

# The efficacy of two different doses of hepatitis B immunoglobulin in interrupting mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis

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## Research article

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# Abstract

**Background:** There isn't consensus about the optimal dose of hepatitis B immunoglobulin (HBIG) in combination with hepatitis B vaccine to preventing mother-to-child transmission (MTCT) of hepatitis B virus (HBV).

**Methods:** We systematically searched MEDLINE, Embase, and Cochrane Library from database inception to Jan 16, 2019 for studies. The primary outcome was HBsAg and/or HBV DNA positive in infants at 6-12 months old. We performed a meta-analysis with a random-effects model to calculate a pooled estimate of MTCT.

**Results:** We included 31 studies, comprising of 12151 infants. There wasn't significant differences in the pooled MTCT rates between 100 IU HBIG group and 200 IU HBIG group (5% vs 5%,  $P = 0.757$ ). When further stratified according to HBeAg status, in HBeAg(+) mothers, 7% (95%CI 4%-11%) infants became chronic HBV infection in 100 IU HBIG group compared to 7% (95%CI 5%-9%) in 200 IU group. The rates were 1% (95%CI 0%-2%) in 100IU group and 0% (95%CI 0%-1%) in 200IU group in infants born to HBeAg(-) mothers, respectively. When further comparing MTCT in infants from mothers with HBV DNA  $\geq 1 \times 10^6$  IU/mL, the pooled MTCT rate was 12% (95%CI 7%-17%) in 100IU group and 8% (95%CI 5%-13%) in 200IU group, respectively. In addition, comparative analysis of four studies concerning two different dosages of HBIG further manifested the comparability.

**Conclusion:** 100 IU HBIG is sufficient in preventing MTCT for infants from chronic hepatitis B infected mothers, regardless of maternal HBeAg status or viral load.

## Background

Hepatitis B virus (HBV) infection remains a major cause of chronic hepatitis and associated morbidity and mortality worldwide<sup>1</sup>. Interrupting mother-to-child transmission (MTCT) has become the main priority for elimination HBV infection, especially in epidemic regions. Universal implementation of hepatitis B vaccine is the key strategy to preventing vertical (mother-to-child transmission) and horizontal transmission, and has manifested prominent effectiveness in reducing MTCT<sup>2,3</sup>.

As a passive immune agent against HBV, the first reported use of hepatitis B immunoglobulin (HBIG) to prevent MTCT was in 1978<sup>4</sup>. A few studies has demonstrated that immediate administration of HBIG play an essential role in the prevention of perinatal HBV infection<sup>5-7</sup>. Since then, active immunoprophylaxis with the hepatitis B vaccine in conjunction with HBIG were extensively administrated and the efficacy of has been fully confirmed<sup>1</sup>.

Nevertheless, there is no consensus on the recommended birth dosage of HBIG. At the very beginning, 0.5 ml HBIG per kg body-weight (1ml = 100 IU) displayed protection for MTCT<sup>7</sup>. A randomized blind controlled trial had further manifested the importance of HBIG (0.5 ml HBIG, 145 IU) in prevention of the perinatally transmission<sup>8</sup>. The recommended dosage of HBIG in different guidelines also varied among different countries. In the United States, the standard dose of HBIG was 0.5 mL for infants born to hepatitis B surface antigen positive (HBsAg(+)) women (HyperHEPATITIS B VACCINE S/D: 220 IU/mL, HepaGam: > 312 IU/mL, Nabi-HB: > 312 IU/mL)<sup>9</sup>. However, 100 IU HBIG was recommended to prevent MTCT in China<sup>10</sup>. Various dosages have been conducted in clinical practice. 100 IU, 200 IU, or even two doses of 200 IU HBIG were given to infants<sup>11-13</sup>. Whereas, considering efficacy and cost, the optimal dose of HBIG is still ambiguous. With the Decision Tree-Markov model and cost-benefit analysis, Yang and his colleagues suggested that the optimal strategies was 200 IU HBIG at birth together with 3 schedules of vaccination<sup>14</sup>. A prospective cohort study conducted by Wei et al. highlighted that one birth dose of 100 IU HBIG was comparable to 200 IU<sup>15</sup>.

Up to present, few studies has compared the efficacy of different dosages of HBIG combined with hepatitis B vaccine in preventing MTCT of hepatitis B virus, and systematic review is absent. Therefore, we performed a systematic review and meta-analysis to assess the effectiveness of 100 IU and 200 IU HBIG, which will provide evidence for developing strategies for MTCT prevention.

## Methods

### Search strategy

This systematic review and meta-analysis was performed using a preplanned protocol (registered in PROSPERO: CRD42019130398). Systematic reviews about the efficacy of different dosages of HBIG in infants had not been found. Firstly, we searched the studies reporting on MTCT after passive-active immunoprophylaxis in HBV mothers, conforming to the Preferred Reporting Items for Systematic reviews and Meta Analysis (PRISMA) guidelines<sup>16</sup>. Two reviewers (SF and NJY) searched PubMed, Embase, and Cochrane Library, for studies published in English or Chinese from inception to Jan 16, 2019. Search strategy included terms related to HBV ( eg, "HBV" or "hepatitis B" or "hepatitis B virus"), infant ( eg, "neonate" or " newborn" or "infant") and Immunization ( eg, "Hepatitis B Vaccines" or "Vaccination" or "vaccin\*" or "Hepatitis B immunoglobulin" or "Immunization" or "Immunoprophylaxis"). Additionally, we also manually screened the reference lists of primary studies and review articles for additional references.

