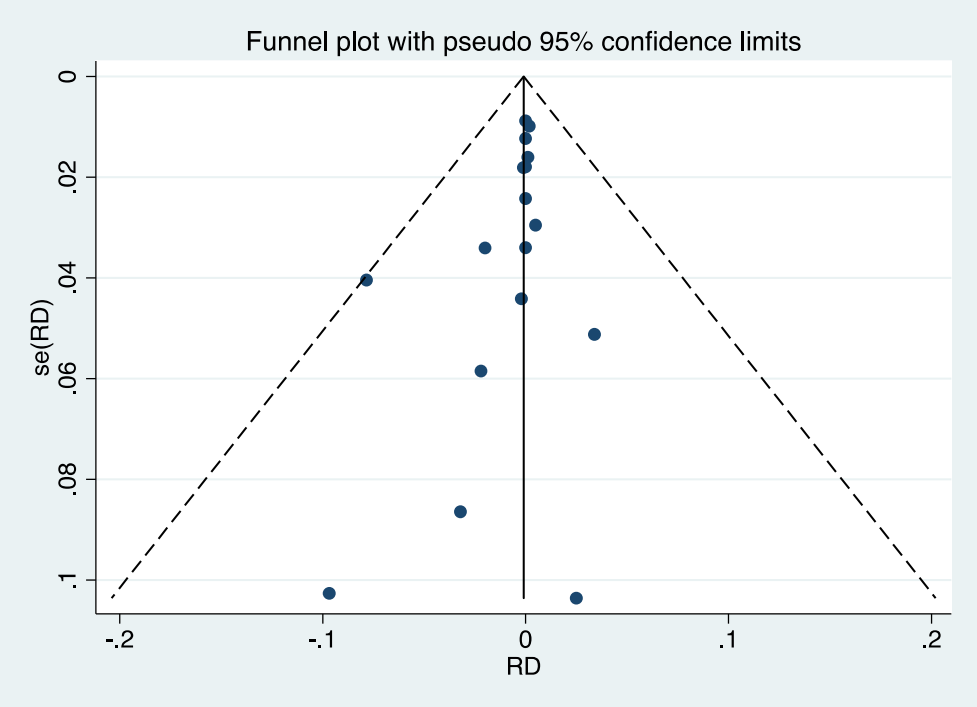
***Fetal deaths, non-RCTs***

- No evidence of publication bias




***Postpartum hemorrhage, non-RCTs***

- No evidence of publication bias



## Appendix AB: GRADE Evidence Profiles

### GRADE review process methods

For each examined treatment comparison, the quality of the evidence studied was evaluated using the Grading of Recommendations Assessment, Development and Evaluation methodology (GRADE). 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 judgments 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, (RC). 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 regards to GRADE criteria:

***Limitations*** – this was rated as 'no serious' only in the following circumstances: for RCTs, if multiple studies (>=2) were of high quality with low risk of bias for the majority of criteria; 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%='no serious', $I^2$>=30&<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, 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 <0.01 (i.e. <10/1000) was allowed for a set of studies to be considered as having 'no serious' limitations in this area.

If the absolute range of the risk difference was >=0.01 and <0.1 then it was considered as having 'serious' limitations, and if it was >=0.1 (i.e. 100 per 1000) then it was considered as having 'very serious' limitations. Note: wherever odds ratios were available, the range of this estimate was used to define imprecision; if no odds ratio was available then risk difference range was used.

***Publication bias*** – An Eggers test with p-value of <0.05 led to assumption of 'possible evidence of publication bias or small study effects' if odds ratios 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 odds ratio was <0.5 and was not considered as imprecise.

