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Research paper

Hepatitis B virus infection among 90 million pregnant women in 2853 Chinese counties, 2015-2020: a national observational study

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ABSTRACT

Background: China has the largest disease burden of hepatitis B virus (HBV) infection and is considered as a major contributor to the global elimination of hepatitis B by 2030. However, the national prevalence of HBV infection among Chinese pregnant women was not reported yet. We evaluated the national and regional prevalence of HBV infection among pregnant women in China between 2015-2020, aiming to provide the latest baseline data.

Methods: We assessed the prevalence of HBV infection from data gathered through a nationwide cross-sectional study of Chinese pregnant women. Data were obtained from the National Integrated Prevention of Mother-to-Child Transmission of HIV, Syphilis and Hepatitis B Programme (iPMTCT Programme) in China, which covered all the 2856 counties from 31 provinces from 2015 to 2020. HBV infection was defined as being tested seropositive for hepatitis B surface antigen (HBsAg).

Findings: A total of 90.87 million pregnant women in mainland China were testing for HBV between 2015 and 2020, with 5.60 million (6.17%, 95%CI: 6.16-6.18%) tested positive for HBsAg. From 2015 to 2020, the prevalence of HBV infection among pregnant women declined by 25.44%, from 7.30% in 2015 to 5.44% in 2020 (p for trend < 0.001), with an estimated annual percentage change (EAPC) of -5.27% (95% CI: -3.19% to -7.32%). Compared with the prevalence in 2015, reginal disparities in eastern, central, and western China were narrowed. Declines were also observed at provincial level and county level. HBV prevalence declined in most provinces (90.3%, 28/31) and counties (76.96%, 2198/2856) from 2015 to 2020. However, disparities still exist.

Interpretation: HBV prevalence in pregnant women in China was intermediate endemic and declined continuously from 2015 to 2020. The decline has been widespread across regions, but disparities remain. Regions with relatively higher disease burden on HBV infection should receive most attention in achieving the 2030 elimination goals.

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Research in context

Evidence before the study

We searched PubMed and ScienceDirect for reports published in English or Chinese before May 30, 2021, with the terms "hepatitis B virus", "China", "pregnant" and "epidemiology", to assess the prevalence of hepatitis B virus (HBV) infection among pregnant women in China. We identified no national survey reporting HBV prevalence among pregnant

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women in China. We identified one article that reported the number of pregnant women tested for HBsAg in China while it did not report HBV prevalence. Other studies were regional surveys among pregnant women in China. The prevalence figures for HBV infection in Chinese pregnant women was not known, especially after the set of global goals for the 2030 elimination of hepatitis B in 2015.

Added value of this study

In this study, we assessed the national and regional prevalence of HBV infection among pregnant women between 2015-2020. To our knowledge, this is the largest population-based cross-sectional study to focus on pregnant women in China. Our findings showed that HBV prevalence in pregnant women in China was intermediate endemic and declined continuously from 2015 to 2020. However, disparities were still observed in the HBV prevalence at provincial level and at county level. Our findings add to the understanding of better prevention and control of HBV in developing countries, after the set of WHO's 2015 set of global goals on the elimination of hepatitis B by 2030.

Implications of all the available evidence

Regions with relatively higher disease burden on HBV infection should receive most attention in achieving the 2030 elimination goals on HBV. It is important to continue the National iPMTCT Programme on hepatitis B and to further strengthen the management of pregnant women infected with HBV in China. Furthermore, the National iPMTCT Programme could provide a unique opportunity and platform to better achieve the 2030 Elimination goals on hepatitis B, by identifying HBV-infected pregnant women and their high-risk family members at the early stage of the disease to improve the incidence and mortality targets on HBV elimination. Better integration of public health and medical services is needed across existing national programmes and resources to establish an integrated prevention and control system that covers prevention, screening, diagnosis, and treatment of HBV infection across the life cycle. Future research should explore the effective strategies to achieve the 2030 Elimination goals on reducing the incidence of new infections and HBV-related mortality based on the National iPMTCT Programme.