### Inclusion and exclusion criteria

Two independent reviewers (SF and NJY) screened the titles and abstracts for eligibility using pre-specified inclusion/exclusion criteria. No type of study restriction was imposed. Our rationale was that inclusion of publications reporting on children, from chronic hepatitis B infected (CHB) women without intervention during pregnancy, were administrated full-course implementation of hepatitis B vaccine and one birth dose of 100IU or 200IU HBIG. The studies were included if they presented the rate of immunoprophylaxis failure, which was defined as HBsAg and/or HBV DNA positive in infants at 6-12months old. We excluded studies in which pregnant women were co-infected with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis D virus (HDV), syphilis, toxoplasmosis, herpes virus, rubella virus, or cytomegalovirus; infants were preterm, congenital abnormality or developmental disorders; sample size<10; or studies published as abstracts only. If there were more than one report from the same research center, we selected the most recent report or the report with the most complete data including subgroup data.

### Data abstraction and quality assessment

Two reviewers independently extracted data according to inclusion/exclusion criteria. We developed a case report form (CRF) to extract the following information from each study: first authors' name, year of publication, study design, countries/regions, maternal hepatitis B e-antigen (HBeAg) status, maternal HBV DNA level before delivery, intervention for infants, dosage of HBIG, time of HBIG administered, time point of immunogenicity assessment, sample size, and relevant outcome data. Disagreements were resolved by consensus with the other authors. We contacted authors to obtain clarification for studies with unclear methods or insufficient data. The quality of the randomized controlled trials (RCTs) was evaluated using the Cochrane Risk of Bias assessment tool, and studies were classified as low risk of bias, unclear/medium risk of bias or high risk of bias. With Newcastle-Ottawa scale (NOS), observational studies with a cumulative score  $\geq 7$ , 4-6, and  $< 4$  were considered as high, fair, and low quality, respectively.

### Statistical analysis

We performed proportion meta-analyses to estimate the rate of immunoprophylaxis failure of two different doses of HBIG, and head-to-head meta-analyses to directly compare the efficacy of 100IU and 200IU HBIG. Statistical analysis

was carried out according to the per-protocol analysis data, and relative risk (RR) and 95% confidence interval (95%CI) were estimated by the Mantel–Haenszel fixed-effects model, or the inverse variance random effects model. The heterogeneity test was assessed using the *chi*-squared test and  $I^2$  statistics, with  $I^2$  statistics 25%-50%, 50%-75%, and > 75% indicated a low, moderate, and high degree of heterogeneity, respectively. Subgroups analyses were performed for potential sources of heterogeneity. Stata (version 13.1; Stata, College Station, TX, USA) was used for proportion meta-analyses, and RevMan 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) for head-to-head meta-analyses. *P* value < 0.05 was considered statistically significant.

## Results

### Characteristics of the eligible studies

Of the 5789 citations and 6 additional manually searched articles evaluated, 359 studies were eligible for full-text review, thirty-one<sup>11,12,15,17-44</sup> of which were included in our analysis. All studies except four<sup>30,31,36,40</sup> were published in English. Included studies were conducted in five countries, China, Turkish, Greece, Australian, and Japan, from 1999 to 2018. Data on study characteristics were shown in Table 1. All enrolled infants were administered with HBIG within 24 h after birth. The levels of HBsAg and/or HBV DNA were detected at 6–12 months old. The methodological quality of the included studies are reported in the appendix Table S1 and Table S2.

Table 1  
Main characteristics of the included studies

First author, year	Country	Study design	Study period	Immunization strategy	Age for assessment	Dosage of HBIG	event	n
Wei 2018 <sup>15</sup>	China	cohort study	2009–2011	HBIG within 12 h + HepB within 12 h, 1,6 m	7 m	100	8	545
						200	12	632
Sheng 2018 <sup>11</sup>	China	cross-sectional study	1/2016–12/2016	HBIG within 12 h + HepB within 12 h, 1,6 m	7 m	100	5	46
He 2018 <sup>17</sup>	China	cohort study	12/2008–5/2016	HBIG within 6 h + HepB within 12 h, 1,6 m	7 m	200	4	34
Chen 2018 <sup>18</sup>	China	cross-sectional study	12/2010–12/2015	HBIG within 12 h + HepB within 12 h, 1,6 m	7 m	200	26	499
Zhu 2017 <sup>19</sup>	China	RCT	NA	HBIG within 24 h + HepB within 24 h, 1,6 m	7 m	200	12	437
Pan 2017 <sup>21</sup>	China	cohort study	5/2008–1/2015	HBIG within 6 h + HepB within 12 h, 1,6 m	7 m	200	5	89
Kang 2017 <sup>22</sup>	China	cross-sectional study	1/2011–7/2011	HBIG within 24 h + HepB within 24 h, 1,6 m	7-12m	100	114	2765
Chen 2017 <sup>23</sup>	China	cohort study	1/2011–6/2015	HBIG within 6 h + HepB within 6 h, 1,6 m	7 m	200	23	168
Zhou 2017 <sup>20</sup>	China	cross-sectional study	8/2012–12/2013	HBIG within 24 h + HepB within 24 h, 1,6 m	7 m	200	2	24
Liu 2016 <sup>28</sup>	China	cohort study	12/2010–12/2012	HBIG + HepB 0,1,6 m	51w	100	19	78

