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

Summary

Background To eliminate mother-to-child transmission (MTCT) of hepatitis B virus (HBV), peripartum antiviral prophylaxis might be required for pregnant women infected with HBV who have a high risk of MTCT despite infant immunoprophylaxis. We aimed to determine the efficacy and safety of peripartum antiviral prophylaxis to inform the 2020 WHO guidelines.

Methods In this systematic review and meta-analysis, we searched PubMed, Embase, Scopus, CENTRAL, CNKI, and Wanfang for randomised controlled trials and non-randomised studies of peripartum antiviral prophylaxis versus placebo or no prophylaxis, with no language restriction, published from database inception until March 28, 2019. We used search terms covering HBV, antiviral therapy, and pregnancy. We included studies that enrolled pregnant women with chronic infection with HBV who received antiviral prophylaxis anytime during pregnancy; that included any of the following antivirals: adefovir, emtricitabine, entecavir, lamivudine, telbivudine, tenofovir alafenamide fumarate, and tenofovir disoproxil fumarate; and that reported the following outcomes: MTCT, indicated by infant HBsAg positivity or HBV DNA positivity, or both, at age 6–12 months, and any infant or maternal adverse events. Two reviewers independently extracted data. Our primary endpoint was MTCT based on infant HBsAg positivity. We assessed pooled odds ratios (ORs) of the efficacy of peripartum antiviral prophylaxis to reduce the risk of MTCT. We assessed safety of prophylaxis by pooling risk differences. The protocol for the systematic review was pre-registered in PROSPERO, CRD42019134614.

Findings Of 7463 articles identified, 595 articles were eligible for full-text review and 129 studies (in 157 articles) were included. The following antivirals were assessed in the meta-analysis: tenofovir disoproxil fumarate 300 mg (19 studies, with 1092 mothers and 1072 infants), lamivudine 100–150 mg (40 studies, with 2080 mothers and 2007 infants), and telbivudine 600 mg (83 studies, with 6036 mothers and 5971 infants). The pooled ORs for randomised controlled trials were similar, at 0·10 (95% CI 0·03–0·35) for tenofovir disoproxil fumarate, 0·16 (0·10–0·26) for lamivudine, and 0·14 (0·09–0·21) for telbivudine. The pooled ORs in non-randomised studies were 0·17 (0·10–0·29) for tenofovir disoproxil fumarate, 0·17 (0·12–0·24) for lamivudine, and 0·09 (0·06–0·12) for telbivudine. We found no increased risk of any infant or maternal safety outcomes after peripartum antiviral prophylaxis.

Interpretation Peripartum antiviral prophylaxis is highly effective at reducing the risk of HBV MTCT. Our findings support the 2020 WHO recommendation of administering antivirals during pregnancy, specifically tenofovir disoproxil fumarate, for the prevention of HBV MTCT.

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For the Chinese translation of the abstract see Online for appendix 1

For the French translation of the abstract see Online for appendix 2

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Unité d'Épidémiologie des Maladies Émergentes, Institut Pasteur, Paris, France (A L Funk PhD, P Boucheron MD, Y Shimakawa MD); **Department of Pediatrics, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada** (A L Funk); **Global Hepatitis Programme, World Health Organization, Geneva, Switzerland** (Y Lu PhD, J van Holten PhD, M Bulterys MD); **Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan** (K Yoshida); **School of Public Health, Peking University, Beijing, China** (T Zhao MSc); **Department of Medicine and Department of Medical Informatics and Clinical Epidemiology, Oregon Health and Science University, Portland, OR, USA** (Prof R Chou MD); **and US Centers for Disease Control and Prevention, Nairobi, Kenya** (M Bulterys)

Correspondence to:
Dr Yusuke Shimakawa, Unité d'Épidémiologie des Maladies Émergentes, Institut Pasteur, Paris 75015, France
yusuke.shimakawa@gmail.com

Introduction

Chronic infection with hepatitis B virus (HBV) is a serious global health problem, affecting approximately 257 million people worldwide in 2015 and causing 900000 deaths annually due to chronic liver diseases, such as cirrhosis and liver cancer.[1] In 2016, 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, elimination of mother-to-child transmission (MTCT) of HBV is crucial because chronic infection is more likely to develop when infection occurs early in life, particularly from birth through MTCT.[3] Moreover, the risk of developing chronic liver diseases might be higher in those who acquired HBV infection through MTCT than in those who acquire it through horizontal transmission later in life.[4,5]

To prevent MTCT, WHO recommends that all infants receive at least three doses of hepatitis B vaccine, with the first dose administered within 24 h of birth.[6] However, the birth dose of hepatitis B vaccine, even if given to neonates combined with passive immunoprophylaxis using hepatitis B immune globulin (HBIG), does not prevent all MTCT,[7] particularly in those born to mothers

Research in context

Evidence before this study

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

Added value of this study

Via a comprehensive literature search that widely covered both predominantly English-language databases and Chinese-language databases, to our knowledge this is the largest and most up-to-date systematic review and meta-analysis on the prevention of MTCT of HBV, including more than twice the number of studies analysed in previously published systematic reviews. Furthermore, we excluded studies with potentially overlapping patient populations. We found high efficacy of three antiviral therapy regimens, including tenofovir disoproxil fumarate 300 mg (19 studies), lamivudine 100–150 mg (40 studies), and telbivudine 600 mg (83 studies), for randomised controlled trials and non-randomised studies of interventions. The large number of studies included enabled us to do subgroup analyses on possible sources of heterogeneity.