1. Introduction

Hepatitis B virus (HBV) infection is a major public health issue, causing high mortality and disease burden worldwide [1]. The World Health Organization (WHO) estimated that 257 million people were living with chronic HBV infection in 2015 [2,3], 1.5 million people were newly infected with chronic HBV infection and 0.82 million died from HBV infection-related causes globally in 2019 [4]. To take action on sustainable development goal 3.3 on combating hepatitis, the World Health Assembly approved the global health sector strategy to eliminate viral hepatitis as a public health threat by 2030, with a target of reducing new infections by 90% and mortality by 65% compared to the 2015 baseline [3]. How to achieve the goals on time is of great concern globally.

As a country with the world's largest burden of HBV infection, China is considered as a major contributor to the global elimination of hepatitis B by 2030 [5]. China has made remarkable progress in the past three decades that it has changed from a highly endemic area into an intermediate endemic area for HBV infection [5-8]. The prevalence of hepatitis B surface antigen (HBsAg) in people aged 1-59 years declined from 9.8% in 1992 to 7.2% in 2006 and HBsAg prevalence in people aged 1-29 years declined from 10.1% in 1992 to 2.6% in 2014 [9]. However, it is unknown to what extent the prevalence of HBsAg is reduced among adults.

Mother-to-child transmission is the predominant mode of HBV infection in high-intermediate endemic areas. Pregnant women are at risk of transmitting HBV to their offspring. 95% of neonates infected with HBV at birth are at risk of developing chronic infection and 15%–40% of them are at risk of developing cirrhosis and liver cancer [8]. Prevention of mother-to-child transmission (PMTCT) of HBV is one of the five core strategies of global HBV elimination by 2030 [3,5]. HBV infection varied greatly in different regions and populations [7,10,11]. Several studies had reported HBV prevalence among pregnant women in some provinces of China or other countries [11-14] and the prevalence among women preparing for pregnancy [7,15]. The prevalence of HBV infection in women of reproductive age and pregnant women in China varied from 3.87% to 9.98% in previous studies [15]. However, the national HBV prevalence among pregnant women in China has not been reported yet. It is urgent to evaluate the current situation and trends of HBV prevalence among pregnant women, especially after the first five years of the global goals on the elimination of hepatitis B by 2030 in 2015.

We did a nationwide cross-sectional study in China to evaluate the national and regional prevalence of HBV infection among pregnant women and disparities of disease burden between 2015 and 2020, using data from all the pregnant women from the National Integrated Prevention of Mother-to-Child Transmission of HIV, Syphilis and Hepatitis B Programme (iPMTCT Programme) in China.

2. Methods

2.1. Study design and participants

This is a nationwide population-based cross-sectional study. We used data from the Management Information System of the National Integrated Prevention of Mother-to-Child Transmission of HIV, Syphilis and Hepatitis B Programme (iPMTCT Programme) from 2015 to 2020 in mainland China. The National iPMTCT Programme, funded by the Government of China, was started in 2011 in 1156 (41%) county-level administrative units (briefly, counties) and expanded to all the 2856 counties nationwide by 2015 [16,17]. All the health-care facilities providing midwifery and antenatal care services were required to participated in the programme [18]. Hepatitis B surface antigen (HBsAg) was required to be tested among the pregnant women during antenatal care following the national standardized procedures [19]. Detailed design, organisation, and implementation of this programme are described elsewhere [17-19]. We included all the pregnant women who were tested for HBsAg in the National iPMTCT Programme which covered all counties in mainland China from 2015 to 2020 in this study (supplemental figure 1). The National iPMTCT Programme did not collect data in Hong Kong, Macao, Taiwan province. For analysis of the aggregated data, the Peking University institutional review board waived review.

2.2. Procedures

Pregnant women were tested for HBsAg when they received antenatal care and above 95% of women attending antenatal care were screened for HBV [19]. To detect seropositivity of HBsAg in pregnant women, enzyme-linked immunosorbent assays (ELISA) was recommended by the implementation plan for the National iPMTCT Programme in 2015 [19]. Quality control was also conducted following the national implementation plan [19]. All the serological tests were conducted at the local laboratories of hospitals as the process of routine medical services and antenatal care. Hepatitis B reagent kits, approved by the China Food and Drug Administration, were chosen by the local laboratories in the hospital for routine medical services on their preference. As for quality con-

trol, an External Quality Assessment (EQA) was conducted every year by the National Center for Clinical Laboratories.