RCT, randomized controlled trial CCT, control clinical trial NA, not applicable h, hour w, week m, month

Event, number of infected infants N, number of total infants

\*The two studies were only eligible for head-to-head analysis, because two dose HepB were used for infants

First author, year	Country	Study design	Study period	Immunization strategy	Age for assessment	Dosage of HBIG	event	n
Zhu 2016 <sup>24</sup>	China	RCT	NA	HBIG within 24 h + HepB within 24 h, 1,6 m	7 m	200	12	477
Yin 2016 <sup>25</sup>	China	case-control study	1/2008-3/2011	HBIG within 6 h + HepB within 6 h, 1,6 m	7 m	200	15	261
Wang 2016 <sup>26</sup>	China	cohort study	7/2012-4/2015	HBIG within 2 h + HepB within 2 h, 1,6 m	7 m	100	16	871
Tan 2016 <sup>27</sup>	China	cohort study	1/2012-3/2015	HBIG within 6 h + HepB within 6 h, 1,6 m	7 m	200	15	320
Pan 2016 <sup>12</sup>	China	RCT	3/2012-6/2013	HBIG within 12 h + HepB within 12 h, 1,6 m	7 m	200	6	88
Wang 2015 <sup>31</sup>	China	cohort study	2009-2013	HBIG 30 min,15d + HepB30min, 1,6m*	7 m	100	0	24
						200	0	55
Tekin 2015 <sup>29</sup>	Turkish	cohort study	5/2013-9/2013	HBIG within 24 h + HepB within 24 h, 1,6 m	24-36w	200	2	54
Deng 2015 <sup>30</sup>	China	CCT	1/2011-1/2014	HBIG + HepB0,1,6 m	6 m	200	4	75
Chen 2015 <sup>32</sup>	China	RCT	2011-2013	HBIG within 24 h + HepB within 24 h, 1,6 m	6 m	100	6	56
Zhang 2014 <sup>33</sup>	China	case-control study	1/2011-6/2011	HBIG + HepB0,1,6 m	7-10m	100	9	176
Kang 2014 <sup>34</sup>	China	Single-arm study	1/2011-6/2011	HBIG at birth + HepB 0,1,6 m	7-10m	100	54	1907

RCT, randomized controlled trial CCT, control clinical trial NA, not applicable h, hour w, week m, month

Event, number of infected infants N, number of total infants

\*The two studies were only eligible for head-to-head analysis, because two dose HepB were used for infants

First author, year	Country	Study design	Study period	Immunization strategy	Age for assessment	Dosage of HBIG	event	n
Yin 2013 <sup>35</sup>	China	unclear	6/2006-3/2010	HBIG within 6 h + HepB within 6 h,1,6 m	7 m	200	9	820
Sun 2012 <sup>36</sup>	China	RCT	2009–2011	HBIG within 12 h + HepB0, 1,6 m	7 m	100	4	240
						200	5	247
Koumbi 2010 <sup>37</sup>	Greece	unclear	NA	HBIG within 24 h + HepB within 24 h, 1,6 m	7 m	200	0	23
Xu 2009 <sup>38</sup>	China	RCT	NA	HBIG within 24h + HepB within 24 h,4,24w	52w	200	5	41
Wiseman 2009 <sup>39</sup>	Australian	prospective, observational study single-arm	8/2002-5/2008	HBIG within 12h + HepB within 12 h,2,4,6 m	9 m	100	4	138
Deng 2008 <sup>40</sup>	China	RCT	9-2006.12	HBIG within 12 h,1 m + HepB0, 1,6m*	8 m	100	14	85
						200	10	96
Xiao 2007 <sup>41</sup>	China	cohort study	9/2001-6/2005	HBIG within 12h + HepB 1d,1,6 m	6 m	100	12	152
Yuan 2006 <sup>42</sup>	China	RCT	11/1999-3/2004	HBIG at birth + HepB within 24 h,1,6 m	12 m	200	17	133
Wang 2002 <sup>43</sup>	China	cohort study	1990–1998	HBIG at birth + HepB 1,2,7 m	7 m	100	21	292
Kato 1999 <sup>44</sup>	Japan	single-arm study	1981–1993	HBIG at birth + HepB within 2 m,3-4m,5-6m	12 m	200	17	203
RCT, randomized controlled trial CCT, control clinical trial NA, not applicable h, hour w, week m, month								
Event, number of infected infants N, number of total infants								
*The two studies were only eligible for head-to-head analysis, because two dose HepB were used for infants								

Among the thirty-one studies included, nine studies evaluated by the Cochrane Risk of Bias assessment tool, consisted of six with low risk of bias and three with unclear/medium risk of bias, the thirteen observational studies evaluated by

NOS score, consisted of eleven with high quality and two with medium quality, while the remaining nine studies could not be evaluated due to unclear design.

### Overall efficacy of different doses HBIG in MTCT

Among thirty-one studies included, twenty-nine studies comprised of 11891 infants were eligible for proportion meta-analyses, and the other two<sup>31,40</sup> including 260 infants were only applied for head-to-head meta-analysis because the infants were administered with two doses of HBIG.