Implications of all the available evidence

From the findings of this meta-analysis, WHO has made a recommendation for administration of tenofovir disoproxil fumarate 300 mg starting from week 28 of pregnancy until at least birth. Most studies were done in Asia, potentially limiting the applicability of findings to other regions with high HBV prevalence such as Africa; hence, more research is needed in these other high-burden areas. Research on the efficacy of peripartum antiviral prophylaxis without hepatitis B immune globulin (HBIG) is urgently needed, given that access to HBIG is restricted in many low-income and middle-income countries.

with high viraemia.[8–10] Consequently, MTCT remains a key contributor to HBV incidence globally, and supplementary interventions to further decrease MTCT are needed.[11]

In 2014, 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 articles in English and identified only one observational study assessing the efficacy of tenofovir disoproxil fumarate, a key first-line anti-HBV therapy. Moreover, little assessment of the potential harms associated with the use of antivirals during pregnancy was done in this review. Consequently, WHO did not make a formal recommendation at that time.[12] Since then, several clinical trials using tenofovir disoproxil fumarate have been published and additional evidence has become available regarding both the risk of post-partum hepatitis B flare in mothers after cessation of antivirals and the risk of changes in bone mineral density in infants of mothers given antivirals while pregnant.[13–16] Thus, we did an updated systematic review and meta-analysis of aggregate data on the efficacy and safety of peripartum antiviral prophylaxis for prevention of MTCT, to inform the new WHO guidelines.[17] Throughout this Article, we use the term peripartum antiviral prophylaxis rather than peripartum antiviral therapy to distinguish between antivirals that are given only for a few months around pregnancy and delivery to prevent MTCT (prophylaxis) and antivirals given to women and mothers over a longer period, most often for their lifetime, for their own health benefit (therapy).

See Online for appendix 3

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we searched PubMed, Embase, Scopus, and CENTRAL, and two Chinese-language (CNKI and Wanfang) databases from database inception until March 28, 2019, with no language restrictions. Our search strategies differed by database, but covered the search terms "HBV" AND "antiviral therapy" AND "pregnancy" (full details of search strategies are in the appendix 3 [pp 3–8]). We considered randomised controlled trials and non-randomised studies of interventions that enrolled pregnant women with chronic HBV infection who received antiviral prophylaxis anytime during pregnancy, and reported the following outcomes with aggregate data: MTCT, indicated by infant HBsAg positivity or HBV DNA positivity, or both, at age 6–12 months, and any infant or maternal adverse events. The following antivirals were eligible for inclusion: adefovir, emtricitabine, entecavir, lamivudine, telbivudine, tenofovir alafenamide fumarate, and tenofovir disoproxil fumarate. Eligible control groups received no intervention or placebo. Non-randomised studies of interventions were eligible if they were described as prospective or retrospective cohort studies, with control populations composed of pregnant women with chronic HBV infection who were followed up during the same time period but

who did not receive antiviral prophylaxis (eg, because they were unwilling). Non-randomised studies with a high risk of bias on the Newcastle-Ottawa Scale (ie, a score of ≤5) were excluded.[18] We also manually searched the references of included studies. Conference abstracts were not considered.

Titles and abstracts of all publications identified through the search were independently screened for inclusion: those identified via PubMed, Embase, Scopus, and CENTRAL were screened by ALF and KY, and those identified via CNKI and Wanfang by YL and TZ. These investigators then reviewed the full text of eligible studies, extracted relevant data using a form that has been piloted by the study team, and assessed the risk of bias in the study using the Cochrane Collaboration tool for randomised controlled trials and the Newcastle-Ottawa Scale for non-randomised studies (appendix 3 pp 13–17).[18,19] A third investigator resolved any discrepancies (YS).

The following data were extracted: study characteristics, number of infants with detectable HBsAg at age 6–12 months, number of infants with detectable HBV DNA at age 6–12 months, and maternal and infant safety outcomes including fetal and neonatal death, preterm birth, congenital abnormalities, post-partum haemorrhage, post-partum hepatitis flare after antiviral discontinuation, 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 assess the same study population unless specifically indicated otherwise by corresponding authors, whom we attempted to contact in all cases. When 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.

The protocol was pre-registered in PROSPERO, CRD42019134614, and this study is reported according to PRISMA guidelines.[20]

Data analysis

We assessed the efficacy of peripartum antiviral prophylaxis by pooling odds ratios (ORs) using the DerSimonian-Laird random-effects model for randomised controlled trials and non-randomised studies separately. Our primary endpoint was MTCT based on infant HBsAg positivity, and our secondary endpoint was MTCT based on infant HBV DNA positivity. We assessed the safety of peripartum antiviral prophylaxis by pooling risk differences using the DerSimonian-Laird random-effects model, rather than ORs, to include studies without events. We intended to do an intention-to-treat analysis, but due to inadequate reporting of loss to follow-up in included studies, we ultimately did a per-protocol analysis, with the denominator being the number of children with complete follow-up. If a specific antiviral was assessed in fewer than three eligible studies then primary and secondary endpoint efficacy meta-analyses were not done. Efficacy subanalyses and safety analyses were only done when three or more studies of the same antiviral were eligible. We assessed statistical heterogeneity using the I^2 statistic. If no significant difference in treatment efficacy was observed between randomised controlled trials and non-randomised studies for a specific antiviral, then these data were combined for subsequent subgroup analyses.

