

Elimination of hepatitis B virus infection in children: experience and challenge in China

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Abstract

Chronic hepatitis B virus (HBV) infection is a serious health issue because of its severe sequelae. Prevention of mother-to-child transmission (MTCT) of HBV is critical to eliminate chronic HBV infection. Here, we reviewed the progress toward the elimination of HBV infection in children in China in the recent decade. A universal hepatitis B vaccination program started from 2002 has been intensified, with the coverage of timely birth dose >95% of all newborn infants from 2012. Since 2011, China has taken a nationwide program to administer hepatitis B immunoglobulin (HBIG) with free of charge in all neonates of HBV-infected mothers, leading to a significant increment of timely use of HBIG. The prevalence of hepatitis B surface antigen (HBsAg) was declined from around 10% among children in 1980s to <0.5% among children born after 2011. Administration of oral antiviral agents in HBV-infected pregnant women with HBV DNA >2 × 10⁵ U/mL during the third trimester is increasing, which will further reduce MTCT of HBV. However, there are some challenges in the elimination of HBV infection in children, which need to overcome by the concerted efforts. Nevertheless, it is anticipated that China will achieve the goal set by the World Health Organization that the prevalence of HBsAg in children aged <5 years is ≤0.1% by 2030.

Keywords: Hepatitis B virus; Mother-to-child transmission; Immunoprophylaxis; HBsAg prevalence; Children; China

Introduction

Chronic hepatitis B virus (HBV) infection, the presence of hepatitis B surface antigen (HBsAg) in circulation over 6 months, is a worldwide serious health problem because of its severe sequelae such as liver cirrhosis and hepatocellular carcinoma, as well as other cancers.^[1] Once infected with HBV, the occurrence of chronic infection depends mainly upon the age; 70% to 90% of newborn infants become chronic carriers, whereas <5% of adolescents and adults develop chronic infection. Thus, the critical strategy to control chronic HBV infection is to prevent infection in infants and young children, particularly to prevent the mother-to-child transmission (MTCT) of HBV. Universal vaccination against hepatitis B in all infants, combined with administration of hepatitis B immunoglobulin (HBIG) in newborn infants of HBsAg-positive mothers, is the cornerstone to prevent chronic HBV infection.

Historically, the prevalence of HBsAg in the general population of China was around 10%.^[2] Thus, China has taken great efforts to control HBV infection by implementation of comprehensive measures, such as hygiene injection, blood donor screening, and particularly immunoprophylaxis against hepatitis B and others in the recent five decades. As a reward, the estimated prevalence of HBsAg in China has been remarkably decreased.^[3] In this review, we summarized the progress and challenges in the elimination of HBV infection in children in China.

Evolution of hepatitis B vaccine and implementation of universal hepatitis B vaccination in China

Hepatitis B vaccine was introduced to China in 1982 after the first hepatitis B vaccine was approved in the USA in 1981.^[4] The commercial plasma-derived hepatitis B vaccine manufactured by China Bio-company became available in 1986. Initially, the vaccine was selectively used

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in individuals with high risk of HBV infection such as neonates of HBsAg-positive mothers due to its limited supply. In 1992, the Ministry of Health of China recommended that all newborn infants be vaccinated against hepatitis B as part of China's Planned Vaccination Program. However, the implementation of hepatitis B vaccination was far from optimum then since the vaccine was not free of charge and whether infants were vaccinated was determined by their parents. After the successful production of recombinant hepatitis B vaccine through transfer of technology from Merck & Dohme Co, USA (recombinant yeast vaccine), and great efforts of Chinese scientists in 1980s and early and mid-1990s (recombinant Chinese Hamster Ovary [CHO] vaccine), China discontinued the production of plasma hepatitis B vaccine in June 1998.^[5] Since 2001, all hepatitis B vaccines used in China have been prepared by recombinant yeast or CHO HBsAgs.^[2,5]