In the proportion meta-analyses, two studies contributed both 100 IU and 200 IU datasets. 7266 infants receiving 100 IU HBIG from twelve studies, and 4625 infants receiving 200 IU HBIG from nineteen studies were included. For 100 IU group, the pooled MTCT rate was 5% (95%CI 3%-7%), and a similar rate was observed in 200 IU group (5%, 95%CI 3%-7%) (Fig. 2a). Of the four studies eligible for head-to-head meta-analyses, 894 infants received 100 IU and 1030 infants received 200 IU HBIG. In addition, there wasn't significant difference in the risk of MTCT between these two groups (RR = 1.08, 95%CI 0.64–1.82, P = 0.77) (Fig. 2b).

### Subgroups analysis by Hepatitis B e antigen (HBeAg) status

A plenty of studies have confirmed that HBeAg is an independent risk factor for MTCT<sup>22</sup>. Data were further stratified to evaluate the effectiveness of the two different doses by maternal HBeAg status. As shown in Fig. 3a, 2319 infants from eighteen studies were born to HBeAg (+) mothers. The pooled MTCT rate was 7% (95%CI 4%-11%) for infants receiving 100 IU HBIG (n = 707), there wasn't obvious difference between 100 IU vs 200 IU group (7%, 95%CI 5%-9%, P = 0.871). Further head-to-head meta-analysis using data from two studies (n = 591) confirmed this result (RR = 0.84, 95%CI 0.39–1.77, P = 0.64) (Fig. 3b). For infants born to HBeAg (-) mothers, the estimated incidence of immunoprophylaxis failure was 1% (95%CI 0–2%) in 100 IU group (n = 1415) and 0% (95%CI 0–1%) in 200 IU group (n = 2157), respectively (Fig. 4).

### Subgroups analysis by maternal HBV DNA level

As we all known, HBV DNA load is closely correlated with MTCT, especially in CHB pregnant women with high viremia<sup>45</sup>. Efficacy of different doses HBIG based on HBV DNA level before delivery was carried out. 12 datasets including 1652 infants provided data of maternal HBV DNA  $\geq 1 \times 10^6$  IU/mL before delivery. As showed in Fig. 5, the pooled MTCT rate was 12% (95%CI 7%-17%) across 686 infants administered 100 IU HBIG and 8% (95%CI 5%-13%) across 966 infants administered 200 IU HBIG, respectively. However, no significant difference was found in these two groups (P = 0.265). Regarding head-to-head meta-analyses for high HBV virus load, there was insufficient sample size to analyze.

## Discussion

To our knowledge, this is the first comprehensive analysis to compare the effectiveness of two different doses of HBIG in preventing MTCT, in which strict inclusion or exclusion criteria was implemented and the definition of hepatitis B virus MTCT was clear and unified for all included studies (defined as HBsAg and/or HBV DNA positive in infants at 6-12months old). Our systematic review emphasized the similar efficacy of different doses of HBIG in preventing hepatitis B virus MTCT, regardless of maternal HBeAg status or HBV DNA virus load before delivery.

HBIG is a purified product of human immunoglobulin from human plasma including high titers of hepatitis B surface antibody and prevent and decrease HBV infection<sup>46</sup>. It is noteworthy that a critical step has been made in preventing hepatitis B virus with combined implementation of HBIG and hepatitis B vaccine in infants.

Previous studies including ours has shown about 29% (95%CI 13%-49%) infants obtained HBV infection from CHB mothers without intervention<sup>8</sup>. In current study, HBIG with hepatitis B vaccine had decreased the rate of MTCT in a great degree, with a pooled rate of 5%. Furthermore, the 100 IU and 200 IU HBIG had shown identical effectiveness in MTCT. The results were consistent with a recent study by Wei et al, which showed that the performance of 100 IU is comparable with 200 IU HBIG in interrupting MTCT of HBV, with the rate of 4.3% in 100 IU and 5.2% in 200 IU (P = 0.669)<sup>15</sup>.

When further subgroup analysis according maternal HBeAg status, a pooled rate of 7% was shown in infants from HBeAg (+) mothers, and no difference was displayed with different doses. Whereas, a pooled MTCT as low as zero (95%CI 0–1%) was shown in 200 IU HBIG group and 1% (95%CI 0–2%) in 100 IU HBIG group among infants from HBeAg (-) mothers. A few studies have showed that Hepatitis B vaccine alone may be sufficient for preventing hepatitis B virus transmission in neonates of HBeAg(-) mothers<sup>47,48</sup>. However, there still were infected cases reported in HBeAg (-) mothers with vaccine only. Considering the high risk of exposure to HBV during delivery and immature immune function of neonates<sup>49</sup>, which increases their vulnerability to infectious agents, MTCT may still occur. Moreover, it is easier for neonates to become chronic carriers once infected with HBV. It should be very cautious to recommend hepatitis B vaccine only to this population.