Pregnant women from 31 provinces were divided into three regions according to their residential addresses to analyses regional disparities: eastern China (including Beijing, Fujian, Guangdong, Jiangsu, Liaoning, Shandong, Shanghai, Tianjin, and Zhejiang), central China (including Anhui, Hainan, Hebei, Heilongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, and Shanxi), and western China (including Chongqing, Gansu, Guangxi, Guizhou, Inner Mongolia, Ningxia, Qinghai, Shaanxi, Sichuan, Tibet, Yunnan, and Xinjiang), which was consistent with previous studies [9,10].

In this study, HBV infection was defined as being tested seropositive for HBsAg [4,19]. Endemicity of HBV infection were defined as low (HBsAg prevalence<2%), lower intermediate (HBsAg prevalence 2-4.99%), higher intermediate (HBsAg prevalence 5-7.99%) and high (HBsAg prevalence ≥8 %) endemic, which were consistent with previous studies [3,20].

All data were collected by the Management Information System, a routine reporting system of the National iPMTCT Programme, which covers all pregnant women who have accessed maternal and child services for PMTCT. Aggregated data on women with HBV infection accessing antenatal care services were reported through the system on a monthly basis. The entry of data was done at county level and the quality of data was re-checked at higher administrative levels, following the national protocol and guidelines [18,19].

2.3. Statistical analysis

We calculated the prevalence of HBsAg and its 95% CI by the entire study group as well as different regions (eastern, western, and central China). We also calculated the prevalence of HBV infection at provincial level and at county level. Chi-square tests were used to compare the prevalence of HBV infection in different years and regions.

We calculated the estimated annual percentage change (EAPC), a summary and widely used indicator to show the trend and annual change over a specified time interval [21,22]. There are many methods to estimate the annual percentage change [23-27]. We chose a most used methods in the field of infectious disease and maternal health [21,22,28] to make it comparable to previous studies. A regression line was fitted to the natural logarithm of HBV prevalence using the formula $y = \alpha + \beta x + \varepsilon$, where y refers to ln (HBV prevalence) and x refers to calendar year. EAPC was calculated as $100 \times (e^{\beta} - 1)$ and its 95% confidence intervals (CIs) was also calculated to assess the temporal trend of the prevalence [21,22]. If the EAPC estimation and its 95% CIs were both <0 (or both >0), HBV prevalence was deemed to be in a decreasing trend (or an increasing trend) in the given time interval [21,22]. In this study, we considered two-sided p values of lower than 0.05 to be statistical significance. All analysis were done with SPSS version 23.0 and Stata software, version 14.

2.4. Role of the funding source

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

3. Results

From 2015 to 2020, there were 91.14 million pregnant women in mainland China, and a total of 90.87 million (99.7%) pregnant women in mainland China were tested for HBsAg in the National iPMTCT Programme between 2015 and 2020. Among these women, 5.60 million (6.17%, 95%CI: 6.16-6.18%) were tested positive for HBsAg (table 1). From 2015 to 2020, the prevalence of HBV infection among pregnant women declined by 25.44%, from 7.30% in 2015 to 5.44% in 2020 ($p_{\text{for trend}} < 0.001$), with an estimated annual percentage change (EAPC) as -5.27% (95% CI: -3.19% to -7.32%).

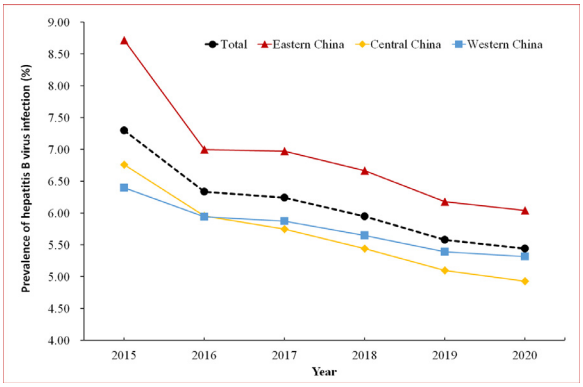

Figure 1. Trends of HBV prevalence among pregnant women in different regions.

Compared with the prevalence 2015, HBV prevalence declined in all three regions, decrseaing from 8.72% to 6.04% in eastern China, from 6.76% to 4.93% in central China, and from 6.40% to 5.43% in western China, respectively (figure 1). Regional disparities also narrowed between 2015 and 2020.