The universal vaccination program against hepatitis B in all infants in the Chinese mainland was launched in 2002, and since then, all newborn infants have received three-dose series of hepatitis B vaccine for free of charge. The program dramatically promoted the vaccination coverage. The timely (within 24 h after birth) birth dose coverage increased from 29.1% in 1997 to 75.8% in 2003, and the complete vaccine series (three doses at 0-, 1-, and 6-month schedule) coverage increased from 70.7% to 89.8%.^[6] With the socioeconomic development, the support of the Global Alliance for Vaccines and Immunization Foundation and the continuous efforts of healthcare works in China, the timely birth dose coverage and complete vaccine series coverage have been maintained >95% since 2012.^[7]

In addition to the universal vaccination program, the China health authority took a nationwide catch-up immunization program to vaccinate the children born between 1994 and 2001 who received no or incomplete hepatitis B vaccination. At least 68 million children received the catch-up vaccination from 2009 to 2011.^[8]

Prevention of MTCT of HBV in infants of HBsAg-positive mothers by passive-active immunoprophylaxis

Because of the high prevalence of HBsAg in childbearing age women, MTCT is a major cause of chronic HBV infection in China. Neonates born to HBsAg-positive mothers are inevitably exposed to HBV during the birth process. Thus, post-exposure prophylaxis, or passive-active immunoprophylaxis, concurrent use of HBIG and hepatitis B vaccine, is required. In the earlier 1980s, HBIG was started to be used for post-exposure prophylaxis in China. Although nationwide passive-active immunoprophylaxis has been recommended for infants of HBsAg-positive mothers since earlier 1990s, the administration of HBIG and hepatitis B vaccine was suboptimal. The average coverage of HBIG in infants was 37.6% (112/298), 55.7% (39/70) in cities, and 32% (73/228) in rural areas, in Jiangsu province, during 2002–2004.^[9] During 2008–2010, just 63.2% (156/247) of the infants in northwest China were administered HBIG.^[10] Even from January to June 2011, only 69.0% (1907/2765) of the infants received HBIG in Yunnan, southwest China.^[11] Several reasons appeared to be associated with the suboptimal immuno-

prophylaxis, including the relatively low prenatal screen for hepatitis B serological markers,^[9] the cost of HBIG charged to parents,^[10] shortage of HBIG supply in some areas, and lack of sufficient knowledge of preventing MTCT of HBV among healthcare workers.^[11]

To overcome the suboptimal adherence to the recommended passive-active immunoprophylaxis in infants of HBsAg-positive mothers, the Chinese Health Authority has taken a nationwide program to provide all infants of HBsAg-positive mothers with charge-free HBIG since July 1, 2011, in addition to the universal hepatitis B vaccination started in 2002. The first clinical guideline for the prevention of MTCT of HBV, released in 2013,^[12] and the national program to control MTCT of HBV, in addition to human immunodeficiency virus (HIV) and syphilis, launched in 2015,^[13] promoted the adherence of recommended immunoprophylaxis measures against hepatitis B. A real-world data analysis in Jiangsu province showed that the timely (within 24 h after birth) administration of HBIG was significantly increased from 76.5% (887/1160) before the program to 98.0% (3910/3989) from July 2011 to June 2016.^[14] Timely administration of HBIG in four provinces, Guangdong, Zhejiang, Shaanxi, and Hebei, representing south, east, west, and north of the Chinese mainland, respectively, was as high as 99.0% (4070/4112) in 2016 and 2017.^[15] The updated clinical guidelines and national protocol for prevention of MTCT of HIV, syphilis, and HBV, both released in 2020,^[16,17] recommended all infants of HBsAg-positive mothers be administered HBIG and hepatitis B vaccine within 12 h (the sooner, the better) after birth, as earlier use of immunoprophylaxis can increase the protective efficacy against MTCT of HBV.^[18]

Blocking MTCT of HBV by oral anti-HBV agents in pregnant women with positive HBeAg and/or high viral loads