Maternal high viremia is an independent risk factor for MTCT<sup>50,51</sup>. In this meta-analysis, 200 IU HBIG showed a higher protective rate than 100 IU HBIG (12% vs. 8%) in infants from CHB mothers with HBV DNA  $\geq 10^6$  IU/mL before delivery, whereas, there was no statistical difference between these two groups (P = 0.265). Wang CM and her colleagues had also shown the similar efficacy of different doses of HBIG in protecting infants from HBV infection, despite 200 IU HBIG exhibited superior to 100 IU in production of HBsAb, which attributed to high dosage of vaccine. In view of above results, 100 IU HBIG may be sufficient, even for infants from high viremia mothers. However, due to lack of head-to-head meta-analysis, further studies are necessary to evaluate efficacy and cost-effectiveness for 200 IU in infants from mothers with HBV DNA  $\geq 10^6$  IU/mL.

This meta-analysis had several limitations. Firstly, there were not insufficient studies for directly comparing the efficacy. Secondly, there were only two studies eligible for head-to-head meta-analysis to evaluate the efficacy in HBeAg (+) mothers. Moreover, limited data were available regarding high HBV DNA, which precluded us from head-to-head meta-analysis. In addition, due to the limitation of primary studies, there were insufficient data to estimate the efficacy in preterm or low birth weight infants, which is a matter of great concern. Finally, as all literature included were published in English or Chinese and the vast majority of data were drawn from studies in China, further researches are essential to generalize the results worldwide.

## Conclusion

In conclusion, our meta-analysis highlighted that similar effectiveness was estimated in 100 IU and 200 IU HBIG combined with hepatitis B vaccine in preventing MTCT, regardless of maternal HBeAg status or HBV DNA virus load before delivery. Owing to the excessively demanding storage condition and unaffordable price in developing countries, with a predominating portion of HBV infected population, 100 IU HBIG combined with hepatitis B vaccine is reasonable to be recommended in preventing MTCT.

## Abbreviations

HBV: Hepatitis B virus; HBIG: hepatitis B immunoglobulin; MTCT: mother-to-child transmission; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e-antigen; CHB: chronic hepatitis B infected; RR: relative risk; CI: confidence

interval

## Declarations

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### Authors' contributions

Guarantor of the article: JF L, TY C

Study design: SF, NJ Y, YL C, YR Z, JF L, TY C

Data collection, data analysis, data interpretation: SF, NJ Y, YC W, Z T

Quality assessment: YY, TT Y, YL F, JL

Drafting of the manuscript: SF, NJ Y, JF L

All authors have approved the final draft of the manuscript.

SF and NJ Y contributed equally to this work and share first authorship

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None.

### Availability of data and materials

All relevant data for this study have been added as additional files.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

All the authors declare that they have no financial and non-financial competing interests.