TDF 300 mg

| 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* | No 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) | High[a] |
| 14 | *Non-randomized controlled trials* | 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 | *Randomized controlled trials* | No 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) | High[c] |
| 7 | *Non-randomized controlled trials* | 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 | *Randomized* | No serious | No serious | No serious | Serious | Not able to examine publication | N/A | 2/367 (0.5) | 1/350 (0.3) | - | **0** (10 | Moderate[e] |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *controlled trials* | | | | | bias. | | | | | fewer - 10 more) | |
| 14 | *Non-randomized controlled trials* | No serious | No serious | No serious | Serious | No evidence of publication bias | None | 0/712 (0.0) | 0/508 (0.0) | - | **0** (10 fewer - 10 more) | Very low[f] |
| **Infant safety: prematurity** | | | | | | | | | | | | |
| 4 | *Randomized controlled trials* | No serious | No serious | No serious | 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-randomized controlled trials* | No serious | No serious | No serious | Serious | Not able to examine publication bias. | None | 8/285 (2.8) | 6/159 (3.8) | - | **10 more** (30 fewer to 40 more) | Very low[h] |
| **Infant safety: congenital abnormalities** | | | | | | | | | | | | |
| 5 | *Randomized controlled trials* | No serious | No serious | No serious | 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-randomized controlled trials* | No serious | No serious | No serious | Serious | Not able to examine publication bias. | None | 2/435 (0.5) | 2/337 (0.6) | - | **0** (20 fewer - 20 more) | Very low[j] |
| **Infant safety: bone mineral density** | | | | | | | | | | | | |
| 1 | *Randomized controlled trials* | 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/cm$^2$); P =0.38) | Low[k] |
| **Maternal safety: miscarriage and stillbirth** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | *Randomized controlled trials* | No serious | No serious | No serious | 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-randomized controlled trials* | No serious | No serious | No serious | Serious | No evidence of publication bias | None | 0/570 (0.0) | 1/520 (0.2) | - | **0** (10 fewer - 10 more) | Very low[m] |
| **Maternal safety: postpartum hemorrhage** | | | | | | | | | | | | |
| 3 | *Randomized controlled trials* | Serious | No serious | No serious | Serious | Not able to examine publication bias. | N/A | 4/177 (2.3) | 5/172 (2.9) | - | **0** (30 fewer - 30 more) | Low[n] |
| 3 | *Non-randomized controlled trials* | No serious | No serious | No serious | Serious | Not able to examine publication bias. | None | 5/188 (2.7) | 3/84 (3.6) | - | **0** (40 fewer - 40 more) | Very low[o] |
| **Maternal safety: postpartum hepatitis flare after treatment discontinuation** | | | | | | | | | | | | |
| 2 | *Randomized controlled trials* | No serious | Serious $I^2$=43.7% | No serious | Serious | Not able to examine publication bias. | N/A | 10/251 (4.0) | 8/257 (3.1) | - | **2 more** (47 fewer - 51 more) | Low[p] |
| 2 | *Non-randomized controlled trials* | No serious | Very serious $I^2$=80.6% | No serious | Very serious | Not able to examine publication bias. | None | 18/105 (17.1) | 12/70 (17.1) | - | **38 fewer** (289 fewer - 212 more) | Very low[q] |

[a]No downgrading
[b]Downgrading due to possible publication bias/small study effects, upgrading due to magnitude of effect.
[c]No downgrading
[d]Upgrading due to magnitude of effect.
[e]No downgrading

[f]No upgrading or downgrading
[g]Downgrading due to imprecision of risk difference estimate
[h] Downgrading due to imprecision of risk difference estimate
[i]No downgrading
[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]No downgrading
[m]No upgrading or downgrading
[n]Downgrading due to 'serious' study design limitations (the majority of RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to imprecision.
[o]Downgrading due to imprecision (OR absolute range >1.0)
[p]Downgrading due to inconsistency, downgrading due to imprecision
[q]Downgrading due to inconsistency, downgrading due to imprecision