We did subgroup analyses for the primary endpoint on the following potential sources of heterogeneity: study design (randomised controlled trial *vs* non-randomised studies), WHO region, timing of treatment start, timing of treatment discontinuation, maternal characteristics (mean viral load at inclusion; HBeAg; HIV, hepatitis C virus [HCV], or hepatitis D virus [HDV] co-infections; HBV genotypes), infant immunoprophylaxis regimen (HBIG, birth dose of hepatitis B vaccine), language used to report the work, quality of the study for non-randomised studies (ie, risk of bias), sample size (smaller studies with ≤30 infants in either the treated or control group *vs* larger studies with >30 infants in both the treated and control groups), and maternal viral load criteria (pre-specified viral load threshold of ≥5·3 $\log_{10}$ IU/mL and mean HBV DNA level reported for participating women *vs* either a pre-specified viral lead threshold of <5·3 $\log_{10}$ IU/mL or no mean HBV DNA level reported). For comparison of randomised controlled trials and non-randomised studies for the primary efficacy analysis, and for all subgroup analyses, we assessed whether or not subgroup effects were present (indicated by a p value of <0·05) using the fixed-effects inverse variance method.

In addition to a priori defined subgroup analyses looking at differences in efficacy outcomes by the time of treatment initiation, and to further explore optimal timing of peripartum antiviral prophylaxis, we did post-hoc meta-analyses including only studies with multiple treatment groups with different treatment start times. These analyses directly compared the efficacy of peripartum antiviral prophylaxis, viral load before treatment initiation, and viral load before delivery for mothers with earlier versus later start of treatment, including pre-pregnancy versus during pregnancy, first trimester (week 0 to week 12 of pregnancy) versus second trimester (week 13 to week 26), and second trimester versus third trimester (week 27 onwards). The analysis of viral load before treatment initiation and the analysis of viral load before delivery involved pooling mean differences in viral load at the various timepoints to generate the standardised mean difference (SMD). Also post hoc, where possible, we examined differences in safety outcomes as per timing of treatment initiation.

When ten or more studies were included in any primary efficacy analysis or subgroup analysis,[21] we assessed them using funnel plots and Egger's test for small-sample effects, which is a potential marker for publication bias.

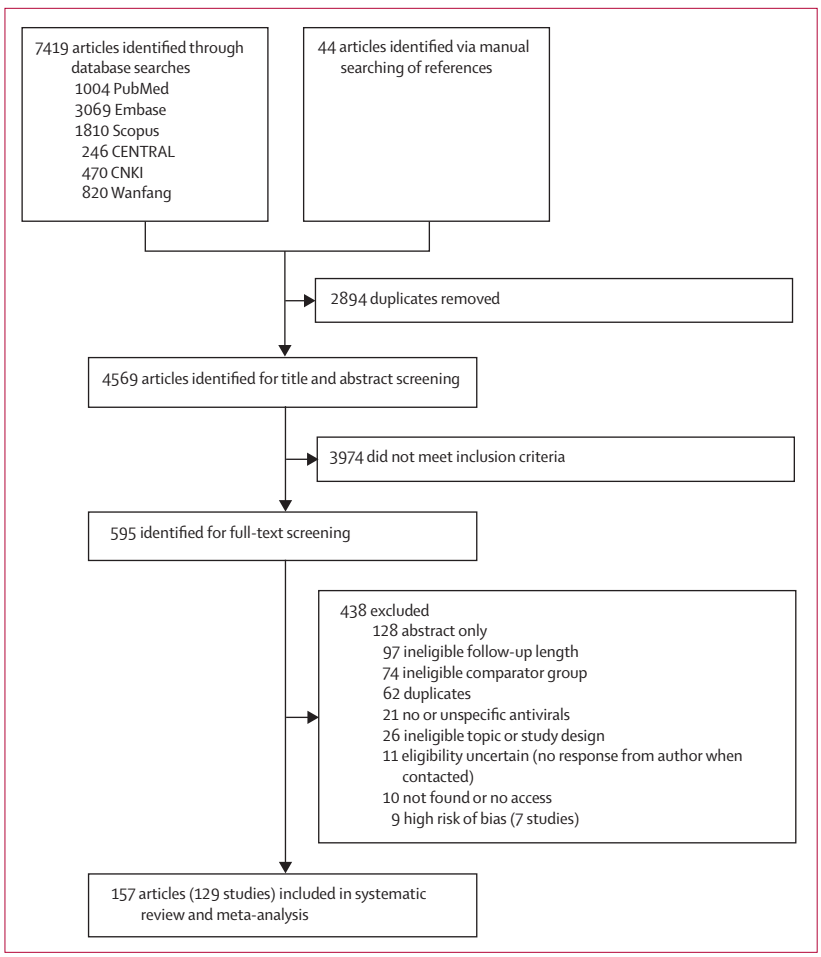

Figure 1: **Study selection**

We assessed the evidence quality for primary efficacy analyses and safety analyses using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework,[22] on the basis of risk of bias, inconsistency, imprecision, indirectness, and reporting bias.

We did all analyses using STATA (version 13.1).

Role of the funding source

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

Results

Of 7463 articles identified, 595 were eligible for full-text screening, and 129 original studies (reported in 157 articles) ultimately met eligibility criteria: 33 randomised controlled trials and 96 non-randomised studies (figure 1). These studies enrolled a total of 18112 HBV-infected mothers (9573 treated, 8539 untreated) and 17582 of the infants who were born to these mothers had complete follow-up (9411 from treated mothers, 8171 from non-treated mothers). The following antivirals were assessed in three or more studies and were therefore assessed in the meta-analysis: tenofovir disoproxil fumarate 300 mg (19 studies, with 1092 mothers and 1072 infants),[13–15,23–44] lamivudine 100–150 mg (40 studies, with 2080 mothers and 2007 infants),[32–35,39,45–88] and telbivudine 600 mg (83 studies, with 6036 mothers and 5971 infants).[30,38,42,43,46,50,56,60,62,64,76,79,80,85,89–173] No meta-analysis could be done for the two eligible studies on telbivudine 100 mg (65 mothers and 65 infants)[51,174] or for the one study each of adefovir 10 mg (42 mothers and 42 infants)[175] and adefovir 500 mg (258 mothers and 254 infants);[176] the results of these studies are summarised in the appendix 3 (pp 18–19).