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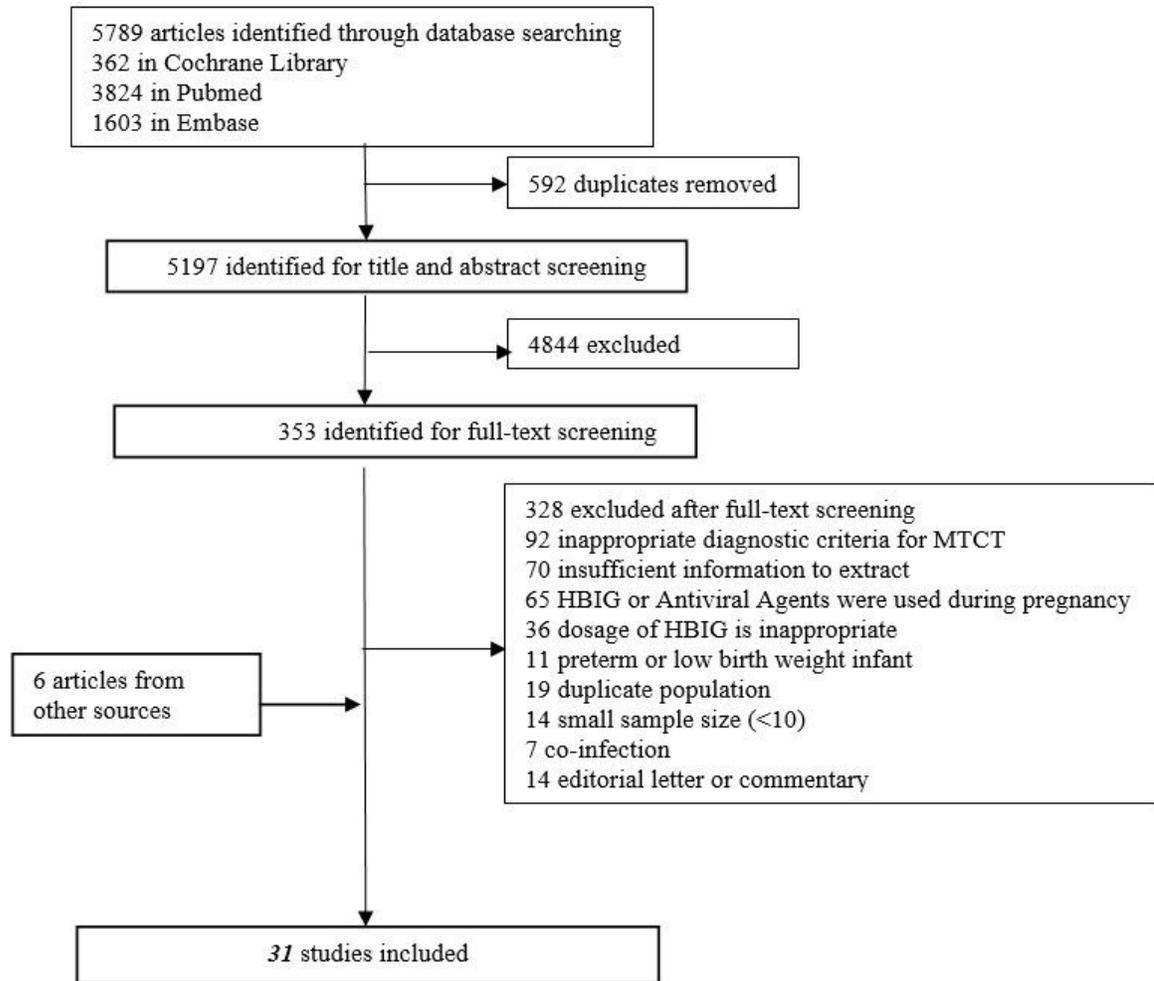
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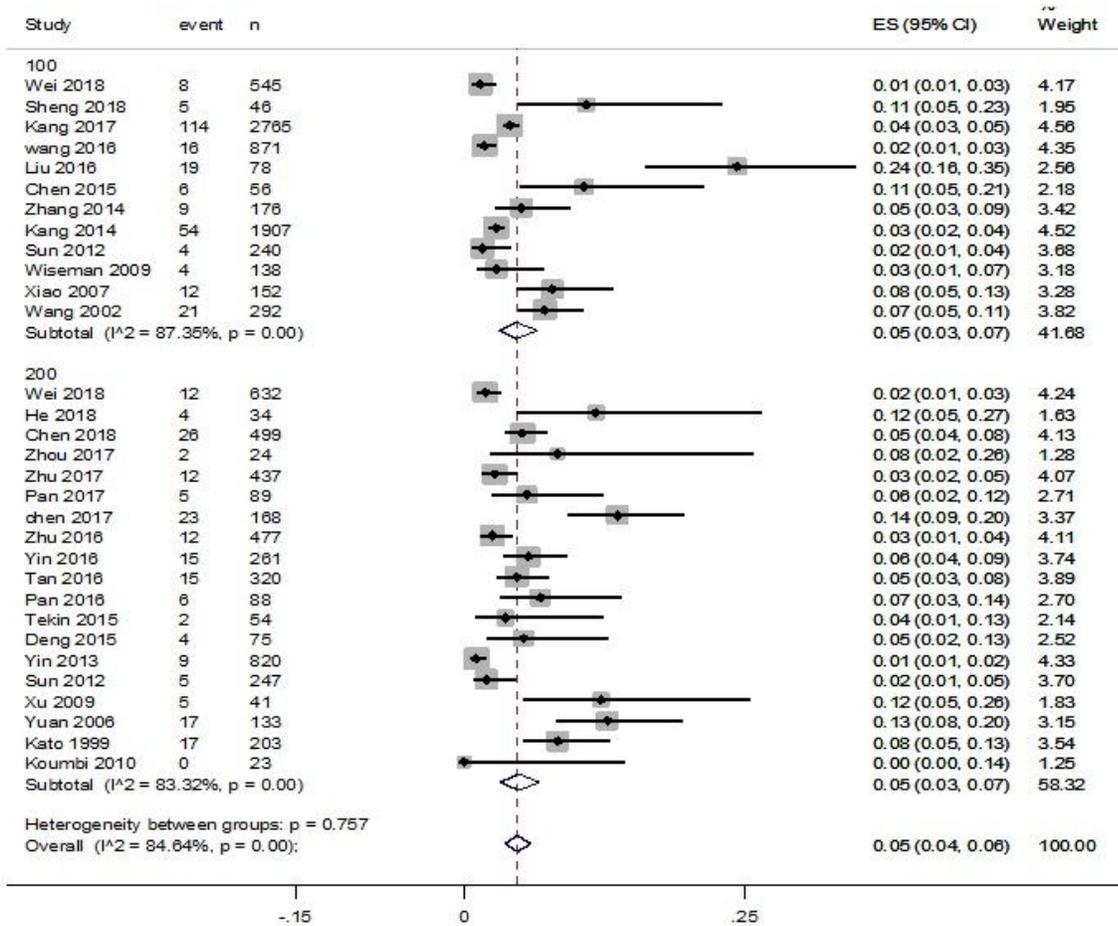
## Figures



**Figure 1**

Flow chart of the study screening and selection for inclusion in the meta-analysis.

