



# New progress towards elimination of mother-to-child transmission of hepatitis B virus in China

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## Abstract

**Background** We conducted an evaluation on the potential data resources for the elimination of hepatitis B virus (HBV) mother-to-child transmission in China, so as to provide reference for WHO and other countries in the validation of HBV elimination of mother-to-child transmission (EMTCT) in a real-world large country setting.

**Methods** We used the indicators set out in *WHO Interim guidance for country validation of viral hepatitis elimination* as the benchmark to evaluate the availability of data and progress against indicators for the elimination validation in China. We used descriptive analysis to illustrate the status of all indicators and parameters.

**Results** According to the indicators which are recommended by WHO for HBV EMTCT validation, the national data in China are attainable, though not for HBV DNA testing for the HBsAg-positive mothers and their subsequent management. The remaining challenges for China are to consider how the national serosurvey might be conducted in future in the context of low HBV prevalence among children under 5 years; to collect systematically the programmatic impact data; to strengthen multi-sectoral collaboration among immunization, maternal and child health, hospital services, as well as other stakeholders.

**Conclusion** The available data on HBV EMTCT are sufficient to support the validation of the elimination of HBV mother-to-child transmission in China.

**Keywords** Hepatitis B · Elimination of mother-to-child transmission · Validation · China

## Introduction

Hepatitis B virus (HBV) infection is a global public health problem responsible for 820,000 deaths in 2019 [1]. The 69th World Health Assembly (WHA) endorsed the Global

Health Sector Strategy for Viral Hepatitis (GHSS), calling for Member States and WHO regions to eliminate viral hepatitis as a public health problem by 2030, defined as a 90% reduction in new infections and a 65% reduction in mortality compared with 2015 [2, 3]. In line with the GHSS, new guidelines for the processes and standards for validation of elimination of viral hepatitis as a public health problem was provided by WHO in 2021. According to those guidelines, WHO suggests the use of absolute impact targets to validate elimination at the national level, instead of the relative reduction targets originally defined in the 2016 GHSS. The main impact indicators and targets for measuring elimination HBV new infection are defined as  $\leq 0.1\%$  HBsAg prevalence in those aged 5 years or less.

China has the highest burden of HBV in the world, with nearly 90 million people living with chronic HBV infection [4–6], and more than 300,000 deaths caused by HBV infection, accounting for almost half of HBV-related deaths worldwide [7, 8]. Most chronic HBV infections are a result of mother-to-child transmission (MTCT) of HBV that occurred before availability of hepatitis B vaccine (HepB).

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In the post-vaccination era, HBV MTCT remains a major route of HBV transmission worldwide [9, 10]. There are between 700,000 and 1,000,000 HBsAg-positive mothers give birth in China each year [11, 12], among those about one-third are HBeAg positive [13], indicating an increased risk of MTCT, resulting more than 50,000 infants infected with HBV on an annual basis [14].

In response, China introduced HepB into the Expanded Program on Immunization in 1992, and the strategies of preventing MTCT (PMTCT) of HBV have been constantly strengthened through quality improvement and evaluation of effectiveness. Several sources of evidence suggested that elimination of MTCT (EMTCT) is on track in China (Fig. 1).

Although WHO has developed a GHSS validation framework to provide guidance on the validation processes, no country has yet validated the elimination of MTCT of HBV and the feasibility of the evidentiary requirements is incompletely known. We conducted an evaluation on data availability and progress towards EMTCT in China to provide other countries for the real-world validation of HBV EMTCT.

## Methods

### Indicator identification

We used the indicators set out in *WHO Interim guidance for country validation of viral hepatitis elimination* as the benchmark to evaluate the availability of data and progress against indicators for the elimination validation in China [15].

