Antiviral Therapy in Chronic Hepatitis B Virus Infection during Pregnancy:

A Systematic Review and Meta-Analysis

Authors:

Robert S. Brown, Jr., MD, MPH[1]

rsb2005@med.cornell.edu

Brian J. McMahon, MD[2]

bdm9@cdc.gov

Anna SF Lok, MD[3]

aslok@umich.edu

John B. Wong, MD[4]

jwong@tuftsmedicalcenter.org

Ahmed T. Ahmed, MBBCh[5,6]

Ahmed.Ahmed1@mayo.edu

Mohamed A. Mouchli, MD[7]

Mouchli.Mohamad@mayo.edu

Zhen Wang, PhD[5,6]

Wang.Zhen@mayo.edu

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version record. Please cite this article as doi:10.1002/hep.28302.

Prokop J Larry, MLS[8]

Prokop.Larry@mayo.edu

Mohammad Hassan Murad, MD, MPH[5,6,9]

Murad.Mohammad@mayo.edu

Khaled Mohammed, MBBCh, MPH[5,6,9]

Mohammed.khaled@mayo.edu

Affiliations:

[1]Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY, USA

[2] Liver Diseases and Hepatitis Program, Alaska Native Tribal Health Consortium, Anchorage, AK, USA

[3]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA

[4]Division of Clinical Decision Making, Tufts Medical Center, Boston, MA, USA

[5]Evidence-Based Practice Research Program, Mayo Clinic, Rochester MN, USA

[6]Knowledge and Evaluation Research, Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, USA

7Division of Hospital Internal Medicine, Mayo clinic, Rochester, Minnesota, USA

[8]Library Public Services, Mayo Clinic, Rochester, MN, USA

[9]Division of Preventive, Occupational and Aerospace Medicine, Mayo Clinic, Rochester, MN, USA

Keywords: mother to child transmission, hepatitis B vaccine, tenofovir, telbivudine, lamivudine

Corresponding author: Robert S. Brown, Jr., MD, MPH, Division of Gastroenterology and Hepatology, Weill Cornell Medical College, 1305 York Avenue, 4th Floor New York, NY 10021. Phone: (646) 962-4463. Email: rsb2005@med.cornell.edu

List of Abbreviations: Hepatitis B virus (HBV), Hepatitis B surface antigen (HBsAg), Hepatitis B e antigen (HBeAg) positive, Mother-to-child transmission (MTCT), Hepatitis B immunoglobulin (HBIG), American Association for the Study of Liver Diseases (AASLD), chronic hepatitis B (CHB), alanine aminotransferase (ALT), cesarean section rate (CS), randomized controlled trials (RCTs), human immunodeficiency viruses (HIV).

Financial Support: This study was supported by a contract from the American Association for the Study of Liver Diseases (AASLD) to M Murad (Mayo Clinic).

Conflict of Interest:

Robert S Brown has received research grants from Gilead and has served as a consultant for Gilead and Bristol Meyers Squibb.

Anna S Lok has received research grants from Bristol-Myers Squibb and Gilead and has served on advisory panels for Gilead, GlaxoSmithKline and Merck.

B McMahon, J Wong, A Ahmed, M Mouchli, Z Wang, P Larry, M Murad, K Mohammed do not have any disclosures.

Abstract:

Introduction: Perinatal or Mother-to-Child transmission (MTCT) of hepatitis B virus (HBV) remains the major risk factor for chronic HBV infection worldwide. In addition to hepatitis B immune globulin (HBIG) and vaccination, oral antiviral therapies in highly viremic mothers can further decrease MTCT of HBV. We conducted a systematic review and meta-analysis to synthesize the evidence on the efficacy and maternal and fetal safety of antiviral therapy during pregnancy. **Methods:** A protocol was developed by American Association for the Study of Liver Diseases (AASLD) guideline writing committee. We searched multiple databases for controlled studies that enrolled pregnant women with chronic HBV infection treated with antiviral therapy. Outcomes of interest were reduction of MTCT and adverse outcomes to mothers and newborns. Study selection and data extraction were done by pairs of independent reviewers. **Results:** We included 26 studies that enrolled 3622 pregnant women. Antiviral therapy reduced MTCT, as defined by infant hepatitis B surface antigen (HBsAg) seropositivity (RR 0.3 (0.2 - 0.4) and infant HBV DNA seropositivity (RR 0.3, (0.2 - 0.5) at 6-12 months. No significant difference was found in the congenital malformation rate, prematurity rate and APGAR scores. Compared to control, lamivudine or telbivudine improved maternal HBV DNA suppression at delivery and during 4-8 weeks postpartum follow up. Tenofovir showed improvement in HBV DNA suppression at delivery. No significant differences were found in postpartum hemorrhage, cesarean section and elevated creatinine kinase rates. **Conclusions:** Antiviral therapy improves HBV suppression and reduces MTCT in women with chronic HBV infection with high viral load compared to the use of HBIG and vaccination alone. The use of telbivudine, lamivudine and tenofovir appear to be safe in pregnancy with no increased adverse maternal or fetal outcome.

Introduction:

Chronic hepatitis B virus (HBV) infection remains an important global health problem. Up to 600,000 of the approximately 240 million carriers worldwide die annually due to chronic hepatitis B (CHB)-related disease (1). Perinatal or mother-to-child transmission (MTCT) is the most common form of transmission of HBV in many high prevalence areas (2, 3) and may occur in up to 90% of mothers who are hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) positive in the absence of prophylaxis (4). This high rate of transmission may be partially due to the high proportion of mothers with active replication and HBeAg positivity during reproductive years (5-8) particularly in Asian countries and regions of the world where HBV genotype C is found (9) as MTCT is associated with high maternal viral load (HBV DNA $> 10^6$ IU/ml) (10-13). Universal prenatal testing of women is therefore recommended, as are hepatitis B vaccination and hepatitis B immunoglobulin (HBIG) administration starting at birth to prevent transmission to the newborn.

Women in their child-bearing years with CHB may need antiviral therapy independent of its impact on MTCT if they have immune active HBV infection. Accordingly, data on the safety of antivirals during pregnancy, and especially their impact on potential teratogenicity, are of paramount importance when counseling pregnant patients with CHB on risks and benefits to their offspring.

Antiviral therapies for CHB have advanced markedly in the last decade. The newer, more potent, nucleos(t)ide analogues durably suppress HBV viremia in most patients. Evolving data for CHB patients show low (0-1%) rates of viral resistance and breakthrough after up to 6 years

of entecavir or tenofovir monotherapy (14, 15). The benefits of long-term virus suppression include slowing of liver disease progression and reversal of fibrosis and cirrhosis (16-18). Although no HBV therapies are currently approved for use in pregnancy, women being treated for CHB may become pregnant. Moreover, pregnant women in the immune tolerant phase of CHB with high HBV DNA levels (>10^7 IU/mL) may want to be considered for antiviral therapy to reduce HBV DNA level and decrease the risk of MTCT that can occur despite neonatal immunoprophylaxis (10) (19). Safety data on the use of anti-HBV therapies are largely derived from HIV positive mothers studied in the Anti-retroviral Pregnancy Registry, which do not report any adverse impact of lamivudine or tenofovir use(20). However, the use of antiviral therapies in pregnancy is controversial and knowledge about the harm and benefit ratio is not widely disseminated among hepatologists and other providers including those specializing in women's health. Therefore, the American Association for the Study of Liver Diseases (AASLD) made this issue a priority for clinical practice guideline development and evidence synthesis. We performed a systematic review and meta-analysis to compare the effect of oral HBV therapy (lamivudine, entecavir, telbivudine or tenofovir) on MTCT prevention, HBV DNA suppression, and on maternal and fetal safety including major birth defect rates.

Methods:

This systematic review follows a protocol developed by a guideline writing group from the AASLD and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (21).

Eligibility Criteria:

We included controlled or comparative studies that enrolled pregnant women diagnosed with chronic HBV infection (characterized by the presence of HBsAg for more than 6 months), who received antiviral therapy and reported the outcomes of interest, including prevention of MTCT of HBV, clinical efficacy, and adverse outcomes from antiviral therapy to both mothers and newborns. Both English and non-English language studies were included. We excluded studies that enrolled infants who did not receive immunization during the first week postpartum; studies of patients co-infected with hepatitis C, D or human immunodeficiency viruses (HIV); patients receiving steroids, chemo/immunotherapy, liver transplant recipients and patients undergoing hemodialysis; and uncontrolled studies or studies published as abstracts only.

Search strategy:

A comprehensive search of Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus was conducted from early 1988 to September 11th 2014. The search strategy was designed and conducted by an experienced librarian (LJP) with input from the principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of antivirals for hepatitis B in pregnancy. Details of the search strategy are available in supplemental Table 1. A manual search of bibliographies of the included studies and relevant systematic reviews was conducted. Content experts from AASLD were also queried for potential references.

Study selection:

Two independent reviewers screened titles and abstracts for potential eligibility in duplicate using an online reference management system (DistillerSR, Evidence Partners, Inc.). Included

abstracts were then reviewed in full text following the same procedure. Disagreements were reconciled by consensus or by a third reviewer.

Data Extraction:

For each study, data extraction was done in duplicate using a standardized, pretested form. A third reviewer compared data and resolved inconsistencies by referring to the full text of the articles. We extracted the following data from each study: study characteristics, patient baseline characteristics, intervention details and outcomes of interest.

Outcomes:

We were interested in the following outcomes: infant outcomes including the risk of vertical transmission, defined by HBsAg seropositivity at 6-12 months or HBV DNA positivity at 6-12 months, APGAR score (1 minute), prematurity rate and congenital malformation rate. Maternal outcomes included HBV DNA suppression, alanine aminotransferase (ALT) normalization, HBeAg loss, HBeAg seroconversion, cesarean section rate (CS), postpartum hemorrhage rate and elevated creatine kinase.

Risk of bias assessment:

Two reviewers independently assessed the risk of bias (i.e., systematic error) using the Cochrane Risk of Bias assessment tool and the Newcastle-Ottawa Scale (NOS) for randomized controlled trials (RCTs) and observational studies, respectively. The quality of evidence (i.e., certainty in the estimates) was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Criteria used to evaluate quality of evidence were risk of

bias, indirectness (surrogate outcomes), imprecision (wide confidence intervals), inconsistency (heterogeneity) and publication bias (22).

Statistical analysis:

For dichotomized outcomes, we calculated the risk ratio and 95% confidence intervals using binomial distribution. We then pooled the log transformed risk ratios using the DerSimonian and Laird random-effect models and estimated heterogeneity using the Mantel-Haenszel model. For continuous outcomes, we calculated the weighted difference in means between the baseline and the longest duration of follow-up for each study and pooled effect size using the DerSimonian and Laird random-effect model. To measure the overall heterogeneity across the included studies, we used the I^2 statistic, where I^2 >50% suggests high heterogeneity. All statistical analyses were conducted using STATA, version 13 (StataCorp LP, College Station, TX). We planned to explore the impact of publication bias using the Egger regression asymmetry test and by constructing funnel plots if a sufficient number of studies (>20) per outcome was available and heterogeneity was low (23).

Results:

The initial search resulted in 734 citations and 3 systematic reviews (24-26) that included the China Biological Medicine Database and summarized additional studies published in Chinese. We eventually included 26 studies. The average weighted Kappa for study selection was 0.82. The study selection process and reasons for exclusions are depicted in figure 1.

Characteristics of the included studies:

Twenty six studies that enrolled a total of 3622 pregnant women were included in the analysis, 10 studies (27-36) were RCTs and 16 studies (37-52) were non randomized studies. Most of the studies (92%) were conducted in China and none in the United States (US). Treatment started in the 2nd or 3rd trimester with an average baseline HBV DNA level of 7.63 log10 IU/mL and average baseline ALT level of 37.7 U/L. In these studies, all infants received hepatitis B vaccine at birth. Table 1 summarizes the characteristics of the studies.