When the recommended passive-active immunoprophylaxis has adhered, the immunoprophylaxis failure almost all occurs in infants born to carrier mothers with HBV DNA levels $>2 \times 10^6$ (6.3) \log_{10} U/mL^[14,18,19-21] or with positive HBeAg.^[22-26] Studies revealed that pregnant women with positive HBeAg have median HBV DNA levels as high as 7.3–8.1 \log_{10} U/mL.^[27-30] Numerous studies demonstrated that administration of oral anti-HBV agents during the third trimester can almost block MTCT of HBV in infants of carrier mothers with high viral loads or positive HBeAg.^[31-39] Recently, both the updated clinical guideline for preventing MTCT of HBV and national program for control of MTCT of HIV, syphilis, and HBV recommend the use of antivirals in pregnant women with positive HBeAg and/or HBV DNA $>2 \times 10^5$ (5.3 \log_{10}) U/mL during the third trimester to block the perinatal HBV infection.^[16,17,40] Thus, more HBV-infected pregnant women with high viral loads or positive HBeAg will receive anti-HBV agents during the third trimester in the future, which will further reduce MTCT of HBV.

Declined prevalence of HBsAg in children

In 1980s, the prevalence of HBsAg peaked to 9.1% among children aged 9 years in cities and to 12.6% in children

aged 5 years in rural areas.^[2] A nationwide survey conducted in 2006, 14 years after the recommendation of and 4 years after the implementation of universal hepatitis B vaccination, showed that the prevalence was reduced to 7.2% in the general population and to 3.2%, 1.4%, and 1.0% in children aged 10–14 years, 5–9 years, and 1–4 years, respectively.^[41] Recently, an epidemiologic study across the Chinese mainland in 2014 revealed that the prevalence was further reduced in children and young adults as shown in Table 1, which also presents the prevalence of HBsAg in children obtained by other independent regional surveys. Overall, the prevalence was <1% in children born after implementation of the universal hepatitis B vaccination in 2002 and was <0.5% among those who were born after implementation of the national program of charge-free HBIG in infants of HBsAg-positive mothers started in 2011.

Improved efficacy of immunoprophylaxis against MTCT of HBV

Earlier clinical trials demonstrated that, after concurrent use of HBIG and hepatitis B vaccine, chronic HBV infection in infants born to carrier mothers with positive HBeAg was about 4.8% (4/83) to 5.7% (9/159), whereas the infection rate was 88.1% (74/84) in controls.^[51,52] The real-world data analysis in developed regions had similar MTCT of HBV to that in clinical trials.^[19,53,54] Recently, clinical studies in China also demonstrated that MTCT of HBV was 4.8% (20/419) to 5.2% (16/306) in infants of HBeAg-positive mothers after passive-active immunoprophylaxis.^[20,21] The actual protective efficacy of HBIG and

hepatitis B vaccine, in the case of adherence to recommended immunoprophylaxis, was comparable to those in clinical studies as well as in developed countries or regions [Table 2].

However, some reports showed that MTCT of HBV in infants of HBeAg-positive mothers was >10% and MTCT still occurred in infants of HBeAg-negative carrier mothers [Table 2]. Detailed analysis identified that a considerable proportion of newborn infants did not receive timely administration of HBIG and/or hepatitis B vaccine.^[9,55,56] Thus, poor adherence to the recommended passive-active immunoprophylaxis is an important cause of MTCT. This indicates the importance of adherence to recommended immunoprophylaxis in the prevention of HBV infection in children.