HBV prevalence varied from 1.88% to 11.99% in 31 provinces in 2020 (figure 2). Two provinces were low endemic (HBsAg prevalence < 2%) in 2020, including Tianjin (1.97%) and Shanxi (1.88%). However, six provinces were still high endemic (HBsAg prevalence ≥ 8%), including Hainan (11.99%), Tibet (11.25%), Jiangxi (10.56%), Fujian (9.97%), Guangdong (9.84%), and Guangxi (9.30%).

From 2015 to 2020, HBV prevalence had gradually declined in most provinces (90.3%, 28/31), with EAPC ranging from -1.83% to -10.60%. The top ten provinces with the highest EAPC of decline were Heilongjiang, Jilin, Shanxi, Ningxia, Yunnan, Hainan, Shaanxi, Shandong, Anhui, and Hebei (table 2). However, the prevalence of HBV infection increased in Tibet, Qinghai, and Xinjiang from 2015 to 2020.

Declines were also observed in the HBV prevalence at county level (supplemental figure 2). The proportion of counties with high endemic (HBV prevalence ≥ 8%) declined from 24.26% (693/2856) in 2015 to 17.54% (501/2856) in 2020. Moreover, HBV prevalence declined in most counties (76.96%, 2198/2856) from 2015 to 2020. However, disparities still exist both at provincial level and at county level.

4. Discussion

To our knowledge, this was the first and largest study that investigated the national HBV prevalence among pregnant women in mainland China. In this population-based cross-sectional study of nearly 90 million pregnant women in mainland China, the total prevalence of HBsAg was 6.17% (95%CI: 6.16-6.18%) between 2015 and 2020. Most previous studies reported province or regional prevalence of HBV infection in China, such as Tianjin (3.8%) [29], Zhejiang (5.9%) [30] and Taiwan (12.4%) [31]. At national level, there were four national epidemiological surveys on investigating HBV infection in the general population in China, which was conducted in 1979 [22], 1992 (including people aged 1-59 years) [32], 2006 (including people aged 1-59 years) [33,34], and 2014 (including people aged 1-29 years) [9], respectively. After 2006, there were no national representative survey conducted in the general population aged 1-59 years, especially for adults. Several studies with large sample size focused on couples at reproductive age in

Table 1
Trends of HBV prevalence among pregnant women in mainland China, 2015-2020

Year	Pregnant women tested for HBV (n)	HBsAg positive (n)	HBsAg prevalence (%, 95 CI)	p for trend
2015	13 928 840	1 016 578	7.30 (7.28, 7.31)	<0.001
2016	18 229 199	1 154 938	6.34 (6.32, 6.35)	
2017	17 385 461	1 085 777	6.25 (6.23, 6.26)	
2018	15 038 592	894 889	5.95 (5.94, 5.96)	
2019	14 355 042	801 072	5.58 (5.57, 5.59)	
2020	11 936 522	649 577	5.44 (5.43, 5.45)	
Total	90 873 656	5 602 831	6.17 (6.16, 6.18)	