## Data review

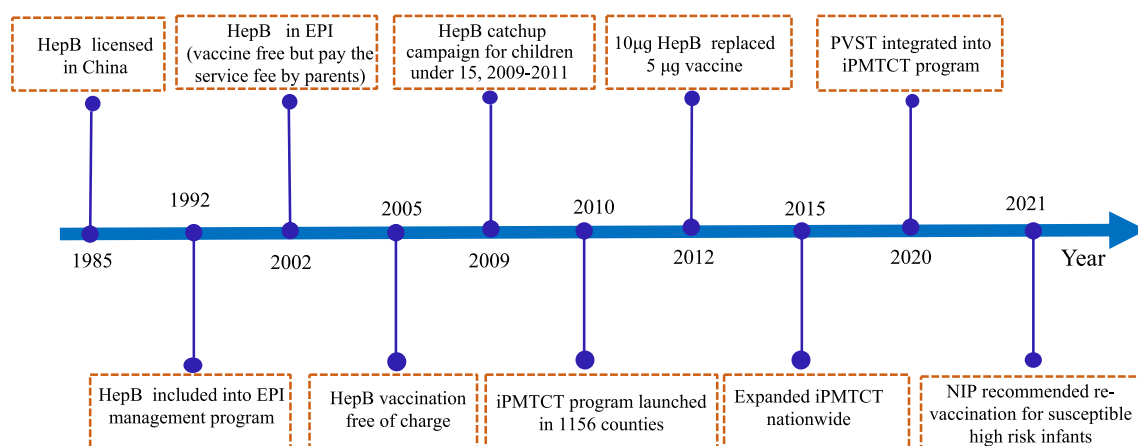
We reviewed national programmatic data (both of the published and unpublished) and peer reviewed literature available. Data were collected from the following: (1) the documents issued by National Health Commission (NHC) or provincial level Health Commissions, including guidelines, national and provincial programs protocols, project reports, and official announcements that were related to the prevention of MTCT of HBV obtained from; (2) China center for disease control and prevention (CDC) providing vaccination coverage for three dose of HepB (HepB3) and timely birth dose (HepB-BD), pregnant women HBsAg screening rate, hepatitis B immunoglobulin (HBIG), and post-vaccination serological testing (PVST); and (3) other supporting information, such as nationwide epidemiological or related studies or special program data on the testing and management of pregnant women, that was searched in two major Chinese medical literature databases (CNKI and Wanfang) and PubMed in English for relevant publications.

## Data analysis

We used descriptive analysis to illustrate the status of all indicators and parameters that were recommended by WHO guidelines for EMTCT.

## Results

In WHO Interim guidance for country validation of viral hepatitis elimination, the criteria for elimination include the attainment of both the impact targets and programmatic targets (Table 1).



**Fig. 1** Progress of HepB vaccination strategy and HBV PMTCT in China

**Table 1** WHO validation indicators for elimination of HBV MTCT, and data availability and progress towards elimination in China

WHO guideline			
Country	Indicators	Measurement	Data resource
China	Universal HepB-BD	Preferred approach: national-level biomarker surveys, if not feasible, a mathematical modeling process may be considered	MOH and China CDC serosurvey data Modeling results
	Targeted timely HepB-BD	Additional approach: MTCT rate through follow-up of HBV-exposed infants in settings using Hep B targeted timely birth dose vaccination	Maternal-child transmission rate data from NIP and MCH after 2020
Progress achieved	Impact targets	<p>≤0.1% HBsAg prevalence among the ≤5-year-old birth cohort (and older children)</p> <p>≤0.1% HBsAg prevalence among the ≤5-year-old birth cohort (and older children) AND Maternal-child transmission rate of ≤2%</p>	<p>0.21% (95% CI:0.07%-0.65%) in 1-4 years children in national serosurvey 2014</p> <p>Model predicts China would reach EMTCT by 2029</p> <p>PVST was integrated in iPMTCT and could be expanded nationwide in 2020</p>
	Programmatic targets (maintain at least 2 years)	<p>≥90% coverage of HepB3</p> <p>≥90% coverage of HepB-BD</p> <p>≥90% HepB3 vaccine coverage</p> <p>≥90% coverage of targeted risk infants timely HepB-BD</p> <p>≥90% coverage of HBsAg antenatal testing among pregnant women</p> <p>≥90% coverage with antivirals for eligible HBsAg-positive pregnant women (plus coverage of HBV-exposed babies with HBIG)</p>	<p>NIP, China CDC</p> <p>HepB data from NIP, China CDC</p> <p>Antenatal testing data from Health year book data Published by NHC</p> <p>HBV-exposed babies with HBIG data from MCH, China CDC</p> <p>No antivirals Data</p> <p>Maintain HepB3 vaccination coverage ≥90% from 2005</p> <p>Maintain HepB-BD coverage ≥90% from 2007</p> <p>Maintain HepB3 vaccination coverage ≥90% from 2005</p> <p>Maintain HepB-BD coverage ≥90% from 2007</p> <p>Pregnant women HBsAg antenatal testing rate ≥99% from 2015</p> <p>HBV-exposed babies with HBIG coverage ≥99% from 2015</p>