Eligible articles were published in English (n=22) or Chinese (n=107). Most studies (121 [94%] of 129) took place in China (appendix 3 pp 20–21). One study was done in both China and the Philippines,[53,54] and one study each was conducted in Thailand,[14,15,23] Turkey,[28] Taiwan,[29] Australia,[32–35] Japan,[39] Egypt,[59] and Ireland.[67] Only eight studies reported HBV genotypes for all enrolled mothers: genotypes B and C in seven Asian studies;[24,29,39,76,128,139,160] and genotypes B, C, D, and E in one Irish study.[67] In 79 (61%) studies, the inclusion criteria specified a high (>5·0 $\log_{10}$ IU/mL) maternal viral load threshold at baseline for all participants. 83 (64%) studies only included women who were HBeAg-positive, nine (7%) studies included a mix of women who were HBeAg-positive and HBeAg-negative,[32,53,59,64,96,111,139,147,152] and one (1%) study[165] only included women who were HBeAg-negative. The remaining 36 (28%) studies did not report on HBeAg-positivity status. All included studies either excluded women co-infected with HIV, HCV, or HDV, or did not report on their prevalence. In most studies (102 [79%] of 129), a timely birth dose of the hepatitis B vaccine and HBIG were provided to neonates. 27 (21%) studies did not clearly indicate timely administration of a birth dose and HBIG.

Five randomised controlled trials assessed tenofovir disoproxil fumarate, of which two had a low risk of bias for most of the main criteria of the Cochrane Collaboration tool for randomised controlled trials[13,14] and the remaining three had a high or unclear risk of bias for most of these criteria.[24,26,27] None of the randomised controlled trials investigating lamivudine (n=8) or telbivudine (n=21) achieved a low risk of bias rating for most of the main criteria; most were either high or unclear risk for performance bias (masking of study personnel), detection bias (masking of outcome assessment), and attrition bias (high loss to follow-up or no reporting of loss to follow-up; appendix 3 pp 34–55). Only six (18%) of the included randomised controlled trials presented adequate details of loss to follow-up;[13,14,26,89,103,106] therefore we were unable to do an intention-to-treat meta-analysis. Of the 96 non-randomised studies, 29 (30%) had a high risk of bias

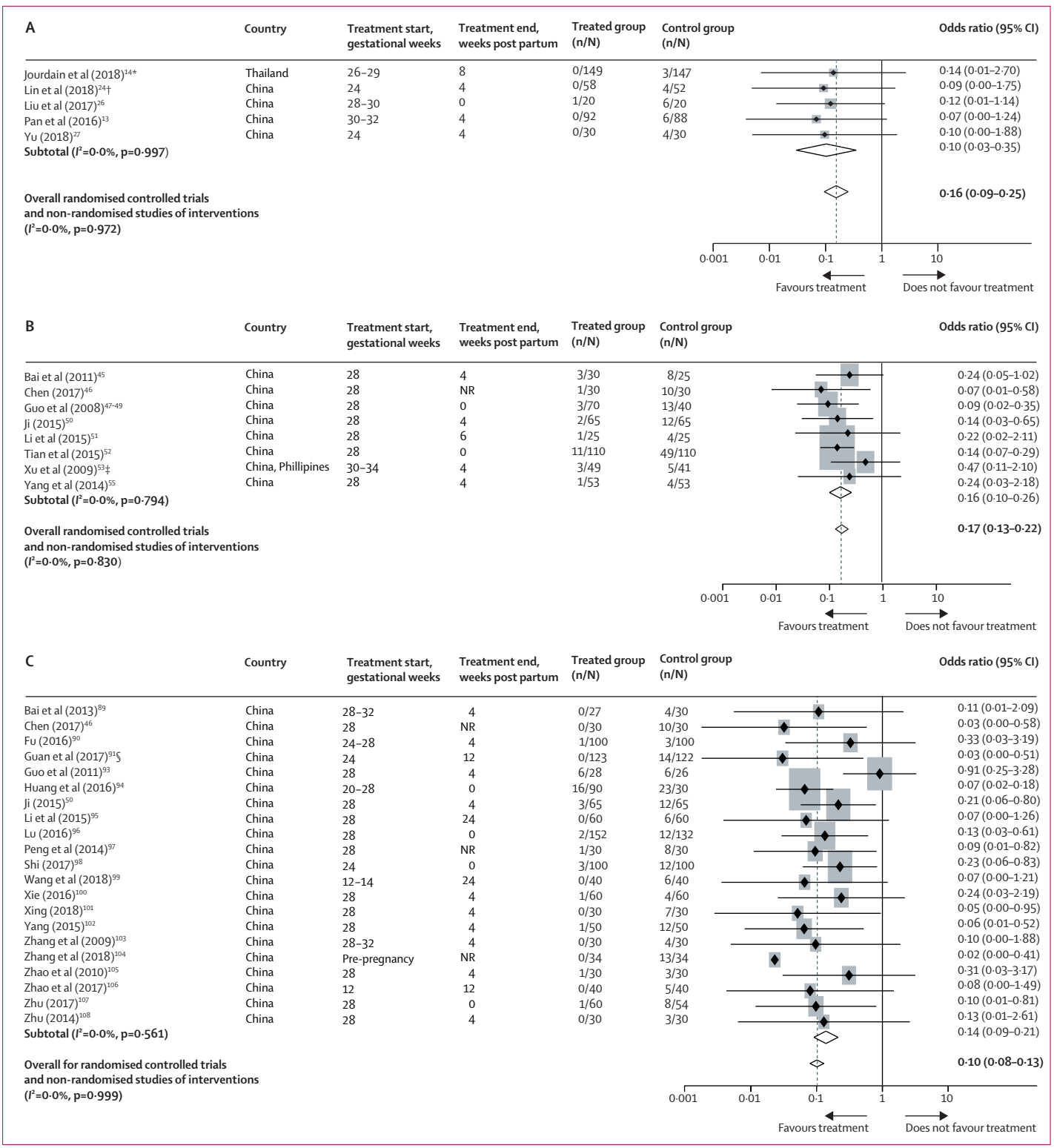

Figure 2: **Efficacy of peripartum antiviral prophylaxis from randomised controlled trials, and overall for randomsied controlled trials and non-randomised studies, using tenofovir disoproxil fumarate 300 mg (A), lamivudine 100–150 mg (B), and telbivudine 600 mg (C) in the prevention of MTCT**