LAM 100-150 mg

| 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* | 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-randomized controlled trials* | 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 | *Randomized controlled trials* | 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-randomized controlled trials* | 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 | *Randomized controlled trials* | Serious | No serious | No serious | Serious | Not possible to examine publication bias. | N/A | 1/439 (0.2) | 1/407 (0.2) | - | **0** (10 fewer - 10 more) | Low[e] |
| 31 | *Non-randomized controlled trials* | No serious | No serious | No serious | Serious | No evidence of publication bias. | None | 0/1571 (0.0) | 0/1686 (0.0) | - | **0** (10 fewer - 10 more) | Very low[f] |
| **Infant safety: prematurity** | | | | | | | | | | | | |
| 2 | *Randomized controlled trials* | Serious | No serious | No serious | Serious | Not possible to examine publication bias. | N/A | 0/123 (0.0) | 0/93 (0.0) | - | **0** (30 fewer – 30 more) | Low[g] |
| 8 | *Non-randomized controlled trials* | Serious | Serious $I^2$ = 55.6% | No serious | 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 | *Randomized controlled trials* | Serious | No serious | No serious | Serious | Not possible to examine publication bias. | N/A | 1/219 (0.5) | 0/222 (0.0) | - | **0** (10 fewer - 20 more) | Low[i] |
| 13 | *Non-randomized controlled trials* | No serious | No serious | No serious | Serious | No evidence of publication bias. | None | 7/626 (1.1) | 5/953 (0.5) | - | **0** (10 fewer - 20 more) | Very low[j] |
| **Maternal safety: miscarriage and stillbirth** | | | | | | | | | | | | |
| 8 | *Randomized controlled trials* | Serious | No serious | No serious | Serious | Not possible to examine publication bias. | N/A | 1/472 (0.2) | 0/409 (0.0) | - | **0 more** (10 fewer - 10 | Low[k] |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | more) | |
| 31 | *Non-randomized controlled trials* | No serious | No serious | No serious | Serious | No evidence of publication bias. | None | 0/1531 (0.0) | 9/1678 (0.5) | - | **0** (10 fewer - 10 more) | Very low[l] |
| **Maternal safety: postpartum hemorrhage** | | | | | | | | | | | | |
| 1 | *Randomized controlled trials* | Serious | Not applicable | No serious | Serious | Not possible to examine publication bias. | N/A | 0/53 (0.0) | 0/53 (0.0) | - | **0** (40 fewer - 40 more) | Very low[m] |
| 7 | *Non-randomized controlled trials* | No serious | No serious | No serious | Serious | Not possible to examine publication bias. | None | 98/558 (17.6) | 61/699 (8.7) | - | **10 more** (10 less - 40 more) | Very low[n] |
| **Maternal safety: postpartum hepatitis flare after treatment discontinuation** | | | | | | | | | | | | |
| 1 | *Randomized controlled trials* | 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-randomized controlled trials* | No serious | Serious $I^2$ = 33.2% | No serious | Serious | Not possible to examine publication bias. | None | 43/364 (11.8) | 19/522 (3.6) | - | **10 fewer** (50 fewer -30 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), downgrading due to imprecision
[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%, downgrading due to imprecision

[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, downgrading due to imprecision.
[n]Downgrading due to imprecision.
[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 some inconsistency >30%, downgrading due to imprecision

LdT 600 mg

| 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* | 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-randomized controlled trials* | 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 | *Randomized controlled trials* | 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 to 250 fewer) | Moderate[c] |
| 45 | *Non-randomized controlled trials* | 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 | *Randomized controlled trials* | Serious | No serious | No serious | Serious | No evidence of publication bias | N/A | 0/1213 (0.0) | 0/1123 (0.0) | - | **0 per 1000** (10 fewer - 10 more) | Low[e] |
| 61 | *Non-* | No | No | No | No | No evidence of publication | None | 2/4539 | 0/4740 | - | **0 per** | Low[f] |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *randomized controlled trials* | serious | serious | serious | serious | bias | | (0.0) | (0.0) | | **1000** (2 fewer - 3 more) | |
| **Infant safety: prematurity** | | | | | | | | | | | | |
| 2 | *Randomized controlled trials* | Serious | No serious | No serious | Serious | Not possible to examine publication bias. | N/A | 1/252 (0.4) | 0/232 (0.0) | - | **0 per 1000** (10 fewer – 20 more) | Low[g] |
| 22 | *Non-randomized controlled trials* | No serious | No serious | No serious | Serious | No evidence of publication bias | None | 104/2175 (4.8) | 120/1959 (6.1) | - | **0 per 1000** (20 fewer - 10 more) | Very low[h] |
| **Infant safety: congenital abnormalities** | | | | | | | | | | | | |
| 4 | *Randomized controlled trials* | Serious | No serious | No serious | Serious | Not possible to examine publication bias. | N/A | 0/326 (0.0) | 0/306 (0.0) | - | **0 per 1000** (10 fewer - 10 more) | Low[i] |
| 36 | *Non-randomized controlled trials* | 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 | *Randomized controlled trials* | Serious | No serious | No serious | Serious | No evidence of publication bias | N/A | 0/1107 (0.0) | 6/1026 (0.6) | - | **1 fewer per 1000** (8 fewer - 6 more) | Low[k] |
| 61 | *Non-randomized controlled* | 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 - | Low[l] |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *trials* | | | | | | | | | | 2 more) | |
| **Maternal safety: postpartum hemorrhage** | | | | | | | | | | | | |
| 2 | *Randomized controlled trials* | 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-randomized controlled trials* | No serious | No serious | No serious | Serious | No evidence of publication bias | None | 86/1549 (5.6) | 78/1840 (4.2) | - | **1 fewer** (10 less - 8 more) | Very low[n] |
| **Maternal safety: postpartum hepatitis flare after treatment discontinuation** | | | | | | | | | | | | |
| 3 | *Non-randomized controlled trials* | No serious | Very serious $I^2$=85.5% | No serious | Very serious | Not possible to examine publication bias. | N/A | 27/431 (6.3) | 26/565 (4.6) | - | **20 less** (60 fewer -110 more) | Very low[o] |

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[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