NHC National Health Commission; MCH Mother-and-child Health; MTCT Mother-to-child transmission; iPMTCT integrated prevention of MTCT; PVST post-vaccination serological test

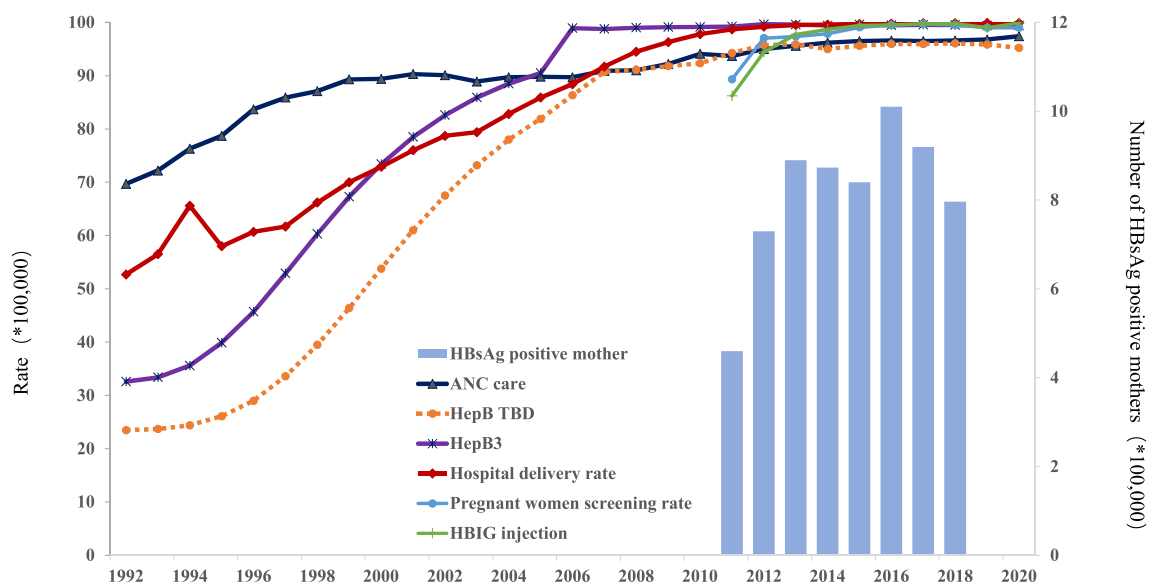
As illustrated in Table 1 and Fig. 1, China has been implementing a universal HepB-BD policy for all newborns, the national data are currently available for the programmatic indicators. Even in terms of criteria for the country with target children for timely HepB-BD, which require higher programmatic indicators, China's national data basically meet the requirements, though not for HBV DNA testing for the HBsAg-positive mothers and their subsequent management.

In China, the coverage of HepB3 and HepB-BD are reported from county-level to the national-level through the National Children Immunization Information System (NCIIS), which was established in 2004. By 2011, the NCIIS received vaccination information for nearly 90% of all newborns [16]. According to NCIIS data, the HepB3 coverage of infant has remained greater than 99% since 2008, and the HepB-BD coverage has remained over 95% since 2013. In 2018, HepB3 coverage in all provinces (excluding Hong Kong, Taiwan and Macao) exceeded 98%, and the HepB-BD coverage in 21 provinces was higher than 95%, though it in Tibet and Qinghai was lower at 62% and 88% respectively (Figs. 2, 3c, d). Even in the COVID-19 pandemic in 2020, China still maintained the infants HepB coverage at high level, with HepB3 reaching 99.4% and HepB-BD reaching 95.2% (Fig. 2).