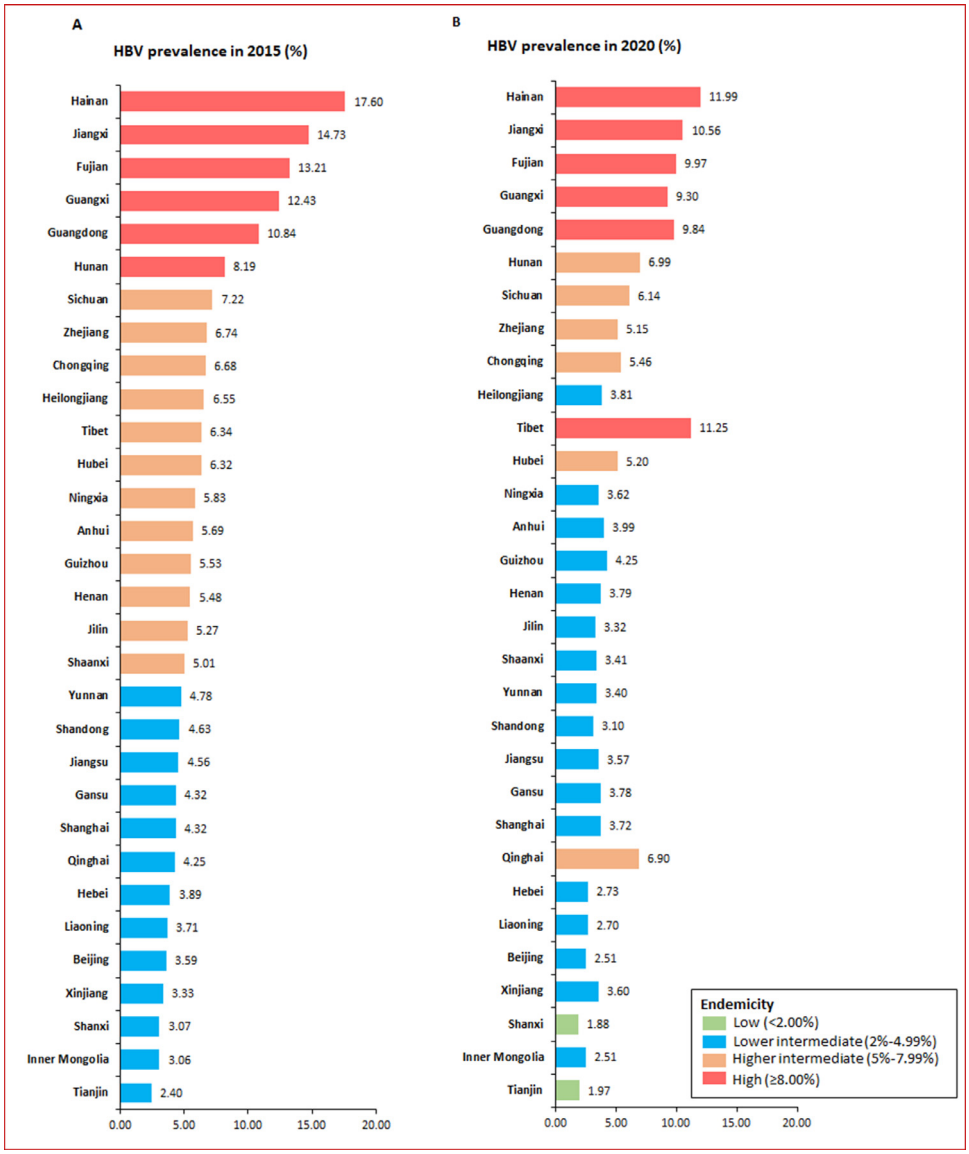

Figure 2. The prevalence of HBV infection among pregnant women and annual percentage change from 2015 to 2020 by province.

China during 2010-2012 [10,15]. The total HBV prevalence of pregnant women in China in our study was lower than the prevalence (6.78%) in women at reproductive age (aged 20-49 years) in the 2006 national survey in China [34,35], higher than the prevalence (4.3%) reported in an epidemiological survey among 0.5 million women at reproductive age during 2010-2012 [15]. Shi et al.[36] did a meta-analysis collecting publications regarding HBsAg among pregnant women between 2002 and 2012 and found that HBsAg prevalence was 7.91% (95% CI: 7.78%-8.03%) during 2002-2012 and 6.29%-7.91% during 2010-2012. The disparities of HBV prevalence between pregnant women and women at reproductive age during the same period might be related to the different characteristics of population in these studies. Moreover, there was higher proportion of pregnant women with advanced age after the implemented the universal "two-child policy" since 2015 [37]. The impact of the two-child policy in China might partially explain the reason of relatively higher prevalence in pregnant women during 2015-2020 than that reported in the women of child-bearing age during 2010-2014. Although there were different results in previous studies, our findings were similar with the result of a meta-analysis in Chinese

Table 2
Ten provinces with the highest estimated annual percentage change of HBV prevalence among pregnant women in mainland China from 2015 to 2020