A



B

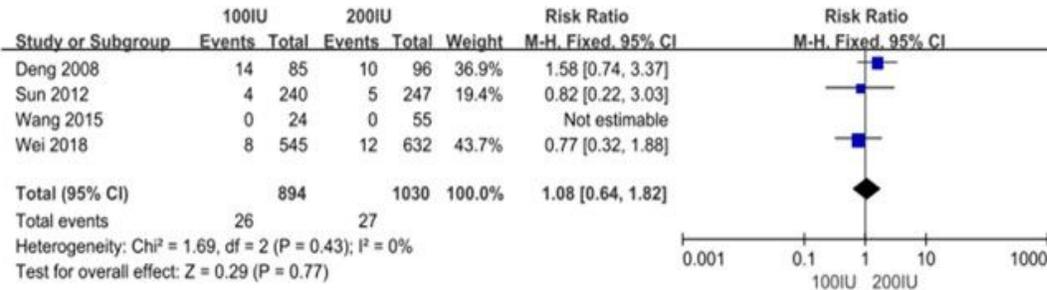
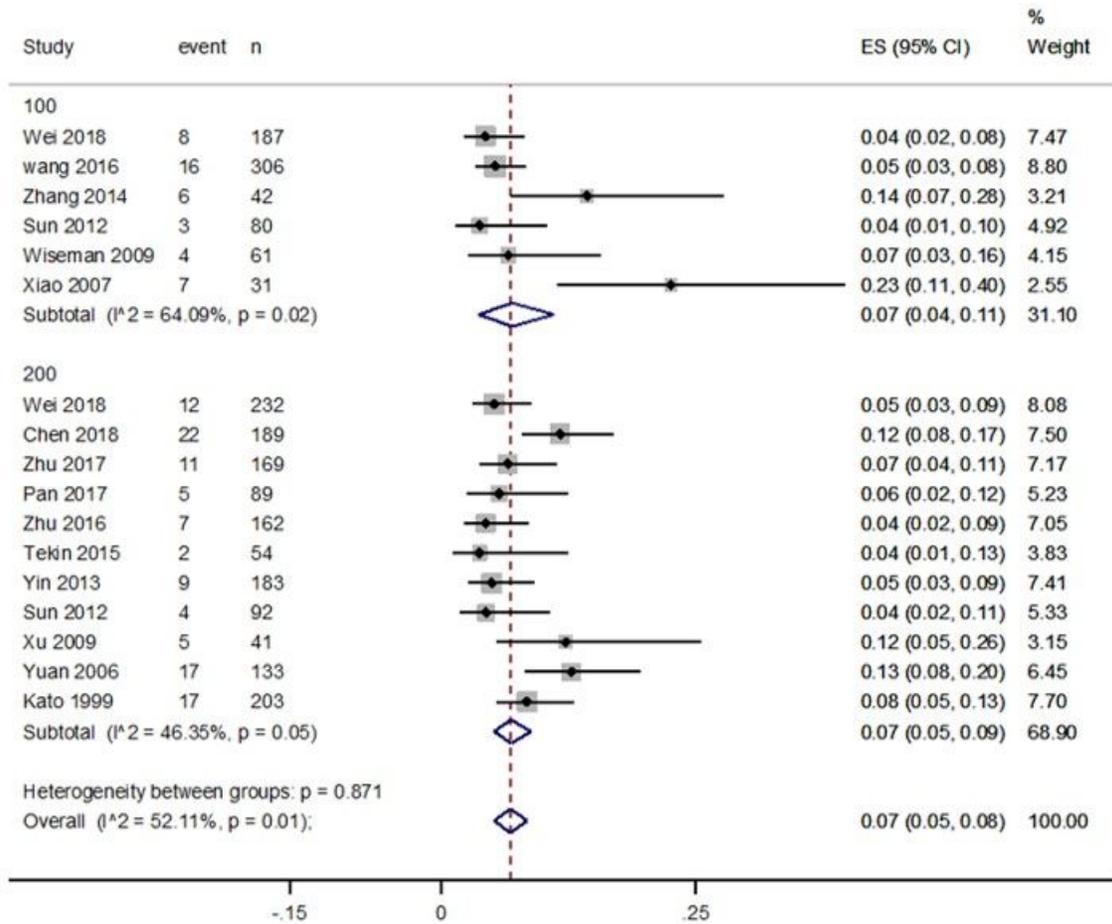


Figure 4

Overall efficacy of 100IU or 200IU HBIG in MTCT. A. Pooled estimates of MTCT rates in infants born to CHB mothers (proportion meta-analyses); B. The rate of immunoprophylaxis failure in infants born to CHB mothers (head to head meta-analyses).