In addition to childhood vaccination and timely HepB-BD vaccination, WHO recommends the screening of pregnant women and assessing their eligibility for antiviral prophylaxis and/or antiviral treatment in order to further reduce the perinatal transmission rates of HBV. In China, an integrated PMTCT (iPMTCT) program for HIV, syphilis and

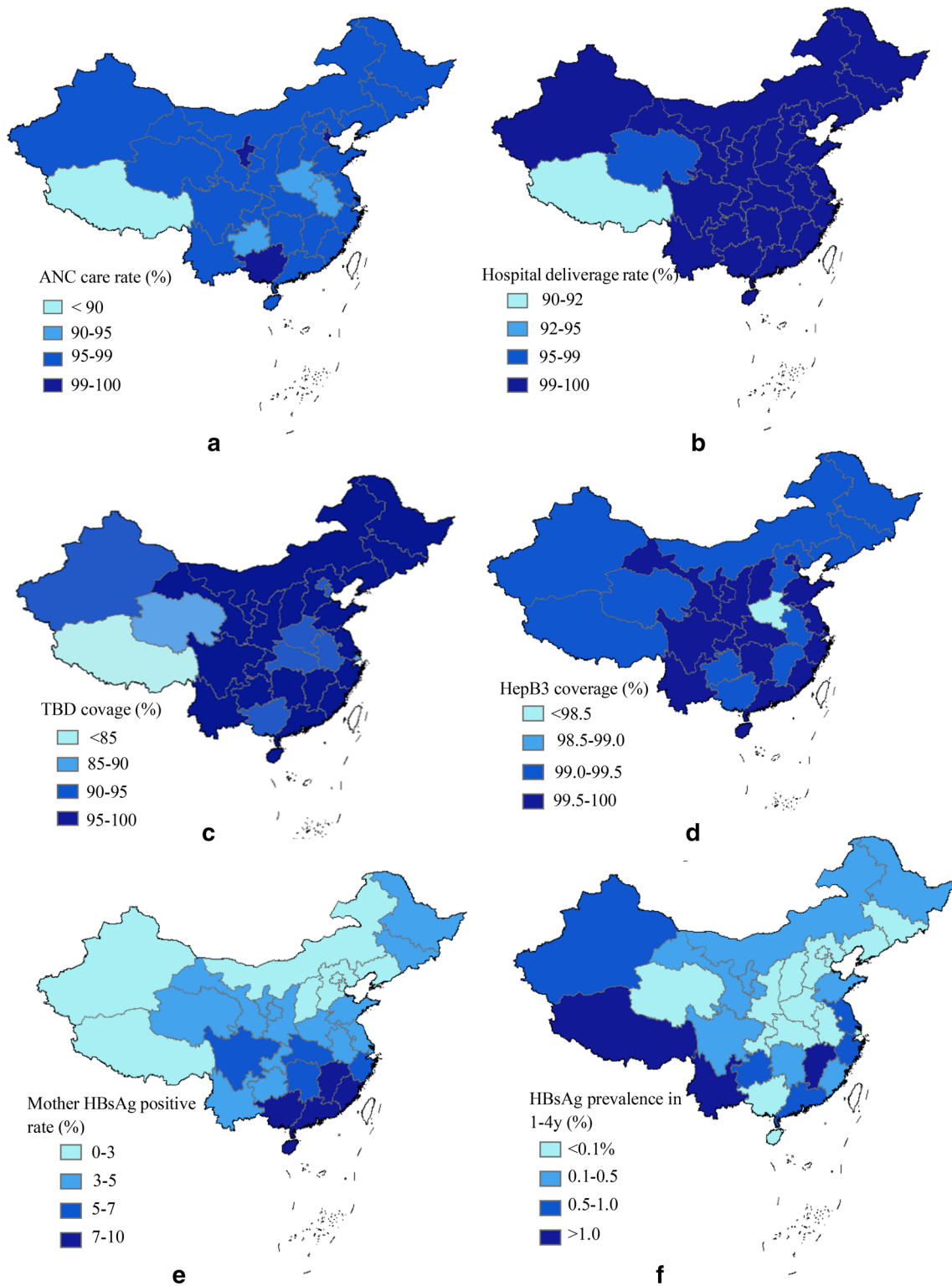
hepatitis B was established in 1,156 counties (representing 41% of counties in China [17]) in 2010. It was expanded nationwide, covering all pregnancies in 2015 [18]. In the iPMTCT project, free HBsAg testing is provided for all pregnant women, as well as the administration of 100 IU hepatitis B immunoglobulin (HBIG) within 24 h after birth (cost-free) for infants born to HBsAg-positive mothers. The National Center for Women and Children's Health (MCH) of China CDC manages the iPMTCT project, while maternal and child healthcare hospitals at provincial, prefectural and county levels implement the program. All the iPMTCT program data are collected through the Maternal Child Health Information Management System. During 2011 to 2020, the HBsAg testing rate for pregnant women increased from 85.3% to 99.5%, peaking in 2016 at more than 1 million (Fig. 2). The data demonstrated that among pregnant women HBsAg screening in 2018, the HBsAg-positive rates vary between regions, with Fujian, Jiangxi, Guangdong and Hainan provinces being more than 10% (Fig. 3e). HBIG coverage for infants born to HBsAg-positive mothers has been greater than 99.5% since 2016 (Fig. 2).