Rank	Province	Prevalence of HBsAg (%) 2015	2020	EAPC (%, 95% CI)[a]
1	Heilongjiang	6.55	3.81	-10.60 (-12.98, -8.15)
2	Jilin	5.27	3.32	-8.86 (-9.67, -8.04)
3	Shanxi	3.07	1.88	-8.81 (-10.24, -7.36)
4	Ningxia	5.83	3.62	-8.77 (-9.73, -7.79)
5	Yunnan	4.78	3.40	-7.87 (-11.77, -3.80)
6	Hainan	17.60	11.99	-7.61 (-8.91, -6.30)
7	Shaanxi	5.01	3.41	-7.43 (-9.95, -4.83)
8	Shandong	4.63	3.10	-7.09 (-9.24, -4.89)
9	Anhui	5.69	3.99	-6.93 (-8.10, -5.75)
10	Hebei	3.89	2.73	-6.57 (-8.49, -4.60)

EAPC, estimated annual percentage change.

pregnant women reported in 2016 (6.9%, 95%CI 6.1%-7.7%). Consistent with the results of previous studies in other populations, our findings indicated that HBV infection was intermediate endemic among Chinese pregnant women. According to the National Health Statistical Yearbook, the hospital delivery rates were 99.9% in China [38]. We calculated the prevalence of HBV among pregnant women who received HBsAg screening and pregnant women who did not get tested for HBsAg were not included in this study. Given that infected women were more likely to have a consultation of HBV infection and tested for HBsAg, the prevalence of HBV infection might be overestimated. Because of the high hepatitis B screening rate of the National iPMTCT Programme (99%), the results of the present study are likely to be the best available evidence of HBV prevalence among pregnant women in mainland China. The results in our study also indicated that HBsAg prevalence among pregnant women have already reached the national target of lower than 6.5% set in the National Plan for the Development of Health Services [39].

Results from the national surveys showed a continuous decline in the prevalence of HBV infection among the general population, especially for the youth. It was reported that HBV prevalence in general population aged 1-29 years declined from 10.1% in 1992 to 5.5% in 2006, and then declined to 2.6% in 2014 [9,34]. The remarkable decline of HBV prevalence among the youth was mainly due to the high vaccination coverages among children and high coverage of timely birth-dose vaccines for PMTCT of HBV in the National iPMTCT Programme [5]. We also observed the trends of decline in the pregnant women in this study. From 2015 to 2020, the prevalence of HBV infection among pregnant women declined by 25.44%, with an estimated annual percentage decline of 5.27%. Our findings indicated the remarkable progress in HBV prevention and control in China. Pregnant women from 2015 to 2020 were almost born between the 1970s and 2000s. Some of them might be benefit from the national immunization policy on infants and children. In 1992, China was among the first developing countries to enact a universal hepatitis B vaccination programme for newborns and infants [9,10]. Before 2002, hepatitis B vaccine was managed as a type 2 vaccine for which parents or adult vaccinees had to pay out-of-pocket [9,10]. China integrated hepatitis B vaccine into the national expanded programme on immunization (EPI) and provided free vaccination since 2002, making the vaccine available at no cost to children through 14 years of age [9,10]. During 2009–2011, China conducted a catch-up campaign for children <15 years of age who were born during 1994–2001 and nearly 68 million children were vaccinated [9]. With the ongoing implementation of the National iPMTCT Programme and other comprehensive interventions on prevention and control of HBV infection, HBV prevalence will continue to decline among adults in the future.