Among included studies, 11 studies compared lamivudine vs control; 9 studies (27, 36, 37, 43-45, 49, 50, 52) compared telbivudine vs control; 2 studies (37) (52) compared lamivudine vs telbivudine; 3 studies (38, 39) (51) compared tenofovir vs control and another study (38) compared tenofovir vs lamivudine.

Five RCTs (28-30, 32, 35) were considered to have low risk of bias while 5 studies (27, 31, 33, 34, 36) were considered to high risk of bias due to unclear/unreported methods of randomization, allocation concealment, blinding, or incomplete outcome data reporting. For non-randomized studies, the overall methodological quality and features were adequate/ appropriate as 60% of the studies reported adequate patient selection methods, comparable study groups, and adequate outcome measures and follow up data. Tables 2 and 3 include detailed description of the risk of bias assessment.

Infant outcomes:

Use of any antiviral therapy compared to control in pregnant women reduced the likelihood of MTCT as defined by infant HBsAg seropositivity (8 RCTs, RR 0.3 (95% CI, 0.2 - 0.4) I^2=63.9%) or infant HBV DNA positivity (5 RCTs, RR 0.3 (95% CI, 0.2 - 0.5) I^2= 47.2%) at 6-12 months (Figure 2). Use of any antiviral compared to control reduced the risk of infant HBsAg

seropositivity and HBV DNA positivity by 13.4% and 18.7% respectively. The quality of evidence was moderate to low, rated down due to risk of bias. This significant reduction persisted when comparing individual drugs vs control at 6-12 months after birth. Lamivudine (Figure 3) reduced infant HBsAg seropositivity by 11.7% (5 RCTs, RR 0.3 (95% CI, 0.2 - 0.6) I^2= 42.4%) and infant HBV DNA positivity by 21.2% (3 RCTs, RR 0.3 (95% CI, 0.2 to 0.6) I^2=47.9%). Telbivudine also reduced infant HBsAg seropositivity by 15.8% (4 RCTs, RR 0.2 (95% CI, 0.1 - 0.5) I^2= 0%) and infant HBV DNA positivity by 16.2% (2 RCTs, RR 0.1 (95% CI, 0.03 to 0.6) I^2= 62.4%) compared to the control group (Figure 4).

In 3 non-randomized studies (38, 39, 51), tenofovir vs control (Figure 5) reduce infant HBsAg seropositivity by 15.8% at 6-12 months follow up (RR 0.2 (95% CI, 0.1 to 0.7) I^2= 0%).

Compared to lamivudine, telbivudine (1 study, RR 1 (95% CI, 0.7 to 1.5) and tenofovir (1 study, RR 2.93 (95% CI, 0.12 to 70.08) showed no statistically significant reduction in infant HBsAg seropositivity at 6-12 months.

When comparing any antiviral therapy vs. control for fetal harms, no statistically significant difference was found in any of the non RCTs reporting on congenital malformation rate, prematurity rate and APGAR scores (Figure 6). The quality of the evidence of infant outcomes was moderate to low, down rated due to risk of bias and imprecision.

Maternal outcomes:

Compared to control, lamivudine improved maternal HBV DNA suppression before delivery (1 cohort, RR 57.1, 95% CI, 3.5 - 921.4) and during 4-8 weeks postpartum follow up (2 cohorts, RR 70.9, (95% CI, 8.5 - 590) I^2=12.2%) . No significant difference was found in maternal ALT normalization.

In studies comparing telbivudine vs control, telbivudine showed improved maternal HBV DNA suppression at delivery (3 cohorts, RR 52.8 (95% CI, 10.7 - 261.8) I^2=0%), at 4 weeks postpartum (2 cohorts, RR 102(95% CI, 14.4 - 722.8) I^2=0%) and at 28 weeks postpartum (1 cohort, RR 1.5 (95% CI, 1.2 - 1.8). When compared to control, pregnant women receiving telbivudine consistently had improved maternal ALT normalization at delivery (2 cohorts, RR 1.5 (95% CI, 1.2 - 1.8) I^2=0%), at 4 weeks postpartum (1 cohort, RR 1.6 (95% CI, 1.1 - 2.3) and at 28 weeks postpartum (1 cohort, RR 1.3(95% CI, 1.04 to 1.6). Telbivudine also significantly increased maternal HBeAg loss at delivery (2 cohorts, RR 1.7 (95% CI, 1.3 - 2.2) I^2=0%), at 4 weeks postpartum (1 cohort, RR 1.6 (95% CI, 1.2 - 2.2) and at 28 weeks postpartum (1 cohort, RR 1.7 (95% CI, 1.2 - 2.29). Tenofovir compared to control showed significant improvement in HBV DNA suppression at delivery (2 cohorts, RR 45.4(95% CI, 9.3 - 222.5) but not ALT normalization or HBeAg seroconversion.

Compared to lamivudine, pregnant women treated with telbivudine had significantly greater HBV DNA suppression at delivery (1 cohort, RR 1.8 (95% CI, 1.3 to 2.6) but not HBeAg loss (RR 1.1 (95% CI, 0.1 to 21.5) or seroconversion (RR 0.6 (95% CI, 0.03 to 15.2).

When comparing any antiviral therapy vs. control for maternal harms, no statistically significant difference was found in postpartum hemorrhage rate, CS rate and elevated creatine kinase rate. The quality of the evidence in maternal outcomes was very low due to the observational nature of the studies, imprecision and indirectness. Figures 7-9 show maternal outcomes reported at delivery in studies comparing lamivudine, telbivudine and tenofovir treatment vs control group respectively. Table 4 summarizes the quality of evidence (GRADE) for infant and maternal outcomes.

Publication bias:

We were unable to evaluate publication bias due to small number of studies for each outcome.

Discussion:

For women who are or may become pregnant, consideration of the potential harms and benefits to the fetus as well as the mother complicate medication treatment decisions is important, such as administering antiviral therapy for CHB during pregnancy. Although the benefit for antiviral therapy is unproven for the many women of childbearing age who are in the immune tolerant phase of CHB, these women have the highest risk of MTCT. Thus characterizing the safety of these medications for the mother and fetus during pregnancy can help inform potential treatment choices for women of child-bearing age. Even for women who are in the immune active phase of CHB infection antiviral treatment may be postponed until after completion of childbearing as long as they have compensated liver disease. Additionally, post-delivery neonatal combined immunoprophylaxis successfully prevents HBV infection in approximately 90% of infants. Thus, prevention of MTCT of HBV does not necessarily mandate antiviral treatment during pregnancy for most women. However, the current failure rate of post-exposure neonatal immunoprophylaxis against MTCT of HBV may be unacceptably high (~9%) in women with high levels of viremia (serum HBV DNA > 10^6 copies/mL; ~2 x10^5 IU/mL) (10).

Among infants who received hepatitis B vaccine starting at birth, this meta-analysis found that antiviral therapy with lamivudine, telbivudine, or tenofovir in pregnant women with high levels of HBV DNA reduced MTCT rates, with over 70% reductions in the rates of infant HBsAg and HBV DNA positivity at 6-12 months post-partum. In non-head-to-head trials, telbivudine showed higher rates of HBV DNA suppression, ALT normalization and HBeAg seroconversion

than lamivudine. For tenofovir, there were insufficient controlled outcome data. No safety issues for maternal or fetal outcomes were identified in our meta-analysis of these studies. Thus antiviral therapy in the third trimester for women who are HBeAg + with a HBV DNA level greater than $2x10^5$ IU/mL to prevent MTCT seems warranted (see the accompanying AASLD Hepatitis B Treatment Guidelines for details).

Although lamivudine, telbivudine and tenofovir are licensed for CHB and HIV treatment, none of these drugs are approved for use in pregnancy. Telbivudine and tenofovir are currently rated pregnancy category B, and lamivudine pregnancy category C, by the United States Food and Drug Administration (US FDA) based primarily on animal data with no clear evidence of harm in sparse human data. However, the substantial experience in the use tenofovir and lamivudine in HIV- infected pregnant women to prevent HIV transmission has not identified any significant safety concerns for either mother or newborn(20). Recent data in women with HIV have reported lower bone mineral content in newborns exposed to tenofovir throughout pregnancy (53), but earlier data did not show any impact on early growth in infants exposed to tenofovir in utero (54), so the significance of this finding is unclear. Additionally, initiating tenofovir, lamivudine, or telbivudine for CHB during pregnancy may be less worrisome because the antiviral agents are usually started in the late second or early third trimester in mothers with high HBV DNA levels to reduce maternal viremia and hence the risk of MTCT of HBV. Concern remains over the propensity to develop viral resistance to lamivudine or telbivudine (55) if it is used throughout the pregnancy or postpartum, rather than restricted to the late second and third trimester. On the other hand, tenofovir has a high resistance barrier with no resistance identified to date after up to 6 years of monotherapy for CHB (56).

The major limitation of this systematic review is the absence of studies warranting high confidence. With a paucity of RCTs, most of the data are derived from cohort studies, which are subject to significant biases, especially selection bias. Additionally, despite a report from the Antiviral Pregnancy Registry finding no increased risk of birth defects for lamivudine or tenofovir (26), data on fetal safety with antivirals remain limited, particularly for telbivudine. Recommendations for management of chronic HBV infection during pregnancy are provided in the updated AASLD guidelines (57).

Conclusion:

In pregnant women with chronic HBV infection, the oral antiviral therapies lamivudine, telbivudine, and tenofovir, lowers HBV DNA level as they do in non-pregnant women and reduce the rates of MTCT. These effects were demonstrated in women who are HBeAg positive with high viral loads ($>10^6$ copies or ~$2x10^5$ IU/mL). The limited safety data suggest no increased risk of adverse maternal or fetal outcomes. Larger scale RCTs of tenofovir are ongoing and these results are eagerly awaited. In the meantime, the use of these agents in women who are HBeAg positive and have HBV DNA > 10^6 copies/mL (20,000 IU/mL) in the third trimester to prevent MTCT is recommended.

References:

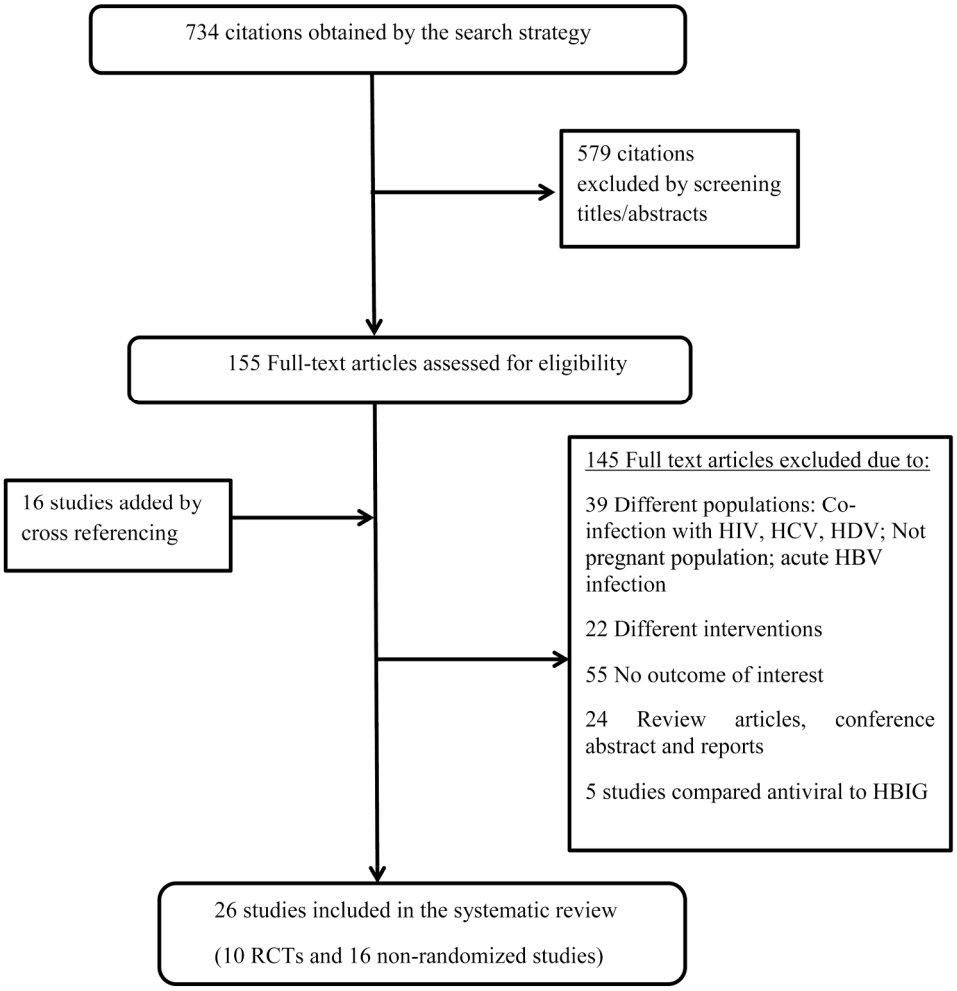
1. Maynard JE. Hepatitis B: global importance and need for control. Vaccine 1990;8 Suppl:S18-20; discussion S21-13.
2. Beasley RP, Hwang LY, Lin CC, Leu ML, Stevens CE, Szmuness W, Chen KP. Incidence of hepatitis B virus infections in preschool children in Taiwan. J Infect Dis 1982;146:198-204.
3. Alter MJ, Hadler SC, Margolis HS, Alexander WJ, Hu PY, Judson FN, Mares A, et al. The changing epidemiology of hepatitis B in the United States. Need for alternative vaccination strategies. JAMA 1990;263:1218-1222.
4. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med 1975;292:771-774.
5. Lok AS, Lai CL, Wu PC, Leung EK, Lam TS. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. Gastroenterology 1987;92:1839-1843.
6. Lok AS, Lai CL. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. Hepatology 1988;8:1130-1133.
7. Liaw YF, Chu CM, Lin DY, Sheen IS, Yang CY, Huang MJ. Age-specific prevalence and significance of hepatitis B e antigen and antibody in chronic hepatitis B virus infection in Taiwan: a comparison among asymptomatic carriers, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. J Med Virol 1984;13:385-391.
8. Stevens CE, Toy PT, Tong MJ, Taylor PE, Vyas GN, Nair PV, Gudavalli M, et al. Perinatal hepatitis B virus transmission in the United States. Prevention by passive-active immunization. JAMA 1985;253:1740-1745.
9. Livingston SE, Simonetti JP, Bulkow LR, Homan CE, Snowball MM, Cagle HH, Negus SE, et al. Clearance of hepatitis B e antigen in patients with chronic hepatitis B and genotypes A, B, C, D, and F. Gastroenterology 2007;133:1452-1457.
10. Wiseman E, Fraser MA, Holden S, Glass A, Kidson BL, Heron LG, Maley MW, et al. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust 2009;190:489-492.
11. Burk RD, Hwang LY, Ho GY, Shafritz DA, Beasley RP. Outcome of perinatal hepatitis B virus exposure is dependent on maternal virus load. J Infect Dis 1994;170:1418-1423.
12. Li XM, Shi MF, Yang YB, Shi ZJ, Hou HY, Shen HM, Teng BQ. Effect of hepatitis B immunoglobulin on interruption of HBV intrauterine infection. World J Gastroenterol 2004;10:3215-3217.
13. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat 2012;19:e18-25.
14. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661-662.
15. Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, Wichroski MJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. Hepatology 2009;49:1503-1514.
16. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology 2006;131:1743-1751.
17. Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, Safadi R, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010;52:886-893.
18. Schiff ER, Lee SS, Chao YC, Kew Yoon S, Bessone F, Wu SS, Kryczka W, et al. Long-term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic hepatitis B. Clin Gastroenterol Hepatol 2011;9:274-276.

19. Shi Z, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. Obstet Gynecol 2010;116:147-159.
20. Brown RS, Jr., Verna EC, Pereira MR, Tilson HH, Aguilar C, Leu CS, Buti M, et al. Hepatitis B virus and human immunodeficiency virus drugs in pregnancy: Findings from the Antiretroviral Pregnancy Registry. J Hepatol 2012.
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open medicine : a peer-reviewed, independent, open-access journal 2009;3:e123-130.
22. Murad MH, Montori VM, Ioannidis JP, Jaeschke R, Devereaux PJ, Prasad K, Neumann I, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. JAMA 2014;312:171-179.
23. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
24. Shi Z, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. Obstetrics & Gynecology 2010;116:147-159.
25. Han L, Zhang HW, Xie JX, Zhang Q, Wang HY, Cao GW. A meta-analysis of lamivudine for interruption of mother-to-child transmission of hepatitis B virus. World Journal of Gastroenterology 2011;17:4321-4333.
26. Lu YP, Liang XJ, Xiao XM, Huang SM, Liu ZW, Li J, Hocher B, et al. Telbivudine during the second and third trimester of pregnancy interrupts HBV intrauterine transmission: a systematic review and meta-analysis. Clinical Laboratory 2014;60:571-586.
27. Zhang L-j, Wang L. [Blocking intrauterine infection by telbivudine in pregnant chronic hepatitis B patients]. Chung Hua Kan Tsang Ping Tsa Chih 2009;17:561-563.
28. Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, Zhang SL, 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.
29. 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]. Chung-Hua Fu Chan Ko Tsa Chih [Chinese Journal of Obstetrics & Gynecology] 2008;43:329-331.
30. Li X-M, Yang Y-B, Hou H-Y, Shi Z-J, Shen H-M, Teng B-Q, Li A-M, et al. Interruption of HBV intrauterine transmission: a clinical study. World Journal of Gastroenterology 2003;9:1501-1503.
31. YF Z. The clinical observation of effect of lamivudine on interrupting mother to infant transmission of chronic HBV on 50 mothers [in Chinese] J Prat Obst Gynecol. 2010;26:367–368.
32. Shi ZJ LX, Yang YB, Ma L. Clinical research on the interruption of mother to child transmission of HBV- a randomized, double-blind, placebo-control study. 6th Annual Global Health Conference. New Haven (CT): Yale University 2009.
33. Guo YZ LS, Ge SL, Wang JH. . Effect of lamivudine treatment combined with active-passive immunization on interrupting mother to infant transmission of HBV [in Chinese] Clin Focus 2008;23:1730–1731.
34. Xiang GJ SJ, Jiang SQ, Hu XB, Qu AL. Evaluation of therapeutic effect in HBV vertical transmission by lamivudine treatment combined with active-passive immunization for pregnant women [in Chinese] Chin Prac Med 2007;2:14–16.
35. Shi MF LX, He J, Yang YB, Hou HY, Zhuang YL, Shen HM. Study of Lamivudine in interruption of HBV intrauterine infection [in Chinese] Clin Med Chin 2005;21:77–78.

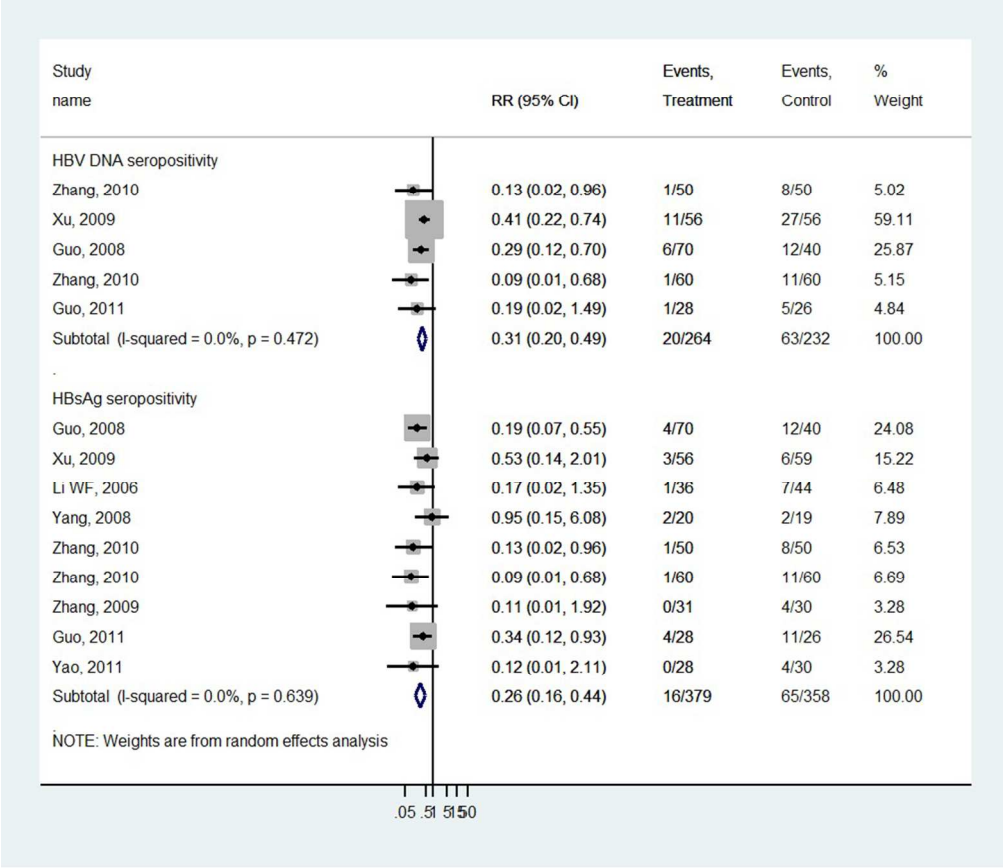
36. Guo HJ ZY. Observation the role of telbivudine in blocking mother-to-child transmission of HBV in pregnant women with high viral load. Journal of CHANGZHI Medical College 2011;25:368-370.
37. Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. Hepatology 2014;60:468-476.
38. Greenup A-J, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U, Holdaway S, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. Journal of Hepatology 2014;61:502-507.
39. Celen MK, Mert D, Ay M, Dal T, Kaya S, Yildirim N, Gulsun S, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. World Journal of Gastroenterology 2013;19:9377-9382.
40. Jiang H-x, Han G-r, Wang C-m, Ji Y. [Maternal-fetal outcomes of lamivudine treatment administered during late pregnancy to highly viremic mothers with HBeAg+ chronic hepatitis B]. Chung Hua Kan Tsang Ping Tsa Chih 2012;20:888-891.
41. Chen R, Liu S-r, Zhang S-y, Tao C-j. [Efficacy of telbivudine in blocking the vertical transmission and the safety observation of discontinuing treatment time after delivery on mother infected with HBV]. Chung Hua Kan Tsang Ping Tsa Chih 2012;20:703-704.
42. Yu M, Jiang Q, Ji Y, Jiang H, Wu K, Ju L, Tang X, et al. The efficacy and safety of antiviral therapy with lamivudine to stop the vertical transmission of hepatitis B virus. European Journal of Clinical Microbiology & Infectious Diseases 2012;31:2211-2218.
43. Pan CQ, Han G-R, Jiang H-X, Zhao W, Cao M-K, Wang C-M, Yue X, et al. Telbivudine prevents vertical transmission from HBeAg-positive women with chronic hepatitis B. Clinical Gastroenterology & Hepatology 2012;10:520-526.
44. Han G-r, Jiang H-x, Wang G-j, Yue X, Wang C-m, Kan N-y, Wu M-m. [Efficacy and safety of telbivudine in pregnant women to prevent perinatal transmission of hepatitis B virus]. Chung Hua Kan Tsang Ping Tsa Chih 2012;20:201-205.
45. Han G-R, Cao M-K, Zhao W, Jiang H-X, Wang C-M, Bai S-F, Yue X, 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. Journal of Hepatology 2011;55:1215-1221.
46. Feng HF ZS. Effect on interruption of hepatitis B virus vertical transmission by lamivudine [in Chinese] J Appl Clin Pediatr 2007;22:1019–1020.
47. Li WF JR, Wei Z, Li Y. . Clinical effect and safety of lamivudine in interruption of chronic HBV maternal to infant transmission [in Chinese] Chin Hepatol. 2006;11:106–107.
48. Han ZH CY, Li LW, Sun XW, Sun YG, Zhao H, Su XS. . Effect and safety of preventing HBV vertical transmission by lamivudine treatment [in Chinese] Chin J Intern Med 2005;44:378.
49. Yao ZC CM, Liao WY, et al. The efficacy and safety of telbivudine in blocking intraterine hepatitis B viral transmission. J Clin Hepatol 2011;14:259-61.
50. Zhang YF HH. Efficacy and safety of telbivudin in preventing mother-to-infant HBV tranmission. Adverse Drug Reactions
Journal fur Gastroenterologische und Hepatologische Erkrankungen 2010;12:157-159.
51. Chen HL, Lee CN, Chang CH, Ni YH, Shyu MK, Chen SM, Hu JJ, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology 2015.
52. Yu M-M, Jiang Q, Ji Y, Wu K-H, Ju L-L, Tang X, Yang Y-F. Comparison of telbivudine versus lamivudine in interrupting perinatal transmission of hepatitis B virus. Journal of Clinical Virology 2014;61:55-60.
53. Siberry GK, Jacobson DL, Kalkwarf HJ, Wu JW, DiMeglio LA, Yogev R, Knapp KM, et al. Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate During Pregnancy. Clin Infect Dis 2015.