Data for non-randomised studies of interventions are shown in the appendix 3 (pp 104–06). MTCT is defined as HBsAg positivity in infants aged 6–12 months. NR=not recorded. MTCT=mother-to-child transmission. *Study population is also reported in Salvadori et al (2019)[15] and Jourdain et al (2016).[23] †Study population is also reported in Liu et al.[25] ‡Study population is also reported in Yang et al (2008).[54] §Study population is also reported in Chen et al (2017).[92]

	Tenofovir disoproxil fumarate 300 mg (n=19)			Lamivudine 100–150 mg (n=40)			Telbivudine 600 mg (n=83)		
	Studies	OR (95% CI)	p value	Studies	OR (95% CI)	p value	Studies	OR (95% CI)	p value
Study design									
Randomised controlled trials	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-randomised studies	14	0·17 (0·10–0·29)	..	32	0·17 (0·12–0·24)	..	62	0·09 (0·06–0·12)	..
Timing of peripartum antiviral prophylaxis 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 peripartum antiviral prophylaxis discontinuation (post partum)									
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	NA	..	2	NA	..	8	0·06 (0·02–0·16)	..
24 weeks	0	NA	..	0	NA	..	6	0·11 (0·04–0·29)	..
Mean maternal viral load at baseline, log_{10} IU/mL									
5·0–5·9	0	NA	0·96	0	NA	NA	1	NA	0·14
6·0–6·9	0	NA	..	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	NA	..	13	0·06 (0·03–0·13)	..
8·0–8·9	3	0·11 (0·02–0·51)	..	2	NA	..	1	NA	..
Maternal HBeAg at baseline									
Positive	11	0·09 (0·04–0·21)	NA	30	0·16 (0·12–0·23)	0·45	52	0·11 (0·08–0·14)	0·65
Negative	0	NA	..	0	NA	..	1	NA	..
Mixed	1	NA	..	4	0·26 (0·08–0·82)	..	6	0·09 (0·04–0·21)	..
Infant immunoprophylaxis regimen									
Timely birth dose of hepatitis B vaccine and 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 birth dose of hepatitis B vaccine or HBIG	5	0·16 (0·06–0·43)	..	9	0·13 (0·06–0·25)	..	18	0·10 (0·06–0·16)	..

HBIG=hepatitis B immunoglobulin. MTCT=mother-to-child transmission. NA=not applicable. OR=odds ratio. *MTCT is defined as HBsAg positivity in infants aged 6–12 months.

Table 1: **Efficacy of peripartum antiviral prophylaxis in the prevention of MTCT* by subgroup**

with a score of 6 and 67 (70%) had low risk of bias with a score of 7–9. No differences were seen in the distributions of risk of bias scores across non-randomised studies examining the three main treatment regimens (appendix 3 pp 56–103).

Peripartum antiviral prophylaxis was associated with a significant reduction in HBsAg positivity in infants aged 6–12 months in both randomised controlled trials and non-randomised studies. The pooled ORs in randomised controlled trials were 0·10 (95% CI 0·03–0·35) for tenofovir disoproxil fumarate, 0·16 (0·10–0·26) for lamivudine, and 0·14 (0·09–0·21) for telbivudine (figure 2). Heterogeneity was not present (I^2=0·0%) in any of the analyses, and the three antiviral regimens were similar in efficacy without any significant difference (p=0·78]). The pooled ORs in non-randomised studies were 0·17 (95% CI 0·10–0·29) for tenofovir disoproxil fumarate, 0·17 (0·12–0·24) for lamivudine, and 0·09 (0·06–0·12) for telbivudine (appendix 3 pp 104–06). Between randomised controlled trials and non-randomised studies, no significant differences in treatment efficacy were observed for each type of antiviral (figure 2; appendix 3 pp 104–06); therefore, these data were merged for subsequent subgroup analysis. Similar efficacies were observed when using infant HBV DNA positivity as an endpoint (appendix 3 pp 107–09). No heterogeneity (I^2=0·0%) was seen in any of the meta-analyses that used HBV DNA positivity as the endpoint, besides that of randomised controlled trials using lamivudine (I^2=39·8%), in which only five studies were included and one outlier (OR 1·28, 95% CI 0·20–8·32)[45] contributed all observed heterogeneity. The individual characteristics (where available) of infants who were infected with hepatitis B through MTCT despite maternal prophylaxis with 300 mg of tenofovir disoproxil fumarate are shown in the appendix 3 (pp 110–11).