Although there was a continuous decline in the total prevalence in pregnant women in China, disparities of HBV prevalence were also observed in regional level. For example, HBV prevalence varied from 1.88% to 11.99% in 2020, which reflected that the province with the highest HBV infection rate (Hainan) was ten times more than that with the lowest prevalence (Shanxi). Six provinces were still high endemic (HBsAg prevalence $\geq$ 8%), including Hainan, Tibet, Jiangxi, Fujian, Guangdong, and Guangxi, although HBV prevalence declined in most provinces. The disparities might be related to the historically high prevalence in these provinces as reported in the 1979 and 1992 national surveys among the general population [33,34,40], when women in our study were born. HBV prevalence in most provinces was declined, except for Tibet, Qinghai, and Xinjiang. Jing Guan et al. conducted an epidemiological survey among people aged 1-29 years in Xinjiang province in 2017 and they also found an increase of HBV prevalence (from 4% in 2006 to 6% in 2017) among adults aged 20-29 years in Xinjiang [41]. One explanation was the relatively low vaccination coverage in there three western provinces. Because of the charging policy for hepatitis B vaccine before 2002, the coverage was relatively high in Eastern and wealthier provinces in central China (80-90%), but was much lower (<40%) in western China and poverty provinces where parents could not afford the vaccine (such as Tibet, Qinghai, and Xinjiang) [42]. Furhat U el al. reported that the vaccination rate in Xinjiang was only 33.92% in 2000s [43]. Another explanation was the disparities of behaviors in different ethnic groups. Tibet and Qinghai had a high proportion of Tibetans and had a relatively higher HBV prevalence in the national survey compared with Han ethnicity among general population [40]. Less awareness of diseases, language barriers, not timely diagnosis and treatment and different health seeking behavior made it harder to prevent and control of HBV infection in these provinces [44]. Moreover, either at the provincial level or at county level, mixed endemic mode was observed in China, that low, intermediate, and high endemic provinces (or counties) exist in the same year. Our findings indicated that, although China has made great achievements in reducing incidence of HBV infection, more attention should be paid on the provinces with relatively disease burden on HBV infection because of the disparities on disease burden and health resources.

The National iPMTCT Programme could provide a unique opportunity and platform to prevent and control of hepatitis B. It is time to take actions. First, by the implementation of the programme, China could timely identify HBV-infected pregnant women and provide a timely endemic map on the distribution of disease burden to make tailored strategies on PMTCT of hepatitis B and to better achieve the 2030 elimination goal of reducing new HBV infections by 90%. Second, the Programme also provides an opportunity to early identify and treat young women to better achieve the target of 65% reduction in HBV-related mortality by 2030. They could be benefit more from the early treatment on prevention disease progression. Third, better integration of public health and medical services is needed across existing national programmes and resources to establish an integrated prevention and control system that covers prevention, screening, diagnosis, and treatment of HBV infection across the life cycle [5]. Future research should explore the effective strategies to achieve the 2030 Elimination goals on reducing the incidence of new infections and HBV-related mortality based on the National iPMTCT Programme.

There were several limitations. First, the National iPMTCT Programme did not collect information on the test for other hepatitis B serological markers (HBeAg, anti-HBs, anti-HBc, anti-HBe, HBV DNA, and birth dose rates). Second, the testing kits of ELISA were used by local hospitals that variations could exist. Third, the use of aggregated data rather than individual data is also the limitation that sociodemographic characteristics (such as age, history of vaccination, high-risk behaviors, coinfected with HIV and receive anti-

retroviral therapy, etc.) of pregnant women were not collected in the National iPMTCT Programme. We could not make further analysis on these factors. For example, we could not make ecological analysis by linking between the changes in HBsAg prevalence in each province and coverage of HBV preventive measures by birth cohort. Moreover, some women underwent two or more pregnancies during the survey years, which made the estimation of HBsAg prevalence complicated. Fourth, a small proportion of HBsAg-positive women were likely to have acute HBV infection, rather than chronic infection, as they were not follow-up at an interval of more than six months.

In conclusion, the prevalence of HBV among pregnant women in China was intermediate endemic (6%) between 2015 and 2020 and declined by 25% from 2015 to 2020. China has made great achievements in prevention and control of HBV infection. However, regional disparities still exists. Concerted efforts should be made in China to achieve the 2030 elimination goals on HBV infection on time, especially for regions with relatively higher disease burden on HBV infection.

Contributors

Jue Liu and Xiaoyan Wang searched the literature, designed the study, collected the data, analyzed the data, interpreted the results, and drafted the report. Qian Wang, Yaping Qiao, Xi Jin, and Zhixin Li collected the data and revised the report. Min Du, Wenxin Yan and Wenzhan Jing analyzed the data and revised the report. Min Liu and Ailing Wang conceived the study, designed the study, supervised the study, interpreted the results, and revised the report. Jue Liu and Xiaoyan Wang made same contribution to this paper. Min Liu and Ailing Wang were co-corresponding authors. All authors contributed to the writing of the report.

Declaration of Competing Interest

We declare that we have no conflicts of interest.

Acknowledgments

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Data sharing statement

Datasets generated and/or analyzed in the present study are available from the corresponding author upon reasonable request.

Editor notes

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2021.100267.

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