The impact target (prevalence of HBsAg among  $\leq 5$ -year-old children) is a proxy for MTCT incidence which is possible to assess serosurvey data. In China, a national hepatitis B serosurvey had been conducted every 5–10 years since 1979, and to date there have been four national HBV prevalence data published, in 1979, 1992, 2006 and 2014. A national hepatitis B and C serosurvey was conducted in 2020 and latest data will be available in 2022. HBsAg prevalence in 1–4 years old



**Fig. 2** ANC care rate, hospital delivery rate, prenatal HBV screening rate, and infant HepB coverage and HBIG administration rate in China, 1992–2020. (Data sources: Hospital delivery rate data from

the Health Statistics yearbook 2021; HepB vaccination data from EPI, China CDC; Prenatal screening rate and HBIG administration data MCH, China CDC)



**Fig. 3** Subnational distribution of the indicators in EMTCT, China, 2018. **a** HBsAg screening rate among pregnant women; **b** hospital delivery rate; **c** hepatitis B vaccine timely birth dose (TBD) within

24h after birth; **d** three doses of hepatitis B vaccine; **e** HBsAg positive rate among pregnant women; **f** HBsAg prevalence among children under 5 years. \* 2014 data

children is part of routine data analysis. According to the 2014 survey data, the national HBsAg prevalence in 1–4 years children was 0.32%, while at the subnational level, 45% (14) of provinces had a HBsAg prevalence of <0.1% in 1–4 years children and so could potentially be classified as having eliminated MTCT of HBV. In Yunnan, Tibet and Jiangxi provinces, HBsAg prevalence among 1–4 years children was > 1% (Fig. 3F).

MTCT rate  $\leq 2\%$  was as an additional approach for the impact targets for those countries with targeted timely HepB-BD for high risk infants, which need through follow-up of HBV-exposed infants. In China, the post-vaccination serological testing (PVST) for HBsAg-positive mothers' infants began in 2016, through a cooperative China-WHO pilot project in eight counties in four provinces of Zhejiang, Jiangxi, Chongqing and Fujian. Testing occurs at 7–12 months of age. By the end of 2019, this project had enrolled nearly 10,579 HBV-exposed infants, including nearly 6600 infants who were eligible for PVST (Table 2). During the prospective follow-up testing for 5,505 infants who received HepB combined with HBIG, 96% displayed seroprotection (anti-HBs positive), and the MTCT rate among the cohort was 1.2%. Nevertheless, 2.7% of infants were susceptible to HBV, indicating the need for revaccination (Table 2).