54. Siberry GK, Williams PL, Mendez H, Seage GR, 3rd, Jacobson DL, Hazra R, Rich KC, et al. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. AIDS 2012;26:1151-1159.
55. Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, Dienstag JL, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 2003;125:1714-1722.
56. Heathcote EJ, Marcellin P, Buti M, Gane E, De Man RA, Krastev Z, Germanidis G, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology 2011;140:132-143.
57. Terrault N BN, Chang K-M, Hwang J, Jonas M, Murad H. AASLD Guidelines for Treatment of Chronic Hepatitis B. http://www.aasld.org/publications/practice-guidelines-0. HEPATOLOGY 2015.

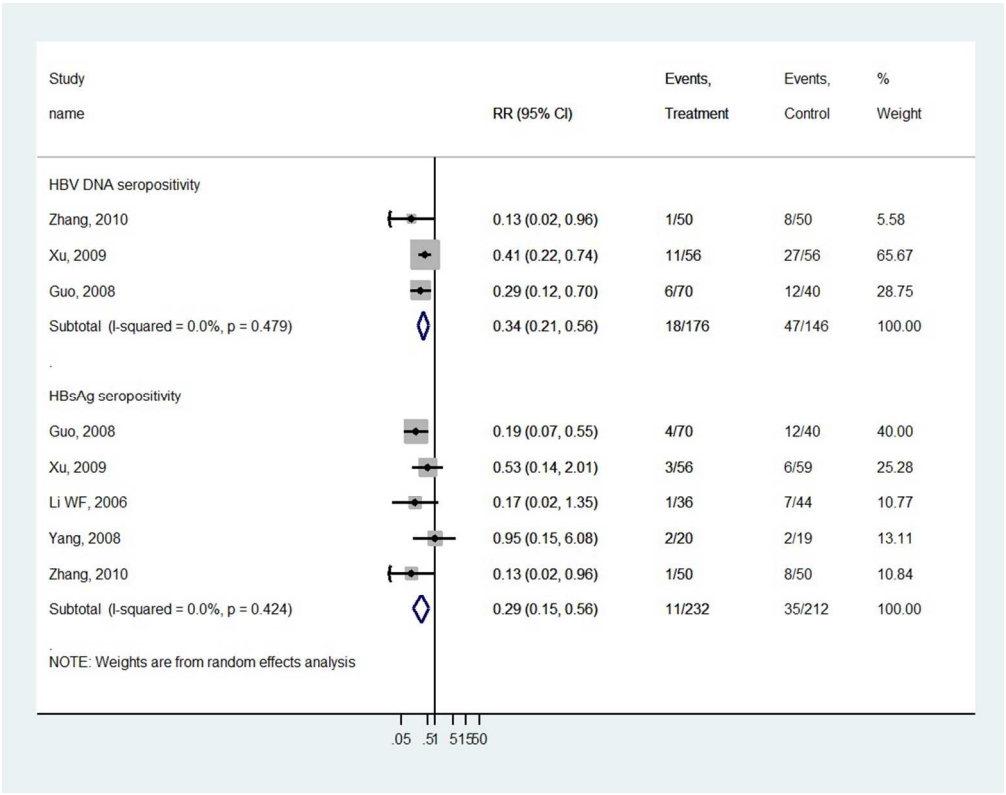
Figure 1: Study selection process:



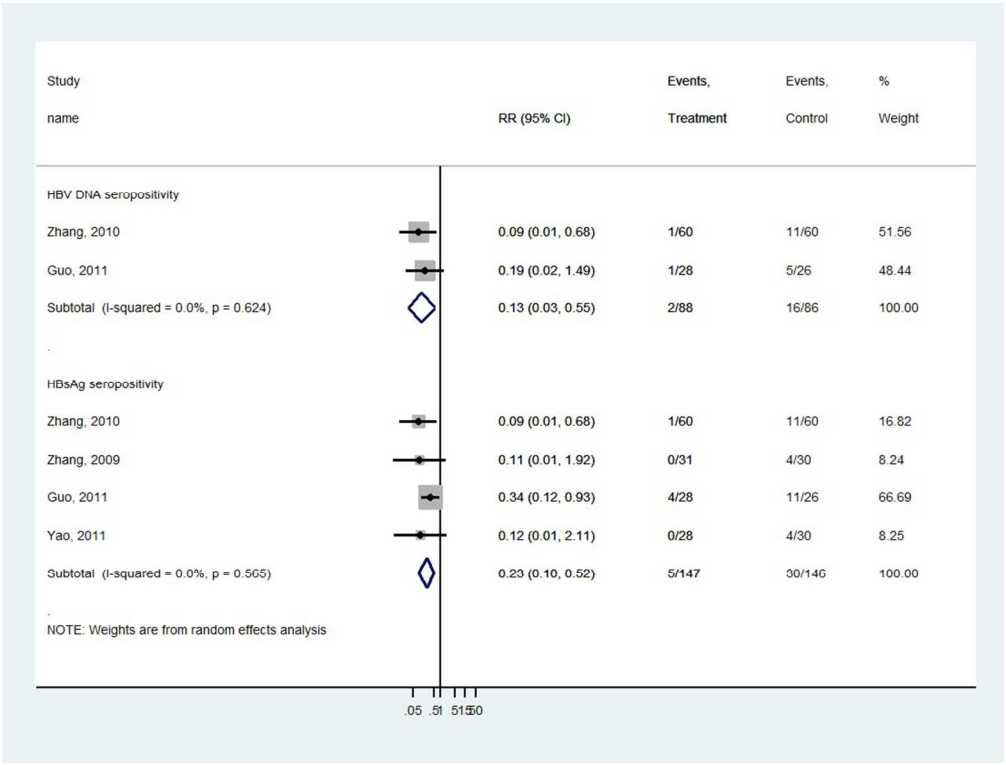
203x223mm (300 x 300 DPI)



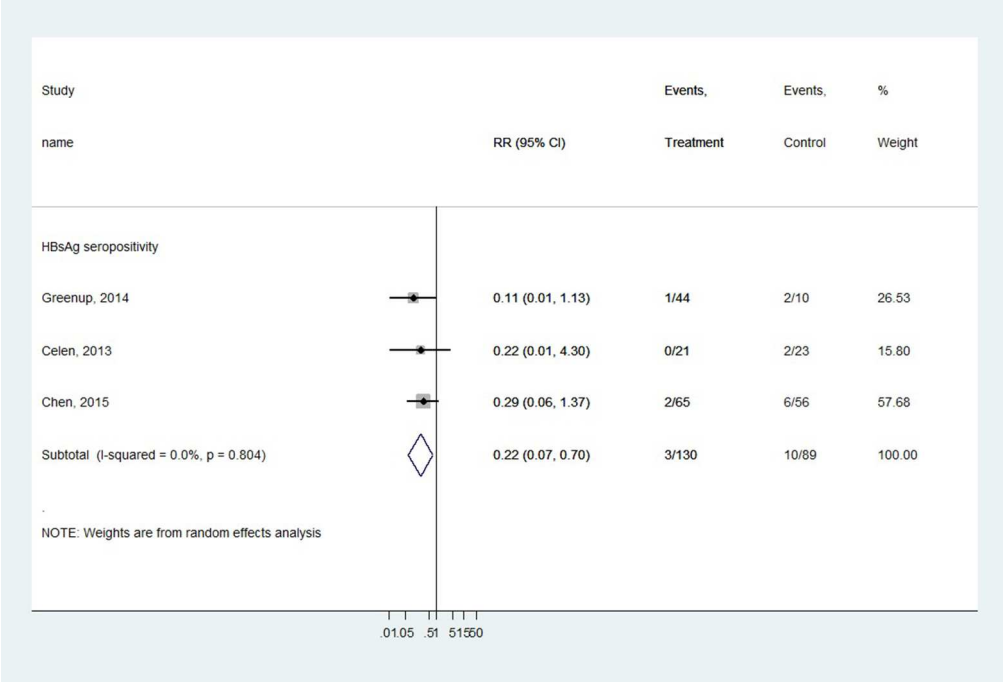
85x73mm (300 x 300 DPI)



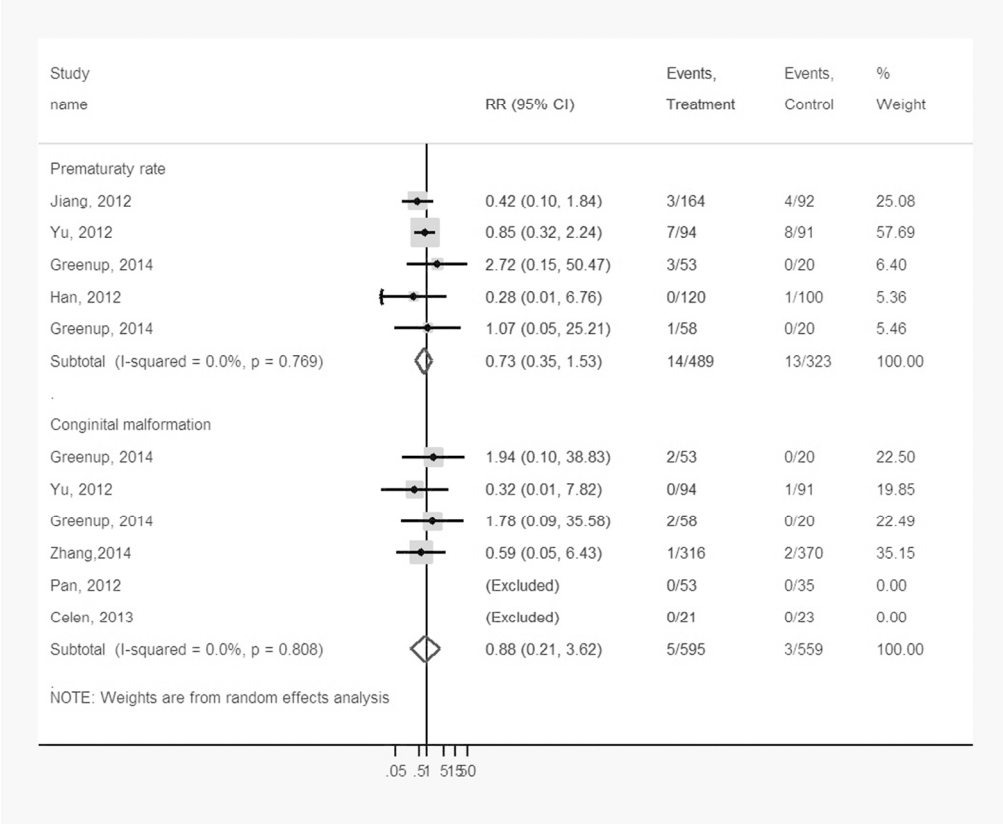
93x73mm (300 x 300 DPI)