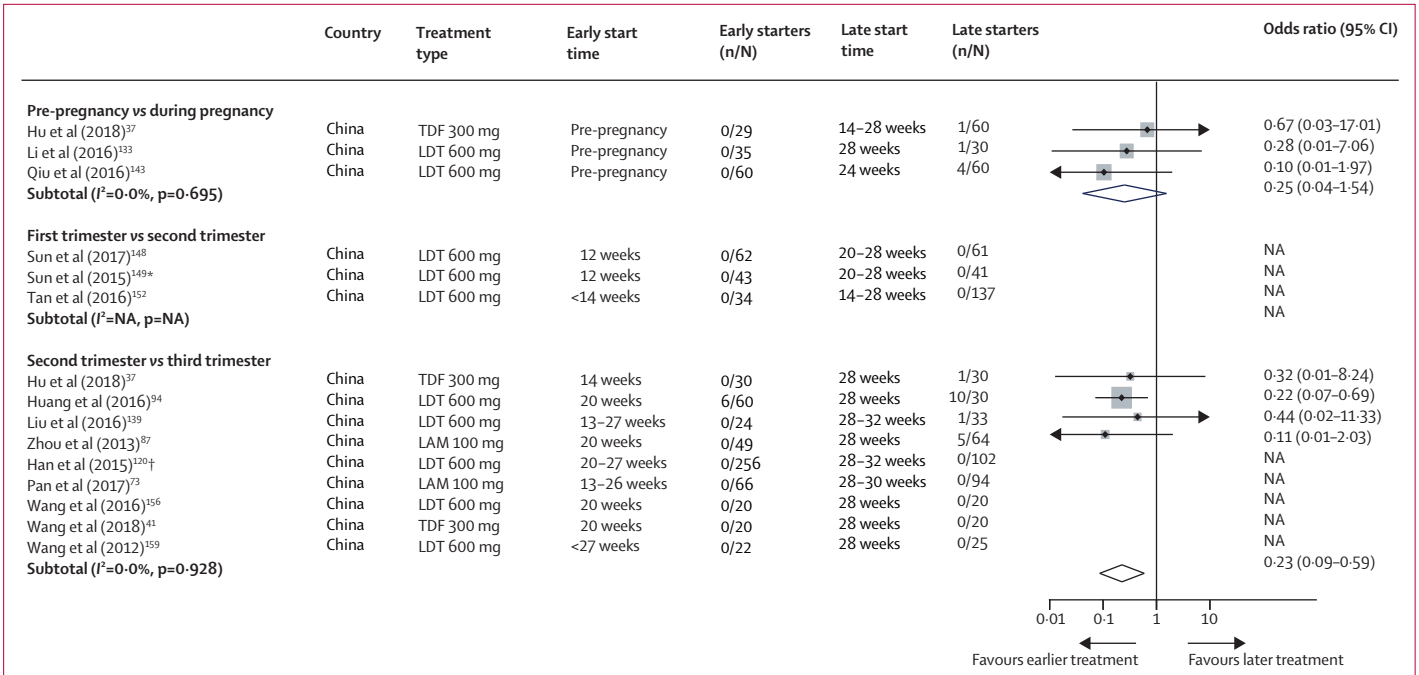

Figure 3: **Post-hoc analysis of efficacy of earlier versus later initiation of peripartum antiviral prophylaxis in the prevention of MTCT**
MTCT is defined as HBsAg positivity in infants aged 6–12 months. LAM=lamivudine. LDT=telbivudine. MTCT=mother-to-child transmission. NA=not applicable. TDF=tenofovir disoproxil fumarate. *Study population is also reported in Sun et al (2013).[150] †Study population is also reported in Han et al (2011),[121] Han et al (2012),[122] Pan et al (2012),[123] Wang et al (2017),[124] and Yu et al (2014).[125]

Efficacy did not vary according to mean maternal viral load at baseline (6·0–6·9 $\log_{10}$ IU/mL, 7·0–7·9 $\log_{10}$ IU/mL, 8·0–8·9 $\log_{10}$ IU/mL), the timing of peripartum antiviral prophylaxis discontinuation (at delivery or 4–8, 12, or 24 weeks post partum), infant immunoprophylaxis regimen, language used to report the study (English or Chinese), risk of bias score for non-randomised studies (high, 6; intermediate, 7; low, 8–9), study sample size (48 studies with ≤30 infants in either the treated or control group *vs* 81 studies with >30 infants in both the treated and control groups), or maternal viral load criteria (table 1; appendix 3 pp 112–38). For any particular antiviral, there were three or more studies only in the Western Pacific WHO region, so we were unable to do our subgroup analysis by this factor. For timing of peripartum antiviral prophylaxis initiation, efficacy did not vary by gestational age at the time of treatment initiation for tenofovir disoproxil fumarate 300 mg or telbivudine 600 mg (table 1). Lamivudine 100–150 mg was associated with greater efficacy with earlier initiation, but compared with later initiation the association was not significant (p=0·06; table 1). 14 studies were eligible for our post-hoc meta-analyses of studies that directly compared different treatment starting times (n=2 of tenofovir disoproxil fumarate, n=10 of telbivudine, and n=2 of lamivudine). Our analysis of those starting in the second versus third trimester suggested that starting treatment in the second trimester might be more effective at reducing MTCT risk (OR 0·23, 95% CI 0·09 to 0·59; figure 3). In this post-hoc meta-analysis dataset, although baseline viral load ($\log_{10}$ IU/mL) did not differ between women in these two treatment timing groups before treatment (SMD 0·01, 95% CI –0·16 to 0·19), women who started treatment earlier (in the second trimester) had significantly reduced viral load before delivery compared with those who started treatment later (ie, in the third trimester; SMD –0·62, –0·77 to –0·46; appendix 3 pp 139–40).