Since the implementation of charge-free HBIG in all infants of HBsAg-positive mothers started in July 2011, the efficacy of immunoprophylaxis against MTCT of HBV has been improved. A cross-sectional analysis of real-world data in four representative provinces, Guangdong, Zhejiang, Shaanxi, and Hebei, conducted between October 2017 and January 2018, showed that, of 4112 infants (2818 [68.5%] from rural areas) of HBsAg-positive mothers born between April 2016 and March 2017, only 35 (0.9%) were infected with HBV.^[15] The results of a real-world data analysis based on 5149 children of HBsAg-positive mothers in Jiangsu province found that before July 2011, MTCT in children of carrier mothers with positive HBeAg was 10.3% (19/185), whereas MTCT was reduced to 5.8% (73/1248) since July 2011.^[14] These data demonstrate that the nationwide program of completely charge-free HBIG and hepatitis B

Table 1: HBsAg prevalence in children in China.

Province and location*	Survey year	Age (yr)	Total children No	HBsAg (+), No (%)	References
Whole country	2014	1–4	12,681	39 (0.3)	Cui <i>et al</i> ^[42]
		5–14	9738	87 (0.9)	
Henan, Central China	2012	1–4	5474	26 (0.5)	Yonghao <i>et al</i> ^[43]
		5–9	4407	32 (0.7)	
		10–14	3326	40 (1.2)	
Guangdong, South China	2013	1–4	825	8 (0.97)	Zhu <i>et al</i> ^[44]
		5–9	1024	12 (1.17)	
		10–14	916	12 (1.31)	
Jiangsu, East China	2014	0.6–3	1270	2 (0.16)	Lin <i>et al</i> ^[45]
		>3–6	822	3 (0.36)	
		>6–9	752	1 (0.13)	
		>9–12	598	6 (1.00)	
Chongqing, Southwest China	2012–2016	1–16	93,326	449 (0.48)	Yue <i>et al</i> ^[46]
Sichuan, Southwest China	2015	1–4	6519	9 (0.14)	Liu <i>et al</i> ^[47]
		5–8	34,689	55 (0.16)	
		9–13	31,415	109 (0.35)	
Zhejiang, East China	2015–2016	1–8	1695	7 (0.41)	Li <i>et al</i> ^[48]
Changchun, Northeast China	2016	<1	382	0 (0)	Wang <i>et al</i> ^[49]
		1–4	1614	3 (0.19)	
		5–14	1413	3 (0.21)	
Yunnan, Southwest China	2017	1.5–5.5	10,691	76 (0.71)	Wang <i>et al</i> ^[50]
		5.6–10.5	14,173	222 (1.57)	
		10.6–15.5	14,941	422 (2.82)	

* This just indicates where the studies were performed, but not to indicate the representative of a province's results, because some of the studies were performed in single hospitals. HBsAg: Hepatitis B surface antigen.

Table 2: MTCT of HBV in children of HBsAg-positive mothers.

Province and location*	HBsAg (-) mothers		HBsAg (+) mothers		References
	Children No	Infection, No (%)	Children No	Infection, No (%)	
Adherence to recommended immunoprophylaxis					
Guangdong, South China	887	0	473	21 (4.44)	Yin <i>et al</i> ^[22]
Liaoning, Northeast China	82	0	167	12 (7.2)	Ding <i>et al</i> ^[23]
Hubei and Xinjiang, Central and Northwest China	647	0	367	29 (7.9)	Zhang <i>et al</i> ^[24]
Jiangsu, East China	126	0	49	4 (8.2)	Evans <i>et al</i> ^[25]
Hubei, Central China	996	0	223	11 (4.9)	Peng <i>et al</i> ^[26]
Jiangsu, East China	2741	0	1248	73 (5.8)	Xu <i>et al</i> ^[14]
Suboptimal adherence to recommended immunoprophylaxis					
Jiangsu, East China	208	0	90	11 (12.1)	Hu <i>et al</i> ^[9]
Henan, Central China	316	8 (2.5)	122	15 (12.3)	Yonghao <i>et al</i> ^[55]
Shaanxi, Northwest China	310	4 (1.3)	189	22 (11.6)	Chen <i>et al</i> ^[56]

* This just indicates where the studies were performed, but not to indicate the representative of a province's results, because most of the studies were performed in single hospitals. HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; MTCT: Mother-to-child transmission.