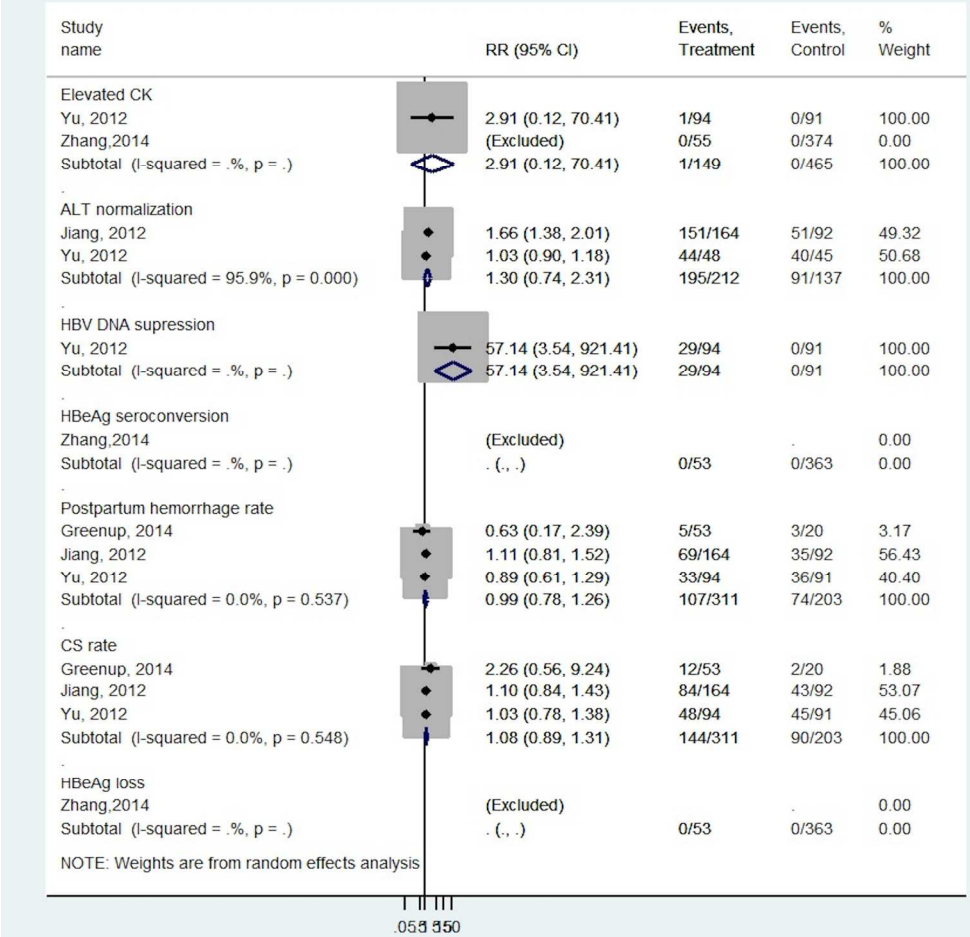
93x70mm (300 x 300 DPI)



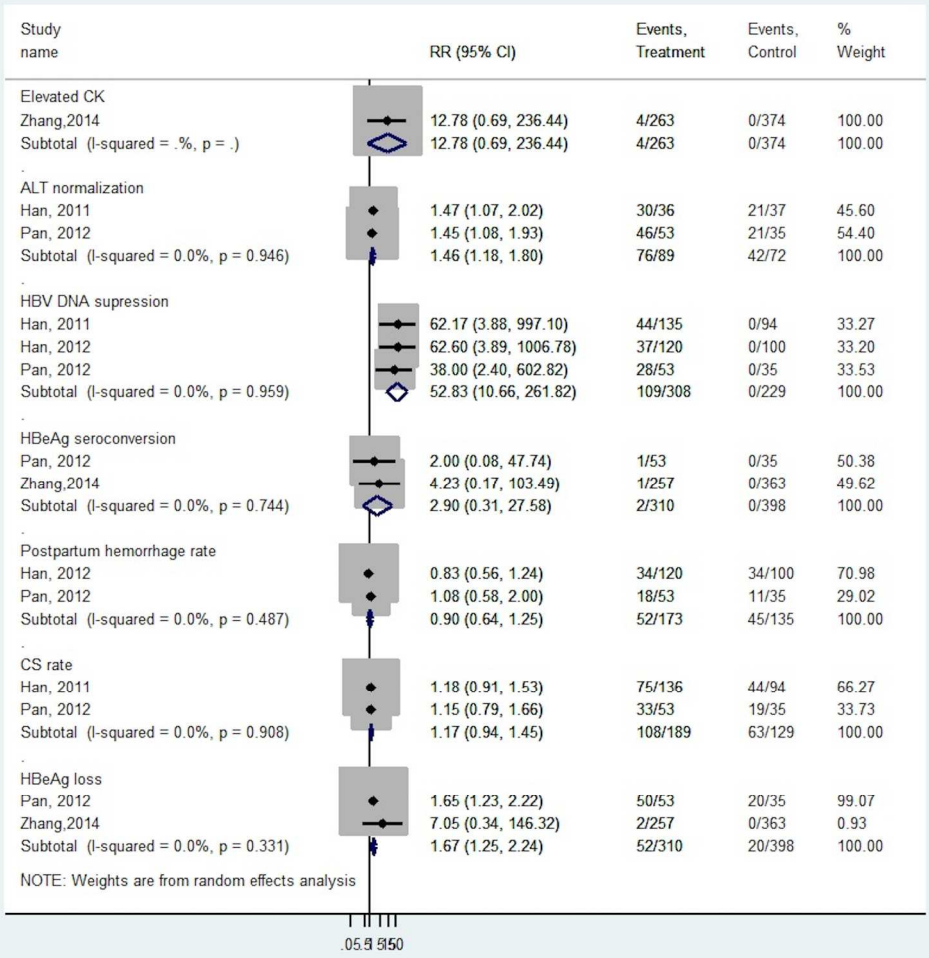
93x63mm (300 x 300 DPI)



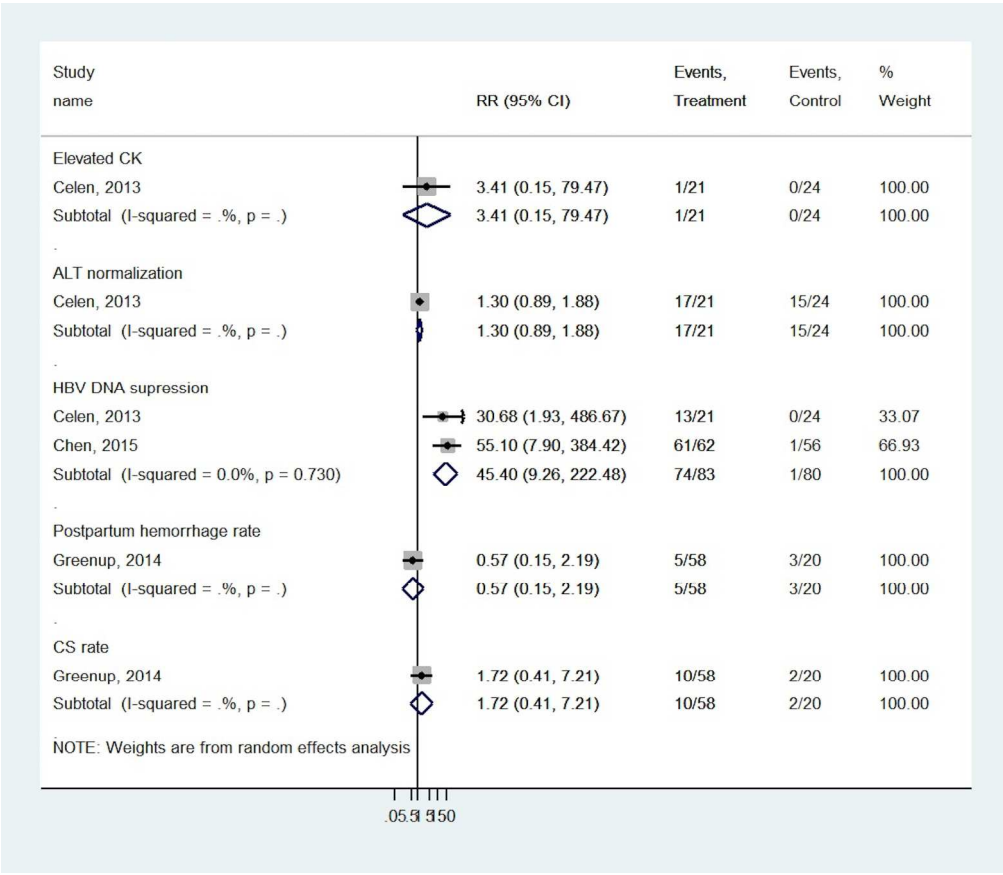
89x73mm (300 x 300 DPI)



226x230mm (300 x 300 DPI)



223x230mm (300 x 300 DPI)



265x230mm (300 x 300 DPI)

Figure 2: Forest plots of infant outcomes for RCTs comparing any antiviral therapy vs control at 6-12 months follow up

Figure 3: Forest plots of infant outcomes for RCTs comparing lamivudine vs control at 6-12 months follow up

Figure 4: Forest plots of infant outcomes for RCTs comparing telbuvidine vs control at 6-12 months follow up

Figure 5: Forest plots of infant outcomes for non-RCTs comparing tenofovir vs control at 6-12 months follow up

Figure 6: Forest plot of congenital malformation and prematurity rates reported for studies comparing any antiviral therapy vs control

Figure 7: Forest plot of maternal outcomes for non-RCTs comparing lamivudine vs control at delivery

Figure 8: Forest plot of maternal outcomes for non-RCTs studies comparing telbivudine vs control at delivery

Figure 9: Forest plot of maternal outcomes for non-RCTs studies comparing tenofovir vs control at delivery

Table 1: Characteristics of the included studies:

Author, year	Interventions	Participants (Mothers) (N)	Country	Age (Years)	Baseline HBV DNA level (log10 IU/mL)	Baseline ALT level (U/L)	Treatment start (gestational weeks)	Treatment discontinuation (postpartum weeks)	HBIG + vaccine (Infants)	Study design
Zhang, 2009(26)	Telbivudine	31	China	20-40	7.4 ± 0.8	NR	32-36	NR	All	RCT
	Control group	30		20-40	7.5 ± 0.5	NR	NA	NA		
Xu, 2009(27)	Lamivudine	89	China	26(19-32)	8.6 ± 0.2	0.4(0.1-5.3) xULN	32	4	HBV vaccine with or without HBIG	RCT
	Control group	61		25(20-36)	8.7 ± 0.2	0.4(0.1-6) xULN	NA	NA		
Yang, 2008(28)	Lamivudine	20	China	20-40	NR	NR	28	4	All	RCT
	Control group	20		20-40	NR	NR	NA	NA		
Li, 2003(29)	Lamivudine	43	China	20-40	7.5 ± 0.5	NR	28	4	All	RCT
	Control group	52		20-40	7.1 ± 1.3	NR	NA	NA		
Zhang, 2010(30)	Lamivudine	50	China	NR	6.8 ± 0.9	NR	28	4	All	RCT
	Control group	50		NR	6.9 ± 1.7	NR	NA	NA		
Shi, 2009(31)	Lamivudine	49	China	NR	7.2 ± 1.9	NR	28	4	All	RCT
	Control group	43		NR	6.4 ± 2.1	NR	NA	NA		
Guo, 2008(32)	Lamivudine	70	China	NR	NR	NR	28	4	All	RCT
	Control group	40		NR	NR	NR	NA	NA		
Xiang, 2007(33)	Lamivudine	21	China	NR	8.0 ± 1.2	NR	28	4	All	RCT
	Control group	18		NR	7.2 ± 0.8	NR	NA	NA		
Shi, 2005(34)	Lamivudine	21	China	NR	8.7 ± 0.7	NR	28	4	All	RCT
	Control group	18		NR	8.9 ± 1.1	NR	NA	NA		
Guo, 2011(35)	Telbivudine	28	China	NR	7.7 ± 4.6	NR	28	4	All	RCT
	Control group	26		NR	7.9 ± 3.5	NR	NA	NA		
Zhang, 2014(36)	Telbivudine	252	China	29.8±6.3	6.9±0.4	30.1±27.9	28-30	4	All	Prospective, open-label, Interventional trial.
	Lamivudine	51		28.4±7.1	6.9±0.4	39.7±26.4	28-30	4		
	Control group	352		28.9±4.6	6.8± 0.5	29.5±20.7	NA	NA		
Greenup, 2014(37)	Tenofovir	58	Australia	30.0± 8.5	7.9 ± 0.8	28(22-36)	32	12	All	Cohort study
	Lamivudine	52		28.0±5.3	7.7 ± 0.6	22(18-30)	32	4		
	Control group	20		28.0±5.0	8 ± 0.04	25(17-31)	NA	NA		
Celen, 2013(38)	Tenofovir	21	Turkey	28.2±4.1	8.3	56(22-71)	18 - 27	4	All	Retrospective study
	Control group	24		26.9±2.9	8.3	52(19-77)	NA	NA		
Jiang, 2012(39)	Lamivudine	164	China	27.3±4.4	7.8±0.8	39.6±26.0	24-32	At delivery	All	Cohort study
	Control group	92		26.4±3.2	7.9±0.6	42.2±0.4	NA	NA		
Chen,	Lamivudine	75	China	NR	7.7±0.5	NR	24-32	4	All	Cohort study