**Table 2** Proportion of non-compliance reasons among infants in four PVST pilot provinces, China, 2016–2019

Items	Numbers [n (%)]
HBsAg-positive mother with prenatal screening	10,393
Enrolled infants in hospital (HepB + HBIG)	10,579
Followed infants after second dose of HepB (at 1 month)	6750 (63.8)
Followed infants after third dose of HepB (at 6 months)	6622 (98.1)
Infants for PVST (at 7–8 months)	5505 (83.1)
Result of PVST for infants <sup>a</sup>	
Protected	5283 (96.1)
Infected	64 (1.2)
Susceptible	148 (2.7)
Unknown	10 (0.2)
Reasons for LTFU <sup>b</sup> of PVST	
Transfer out of birthplace	177 (15.8)
Refuse/failure of blood collection	595 (53.2)
Want to delay blood collection	103 (9.2)
Self-test with no feedback for CDC	97 (8.7)
Mis-connection information	93 (8.3)
Others	53 (4.7)

<sup>a</sup>PVST results unknown: refer just testing for HBsAg negative, without anti-HBs testing result

<sup>b</sup>LTFU lost to follow-up

## Discussion

The GHSS for Viral Hepatitis 2016–2021 defines the EMTCT of hepatitis B as achievement of a 90% reduction in new chronic infections, equivalent to 0.1% prevalence of HBsAg among 5-year-old children [3, 19]. In order to reach this elimination target, a comprehensive package of interventions is required, including provision of recommended, evidence based EMTCT interventions during the antenatal period, birth and the postnatal periods in addition to high HepB-BD and HepB3 vaccine coverage.

Progress towards and the validation of EMTCT for HBV in China appear promising. As it demonstrated, China has been implementing a systematic program to interrupt the HBV MTCT and has a robust system to monitor the progress, it is systematic and the data are published over time. The country has a well-established NCIIS as well, which can provide continuous monitoring data on newborns vaccination coverage data. The NCIIS was established in 2004 and achieved the monthly report by township in 2010. By 2011, nearly 90% of newborns vaccination information could be recorded in NCIIS [20]. China has very high coverages of universal antenatal HBsAg testing and TBD vaccination. Yu's studies showed that the routine immunization could continue efficiently run during the COVID-19 pandemic and response in 2020 in China, which ensured China maintaining 9 years for HepB-BD coverage  $\geq 95\%$  and 14 years for HepB3  $\geq 99\%$ . To further increase the timeliness of birth dose as HBV post-exposure prophylaxis, in 2020 the National Immunization Advisory Committee (NIAC) recommended administration of the HepB-BD within 12 h of birth for infants born to HBsAg-positive mothers; the previous recommendation had been administration of a HepB-BD within 24 h of birth [21].

High viral load HBV infection is often observed in HBeAg-positive women and is associated with an elevated risk of transmission, even with vaccine prophylaxis and HBIG [14, 22]. New strategies are becoming available to prevent MTCT, including use of tenofovir for mothers with a viral load  $\geq 200,000$  IU/mL [23–25]. In 2020 WHO recommended the pregnant women with high hepatitis B viral loads to be offered tenofovir from week 28 of pregnancy further reduce risk of vertical HBV transmission [19]. Implementation of this recommendation has challenges, particularly in low resource and rural settings. Operationalizing this in whole country will require a new national strategy for the delivery of perinatal antiviral treatment as antiviral prophylaxis is currently available in a limited number of tertiary hospitals [26–28]. In the interim, in an effort to standardize clinical management with antiviral prophylaxis, professional societies, including the China Foundation for Hepatitis Prevention and Control



(CFHPC), the Chinese Society of Hepatology, and the Chinese Society of Infectious Diseases, have issued antiviral prophylaxis guidelines [23, 29]. The rate of HBV viral load testing of HBsAg-positive pregnant women is very low, possibly due to the cost of the test or the lack of clear testing requirements. In the PVST pilot project described above, the HBV DNA testing rate was < 1% among HBV infected mothers [30, 31], implying that antiviral prophylaxis rates are either lower or not properly targeted. However, HBeAg positivity is an alternative indicator based on the 2020 WHO PMTCT recommendations for the use of antivirals in HBsAg-positive pregnant women, and in China, all pregnant women who are HBsAg positive should be tested for HBeAg, which makes it more feasible to implement antiviral therapy based on the status of HBeAg.