vaccine in all newborn infants of HBsAg-positive mothers has greatly improved the efficacy of immunoprophylaxis against MTCT of HBV, and the efficiency of immunoprophylaxis is comparable to that in advanced countries or regions.^[19,53,54,57]

Declined prevalence of HBsAg in pregnant women

The nationwide surveys showed that HBsAg prevalence among women at childbearing age in 1980s was around 10%.^[2] In 2002–2004, 16–18 years after the availability of hepatitis B vaccine produced in China, HBsAg prevalence in 6398 pregnant women at the second trimester across Jiangsu province was reduced to 6.7%.^[58] From July 2011 to June 2016, the average HBsAg prevalence based on the pregnancy population from two county-level cities and one county in south, middle, and north Jiangsu, respectively, was 5.2% (1814/34,614), 5.5% (3397/62,053), and 5.7% (3393/59,296), respectively.^[14] In Rugao city, in the middle of Jiangsu, the HBsAg prevalence in all pregnant women tended to decline over time, from 6.4% (414/6449) in 2011 to 4.9% (281/5760) in 2016.^[59] As the HBsAg prevalence in teenagers and young adults at 15–29 years of age in 2014 was 4.4% (409/9294),^[42] it is predictable that the HBsAg prevalence in pregnant women will continuously decline in the coming years. The reduced HBsAg prevalence in pregnant women will lead to less MTCT of HBV.

Challenges in the elimination of HBV infection in children in China

China has a vast, geographically diverse territory and world's largest population, and the economic development is quite uneven. Despite the great success in preventing HBV infection over the last 40 years, there are some challenges in achieving the goal to eliminate novel chronic HBV infection in children.

Suboptimal coverage of timely birth dose vaccine in rural or remote areas

Overall, the rate of untimely birth dose in children at 1–4 years age in the Chinese mainland surveyed in 2014 was as

high as 10.1%, and HBsAg prevalence was higher in these children than that in timely vaccinated children (0.9% [11/1274] *vs.* 0.2% [28/11,313]).^[60] Even in Ningbo, an economically prosperous city of Zhejiang province, the coverage of hepatitis B vaccination was 99.9% (18,384/18,397) but the timely birth dose was only 88.1% (16,209/18,397) in infants of HBsAg-positive mothers during 2013–2018.^[61] The situations seemed to be more serious in some remote areas, particularly in rural areas of western China. In 2015, only 71.2% (765/1074) of the infants in rural areas in Yunnan province received timely birth dose vaccine.^[50] In 2016, just about 80.2% (1547/1929) of the infants in 14 rural counties of seven provinces (Gansu, Guizhou, Qinghai, Yunnan, Sichuan, Tibet, and Xinjiang) in west China were timely vaccinated.^[62] The relatively lower coverage of timely birth dose resulted in relatively higher HBsAg prevalence in these areas.^[50] The updated nationwide program for preventing HIV, syphilis, and HBV, released by China Health Committee in 2020, would be helpful to promote the use of timely birth dose vaccine in all infants.

Missed or delayed use of HBIG in newborn infants of HBsAg-positive mothers

A proportion of newborn infants of HBsAg-positive mothers were not administered HBIG shortly after birth, which appears to be an important reason of MTCT of HBV.^[11,24,55,63] In Ningbo city, only 80.6% (14,827/18,397) of the infants received HBIG within 24 h after birth during 2013–2018.^[61] The main reasons include neonates with poor health conditions and/or preterm birth^[10,11,61] and no HBIG supply in delivery rooms. Actually, premature birth is not a contradiction of HBIG administration. The other reasons include unknown HBsAg state at delivery due to the absence of prenatal screen, usually in mobile populations, and in rare cases, tentatively concealing the positive HBsAg because of worry about the discrimination. Thus, public health education should be emphasized in healthcare workers and general population. HBIG should be stored in delivery rooms to ensure its immediate use. Additionally, more efforts should be taken to ensure that all pregnant

women are screened for HBsAg in the first or second trimester.