A



B

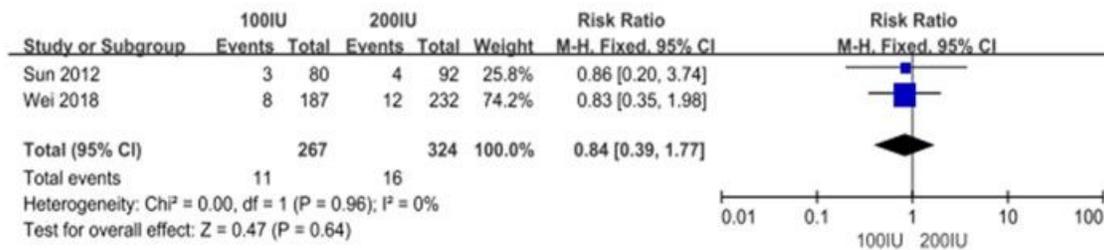
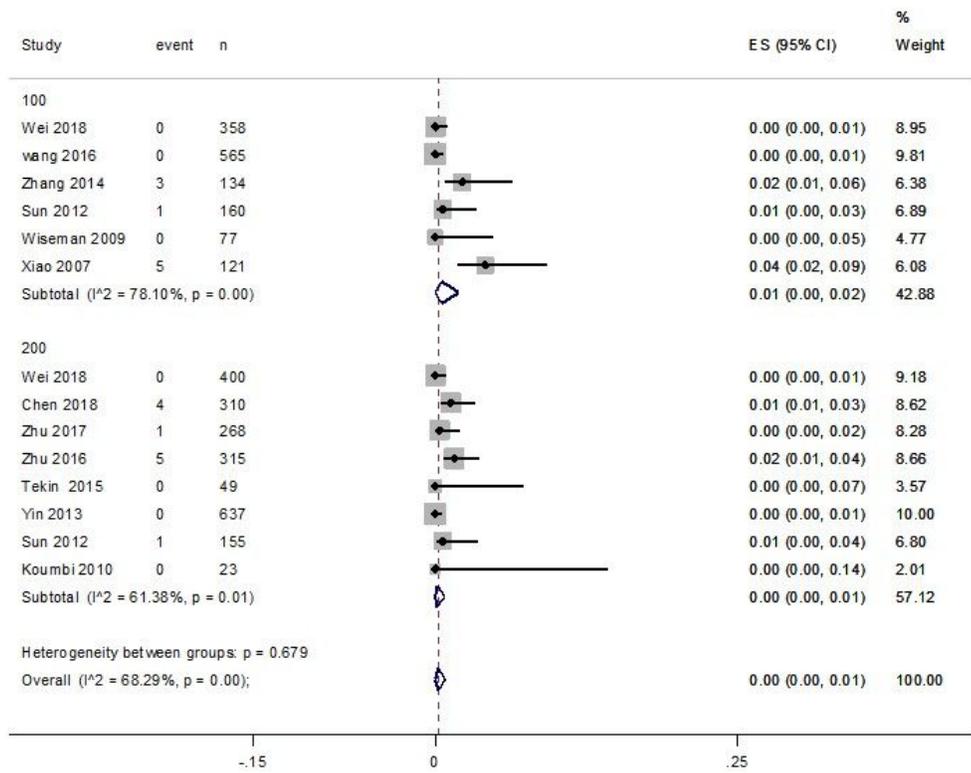


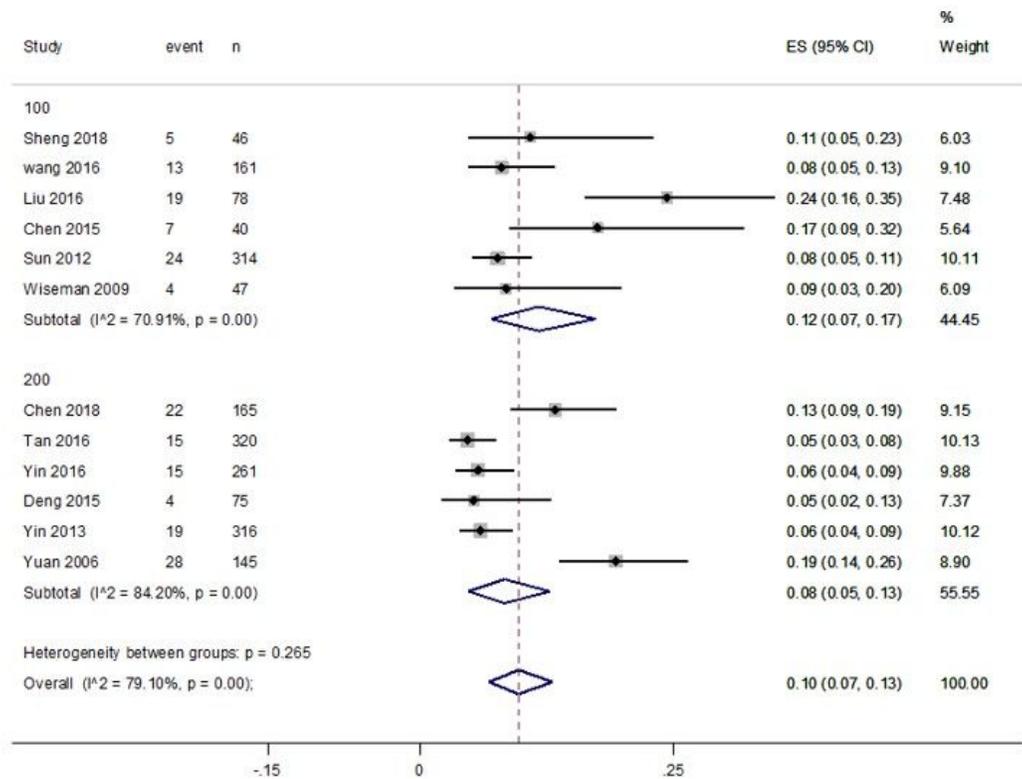
Figure 6

Subgroups analysis by Hepatitis B e antigen (HBeAg) status in MTCT A. Pooled estimates of MTCT rates in infants born to HBsAg+/HBeAg+ mothers (proportion meta-analyses); B. The rate of immunoprophylaxis failure in infants born to HBsAg+/HBeAg+ mothers (head to head meta-analyses).



**Figure 8**

Pooled estimates of MTCT rates in infants born to HBsAg+/HBeAg- mothers



**Figure 10**

Pooled estimates of MTCT rates in infants born to high viremia mothers (HBV DNA  $\geq 1 \times 10^6$  IU/mL).

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