We found no evidence that peripartum antiviral prophylaxis was associated with an increased risk of fetal death or post-partum haemorrhage; however, the number of events was small and the estimates were imprecise (table 2; appendix 3 pp 141–46). We also found no association between cessation of tenofovir disoproxil fumarate (four studies), lamivudine (six studies), or telbivudine (three studies) and increased risk of post-partum hepatitis B flare, on the basis of evaluation of hepatitis flare at a fixed time in the intervention group and a matched period in the control group (table 2; appendix 3 pp 147–58). We found moderate to substantial heterogeneity in the meta-analysis of post-partum hepatitis B flare after treatment cessation for tenofovir disoproxil fumarate (I^2=66·5%) and lamivudine (I^2=46·5%), and considerable heterogeneity (I^2=85·5%) in this meta-analysis for telbivudine. The definition of flare varied across studies; however, most cases were mild and spontaneously recovered, and none progressed to hepatic decompensation (appendix 3 pp 147–58). One tenofovir disoproxil fumarate study investigated antiviral resistance for all

	Tenofovir disoproxil fumarate 300 mg (n=19)				Lamivudine 100–150 mg (n=40)				Telbivudine 600 mg (n=83)			
	Valuable studies	Events/participants		Weight risk difference (95% CI)	Evaluable studies	Events/participants		Weight risk difference (95% CI)	Evaluable studies	Events/participants		Weight risk difference (95% CI)
		Treated	Control			Treated	Control			Treated	Control	
Maternal safety												
Fetal death	19	3/1097	1/881	0·003 (–0·006 to 0·012)	39	1/2003	9/2087	0·000 (–0·006 to 0·005)	81	3/5645	20/5823	–0·001 (–0·003 to 0·002)
Post-partum haemorrhage	6	9/365	7/256	–0·001 (–0·024 to 0·022)	8	98/611	61/752	0·008 (–0·012 to 0·028)	19	125/1729	116/2020	–0·001 (–0·010 to 0·008)
Post-partum hepatitis B flare*	4	28/356	20/327	–0·020 (–0·082 to 0·041)†	6	59/447	34/568	–0·020 (–0·071 to 0·030)†	3	27/431	26/565	0·022 (–0·064 to 0·109)‡
Infant safety												
Neonatal death	19	2/1079	1/858	0·000 (–0·009 to 0·009)	39	1/2010	1/2093	0·000 (–0·006 to 0·006)	82	2/5752	0/5863	0·000 (–0·002 to 0·003)
Preterm birth	9	19/622	22/479	–0·003 (–0·024 to 0·019)	10	14/609	11/399	0·000 (–0·025 to 0·025)†	24	105/2427	120/2191	–0·001 (–0·010 to 0·008)
Congenital abnormalities	14	4/802	5/687	–0·002 (–0·013 to 0·009)	16	8/845	5/953	0·003 (–0·007 to 0·014)	40	11/3585	9/2983	0·000 (–0·004 to 0·004)

*After drug cessation. †Moderate to substantial heterogeneity in estimate (I^2≥30% and <75%). ‡Considerable heterogeneity in estimate (I^2≥75%).

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

women and found no HBV mutations related to antiviral therapy.[24] By contrast, two of four studies of lamivudine[61,67,76,85] and three of seven studies[76,110,121,128,133,139,148] of telbivudine detected drug-resistant mutations in some mothers who had been treated. We were not able to do a meta-analysis of antiviral resistance because of considerable variation in timing of testing and the population tested. We found no differences in risk of any maternal safety outcomes by timing of treatment initiation (appendix 3 pp 159–72).

We found no evidence that peripartum antiviral prophylaxis was associated with an increased risk of neonatal death, preterm birth, or congenital abnormalities; however, the number of events was small and so the estimates were imprecise (table 2; appendix 3 pp 173–81). Only one tenofovir disoproxil fumarate study investigated bone mineral density changes in children in both groups, with no significant difference detected.[14,15] We found no differences in risk of any infant safety outcomes by timing of treatment initiation (appendix 3 pp 159–172). We found heterogeneity (I^2=43·0%) in the meta-analysis of the risk of preterm birth after lamivudine 100–150 mg, largely due to two outlying studies, both of which were non-randomised studies that started treatment very early (pre-pregnancy or in the first trimester; appendix 3 p 177).[64,72]

In our assessment of risk of bias across studies, funnel plots and the Egger's test did not indicate small-sample effects in randomised controlled trials. However, in non-randomised studies, we found evidence of potential small-sample effects for the efficacy of each of the treatment types (appendix 3 pp 182–92).

The GRADE evidence quality for the primary endpoint, based on randomised controlled trials, was high for tenofovir disoproxil fumarate and moderate for lamivudine and telbivudine (due to high or unclear risk of bias in most studies; appendix 3 pp 193–203). Although the GRADE score was lower for non-randomised studies, the results of these studies were consistent with randomised controlled trials. For some safety outcomes evaluated by randomised controlled trials, including fetal death, neonatal death, and congenital abnormalities, the GRADE score was ranked as moderate for tenofovir disoproxil fumarate and low for lamivudine and telbivudine. By contrast, the GRADE scores for post-partum haemorrhage and post-partum flare were low or very low for all types of antivirals. We were not able to do GRADE evidence quality analysis for antiviral resistance because of inconsistencies in the method of reporting this safety measure in included studies.

Discussion

We found evidence to support the efficacy and safety of peripartum antiviral prophylaxis using three different types of nucleoside and nucleotide analogues—namely, tenofovir disoproxil fumarate, lamivudine, and telbivudine. Our meta-analysis of randomised controlled trials showed that these antivirals were associated with similar reductions in the likelihood of MTCT. For safety outcomes, we found no evidence for an increased risk associated with any of the antivirals examined, although some findings were based on few events. However, our systematic review also suggested the low barrier to resistance of early generation nucleoside and nucleotide analogues (lamivudine and telbivudine).[12,177] Consequently, WHO recommends tenofovir disoproxil fumarate for HBV-infected women with high viral load to prevent MTCT.

An important strength of our systematic review was our comprehensive search of the scientific literature, which covered both predominantly English-language

databases and Chinese-language databases. We used this method because many studies on HBV MTCT have been published in Chinese-language articles that are not indexed on predominantly English-language databases. Hence we included more than twice the number of studies compared with previous systematic reviews on this topic.[178–184] The large number of studies included enabled us to do subgroup analyses for efficacy, and to evaluate safety with outcomes that are reported relatively rarely. Additionally, we excluded articles assessing the same patient group to avoid double-counting and overweighting of the same study samples; the inclusion of overlapping patient populations in other systematic reviews has been criticised.[185] We also excluded poorly conducted non-randomised studies that had a high risk of bias. Subsequently, we found no evidence of differences in efficacy estimates between studies by language of publication, nor between studies with smaller versus larger sample sizes.

The optimal timing to start and stop peripartum antiviral prophylaxis 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 post partum.[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 earlier start might be linked to increased viral load reduction in women who are treated earlier. However, this finding should be cautiously interpreted as it is based on only a few studies (n=4)[37,87,94,139] and events (23 total). Moreover, only two of the studies included in this post-hoc analysis used tenofovir disoproxil fumarate 300 mg; hence more research is needed on this topic before any conclusion can be made. WHO recommends starting peripartum antiviral prophylaxis from week 28 of pregnancy, pending additional evidence to support earlier administration.[17]

No difference was observed in the efficacy of peripartum antiviral prophylaxis when cessation was at the time of childbirth versus at 4–8 weeks post partum, suggesting that peripartum antiviral prophylaxis could be stopped immediately after delivery. However, another concern is post-partum hepatitis flare. In pregnant women infected with HBV who do not take concurrent antiviral therapy, suppression in maternal immunity during pregnancy followed by its rapid reconstitution after childbirth could trigger a post-partum flare. Early studies have reported that initiating antivirals during pregnancy and their withdrawal at delivery might further increase the risk of post-partum flares.[188] In our meta-analysis we did not observe any difference in the risk of post-partum flares between the treated group after discontinuation of peripartum antiviral prophylaxis and controls; however, none of these comparative studies stopped peripartum antiviral prophylaxis at the time of childbirth. In four included studies in which all women were HBeAg-positive, and that only reported on post-partum hepatitis B flare in the treated group, the range of flare risk for women stopping treatment at childbirth was 3·5–19·2% (appendix 3 pp 147–158).[67,84,109,145] This range overlaps with that previously reported for non-treated women who were HBeAg positive (14·2–40·0%).[189,190] Few studies were included in the safety meta-analysis for post-partum hepatitis flare and the GRADE evidence quality was low or very low for all treatment types for this outcome. All meta-analyses for all treatments that assessed post-partum hepatitis flare had high heterogeneity, which is probably due to the small number of eligible studies included in the analysis and important differences in both the safety outcome definitions used and the treatment regimen timing across these studies. Most flares described in the studies were mild and self-limiting, only a few required antiviral therapy, and none developed into hepatic decompensation.

Our review had several potential limitations. Only two (6%) of 33 randomised controlled trials were assessed as having an overall low risk of bias. Only six (18%) of the included randomised controlled trials presented adequate details of loss to follow-up, which restricted our ability to do an intention-to-treat meta-analysis. Furthermore, although non-randomised studies with a very high risk of bias were excluded from our analysis, 30% of the remaining non-randomised studies had a score of 6 (high) on the Newcastle-Ottawa Scale, indicating multiple methodological limitations. Many of the included studies had small sample sizes (≤30 infants) in either the treated or control group, although subgroup analysis showed no difference in efficacy estimates between smaller and larger studies for any treatment type. Some subgroup meta-analyses had few (ie, <5) eligible studies, such as those examining differences in efficacy by mean maternal viral load at baseline; therefore, these results should be interpreted cautiously. This is a meta-analysis of aggregate data, and so we were restricted in our examination of some topics of interest, such as differences in efficacy by maternal viral load, which might be better assessed using a meta-analysis of individual participant data. Importantly, most of the studies included were done in Asia, particularly in China. Of the seven studies done outside of China, only one from each of Thailand and Taiwan had more than 30 infants in both treated and control groups. Therefore, our meta-analysis has little representation of diverse populations and the applicability of our findings to other regions is uncertain. For example, in sub-Saharan Africa—another area with high HBV prevalence—the major HBV genotypes, natural history of chronic infection with HBV, and the current standard of care all differ from those in Asia.[191,192] Many African countries have little coverage of a birth dose of hepatitis B vaccine and are without access to either HBIG or HBV DNA testing. No studies in this systematic review assessed the efficacy of peripartum antiviral prophylaxis without HBIG (ie, with a birth dose alone), indicating an important research gap. Assessment is ongoing to assess the

efficacy of a birth dose plus peripartum antiviral prophylaxis versus a birth dose alone (NCT03343431).

Based on the evidence provided by this study and a companion systematic review[9] that addressed HBV DNA thresholds for identifying pregnant women at risk of MTCT, WHO recommends administering tenofovir disoproxil fumarate to pregnant women infected with HBV with a high viral load (≥5·3 $\log_{10}$ IU/mL [≥200 000 IU/mL]) from week 28 of pregnancy until at least childbirth to prevent MTCT, in addition to three doses of hepatitis B vaccination including a birth dose to the neonate.[17] To accelerate global HBV elimination by 2030, promotion of the uptake of peripartum antiviral prophylaxis into routine health care is essential, particularly in low-income and middle-income countries that have the highest HBV disease burden.

Contributors

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

Declaration of interests

RC received personal fees from WHO for the role of methodologist for the WHO Global Hepatitis Programmes. All other authors declare no competing interests.

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