2012(40)	Control group	28		NR	7.3±0.4	NR	NA	NA		
Yu, 2012(41)	Lamivudine	94	China	26.4±4.2	6.9±0.4	45.0	24-32 .	Continued for variable duration after delivery	All	Cohort study
	Control group	91		25.8	7.0±0.6	45.0	NA	NA		
Pan, 2012(42)	Telbivudine	53	China	27(21-34)	8.08 (6.6–9.4)	60.4(41.4-422)	12-30	Continued for variable duration after delivery	All	Prospective, non-randomized open-label trial
	Control group	35		27(21-33)	8.1 (6.8–9.1)	63.2(42.4-262.5)	NA	NA		
Han, 2012(43)	Telbivudine	120	China	26.0±3.5	7.3±0.5	31.0±32.2	20-32	4	All	Cohort study
	Control group	100		26.4±3.2	7.3±0.6	31.5±35.1	NA	NA		
Han, 2011(44)	Telbivudine	135	China	27(20-38)	7.4 ± 0.6	35.7 ± 43.4	20-32	4	All	Cohort study
	Control group	94		26(20-35)	7.3 ± 0.6	42.5 ± 40.1	NA	NA		
Feng, 2007(45)	Lamivudine	48	China	NR	8.3 ± 1.2	NR	28	4	All	RCT
	Control group	42		NR	8.3 ± 1.9	NR	NA	NA		
Li, 2006(46)	Lamivudine	36	China	NR	6.9 ± 0.8	NR	28	4	All	RCT
	Control group	44		NR	> 5.00	NR	NA	NA		
Han, 2005(47)	Lamivudine	43	China	NR	7.2 ± 0.9	NR	28	4	All	RCT
	Control group	35		NR	> 5.6	NR	NA	NA		
Zhang, 2010(49)	Telbivudine	60	China	NR	NR	NR	28	4	All~~NR~~	RCT
	Control group	60		NR	NR	NR	NA	NA		
Yao, 2011(48)	Telbivudine	28	China	NR	7.5 ± 0.6	NR	28	4	All	RCT
	Control group	30		NR	7.5 ± 0.7	NR	NA	NA		
Chen, 2015(50)	Tenofovir	62	Taiwan	32.5±3.2	8.2±0.5	16.6±14.4	28	4	All	Open-labeled, non-randomized controlled trial.
	Control group	56		32.4±3.1	8.2±0.4	23.3±36.2	NA	NA		
Yu, 2014(51)	Telbivudine	233	China	26.8±3.9	7.8 ± 0.8	57.6 ± 83.5	8-32	At delivery	All	Cohort study
	Lamivudine	154		26.7±3.5	7.7 ± 0.7	56.3 ± 82.7	NA	NA		

Table 2: Risk of bias assessment for the included RCTs:

Author, year	Sequence generation	Allocation concealment	Blinding of participants, personnel and assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Risk of bias
Zhang, 2009(26)	Unclear	Unclear	Unclear	No missing outcome	All prespecified outcomes reported	No	Unclear
Xu, 2009(27)	Unclear	Sequentially numbered drug containers of identical appearance	Adequate blinding	One arm of data missing for ethics	All pre specified outcomes reported	No	Low
Yang, 2008(28)	Random number table	Sequentially numbered drug containers of identical appearance	Adequate blinding	No missing outcome data	All prespecified	No	low
Li, 2003(29)	Computer random Number generator	Unclear	Measurement not influenced by lack of blinding	No missing outcome data	All prespecified outcomes reported	No	Low
Zhang, 2010(30)	Unclear	Unclear	Unclear	Unclear	None	None	Unclear
Shi, 2009(31)	Computer random number generator	Sequentially numbered drug containers of identical appearance	Adequate blinding	Missing outcomes have no impact on effect size	All prespecified outcomes reported	No	Low
Guo, 2008(32)	Adequate	Unclear	Unclear	No missing outcome	All prespecified outcomes reported	No	Unclear
Xiang, 2007(33)	Adequate	Unclear	Unclear	No missing outcome	All prespecified outcomes reported	No	Unclear
Shi, 2005(34)	Random table	Unclear	Measurement not influenced by lack of blinding	No missing outcome data	All prespecified outcomes reported	No	Low
Guo, 2011(35)	Unclear	Unclear	No blinding	No missing outcome data	All prespecified outcomes reported	No	High/ unclear

Table 3: Risk of bias assessment for the observational studies:

Author, Year	Selection		Comparability		Outcome	
	Representativeness of the exposed cohort	**Selection of the non-exposed cohort**	**Comparability of cohorts on the basis of the design or analysis.**	**Assessment of outcome**	**Was follow up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**
Zhang, 2014(36)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for any additional factors	Record linkage	Yes	Adequate
Greenup, 2014(37)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for any additional factors	Record linkage	Yes	Adequate
Celen, 2013(38)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate
Jiang, 2012(39)	No description	Drawn from the same community as the exposed cohort	Study controls for most important factor	No description	Yes	Adequate
Chen, 2012(40)	No description	Drawn from the same community as the exposed cohort	Study controls for most important factor	No description	No	Unclear
Yu, 2012(41)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate
Pan, 2012(42)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate
Han, 2012(43)	No description	Drawn from the same community as the exposed cohort	Study controls for most important factor	No description	Unclear	unclear
Han, 2011(44)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate
Feng, 2007(45)	No description	No description	No description	No description	No description	No description
Li, 2006(46)	No description	No description	No description	No description	No description	No description
Han, 2005(47)	No description	No description	No description	No description	No description	No description
Yao, 2011(48)	No description	No description	No description	No description	No description	No description
Zhang, 2010(49)	No description	No description	No description	No description	No description	No description
Chen, 2015(50)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for any additional factors	Record linkage	Yes	Adequate
Yu, 2014(51)	somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Independent blind assessment	Yes	Adequate

Supplemental table 1: Detailed Search Strategy:

Ovid

Database(s): Embase 1988 to 2014 Week 36, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials August 2014, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 2014
Search Strategy:

#	Searches	Results
1	exp Hepatitis B/dt	26394
2	("hepatitis B" or "serum hepatitis" or "hippie hepatitis" or "injection hepatitis" or "hepatitis type B").mp.	178415
3	1 or 2	178415
4	exp Antiviral Agents/	915473
5	exp antivirus agent/	611278
6	("1-Deoxynojirimycin" or absouline or "abt 333" or "abt 450" or Acetylcysteine or aciclovir or "acyclouridine derivative" or Acyclovir or "adenine xyloside" or "adenosine dialdehyde" or afovirsen or "al 721" or alamifovir or alisporivir or "aln rsv 01" or "alvircept sudotox" or amantadine or amenamevir or amidapsone or amitivir or "ammonium trichloro dioxyethylene o o tellurate" or amsacrine or "ana 975" or "anti viral agent" or AntiRetroviral* or "Anti-Retroviral*" or antiretrovirus or antiviral* or "anti-viral*" or Aphidicolin or arasangivamycin or arbidol or arildone or astodrimer or asunaprevir or avarol or avarone or avridine or "azd 7295" or balapiravir or bavituximab or "behenyl alcohol" or benzimidavir or besifovir or boceprevir or bonaphthone or "Brefeldin A" or brincidofovir or Bromodeoxyuridine or bropirimine or buciclovir or carbocyclic or carbodine or carrageenan or cidofovir or ciluprevir or clevudine or "cpg 10101" or crofelemer or cyclaradine or "cyclosporin A" or cytarabine or daclatasvir or damavaricin or danoprevir or dasabuvir or deitiphorin or deleobuvir or denotivir or deoxyaristeromycin or Deoxyglucose or deoxypenciclovir or deoxyribavirin or desciclovir or detiviciclovir or "didemnin A" or "didemnin B" or Dideoxyadenosine or Dideoxynucleoside* or disoxaril or "distamycin 5" or "distamycin A" or Ditiocarb or droxinavir or edoxudine or elbasvir or "enisamium iodide" or enviroxime or epetirimod or eudistomin or exbivirumab or faldaprevir or famciclovir or favipiravir or felvizumab or fiacitabine or fialuridine or filibuvir or Filipin or florenal or "flucytosine arabinoside" or fomivirsen or foravirumab or fosarilate or foscarnet or fosdevirine or fucoidin or "gamma venin" or ganciclovir or "gene expression modulator" or grazoprevir or "gs 9256" or "guanine 7 oxide" or hypericin or "hypoxanthine arabinoside" or idoxuridine or "idoxuridine derivative" or "idx 184" or imexon or imiquimod or "Inosine Pranobex" or iododeoxycytidine or ipilimumab or isatoribine or "isis 13312" or "isis 14803" or laninamivir or larifan or ledipasvir or letermovir or levovirin or lexithromycin or libivirumab or litomeglovir or lomibuvir or mericitabine or merimepodib or Methisazone or methisoprinol or methylcytidine or metisazone or miravirsen or moroxydine or motavizumab or "mycophenolic acid" or "Myxovirus resistance protein" or "n bromoacetyldistamycin A" or narlaprevir or neceprevir or "neominophagen C" or nesbuvir or netivudine or netropsin or nivocasan or omaciclovir or ombitasvir or oseltamivir or palivizumab or penciclovir or "penciclovir triphosphate" or peramivir or "phosphonoacetic acid" or "Phosphonoacetic Acid" or pirazofurin or pirodavir or pleconaril or pocapavir or "pokeweed antivirus protein" or "Poly A-U" or "Poly I-C" or pritelivir or pseudohypericin or "pyran copolymer" or "Pyran Copolymer" or radavirsen or rafivirumab or "recombinant intercellular adhesion molecule 1" or regavirumab or resiquimod or ribavirin or "ribavirin derivative" or rifabutin or rimantadine or rintatolimod or riodoxol or rociclovir or rupintrivir or samatasvir or sangivamycin or "sangivamycin derivative" or "scopadulcic acid B" or setrobuvir or sevirumab or simeprevir or sofosbuvir or sorivudine or sovaprevir or streptovaricin or Streptovaricin or streptovirudin or suramin or suvizumab or synadenol or synguanol or taribavirin or tebrofen or tecovirimat or tegobuvir or telaprevir or telbivudine or "Tenuazonic Acid" or "thiarubrine A" or "thiophene A" or "thymine arabinoside" or tilorone or Tilorone or "tilorone derivative" or tiviciclovir or tomeglovir or torcitabine or trifluridine or tromantadine or tunicamycin or tuvirumab or umifenovir or "uracil arabinoside" or valaciclovir or valganciclovir or valomaciclovir or valopicitabine or valtorcitabine or vaniprevir or vapendavir or	747307