Routine PVST can assess an infant's response to TBD and HepB3 vaccination schedule and provide programs with data to better understand real-world effectiveness of PMTCT interventions for HBV. Both WHO and the US CDC now recommend PVST of infants born to HBsAg-positive mothers [32–34]. Thus far, only a few developed countries have successfully implemented routine PVST for infants born at risk for HBV. The China-WHO Projects confirmed the feasibility of PVST in China [35], leading to a national PVST recommendation with rollout in 2020. Financing for PVST is covered by the iPMTCT program, and PVST has been included in the updated national iPMTCT guidelines [36]. The 2021 edition of the National Immunization Program Guidelines recommends that infants shown by PVST to be susceptible to HBV infection should be revaccinated with a three HepB vaccine schedule, which are provided by government at no cost to families [21]. Increasing PVST follow-up and testing rates, and data sharing and strengthening data management systems will be critically important to optimize the PVST initiative. Implementation of a national PVST strategy makes it possible to track the MTCT rate for at-risk children in near-real time and will provide a critical data source for evidence of HBV EMTCT during validation.

Regular serological biomarker surveys are the methods of reference to estimate the prevalence of chronic infections in the general population and are recommended by WHO [37]. China has conducted five national HBV serosurveys since 1979, with the most recent to be published in 2022. However, now that the prevalence of HBV infection among children is very low, serological surveys to assess HBsAg prevalence among children will require ever-larger sample sizes to have statistical confidence in the point estimate of HBsAg prevalence among young children, and of achieving the 2030 target of 0.1%. Large serological surveys of children are challenging financially

and logistically. Use of multiple sampling methods with the addition of mathematical modeling that includes PVST data is a potential solution to this challenge.

In China, modeling has proven to be useful to better understand the epidemiology and evaluate the national effort to eliminate MTCT of HBV. Recently, a simulation model of the HBV epidemic in China was developed and calibrated to HBsAg and HBeAg prevalence from sequential national serosurveys and HBV-related cancer deaths. This model predicted that if the current high levels of prevention interventions are sustained (TBD = 96%, HepB3 = 99%, HBIG = 99%), China will achieve the 2030 WHO elimination target by 2029. According to the transmission model, increasing TBD vaccination from 96% to 99% would prevent 54,000 new chronic infections by 2030 and would lead to achieving the WHO target by 2025, just four years from now [38].

There already exists sufficient data for HBV PMTCT in China to support the validation of the elimination of HBV MTCT. However, the remaining challenges to achieve the 2030 elimination target are: First, China needs to consider how the national serosurvey might be conducted in future in the context of low HBV prevalence among children under 5 years; second, programmatic impact data will need to be collected systematically in order to effectively monitor the progress, including for those variables relating to iPMTCT, PVST, and antiviral treatment data for pregnant women, as well as to support the triangulation of multiple sources of data for calibration and validation; third, China needs to strengthen multi-sectoral collaboration among immunization, maternal and child health, hospital services, as well as other stakeholders, particularly with regard to the management of high HBV viral load pregnant women. With these efforts, China should be in a position to be able to provide complete and systematical data sufficient for validating the elimination of mother-to-child transmission of hepatitis B virus in the near future.

## Conclusion

In summary, there already exists sufficient data for HBV PMTCT in China to support the validation of the elimination of HBV MTCT. All the evidences indicate that elimination of MTCT of HBV by 2030 is quite promising in China.

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## Declarations

**Conflict of interest** Hui Zheng, Nick Walsh, Olufunmilayo Lesi and Fuqiang Cui have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

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