Front. Med. 2020, 14(1): 21–29
https://doi.org/10.1007/s11684-020-0744-2

REVIEW

Eliminating mother-to-child transmission of HBV: progress and challenges in China

Wenzhan Jing, Jue Liu, Min Liu (✉)

Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China

Abstract **China has the world's largest burden of hepatitis B virus (HBV) infection, but the country has made considerable progress in preventing its mother-to-child transmission (MTCT) in the past three decades. This feat is made possible due to the high coverage of birth-dose hepatitis B vaccine (HepB, > 95%), hepatitis B surface antigen (HBsAg) screening for pregnant women (> 99%), and hepatitis B immunoglobulin plus HepB for newborns whose mothers are HBsAg positive (> 99%). Studies on the optimal antiviral treatment regimen for pregnant women with high HBV-DNA load have also been conducted. However, China still faces challenges in eliminating MTCT of HBV. The overall HBsAg prevalence among pregnant women is considered an intermediate endemic. The prevalence of HBsAg among pregnant women from remote, rural, or ethnic minority areas is higher than that of the national level because of limited health resources and public health education for HBV. The coverage for maternal and child healthcare and immunization services should be improved, especially in western regions. Integration of current services to prevent MTCT of HBV with other relevant health services can increase the acceptability, efficiency, and coverage of these services, particularly in remote areas and ethnic minority areas. By doing so, progress toward key milestones and targets to eliminate hepatitis B as the main public health threat by 2030 can be achieved.**

Keywords hepatitis B virus; mother-to-child transmission; progress; challenge

Introduction

Chronic hepatitis B virus (HBV) infection remains endemic and continues to cause significant morbidity and mortality [1]. Mother-to-child transmission (MTCT) of HBV is defined as a mechanism through which mothers with positive hepatitis B surface antigen (HBsAg) transmit HBV to their offspring [2]. MTCT is the major route of HBV transmission and an important factor for the reservoir of chronic HBV infection in many parts of the world, especially in China and Southeast Asia [3].

The World Health Organization (WHO) estimated that in 2015, 257 million individuals, accounting for 3.5% of the population, were living with HBV infection globally [4]; 65 million women of childbearing age were chronically infected and at risk of transmitting HBV to their offspring [4]. Also, 90% of infants infected with HBV at birth are at risk of chronicity [5,6], and 15%–40% of them will develop cirrhosis and liver cancer [6,7]. In 2015, approximately 887 000 persons died due to complications of chronic HBV infection globally [4], leading to a massive public health burden [4,8].

China has the world's largest burden of HBV infection [9]. The WHO estimated that in China, approximately 6% of women giving birth are living with HBV [10], among which the hepatitis B e antigen (HBeAg)-positive rate is up to 30% [11,12]; as such, the risk of MTCT of HBV and the accumulation of chronic HBV infections are high [3,8,11]. In 2016, mortality due to HBV-related liver diseases in China accounted for more than 30% of the global mortality from HBV (0.31 million/0.89 million) [13]. Given the low coverage of diagnosis and treatment of hepatitis B in China [13], most patients progress to an advanced stage. Therefore, mortality due to HBV-related liver cancer in China accounted for more than 60% of the global rate (0.22 million/0.32 million) in 2016 [14].

The 194 Member States of the WHO committed to eliminating viral hepatitis as a public health threat by 2030

Received July 19, 2019; accepted December 18, 2019
Correspondence: Min Liu, liumin@bjmu.edu.cn

through five synergistic core interventions, including the third-dose of hepatitis B vaccine (HepB) covering 90%, and the approach of preventing MTCT of HBV covering 90% [4,15]. Adherence to safe, effective, and sustainable strategy to prevent MTCT of HBV is critical to decrease HBsAg prevalence among children under five years to $< 0.1\%$ by 2030 in China and worldwide [15]; as such, every child will have the best chance to start a healthy life free from preventable infections [16].

Progress in preventing MTCT of HBV in China

The Chinese government has begun to prevent and control HBV transmission since 1992. The following policies and measures were formulated and implemented to prevent MTCT of HBV directly or indirectly (Fig. 1): (1) Universal HepB immunization strategy in which HepB was integrated to routine childhood immunization and thereby contributed to the decrease in HBsAg prevalence among currently pregnant women. (2) Preventing MTCT of HBV for infants born to mothers who are HBsAg positive. Pregnant women are screened for HBsAg. Timely birth-dose of HepB and extra hepatitis B immunoglobulin (HBIG) is given to infants whose mothers are HBsAg positive within 24 h after birth (or as early as possible after delivery). Another two doses of HepB are administered in strict compliance with the national immunization schedule. (3) Administration of antiviral therapy for pregnant women in the third trimester infected with HBV. Pregnant women with indications for treatment can receive antiviral therapy during the third trimester to decrease the risk of MTCT of HBV.

Universal HepB immunization strategy

Three decades of escalating HepB policies for children have contributed to the decrease in HBsAg prevalence in the whole population in China, as well as among currently pregnant women. In 1992, China recommended HepB for the routine immunization of infants in response to the call of World Health Assembly; however, parents had to pay out of pocket [12]. In 2002, China integrated HepB into an expanded program on immunization, making it free for infants [17]. From 2002 to 2009, the Chinese government collaborated with Global Alliance for Vaccine and Immunization (GAVI) to provide free HepB in the western regions and 223 poverty-affected counties of the central region to work against regional inequalities in terms of HepB coverage [18]. From 2009 to 2011, China launched a HepB catch-up campaign for children younger than 15 years old [13]. In 2012, China replaced 5 μg of HepB with 10 μg, thereby further reducing the risk of HBV infection in children [19]. Timely birth-dose of HepB is the key intervention to prevent HBV infection among infants [15]. The increase in the rural hospital delivery rate (from 94.7% in 2009 up to 99.8% in 2017) ensured the timely birth-dose of HepB among newborns, thereby decreasing the gap of HepB birth-dose coverage between urban and rural areas [20].

The HepB policy for children was escalated, and the national coverage with third-dose of HepB for infants increased from 30% in 1992 to 99.58% in 2015; the national coverage with timely birth-dose HepB increased from 22.2% in 1992 to 95.61% in 2015 [13,21,22]. China has achieved the WHO target of 90% coverage for the third-dose of HepB and the timely birth-dose of HepB [13]. With the increase in HepB coverage, HBsAg prevalence decreased significantly among children under 5 years old, from 9.67% in 1992 to less than 0.3% in 2014 [23,24]. A big gap to the WHO target of 0.1% prevalence of HBsAg remains among children under 5 years old by 2030. Additionally, data from national surveys in China showed that individuals aged 15–29 years old had an HBsAg-positive rate of 9.8% in 1992, 8.4% in 2006, and 4.4% in 2014 [23]; as such, the HBsAg-positive rate in the population with a high fertility rate has a declining trend. Currently, the prevalence of HBsAg among pregnant women is approximately 6% in China [10]. In brief, the increase in HepB coverage among children contributed to the decrease in HBsAg prevalence among currently pregnant women and is beneficial for preventing MTCT of HBV at present.

Preventing MTCT of HBV for infants born to mothers who are HBsAg positive

Despite high coverage of HepB, MTCT is possibly the primary route of chronic HBV infection in China, accounting for 40%–50% of new HBV infections [11,25]. Effective prevention of MTCT should be implemented to control the HBV epidemic [25].

China's Integrated Prevention of MTCT of HIV, Syphilis, and HBV program (iPMTCT program) was launched in 2010 [26,27]. In February 2011, the National Health Commission issued the protocol for the iPMTCT program [28], requiring pregnant women to undergo HBsAg screening and children whose mothers are HBsAg positive to be provided with extra free HBIG (100 IU) within 24 h after birth; aside from such steps, three doses of HepB should be administered in accordance with the national childhood immunization programs. By 2013, the iPMTCT program covered 41% (1156/2853) of counties and expanded to 1638 counties in 2014 [27]. The 2015 edition of the Protocol for iPMTCT program was issued to extend the program nationwide, requiring all pregnant women (including the floating population) to

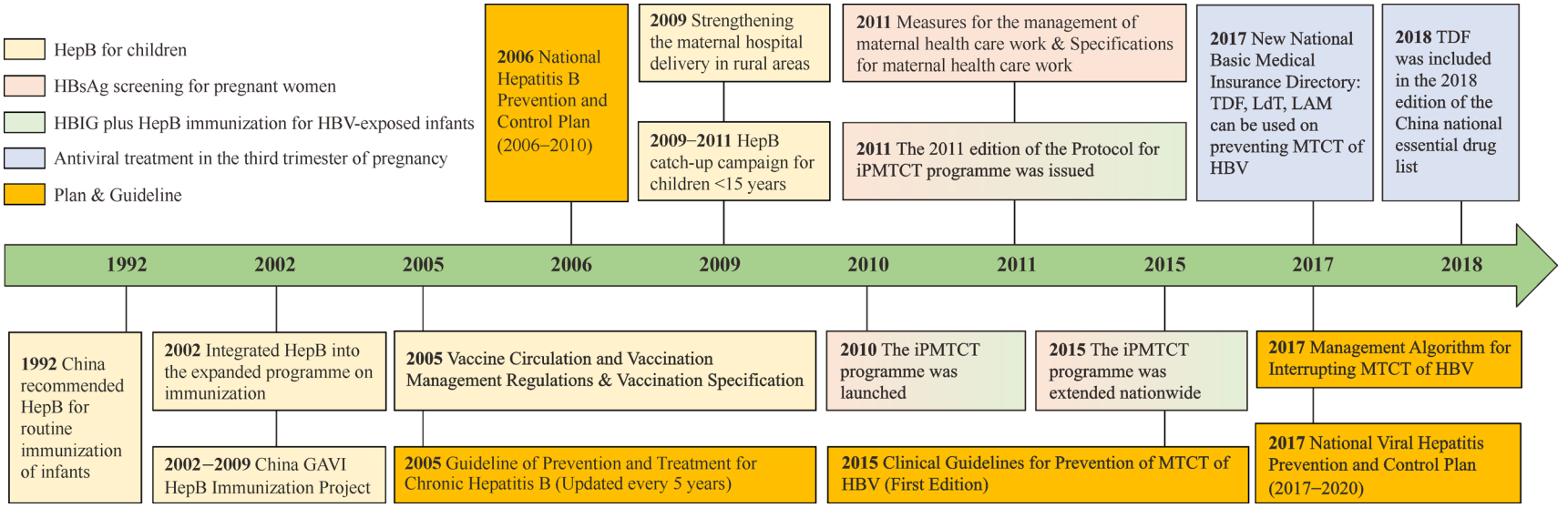

Fig. 1 Major policies and measures to prevent MTCT of HBV in China. HBV, hepatitis B virus; HepB, hepatitis B vaccine; HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immunoglobulin; GAVI, Global Alliance for Vaccine and Immunization; MTCT, mother-to-child transmission; iPMTCT, integrated prevention of mother-to-child transmission; TDF, tenofovir disoproxil fumarate; LdT, tebivudine; LAM, lamivudine.

undergo HBsAg screening, requiring that HBIG should be provided preferably within 12 h after birth (or as early as possible) for newborns whose mothers are HBsAg positive [26]. China also established the Elimination of MTCT of HIV, Syphilis, and HBV program (EMTCT) in 2016 [29]. In September 2017, the EMTCT pilot project was launched in Zhejiang, Guangdong, and Yunnan provinces in preparation for national strategies and work programs [30].

The HBsAg screening rates among pregnant women in 41% of counties were 89.29% in 2011, 97.10% in 2012, and 97.40% in 2013, respectively [27]; the HBIG injection rates among newborns whose mothers are HBsAg positive were 86.21% in 2011, 94.42% in 2012, and 97.74% in 2013, respectively [27]. In 2017, the national coverage of HBsAg screening test among pregnant women exceeded 99.5% and nearly all (99.7%) infants exposed to HBV received HBIG at birth [29].

Administering HBIG and HepB to infants born to mothers who are HBsAg positive to prevent MTCT of HBV is highly effective. Nevertheless, infants born to pregnant women with high HBV-DNA load are still infected [11]. A higher failure rate of HBIG plus HepB was observed among infants born to mothers with HBeAg-positive and high HBV-DNA load than that of infants born to mothers with HBeAg-negtive or low HBV-DNA load [31,32]. A meta-analysis estimated that the failure rate was 4.87% in the Chinese population, and the failure rate of infants with mothers who are HBeAg positive (9.66%) was higher than that of infants whose mothers are HBeAg negative (1.16%) [31]. In addition, the pre-delivery HBV-DNA level of mothers is positively correlated with the risk of MTCT of HBV [32,33]. Zou *et al.* showed that when the HBV-DNA levels of mothers were stratified to < 6, 6–6.99, 7–7.99, and $\geqslant 8$ $\log_{10}$ copies/mL, the failure rates in the Chinese population were 0%, 3.2% (3/95), 6.7% (19/282), and 7.6% (5/66), respectively; infants born to mothers who are HBeAg positive with HBV-DNA levels $\geqslant 6$ $\log_{10}$ copies/mL contributed to the failure rate [32]. The findings of Peng *et al.* were in accordance with the previous study, showing that the failure rates were 0.9% (11/1219), 2.6% (11/422), 4.9% (11/223), 7.7% (11/143), and 8.9% (11/124), respectively, when mothers are HBsAg positive, HBV-DNA positive, HBeAg-positive, high HBV-DNA level ($> 10^7$ copies/mL), and both HBeAg-positive and high HBV-DNA level [34].

However, recently published studies reported that administering HBIG plus HepB as early as possible after birth resulted in pretty low failure rates among infants whose mothers are HBsAg positive [35,36]. A prospective cohort study [36] in China showed that the perinatal infection rate was 1.5% (8/545) if one dose of 100 IU HBIG was given within 12 h of birth, followed by completion of three doses of HepB series. A randomized controlled trial [35] in Thailand reported that only 2% (3/147) of infants whose mothers are HBeAg positive resulted in HBsAg-positive status if the median time from birth to administration of HBIG and HepB was less than 2 hours.

Postvaccination serological testing is also important for evaluating the effects of immunization and identifying HBV infection among infants [37]. The 2015 edition of the Protocol for iPMTCT program suggested that post-vaccination serological test could be done for children with mothers who are HBsAg positive after the completion of HepB series to determine whether HBV exposure is effectively prevented [26]. The Chinese Center for Disease Control and Prevention coordinated with the WHO to launch the first postvaccination serological test pilot program in Fujian, Jiangxi, Zhejiang, and Chongqing from June 2016 to December 2017 to monitor the HBV status of infants with HBsAg-positive mothers; the implementation of this pilot program could provide guidance for future strategies [38].

Antiviral therapy for HBV-infected pregnant women in the third trimester

Although the current HBIG plus HepB immunization strategy for preventing MTCT of HBV has been implemented successfully in China, challenges still remain. Under the current HBIG plus HepB immunization strategy, more than 50 000 children are born with HBV annually in China [10], and these individuals might become chronic HBV carriers in the future [39].

Several studies involving Chinese populations suggested that antiviral treatment is effective in decreasing the risk of MTCT among infants born to mothers with high HBV-DNA load when given with birth-dose HepB and HBIG [25,40–42]. Pan *et al.* [40] indicated that among mothers who are HBeAg positive with HBV-DNA $>$ 200 000 IU/mL during the third trimester, tenofovir disoproxil fumarate (TDF) therapy from 30 weeks to 32 weeks of gestation until 4 weeks after the birth resulted in a threefold reduction in MTCT from 18% (18/100) to 5% (5/97) by intention-to-treat analysis. Sheng *et al.* [41] showed that for pregnant women with HBV DNA $>$ 5 $\log_{10}$ IU/mL but normal alanine aminotransferase (ALT) levels, telbivudine (LdT) therapy is effective in reducing MTCT of HBV (9.5% [2/21] vs. 0% [0/97] in the observation group and treatment group, respectively). Wang *et al.* [42] suggested that TDF therapy for mothers who are HBeAg positive with HBV-DNA $>$ 6 $\log_{10}$ IU/mL between 24–33 weeks of gestation and delivery reduced the MTCT rate among infants to 0.7% (1/144) in a real-world setting. These studies demonstrated that during or after antiviral treatment,

elevated ALT was observed among mothers; no severe adverse effects were observed among mothers or infants; and antiviral treatment was not found to increase the risk of birth defects.

China's Guideline of Prevention and Treatment for Chronic Hepatitis B (2015 update) [43] recommended that for pregnant women with HBV DNA $> 2 \times 10^6$ IU/mL in the second and third trimesters, TDF, LdT, or lamivudine (LAM) could be administered from 24 weeks to 28 weeks of gestation to delivery after full discussion was made and with informed consent. In 2017, TDF and LdT were recommended for antiviral therapy by China' Management Algorithm for Interrupting MTCT of HBV [37].

LdT and LAM are categorized as class B drugs by the National Basic Medical Insurance in 2009. TDF is recommended by the WHO as the preferred antiviral treatment for pregnant women who are HBV positive with indications due to good resistance profile and extensive safety data [3]; this drug was included in the national first price negotiation catalog of pilot drugs in 2016, and its cost was sharply reduced from 49 CNY per day to 16.6 CNY per day [44]. Subsequently, TDF was successfully incorporated into the National Basic Medical Insurance in 2017 and was included in the 2018 edition of the China national essential drug list [45]. To date, TDF, LdT, or LAM recommended in the guideline can be reimbursed as class B drugs in China [46], thereby ensuring the availability and affordability of antiviral treatment to prevent MTCT of HBV.

Challenges and suggestions for eliminating MTCT of HBV in China

Comprehensively decreasing HBsAg prevalence among pregnant women

HBsAg prevalence among pregnant women has declined, but regional differences still remain. Zhao *et al.*' study in Ali, Tibet showed that the total HBsAg-positive rate of pregnant women was 17.19% (143/832) with a difference in urban (13.66%, 56/410) and rural areas (20.62%, 87/422) and higher than that of the national level [47]. Moreover, 46.85% (67/143) of women who are HBsAg positive are living with HBeAg and hepatitis B core antibody (HBcAb) [47]; this finding indicates the high risk of MTCT of HBV in Ali. Cui *et al.* showed that regardless of the regions, the HBsAg prevalence among pregnant women in the rural areas was higher than that in the urban areas in China [48]. Li *et al.* showed that the HBsAg-positive rate of reproductive women was 4.5% (279/5963) in Yunnan Province, and the minority had a higher HBsAg-positive rate, especially among Wa, Lahu, and Dai ethnic minorities [49].

Several underlying factors may have contributed to the higher HBsAg prevalence among pregnant women from remote, rural, or ethnic minority areas than that of national level in China. First is the limited economic and health resources. Although China enacted a universal HepB program in the 1990s, parents had to pay out of pocket for HepB [12]. Given the disparity in regional economic and health development, HepB vaccination was conducted mainly in large cities and the relatively developed eastern region in China in the 1990s [12,50]. The surveyed coverages of HepB among infants considerably varied in different regions in 2002: the surveyed coverages with the three doses of HepB in the eastern, central, and western regions were 88.8%, 65.51%, and 46.89%, respectively [17]; the surveyed coverages with the timely birth-dose of HepB were 81.7%, 51.4%, and 25.6%, respectively [18]. As yesterday's children become today's adults, a higher HBsAg prevalence among today's pregnant women was observed in remote and rural areas than that of developed and urban areas. Second, public health education for HBV is limited and awareness of the hazards of HBV infection is low, resulting in less active screening and prevention of HBV in these areas [47]. Finally, some special customs in several ethnic minority gathering areas may lead to the frequent occurrence of high-risk behaviors. Therefore, additional strategies should be implemented to decrease HBsAg prevalence among pregnant women, especially in remote, rural, or ethnic minority areas; such methods include strengthening the implementation of the universal HepB program, intensifying public health education to avoid high-risk behaviors, and emphasizing HBV screening and prevention.

After three decades of escalating HepB policy for children, China has achieved the WHO targets of 90% coverage for third-dose of HepB and timely birth-dose of HepB to eliminate hepatitis B by 2030. However, the coverage of the birth-dose of HepB is not high in some weak areas, especially in western region with a relatively backward economy; thus, attention should be given to these areas [19]. For instance, the coverage of the timely birth-dose of HepB was only 90.80% in the western region in 2015, which was under the national coverage level of 95.61% [22]. The less than 90% coverage of the timely birth-dose of HepB was reported among 35.46% of counties in the western region in 2015 and considerably higher than the national proportion of 23.61% [22].

Apart from integrating HepB into routine childhood immunization programs, as step which naturally decreased HBsAg prevalence among currently pregnant women, active measures should be implemented.

Ensure high coverage of HBsAg screening for pregnant women and HBIG plus HepB immunization for HBV-exposed infants

The iPMTCT program has basically covered the whole

target population in China; the coverage of HBsAg screening among pregnant women and HBIG for HBV-exposed infants have exceeded 99% in 2017 [29]. However, regional differences may still exist given the limited maternal and child healthcare capacity in underdeveloped areas; for example, the coverage of HBsAg screening among pregnant women in Qinghai and Tibet were only 49.2% and 85.5%, respectively, in 2015 [51]. Improving the coverage of HBsAg screening for pregnant women is still a vital problem in underdeveloped areas.

Timely HBIG plus birth-dose of HepB immunoprophylaxis and strict compliance with the immunization schedule for infants born to mothers who are HBsAg positive is crucial to prevent MTCT of HBV [37]. According to the recommendations of the Advisory Committee on Immunization Practices, HBIG and the birth-dose of HepB should be administered to infants whose mothers are HBsAg positive within 12 h after birth (preferably immediately after delivery) rather than within 24 h [52]. Several recent studies reported that if HBIG plus HepB were provided as early as possible after birth, the failure rate was unexpectedly low [35,36]; this finding underscores the importance of the early timing of HBIG and vaccine. Therefore, effort should be dedicated to ensure the prompt administration of HBIG and the birth-dose of HepB for infants whose mothers are HBsAg positive to prevent MTCT of HBV.

Prevention of MTCT of HBV is mainly performed in medical institutions within 24 h after birth. The nationwide hospital delivery rate was 99.9% in 2018 but only 89.6% in the county of Tibet [53]. The hospital delivery rate of 74 districts or counties (28 in Tibet, 26 in Sichuan, and 10 in Qinghai) was less than 96% in 2017, and the total number of live births in these 74 districts or counties was 112 099 in 2017 [54]. Therefore, ensuring the timely HBIG plus HepB immunization in remote areas with low hospital delivery rates, such as ethnic minority areas in Tibet, Sichuan, and Qinghai, remains a challenge [51]. Joint efforts of the central and local government are needed to find local solutions for eliminating hepatitis B.

In addition, the results of maternal HBV screening are registered in maternal and child healthcare institutions, whereas information on infant vaccination are collected by the national immunization program in China. Currently, no existing cross platform for sharing between these two systems is implemented [38]. No existing national system is used to collect follow-up data on outcomes of children exposed to HBV [29]; thus, studies based on big data to evaluate the efficacy of preventing MTCT of HBV are lacking. Therefore, effort should be exerted to establish a national postvaccination serological test information system. This system should be integrated with maternal screening and the children vaccination information system at the national level.

Strengthen the efficacy and safety study of antiviral therapy for pregnant women infected with HBV

Several studies reported that antiviral treatment effectively reduces the risk of MTCT among mothers with a high HBV-DNA level [40,55]. However, Jourdain *et al.*' study [35] in Thailand did not identify the added value or difference between HepB plus HBIG and short-term antiviral treatment to prevent MTCT of HBV; the results reaffirmed the importance of hepatitis B immunization and probably reminded people not to overtreat. Controversies exist on the use of antiviral therapy to prevent MTCT of HBV [7]. The WHO currently does not formally recommend the routine use of antiviral therapy to prevent MTCT of HBV due to a lack of sufficient evidence supporting its implementation [3]. The major guidelines recommending antiviral treatment for pregnant women are not uniform for the optimal threshold of HBV DNA for antiviral therapy, the start time, and withdrawal time of the oral antiviral drugs [43,56–58]. The WHO has begun to develop a guideline to stop MTCT of HBV owing to the emerging new evidence and is scheduled to be completed by mid-2020 [59].

In-depth research is needed on the efficacy and safety of antiviral therapy in the third trimester of pregnancy to obtain solid evidence. Considerable attention should be given to determining the risks of toxicity to babies, including breastfeeding, growth and development; and be given to the potential harms to pregnant women, such as drug resistance due to short-term antiviral therapy, progression of liver disease, or fulminant hepatitis after postpartum discontinuation [3]. Additionally, analysis on the health economics of antiviral therapy in the third trimester are rare in the country and abroad; relevant research is needed to optimize strategies on preventing MTCT of HBV. At present, such challenges are experienced in China and abroad, and joint efforts are needed to eliminate hepatitis B.

Conclusions

The Chinese government has made considerable progress in preventing the MTCT of HBV in the past three decades by mandating close collaboration between maternal and child healthcare institutions and immunization departments. Currently, prevention of MTCT of HBV is conducted nationwide through universal HepB for all infants, HBsAg screening among pregnant women, and timely HBIG plus birth-dose of HepB for newborns with mothers who are HBsAg positive. Meanwhile, studies on the optimal antiviral treatment regimen for pregnant women with high HBV-DNA load have been explored. However, China still faces challenges in eliminating MTCT of HBV, especially in remote western regions.

Improved integration of current services that prevent MTCT of HBV with other relevant health services can increase the acceptability, efficiency, and coverage of current services. As such, progress toward key milestones and targets to eliminate hepatitis B as the main public health threat by 2030 can be achieved.

Acknowledgements

This study was supported by the grant from the National Natural Science Foundation of China (Nos. 71874003, 71934002, and 81703240).

Compliance with ethics guidelines

Wenzhan Jing, Jue Liu, and Min Liu have no conflicts of interest to declare. This manuscript is a review article and does not involve a research protocol requiring approval by a relevant institutional review board or ethics committee.

References

1. Cheung KW, Seto MTY, Lao TTH. Prevention of perinatal hepatitis B virus transmission. Arch Gynecol Obstet 2019; 300(2): 251–259
2. Chinese Medical Association Obstetrics and Gynecology Branch. Clinical guidelines for prevention of mother-to-child transmission of hepatitis B virus (1st Edition). Chin J Obstet Gynecol (Zhonghua Fu Chan Ke Za Zhi) 2013; (2): 151–154 (in Chinese)
3. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva, Switzerland: World Health Organization, 2015. http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf;jsessionid = C45FBB6C849F7F96F2213274A3FE2336?sequence = 1 (accessed May 15, 2018)
4. World Health Organization. Global hepatitis report, 2017. Geneva, Switzerland: World Health Organization, 2017. http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/# (accessed January 12, 2018)
5. Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009; 373 (9663): 582–592
6. Wang FS, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. Hepatology 2014; 60(6): 2099–2108
7. Yin RX, Liu ZH, Liu ZH, Li J, Zhuang H, Dou XG, Hou JL. Getting to zero mother-to-child transmission of hepatitis B virus: dream and challenge. Chin J Hepatol (Zhonghua Gan Zang Bing Za Zhi) 2018; (4): 262–265 (in Chinese)
8. Trépo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet 2014; 384(9959): 2053–2063
9. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol 2018; 3(6): 383–403
10. World Health Organization. Tenofovir reduces mother-to-child transmission of hepatitis B: new study. Geneva, Switzerland: World Health Organization, 2016. https://www.who.int/hepatitis/news-events/hbv-mtct-tenofovir/en/ (accessed January 15, 2019)
11. Xu Y, Liu H, Wang Y, Hao R, Li Z, Song H. The next step in controlling HBV in China. BMJ 2013; 347: f4503
12. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, Zhang Y, Liu J, Gong X, Chen Y, Wang F, Zheng H, Wang F, Guo J, Jia Z, Ma J, Wang H, Luo H, Li L, Jin S, Hadler SC, Wang Y. Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. Vaccine 2009; 27(47): 6550–6557
13. Liu J, Liang W, Jing W, Liu M. Countdown to 2030: eliminating hepatitis B disease, China. Bull World Health Organ 2019; 97(3): 230–238
14. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME). 2018. http://ghdx.healthdata.org/gbd-results-tool (accessed April 20, 2018)
15. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021. Geneva, Switzerland: World Health Organization, 2016. http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/ (accessed March 29, 2018)
16. World Health Organization. Regional Office for the Western Pacific. Regional framework for the triple elimination of mother-to-child transmission of HIV, hepatitis B and syphilis in Asia and the Pacific, 2018–2030. Geneva, Switzerland: World Health Organization, 2018. http://iris.wpro.who.int/handle/10665.1/14193 (accessed April 10, 2018)
17. Cui F, Liang X, Gong X, Chen Y, Wang F, Zheng H, Wu Z, Miao N, Hadler SC, Hutin YJ, Luo H, Yang W. Preventing hepatitis B though universal vaccination: reduction of inequalities through the GAVI China project. Vaccine 2013; 31(Suppl 9): J29–J35
18. Cui F, Luo H, Wang F, Zheng H, Gong X, Chen Y, Wu Z, Miao N, Kane M, Hennessey K, Hadler SC, Hutin YJ, Liang X, Yang W. Evaluation of policies and practices to prevent mother to child transmission of hepatitis B virus in China: results from China GAVI project final evaluation. Vaccine 2013; 31(Suppl 9): J36–J42
19. National Health Commission of the People's Republic of China. The National Health Commission held a press conference on July 25, 2017 (in Chinese) http://www.nhc.gov.cn/xcs/s3574/201707/10ae796284de4d40a58b36502e145961.shtml (accessed April 10, 2019)
20. National Health Commission of the People's Republic of China. The 2018 China Health Statistics Yearbook. Beijing: China Union Medical University Press, 2018 (in Chinese)
21. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, Zhang Y, Liu J, Gong X, Chen Y, Wang F, Zheng H, Wang F, Guo J, Jia Z, Ma J, Wang H, Luo H, Li L, Jin S, Hadler SC, Wang Y. Evaluation of the impact of hepatitis B vaccination among children born during 1992–2005 in China. J Infect Dis 2009; 200(1): 39–47
22. Cui J, Cao L, Zheng J, Cao L, Duo M, Xiao Q. Reported coverage of vaccines in the National Immunization Program of China, 2015. Chin J vacc and imm (Zhongguo Yi Miao He Mian Yi) 2017; (6): 601–607 (in Chinese)
23. Cui F, Shen L, Li L, Wang H, Wang F, Bi S, Liu J, Zhang G, Wang F, Zheng H, Sun X, Miao N, Yin Z, Feng Z, Liang X, Wang Y. Prevention of chronic hepatitis B after 3 decades of escalating vaccination policy, China. Emerg Infect Dis 2017; 23(5): 765–772
24. Xia GL, Liu CB, Cao HL, Bi SL, Zhan MY, Su CA, Nan JH, Qi XQ. Prevalence of hepatitis B and C virus infections in the general

Chinese population. Results from a nationwide cross-sectional seroepidemiologic study of hepatitis A, B, C, D, and E virus infections in China, 1992. Int Hepatol Commun 1996; 5(1): 62–73

25. Thio CL, Guo N, Xie C, Nelson KE, Ehrhardt S. Global elimination of mother-to-child transmission of hepatitis B: revisiting the current strategy. Lancet Infect Dis 2015; 15(8): 981–985
26. National Health Commission of the People's Republic of China. Comprehensive Prevention of Mother-to-Child Transmission for HIV, Syphilis and Hepatitis B. April, 2015 (in Chinese) http://www.nhfpc.gov.cn/fys/s3581/201506/4f2123fa955a44afa75a75da2ad35d6e.shtml (accessed April 22, 2018)
27. Wang AL, Qiao YP, Wang LH, Fang LW, Wang F, Jin X, Qiu J, Wang XY, Wang Q, Wu JL, Vermund SH, Song L. Integrated prevention of mother-to-child transmission for human immunodeficiency virus, syphilis and hepatitis B virus in China. Bull World Health Organ 2015; 93(1): 52–56
28. National Health Commission of the People's Republic of China. Prevention of Mother-to-Child Tansmission for Human Immunodeficiency Virus, Syphilis and Hepatitis B Virus Work Plan. 2011 (in Chinese) http://www.nhfpc.gov.cn/fys/s3581/201102/a0c03b2192a1483384b4f798d9ba603d.shtml (accessed March 28, 2018)
29. Wang A, Qiao Y, Dou L, Wang Q, Wang X, Su M, Li Z, Huang X, Yang Y, Jin X, Song L. Challenges of eliminating mother-to-child transmission of HIV, syphilis and hepatitis B in China: a cross-sectional survey. Lancet 2018; 392(Supplement 1): S55
30. Yuhang Government, Zhejiang Province, China. Yuhang Becomes a National Pilot Area to Eliminate of Mother-to-Child Transmission for HIV, syphilis and hepatitis B virus Project. September 2017 (in Chinese) http://www.yuhang.gov.cn/zjyh/jryh/news/201709/t20170914_1100547.html (accessed April 29, 2018)
31. Lin X, Guo Y, Zhou A, Zhang Y, Cao J, Yang M, Xiao F, Zhang B, Du Y. Immunoprophylaxis failure against vertical transmission of hepatitis B virus in the Chinese population: a hospital-based study and a meta-analysis. Pediatr Infect Dis J 2014; 33(9): 897–903
32. 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(2): e18–e25
33. Wiseman E, Fraser MA, Holden S, Glass A, Kidson BL, Heron LG, Maley MW, Ayres A, Locarnini SA, Levy MT. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust 2009; 190(9): 489–492
34. Peng S, Wan Z, Liu T, Zhu H, Du Y. Incidence and risk factors of intrauterine transmission among pregnant women with chronic hepatitis B virus infection. J Clin Gastroenterol 2019; 53(1): 51–57
35. Jourdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khamduang W, Tierney C, Salvadori N, Cressey TR, Sirirungsi W, Achalapong J, Yuthavisuthi P, Kanjanavikai P, Na Ayudhaya OP, Siriwachirachai T, Prommas S, Sabsanong P, Limtrakul A, Varadisai S, Putiyanun C, Suriyachai P, Liampongsabuddhi P, Sangsawang S, Matanasarawut W, Buranabanjasatean S, Puernngooluerm P, Bowonwatanuwong C, Puthanakit T, Klinbuayaem V, Thongsawat S, Thanprasertsuk S, Siberry GK, Watts DH, Chakhtoura N, Murphy TV, Nelson NP, Chung RT, Pol S, Chotivanich N. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. N Engl J Med 2018; 378(10): 911–923
36. Wei KP, Zhu FC, Liu JX, Yan L, Lu Y, Zhai XJ, Chang ZJ, Zeng Y, Li J, Zhuang H. The efficacy of two different dosages of hepatitis B immunoglobulin combined with hepatitis B vaccine in preventing mother-to-child transmission of hepatitis B virus: a prospective cohort study. Vaccine 2018; 36(2): 256–263
37. Hou J, Cui F, Ding Y, Dou X, Duan Z, Han G, Jia J, Mao Q, Li J, Li Z, Liu Z, Wei L, Xie Q, Yang X, Zhang H, Zhuang H. Management algorithm for interrupting mother to child transmission of hepatitis B virus. Clin Gastroenterol Hepatol 2019; 17(10): 1929–1936.e1
38. Zheng H, Zhang GM, Chan PL, Wang FZ, Rodewald LE, Miao N, Sun XJ, Yin ZD, Edwards J, Wang HQ. Compliance among infants exposed to hepatitis B virus in a post-vaccination serological testing program in four provinces in China. Infect Dis Poverty 2019; 8(1): 57
39. Fan R, Yin X, Liu Z, Liu Z, Lau G, Hou J. A hepatitis B-free generation in China: from dream to reality. Lancet Infect Dis 2016; 16(10): 1103–1105
40. Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, Zhang H, Zou H, Zhu B, Zhao W, Jiang H; China Study Group for the Mother-to-Child Transmission of Hepatitis B. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med 2016; 374(24): 2324–2334
41. Sheng Q, Ding Y, Li B, Han C, Li Y, Zhang C, Bai H, Wang J, Zhao L, Xia T, An Z, Zhang M, Dou X. Efficacy and safety of nucleos(t)ide analogues to prevent hepatitis B virus mother-to-child transmission in pregnant women with high viremia: real life practice from China. Int J Med Sci 2018; 15(8): 796–801
42. Wang M, Bian Q, Zhu Y, Pang Q, Chang L, Li R, Tiongson BC, Zhang H, Pan CQ. Real-world study of tenofovir disoproxil fumarate to prevent hepatitis B transmission in mothers with high viral load. Aliment Pharmacol Ther 2019; 49(2): 211–217
43. Hou J, Wang G, Wang F, Cheng J, Ren H, Zhuang H, Sun J, Li L, Li J, Meng Q, Zhao J, Duan Z, Jia J, Tang H, Sheng J, Peng J, Lu F, Xie Q, Wei L; Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases, Chinese Medical Association. Guideline of prevention and treatment for chronic hepatitis B (2015 Update). J Clin Transl Hepatol 2017; 5(4): 297–318
44. National Health Commission of the People's Republic of China. Reply to the No. 3268 of the Fourth Session of the Twelfth National People's Congress. 2016 (in Chinese) http://www.nhfpc.gov.cn/zwgk/jianyi/201611/2f1b4892160040c4ac3ba3eccfc2873d.shtml (accessed April 23, 2018)
45. Liu J, Liu M. Progress and challenges in achieving the WHO goal on 'Elimination of Hepatitis B by 2030' in China. Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi) 2019; 40(6): 605–609 (in Chinese)
46. Ministry of Human Resources and Social Security of the People's Republic of China. National Basic Medical Insurance, Industrial Injury Insurance and Maternity Insurance Drug List (2017 Edition). 2017 (in Chinese) http://www.mohrss.gov.cn/SYrlzyhshbzb/shehuibaozhang/zcwj/201702/t20170223_266775.html (accessed March 29, 2018)
47. Zhao H, Ma X, Zhang L, Liu X, Ciren L, Song C. Status of hepatitis B virus infection in pregnant women and infants in Ali, Tibet. China Trop Med (Zhongguo Re Dai Yi Xue) 2018; 18(12): 1218–1221 (in Chinese)
48. Cui F, Woodring J, Chan P, Xu F. Considerations of antiviral treatment to interrupt mother-to-child transmission of hepatitis B virus in China. Int J Epidemiol 2018; 47(5): 1529–1537

49. Li G, Chen J, Xie Z, Li X, Zhang Y, Zhang J. HBsAg screening results of 10018 cases of pregnant women, Yunnan, 2013–2016. Mod Prev Med (Xian Dai Yu Fang Yi Xue) 2018; 45(13): 2350–2353, 2441 (in Chinese)
50. National Health Commission of the People's Republic of China. WHO awards recognition for the prevention and control of hepatitis B in children in China. 2014 (in Chinese) http://www.nhfpc.gov.cn/gjhzs/ptpxw/201402/0f6349b5c3c243f89238e8d84c17bed0.shtml (accessed April 20, 2018)
51. National Health Commission of the People's Republic of China. National maternal and child health monitoring and annual report communication. 2016 (in Chinese) http://www.mchscn.org/Article_Show.asp?ArticleID = 651 (accessed July 30, 2018)
52. Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, Nelson NP. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018; 67(1): 1–31
53. National Health Commission of the People's Republic of China. The 2019 China Health Statistics Yearbook. Beijing: China Union Medical University Press, 2019 (in Chinese)
54. National Health Commission of the People's Republic of China. National maternal and child health monitoring and annual report communication. 2018 (in Chinese) http://www.mchscn.org/Article_Show.asp?ArticleID = 694 (accessed July 30, 2019)
55. 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 (2): 468–476
56. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016; 63(1): 261–283
57. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67(4): 1560–1599
58. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67(2): 370–398
59. World Health Organization. WHO begins guideline development to stop mother-to-child transmission of hepatitis B. Geneva, Switzerland: World Health Organization, 2019. https://www.who.int/hepatitis/news-events/hbv-mtc-guidelines-development/en/(accessed October 20, 2019)