	vedroprevir or vidarabine or Vidarabine or viracine or "viral inhibitor*" or virantmycin or virostatic* or viroxime or virucidal* or virucide* or "virus repressor*" or virustatic* or xanthogenate or "xenazoic acid" or zanamivir or Zanamivir or zinviroxime).mp.	
	4 or 5 or 6	1208899
	exp Interferons/	453504
	exp interferon/	453504
0	("cl 884" or cl884 or ifn or interferon* or interferone* or interferonogen* or interferron* or "interleukin 28A" or "interleukin 29" or "interleukin 6" or leif or peginterferon* or peginterferone* or peginterferonogen* or peginterferron*).mp.	628658
1	8 or 9 or 10	628758
2	exp Pregnancy/	1080989
3	(pregnan* or gestation* or "child bearing" or childbearing).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui, tx, ct]	1448492
4	12 or 13	1463788
5	3 and (7 or 11) and 14	1340
6	exp evidence based medicine/	721205
7	exp meta analysis/	134011
8	exp Meta-Analysis as Topic/	29510
9	exp "systematic review"/	79207
0	exp Guideline/ or exp Practice Guideline/	344377
1	exp controlled study/	4512490
2	exp Randomized Controlled Trial/	723249
3	exp triple blind procedure/	68
4	exp Double-Blind Method/	342895
5	exp Single-Blind Method/	51259
6	exp latin square design/	276
7	exp Placebos/	267995
8	exp Placebo Effect/	7231
9	exp comparative study/	2459742
0	exp Cross-Sectional Studies/	307288
1	exp Cross-Over Studies/	101407
2	exp Cohort Studies/	1680397
3	exp longitudinal study/	1065024
4	exp retrospective study/	864314
5	exp prospective study/	701082
6	exp population research/	68087
7	exp observational study/	65081
8	exp clinical trial/	1728711
9	clinical study/	53598
0	exp Evaluation Studies/	208013
1	exp Evaluation Studies as Topic/	1130031
2	exp Twin Study/	31182
3	exp quantitative study/	5818
4	exp validation studies/	113515
5	exp experimental study/	14612

6	exp quasi experimental study/	2028
7	exp field study/	1531
8	in vivo study/	189705
9	exp panel study/	373
0	exp Pilot Projects/	171018
1	exp pilot study/	171018
2	exp prevention study/	2120
3	exp replication study/	949
4	exp theoretical study/	1368248
5	exp Feasibility Studies/	99507
6	exp Models, Theoretical/	1387826
7	exp trend study/	11365
8	exp correlational study/	11312
9	exp case-control studies/	784804
0	exp confidence interval/	122062
1	exp regression analysis/	570654
2	exp proportional hazards model/	94889
3	exp multivariate analysis/	343014
4	"limit follow up studies to medline only. embase maps to follow up".ti.	0
5	exp follow up studies/	1343640
6	exp case study/	1738225
7	"limit case study above to embase only. medline maps to case report".ti.	0
8	odds ratio/	383358
9	"limit odds ratio above to embase. medline maps to risk".ti.	0
0	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or guideline* or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo or random* or control* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or compar* or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analys*" or "cross-sectional survey*" or "cross-sectional design*" or "prevalence study" or "prevalence analys*" or "prevalence survey*" or "disease frequency study" or "disease frequency analys*" or "disease frequency survey*" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or longitudinal* or "retrospective study" or "retrospective survey" or "retrospective analysis" or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "population study" or "population survey" or "population analysis" or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or "follow-up study" or "follow-up survey" or "follow-up analysis" or "observational study" or "observational survey" or "observational analysis" or "case study" or "case series" or "clinical series" or "case studies" or "clinical study" or "clinical trial" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "twin study" or "twin survey" or "twin analysis" or "quantitative study" or "quantitative analys*" or "validation study" or "validation survey" or "validation analysis" or "experimental study" or "experimental analysis " or "quasi experimental study" or "quasi experimental analysis" or "quasiexperimental study" or "quasiexperimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or "prevention study" or "prevention survey" or "prevention analysis" or "replication study" or "replication analysis " or "theoretical study" or "theoretical analysis " or "feasibility study" or "feasibility analysis " or "trend study" or "trend survey" or "trend analysis" or (correlation* adj2 study) or (correlation* adj2 analys*) or "case control study" or "case base study" or	22128887

	"case referrent study" or "case referent study" or "case compeer study" or "case comparison study" or study or trial or pilot or "odds ratio" or "confidence interval" or "regression analysis" or "hazards model" or "change analysis").mp.	
1	from 65 keep 793339-1301733	508395
2	from 66 keep 1-25622	25622
3	from 68 keep 1-318765	318765
4	or/16-63	12606394
5	or/70-74	23255184
6	15 and 75	934
7	from 15 keep 962-1300	339
8	limit 77 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews or twin study or validation studies) [Limit not valid in Embase,CCTR,CDSR; records were retained]	83
9	76 or 78	934
0	limit 79 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	41
1	79 not 80	893
2	from 15 keep 1301-1340	40
3	81 or 82	916
4	83 not (exp animals/ not exp humans/)	885
5	from 83 keep 896-916	21
6	84 or 85	906
7	remove duplicates from 86	735

Scopus

1 TITLE-ABS-KEY("hepatitis B" or "serum hepatitis" or "hippie hepatitis" or "injection hepatitis" or "hepatitis type B")

2 TITLE-ABS-KEY("1-Deoxynojirimycin" OR absouline OR "abt 333" OR "abt 450" OR Acetylcysteine OR aciclovir OR "acyclouridine derivative" OR Acyclovir OR "adenine xyloside" OR "adenosine dialdehyde" OR afovirsen OR "al 721" OR alamifovir OR alisporivir OR "aln rsv 01" OR "alvircept sudotox" OR amantadine OR amenamevir OR amidapsone OR amitivir OR "ammonium trichloro dioxyethylene o o tellurate" OR amsacrine OR "ana 975" OR "anti viral agent" OR AntiRetroviral* OR "Anti-Retroviral*" OR antiretrovirus OR antiviral* OR "anti-viral*" OR Aphidicolin OR arasangivamycin OR arbidol OR arildone OR astodrimer OR asunaprevir OR avarol OR avarone OR avridine OR "azd 7295" OR balapiravir OR bavituximab OR "behenyl alcohol" OR benzimidavir OR besifovir OR boceprevir OR bonaphthone OR "Brefeldin A" OR brincidofovir OR Bromodeoxyuridine OR bropirimine OR buciclovir OR carbocyclic OR carbodine OR carrageenan OR cidofovir OR ciluprevir OR clevudine OR "cpg 10101" OR crofelemer OR cyclaradine OR "cyclosporin A" OR cytarabine OR daclatasvir OR damavaricin OR danoprevir OR dasabuvir OR deitiphorin OR deleobuvir OR denotivir OR deoxyaristeromycin OR Deoxyglucose OR deoxypenciclovir OR deoxyribavirin OR desciclovir OR detiviciclovir OR "didemnin A" OR "didemnin B" OR Dideoxyadenosine OR Dideoxynucleoside* OR disoxaril OR "distamycin 5" OR "distamycin A" OR Ditiocarb OR droxinavir OR edoxudine OR elbasvir OR "enisamium iodide" OR enviroxime OR epetirimod OR eudistomin OR exbivirumab OR faldaprevir OR famciclovir OR favipiravir OR felvizumab OR fiacitabine OR fialuridine OR filibuvir OR Filipin OR florenal OR "flucytosine arabinoside" OR fomivirsen OR foravirumab OR fosarilate OR foscarnet OR fosdevirine OR fucoidin OR "gamma venin" OR ganciclovir OR "gene expression modulator" OR grazoprevir OR "gs 9256" OR "guanine 7 oxide" OR hypericin OR "hypoxanthine arabinoside" OR idoxuridine OR "idoxuridine derivative" OR "idx 184" OR imexon OR imiquimod OR "Inosine Pranobex" OR iododeoxycytidine OR ipilimumab OR isatoribine OR "isis 13312" OR "isis 14803" OR laninamivir OR larifan OR ledipasvir OR letermovir OR levovirin OR lexithromycin OR libivirumab OR litomeglovir OR lomibuvir OR mericitabine OR merimepodib OR Methisazone OR methisoprinol OR methylcytidine OR metisazone OR miravirsen OR moroxydine OR motavizumab OR "mycophenolic acid" OR "Myxovirus resistance protein" OR "n bromoacetyldistamycin A" OR narlaprevir OR neceprevir OR "neominophagen C" OR nesbuvir OR netivudine OR netropsin OR nivocasan OR omaciclovir OR ombitasvir OR oseltamivir OR palivizumab OR penciclovir OR "penciclovir triphosphate" OR peramivir OR "phosphonoacetic acid" OR "Phosphonoacetic Acid" OR pirazofurin OR pirodavir OR pleconaril OR pocapavir OR "pokeweed antivirus protein" OR "Poly A-U" OR "Poly I-C" OR pritelivir OR pseudohypericin OR "pyran copolymer" OR "Pyran Copolymer" OR radavirsen OR rafivirumab OR "recombinant intercellular adhesion molecule 1" OR regavirumab OR resiquimod OR ribavirin OR "ribavirin derivative" OR rifabutin OR rimantadine OR rintatolimod OR riodoxol OR rociclovir OR rupintrivir OR samatasvir OR sangivamycin OR "sangivamycin derivative" OR "scopadulcic acid B" OR setrobuvir OR sevirumab OR simeprevir OR sofosbuvir OR sorivudine OR sovaprevir OR streptovaricin OR Streptovaricin OR streptovirudin OR suramin OR suvizumab OR synadenol OR synguanol OR taribavirin OR tebrofen OR tecovirimat OR tegobuvir OR telaprevir OR telbivudine OR "Tenuazonic Acid" OR "thiarubrine A" OR "thiophene A" OR "thymine arabinoside" OR tilorone OR Tilorone OR "tilorone derivative" OR tiviciclovir OR tomeglovir OR torcitabine OR trifluridine OR tromantadine OR tunicamycin OR tuvirumab OR umifenovir OR "uracil arabinoside" OR valaciclovir OR valganciclovir OR valomaciclovir OR valopicitabine OR valtorcitabine OR vaniprevir OR vapendavir OR vedroprevir OR vidarabine OR Vidarabine OR viracine OR "viral inhibitor*" OR virantmycin OR virostatic* OR viroxime OR virucidal* OR virucide* OR "virus

repressor*" OR virustatic* OR xanthogenate OR "xenazoic acid" OR zanamivir OR Zanamivir OR zinviroxime)

3 TITLE-ABS-KEY("cl 884" OR cl884 OR ifn OR interferon* OR interferone* OR interferonogen* OR interferron* OR "interleukin 28A" OR "interleukin 29" OR "interleukin 6" OR leif OR peginterferon* OR peginterferone* OR peginterferonogen* OR peginterferron*)