Post-vaccination serologic test in infants of HBsAg-positive mothers

A prerequisite to estimate the protective efficacy against MTCT of HBV is to perform post-vaccination serologic test (PVST) in infants of HBsAg-positive mothers. However, the HBsAg test is not performed in most of the infants born to HBsAg-positive mothers in the real-world practice,^[14,15] although the guidelines recommend doing so.^[12,40] Even in the prospective studies that provided serologic tests with free of charge, around 15% of the parents who initially agreed to follow-up their infants declined PVSTs.^[18,35] In four provinces, Chongqing, Zhejiang, Jiangxi, and Fujian, where the PVST program has been implemented, the actual test was performed in less than half of targeted infants.^[64] The low performance of PVST may influence the accuracy of estimating the protective efficacy of immunoprophylaxis. Thus, health education should be emphasized to increase PVST in infants of HBsAg-positive mothers.

The accuracy of hepatitis B serologic tests

Studies showed that 644 (11.9%) of 5419 pregnant women who were initially diagnosed with HBV infection based on the positive HBsAg results measured in hospitals of three provinces of south China turned out to be negative HBsAg in the further test in provincial centers for disease control (CDC).^[65] Of 10 infants who were tested HBsAg positive in the local CDC laboratory, only 3 were confirmed to be positive, and 7 others were tested negative in a national laboratory.^[66] The findings that a high proportion of successful vaccinees became HBsAg positive even in the presence of anti-HBs are likely caused by the false-positive results.^[67,68] Thus, efforts should be taken to improve the quality of testing HBsAg as well as other hepatitis B serological markers.

Administration of oral antiviral agents in HBsAg-positive pregnant women

Currently, administration of oral antiviral agents in HBsAg-infected women with high viral loads is recommended to further reduce MTCT of HBV, although the optimal management requires more studies to clarify some issues.^[69,70] The cut-off of HBV DNA for the administration of oral antivirals is set up to be $>2 \times 10^5$ ($5.3 \log_{10}$) U/mL.^[16,17,40] However, the quantification of HBV DNA is not widely performed in many township hospitals and local maternal and children's hospitals of China, which may limit the administration of anti-HBV agents in pregnant women with high viral loads. To overcome this issue, HBeAg is proposed to be a surrogate marker of high viral load^[40,69,71] since HBeAg positivity is well correlated with high viral loads and the median HBV DNA levels in pregnant women is as high as 7.3 to 8.1 \log_{10} U/mL, and the proportion of HBV DNA $>2 \times 10^5$ ($5.3 \log_{10}$) U/mL is about 90%.^[27-30] The detection of HBeAg is inexpensive and requires no specific techniques and can be performed in all hospitals where the detection

of HBsAg is performed. Nevertheless, the quality of testing hepatitis B serological markers should be improved to ensure the accuracy of HBeAg test.

In addition, administration of oral anti-HBV agents in HBsAg-infected pregnant women with high viral loads appears to be suboptimal in towns and rural areas, which will influence the efficacy of prevention of MTCT of HBV. Intensifying educations in healthcare workers who provide prenatal care in towns and rural areas is necessary to overcome this challenge.

Conclusions

Substantial progress has been achieved in the elimination of chronic HBV infection in children as well as in young adults in China since the implementation of universal infant vaccination against hepatitis B and the national program of administration of HBIG with free of charge in all infants of HBsAg-positive mothers. Future efforts are required to focus on improving the timely coverage of both HBIG and hepatitis B vaccine in newborn infants of HBsAg-positive mothers in towns and rural areas and adequately administering oral anti-HBV agents in HBsAg-positive mothers with positive HBeAg and/or high viral loads. It is anticipated that China will achieve the goal of $\leq 0.1\%$ HBsAg prevalence in children aged younger than 5 years by 2030, which was set by the World Health Organization.

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Conflicts of interest

None.

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