4 TITLE-ABS-KEY(pregnan* or gestation* or "child bearing" or childbearing)

5 TITLE-ABS-KEY((evidence W/1 based) OR (meta W/1 analys*) OR (systematic* W/3 review*) OR (guideline*) OR (doubl* W/1 blind*) OR (doubl* W/1 mask*) OR (singl* W/1 blind*) OR (singl* W/1 mask*) OR (tripl* W/1 blind*) OR (tripl* W/1 mask*) OR (trebl* W/1 blind*) OR (trebl* W/1 mask*) OR "latin square" OR placebo OR random* OR control* OR multivariate OR "comparative study" OR "comparative survey" OR "comparative analysis" OR compar* OR (intervention* W/2 study) OR (intervention* W/2 trial) OR "cross-sectional study" OR "cross-sectional analys*" OR "cross-sectional survey*" OR "cross-sectional design*" OR "prevalence study" OR "prevalence analys*" OR "prevalence survey*" OR "disease frequency study" OR "disease frequency analys*" OR "disease frequency survey*" OR crossover OR "cross-over" OR cohort* OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR longitudinal* OR "retrospective study" OR "retrospective survey" OR "retrospective analysis" OR retrospectiv* OR "prospective study" OR "prospective survey" OR "prospective analysis" OR prospectiv* OR "population study" OR "population survey" OR "population analysis" OR "concurrent study" OR "concurrent survey" OR "concurrent analysis" OR "incidence study" OR "incidence survey" OR "incidence analysis" OR "follow-up study" OR "follow-up survey" OR "follow-up analysis" OR "observational study" OR "observational survey" OR "observational analysis" OR "case study" OR "case series" OR "clinical series" OR "case studies" OR "clinical study" OR "clinical trial" OR "evaluation study" OR "evaluation survey" OR "evaluation analysis" OR "twin study" OR "twin survey" OR "twin analysis" OR "quantitative study" OR "quantitative analys*" OR "validation study" OR "validation survey" OR "validation analysis" OR "experimental study" OR "experimental analysis " Or "quasi experimental study" OR "quasi experimental analysis" OR "quasiexperimental study" OR "quasiexperimental analysis" OR "field study" OR "field survey" OR "field analysis" OR "in vivo study" OR "in vivo analysis" OR "panel study" OR "panel survey" OR "panel analysis" OR "prevention study" OR "prevention survey" OR "prevention analysis" OR "replication study" OR "replication analysis " OR "theoretical study" OR "theoretical analysis " OR "feasibility study" OR "feasibility analysis " OR "trend study" OR "trend survey" OR "trend analysis" OR (correlation* W/2 study) OR (correlation* W/2 analys*) OR "case control study" OR "case base study" OR "case referrent study" OR "case referent study" OR "case compeer study" OR "case comparison study" OR study OR trial OR pilot OR "odds ratio" OR "confidence interval" OR "regression analysis" OR "hazards model" OR "change analysis")

6 1 and 2 and 3 and 4 and 5

7 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

8 6 and not 7

9 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)

10 8 and not 9

Supplemental Table 2: Quality of evidence summary:

Intervention	Outcome (Follow up)	No. of participants (Study design)	Quality of the evidence (GRADE)	Relative effect (95% CI)
Infant outcomes:				
Any antiviral vs none	Infant HBsAg seropositivity (6-12 m)	737 (8 RCTs)	⊕⊕⊕◯[1] MODERATE	**RR 0.26** (0.16 to 0.44)
	Infant HBsAg seropositivity (6-12 m)	1190 (9 observational studies)	⊕◯◯◯[1] VERY LOW	**RR 0.21** (0.12 to 0.38)
	Infant HBV DNA positivity (6-12 m)	496 (5 RCTs)	⊕⊕◯◯[13] LOW	**RR 0.31** (0.20 to 0.49)
	Infant HBV DNA positivity (6-12 m)	90 (1 observational studies)	⊕◯◯◯[13] VERY LOW	**RR 0.38** (0.17 to 0.84)
	Congenital malformation rate	1154 (4 observational studies)	⊕◯◯◯[14] VERY LOW	**RR 0.88** (0.21 to 3.62)
	Prematurity rate	812 (5 observational studies)	⊕◯◯◯[4] VERY LOW	**RR 0.73** (0.35 to 1.53)
Lamivudine vs None	Infant HBsAg seropositivity (6-12 m)	444 (5 RCTs) 6-12 months	⊕⊕⊕◯[1] MODERATE	**RR 0.29** (0.15 to 0.56)
	Infant HBsAg seropositivity (6-12 m)	662 (5 observational studies) 6-12 months	⊕◯◯◯[1] VERY LOW	**RR 0.12** (0.03 to 0.45)
	Infant HBV DNA positivity (6-12 m)	322 (3 RCTs) 6-12 months	⊕⊕◯◯[13] LOW	RR 0.34 (0.21 to 0.56)
	Infant HBV DNA positivity (6-12 m)	90 (1 observational study) 6-12 months	⊕◯◯◯[13] VERY LOW	**RR 0.38** (0.17 to 0.84)
	APGAR score	289 (2 observational studies)	⊕◯◯◯[13] VERY LOW	Means differences 0.012 (-0.75 to 0.47)
	Congenital malformation rate	493 (2 observational studies)	⊕◯◯◯ VERY LOW	RR 0.84 (0.09 to 7.4)
	Prematurity rate	514 (3 observational studies)	⊕◯◯◯ VERY LOW	RR 0.76 (0.35 to 1.65)
Telbivudine vs control	Infant HBsAg seropositivity (6-12 m)	293 (4 RCTs) 6-12 months	⊕⊕⊕◯[1] MODERATE	**RR 0.23** (0.10 to 0.52)
	Infant HBsAg seropositivity (6-12 m)	309 (2 observational studies) 6-12 months	⊕◯◯◯[1] VERY LOW	**RR 0.06** (0.01 to 0.49)
	Infant HBV DNA seropositivity (6-12 m)	174 (2 RCTs) 6-12 months	⊕⊕◯◯[13] LOW	RR 0.13 (0.03 to 0.55)
	APGAR score	815 (3 observational studies)	⊕◯◯◯[4] VERY LOW	Means difference -0.009 (-0.048 to 0.03)
	Prematurity rate	220 (1observational studies)	⊕◯◯◯[4] VERY LOW	RR 0.28 (0.01 to 6.76)

Tenofovir vs control	Infant HBsAg seropositivity (6-12 m)	219 (2 observational study)	⊕⊕◯◯ LOW	**RR 0.22** (0.07 to 0.70)
	Congenital malformation rate	122 (2 observational studies)	⊕◯◯◯[4] VERY LOW	RR 1.7 (0.01 to 28.8)
	Prematurity rate	78 (1 observational study)	⊕◯◯◯[4] VERY LOW	RR 1.07 (0.05 to 25.21)
Telbivudine vs lamivudine	Infant HBsAg seropositivity (at birth)	684 (2 observational studies)	⊕◯◯◯[14] VERY LOW	RR 0.98 (0.65 to 1.48)
	Prematurity rate	387 (1 observational study)	⊕◯◯◯[4] VERY LOW	RR 1.89 (0.55 to 7.21)
Tenofovir vs Lamivudine	Infant HBsAg seropositivity (at birth)	87 (1 observational study)	⊕◯◯◯[4] VERY LOW	**RR 2.93** (0.12 to 70.08)
	Congenital malformation rate	111 (1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.46 (0.04 to 4.9)
	Prematurity rate	111 (1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.3 (0.03 to 2.84)
Maternal Outcomes:				
Lamivudine vs control	Maternal HBV DNA suppression (at delivery)	185 (1 observational study)	⊕◯◯◯[34] VERY LOW	RR 57.14 (3.54 to 921.41)
	Maternal HBV DNA suppression (4-8 weeks postpartum)	581 (2 observational studies)	⊕◯◯◯[34] VERY LOW	RR 70.93 (8.53 to 589.96)
	ALT normalization (at delivery)	349 (2 observational studies)	⊕◯◯◯[134] VERY LOW	RR 1.3 (0.74 to 2.31)
	Postpartum hemorrhage rate	115 (1 RCT)	⊕⊕◯◯[14] LOW	RR 0.96 (0.7 to 1.31)
	Postpartum hemorrhage rate	514 (3 observational studies)	⊕◯◯◯[14] VERY LOW	RR 0.99 (0.78 to 1.26)
	Cesarean section rate	115 (1 RCT)	⊕⊕◯◯[14] LOW	RR 0.96 (0.71 to 1.3)
	Cesarean section rate	514 (3 observational studies)	⊕◯◯◯[14] VERY LOW	RR 1.08 (0.89 to 1.31)
	Elevated Creatinine kinase rate	185 (1 observational study)	⊕◯◯◯[34] VERY LOW	RR 2.9 (0.12 to 72.03)
Telbivudine vs control	Maternal HBN DNA Suppression (at delivery)	537 (3 observational studies)	⊕◯◯◯[34] VERY LOW	RR 52.83 (10.66 to 261.82)
	Maternal HBN DNA Suppression (4 weeks postpartum)	685 (2 observational studies)	⊕◯◯◯[34] VERY LOW	RR 102.94 (14.4 to 722.83)
	Maternal HBN DNA Suppression (28 weeks postpartum)	88 (1 observational study)	⊕◯◯◯[34] VERY LOW	RR 42 (2.65 to 664.73)
	ALT normalization (at delivery)	161 (2 observational	⊕◯◯◯[3]	RR 1.46

		studies)	VERY LOW	(1.18 to 1.8)
	ALT normalization (4 weeks postpartum)	88 (1 observational study)	⊕◯◯◯[3] VERY LOW	RR 1.59 (1.1 to 2.31)
	ALT normalization (28 weeks postpartum)	88 (1 observational study)	⊕◯◯◯[3] VERY LOW	RR 1.29 (1.04 to 1.62)
	Maternal HBeAg loss (at delivery)	708 (2 observational studies)	⊕◯◯◯[3] VERY LOW	RR 1.67 (1.25 to 2.24)
	Maternal HBeAg loss (4 weeks postpartum)	88 (1 observational study)	⊕◯◯◯[3] VERY LOW	RR 1.64 (1.24 to 2.15)
	Maternal HBeAg loss (28 weeks postpartum)	88 (1 observational study)	⊕◯◯◯[3] VERY LOW	RR 1.67 (1.22 to 2.29)
	Maternal HBeAg seroconversion (at delivery)	708 (2 observational studies)	⊕◯◯◯[34] VERY LOW	RR 2.9 (0.31 to 27.58)
	Maternal HBeAg seroconversion (4 weeks postpartum)	88 (1 observational study)	⊕◯◯◯[34] VERY LOW	RR 3.33 (0.16 to 67.42)
	Maternal HBeAg seroconversion (28 weeks postpartum)	88 (1 observational study)	⊕◯◯◯[34] VERY LOW	RR 11.33 (0.67 to 190.29)
	Cesarean section rate	318 (2 observational studies)	⊕◯◯◯[4] VERY LOW	RR 1.17 (0.94 to 1.45)
	Postpartum hemorrhage	308 (2 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.9 (0.64 to 1.25)
	Elevated Creatinine kinase rate	637 (1 observational study)	⊕◯◯◯[34] VERY LOW	RR 12.78 (0.69 to 236.44)
Tenofovir vs control	Maternal HBN DNA Suppression (at delivery)	2(observational studies)	⊕◯◯◯[34] VERY LOW	RR 45.4 (9.26 to 222.48)
	Maternal HBeAg seroconversion (at delivery)	1(observational studies)	⊕◯◯◯[34] VERY LOW	RR 6.33 (0.33 to 119.97)
	ALT normalization (before delivery)	45 (1 observational study)	⊕◯◯◯[34] VERY LOW	RR 1.3 (0.89 to 1.88)
	Cesarean section rate	78 (1 observational study)	⊕◯◯◯[4] VERY LOW	RR 1.72 (0.41 to 7.21)
	Postpartum hemorrhage	78 (1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.57 (0.15 to 2.19)
	Elevated Creatinine kinase rate	45 (1 observational study)	⊕◯◯◯[34] VERY LOW	RR 3.41 (0.15 to 79.47)
Telbivudine vs Lamivudine	Maternal HBV DNA suppression (at delivery)	387 (1 observational study)	⊕◯◯◯[3] VERY LOW	RR 1.83 (1.28 to 2.61)
	Maternal HBV DNA suppression	303	⊕◯◯◯[34]	RR 1.24

	(4 weeks postpartum)	(1 observational study)	VERY LOW	(0.78 to 1.97)
	Maternal HBeAg loss (at delivery)	310 (1 observational study)	⊕◯◯◯[3,4] VERY LOW	RR 1.05 (0.05 to 21.49)
	Maternal HBeAg seroconversion (at delivery)	310 (1 observational study)	⊕◯◯◯[3,4] VERY LOW	RR 0.63 (0.03 to 15.21)
	Cesarean section rate	387 (1 observational study)	⊕◯◯◯[4] VERY LOW	RR 1.05 (0.86 to 1.3)
	Elevated Creatinine kinase rate	318 (1 observational study)	⊕◯◯◯[3,4] VERY LOW	RR 1.91 (0.1 to 34.96)
Tenofovir vs Lamivudine	Cesarean section rate	111 (1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.76 (0.36 to 1.62)

Footnotes:

1. Increased risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision