

Strategy vaccination against Hepatitis B in China

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Hepatitis B (HB) is a serious public health problem in China. Up to now, the hepatitis B virus (HBV) vaccination was the most cost-effective way to prevent HBV infection. Since 1992, when the Chinese government prioritized implementing the HBV vaccinations for newborns, China began to see a larger reduction in HBV infections. For children under 5 years, the prevalence of hepatitis B surface antigen (HBsAg) has decreased to 1.0%. However, many additional challenges for the prevention and control of HBV infection in China remain. There is a lack of knowledge of the significant impact of the HBV vaccination for the general public with 93 million HBV carriers and chronic HBV patients as infection sources. Therefore, the HBV vaccine application should focus on the optimization of immunization strategies according to HBV prevalence characteristics, improve the public's knowledge of HBV vaccinations, and help to ensure the protective effects of the HBV vaccine.

Introduction

It is well known that the hepatitis B virus (HBV) has contributed to an extremely high burden of liver disease worldwide. The World Health Organization (WHO) reported that over 240 million people have chronic HBV infections and 2 billion people have been infected by HBV. Annually, more than 780 thousand HBV patients die from complications such as hepatic decompensation, cirrhosis, and hepatocellular carcinoma (HCC).^{1,2} The hepatitis B vaccination is the most effective measure to prevent HBV infection and its consequences. In order to reduce the world population's prevalence of HBV infection, research has confirmed that the hepatitis B vaccination should also be administered to infants and adolescents to block the horizontal transmission of HBV, in addition to proper vaccination of newborns at birth and control of HBV transmission from mother to child.³

The first HBV vaccine was introduced in 1982. Government delegates to the World Health Assembly agreed in May 1992 that all countries should integrate hepatitis B vaccinations into their national immunization programs by 1997.⁴ As of 2012, 183 countries had incorporated a hepatitis B vaccine as an integral part of their national infant immunization programs and an estimated 79% of the 2008 birth cohort received 3 doses of the hepatitis B vaccine.² In the United States, a primary focus of this

strategy was universal vaccinations of infants to prevent early childhood HBV infection and to eventually protect adolescents and adults from infection. Other components included routine screening of all pregnant women for hepatitis B surface antigen (HBsAg) and postexposure immunoprophylaxis of infants born to HBsAg-positive women, vaccinations of children and adolescents who were not previously vaccinated, and vaccinations of unvaccinated adults at increased risk for infection.^{5,6} Taiwan started vaccinations on neonates born to mothers who were HBV carriers in 1984, then expanded the vaccination program to all newborns in 1986. They started to vaccinate children less than 4 years of age and healthcare workers in 1987, family members of HBV carriers and children aged 5 to 9 years in 1988, adolescents aged 10 to 19 years in 1989, young people aged 20 to 39 years and adults in 1990, and the population older than 40 years of age in 1991. Vaccinations have reduced the prevalence of HBV infection, decreased the number of acute and chronic hepatitis B cases, and also greatly lowered the incidence of hepatic cirrhosis and cancer.⁷

China's government listed the application of HBV vaccine as a priority of public health works. The prevention and control of the HBV infection has already been successfully implemented through newborn HBV vaccinations for years. For Chinese children, the prevalence of HBsAg has declined significantly. Since 1992, 90 million cases were prevented against the HBV infection and 24 million HBV carriers were decreased.⁸ In 2014, the WHO awarded China's government the prize for the achievement of prevention against HBV infection for children in China. However, many challenges remain for the prevention and control of the HBV infection in China. One of the biggest challenges is the lack of knowledge of the significance of the HBV vaccination for the prevention and control of the HBV infection. Key factors should include how to improve the knowledge and confidence of the HBV vaccination under the impact of bias media reporting on vaccine immunization, and ensuring the rate of timely (within 24 hours of birth) HBV vaccine birth-dose vaccination and 3-doses HBV vaccine coverage nationwide.

The manufacture and management of HBV vaccines in China

In 1983, Beijing Tiantan Biological Products Co., Ltd. successfully developed a plasma derived HBV vaccine. This kind of HBV vaccine was manufactured on a large scale and launched in 1985. Because of the potential risk of transmission of live HBV and other blood-borne pathogens, and the limitation of blood donor numbers, the domestic hepatitis B vaccine in Chinese Hamster Ovary (CHO) cell and the hepatitis B vaccine in yeast

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(Merck & Co., Inc.) were successfully approved for marketing in the 1990s. In 1988, the Institute of Virology at the Chinese Academy of Preventive Medicine developed the CHO cell line for production of the hepatitis B vaccine. Changchun Institute of Biological Products Co., Ltd. established the technology of the pilot scale and submitted manufacture application. Finally, they achieved the pre-manufacture license in 1992 and acquired the drug-manufacturing certificate in 1996. Beijing Tiantan and Shenzhen Kangtai Biological Products Co., Ltd. introduced the production technology of recombinant DNA hepatitis B vaccine from Merck & Co., Inc. in 1992, received the drug certificate and launched the products in 1995. In 2004, recombinant DNA hepatitis B vaccine in *Hansenula Polymorpha* was developed by Dalian Hissen Bio-pharm. Co., Ltd. and was approved for marketing. Since June 30, 1998, China's government mandated stopping the production of the plasma-derived hepatitis B vaccine and forbid the application of this kind of vaccine in 2000. Since then, Hepatitis B vaccines manufactured in yeast or mammalian cells using recombinant DNA technology replaced plasma-derived hepatitis B vaccines nationwide.

With the development of the recombinant DNA hepatitis B vaccines over the past several decades, vaccine manufacturers have not only increased productivity by improving the vaccine production technology but also developed various dosage forms of hepatitis B vaccines in order to meet clinical demands. Currently, the hepatitis B vaccine dosages included in Chinese Pharmacopoeia, 2010 version are 5 µg/dose, 10 µg/dose, and 20 µg/dose. Until now, a total of 6 enterprises are producing hepatitis B vaccines in China using *Saccharomyces cerevisiae*, *hansenula polymorpha* and CHO cell with 2 enterprises each. These 6 enterprises produce various formulations containing antigen of 10 µg/dose (6 enterprises), 20 µg/dose (5 enterprises except 1 enterprise producing in *hansenula polymorpha*) and 60 µg/dose (1 enterprise producing in *Saccharomyces cerevisiae*). To further enhance the protective effects of the hepatitis B vaccines, the 5 µg/dose formulation has been discontinued since 2012 and a 60 µg/dose formulation mainly for immunocompromised population and non-response to HBV vaccine has been approved for marketing. Since 2010, Chinese authorities have not permitted the use of thiomersal as a preservative during the manufacturing process of the hepatitis B vaccines. The lot release management system for hepatitis B vaccines was initiated since 2002. Implementation of the Chinese pharmacopoeia 2010 version has greatly improved the quality of hepatitis B vaccines in China, and also met the international standards for the vaccines. For each lot of hepatitis B vaccines, the qualification certificate cannot be issued until the production record and sample are reviewed and tested. In recent years, more than 300 lots per year of hepatitis B vaccines were granted qualification certificate, which contained more than 100 million doses and approximately 80% was yeast-derived vaccine.

China's national planning of HBV immunization strategies

HBV immunization was introduced in China in 1987. The HBV vaccine was first recommended for routine vaccination of

infants formulated by the Ministry of Health of the People's Republic of China on January 1, 1992, with the first dose to be administered within 24 hours of birth and subsequent doses at ages one and 6 months. However, because of high vaccine prices and user fees charged to parents by local health departments for vaccine purchase and administration, until 2002, infant vaccination occurred primarily in large cities of the wealthier eastern provinces. China integrated HBV vaccines into the Expanded Program of Immunization (EPI) in 2002, when the cost of HBV vaccines was paid by the government, while administration fees of HBV vaccinations (up to \$1.10 per dose) continued to be charged to the parents.⁹ Also in 2002, the China Ministry of Health began a project with the Global Alliance for Vaccines and Immunization (GAVI) to ensure HBV vaccine availability in China's poorest provinces and counties. The 5-year China-GAVI project provided free HBV vaccines, targeting approximately 5.6 million children born each year in 12 western provinces and in government-designated poor counties in 10 middle provinces, covering approximately 36% of China's child population.¹⁰ In 2005, a new vaccination regulation abolished all charges and user fees for all nationally recommended vaccines, including the hepatitis B in China.^{11,12} These HBV immunization strategies were regarded as successful methods and have resulted in reduced HBsAg prevalence among children under 5 years old to less than 1% and prevented an estimated 1620 million additional HBV carriers.⁸ Also, these strategies have been estimated to achieve a cost-effectiveness of 1:51.¹³

Immunization strategies for HBsAg positive mothers

Currently, most pregnant women have their HBsAg status checked in the hospital even though it is not mandatory. Guidelines on prevention and treatment of chronic hepatitis B in China (2010) indicated that to prevent perinatal transmission, neonates born to HBsAg positive mothers should receive a combination of immunization with the hepatitis B vaccine of either 10 µg recombinant yeast vaccine or 20 µg CHO vaccine and 100 IU of hepatitis B immunoglobulin within 24 hours after birth or within 12 hours after delivery. By combining the hepatitis B vaccine together with the HBIG injection, a 95–97% protective rate could be achieved in those neonates born to HBsAg-positive mothers.¹⁴

Immunization strategies for children and high risk populations among adults

Under the implementation of the national immunization strategy for newborn infants, China has been transferred to an area with HBV intermediate endemicity or low endemicity.⁸ Many older children, adolescents and adults were born prior to universal vaccination. Catch-up strategies targeted at unvaccinated people in older age groups might be needed to speed up the development of population-based immunity and to accelerate the decline in incidence of acute hepatitis B.

Therefore for children with incomplete, none, or unknown HBV vaccination history, China's government proposed the catch-up strategies based on effectively implementing a neonatal

HBV immunization plan. From 2002 to 2006, 16 provinces carried out the catch-up strategies for children born from 2002 to 2005 and 8.2 million doses of the HBV vaccine were administered. In 2007, more than 7 million doses of the HBV vaccine were immunized to children less than 15 years old, without HBV vaccination history in Jiangsu, Qinghai, Zhejiang, Tianjin and Shandong provinces.¹² With more attention to prevent HBV, all children less than 15 years of age who were never or incompletely immunized with the HBV vaccine had to be immunized by catch-up HBV vaccinations from 2009 to 2011. China's government paid the immunization fees.¹⁵

Among adults, ongoing HBV transmission occurs primarily among unvaccinated adults with risk behaviors for HBV transmission and among household contacts and sex partners of persons with chronic HBV infection. Although a national HBV immunization strategy for adults has not been developed in China till now, the Technical Guide for Adult Hepatitis B Immunization in China was published in 2011. The guidelines suggested that immunization with 3 doses of 20 µg HBV vaccines at 0, 1, and 6 months was voluntary for adults aged 18 years and older, who were unvaccinated, incompletely vaccinated or it was unknown if they had been vaccinated with the HBV vaccine. Pre-vaccination HBV serological testing is not recommended as routine practice. Currently China's government cannot afford the expenses of the HBV vaccines and administration fees.¹⁵

Immunization strategies for high-risk population

Combined with the WHO position paper, the recommendations of the United States Center For Disease Control (CDC) and the Guideline of Prevention and Treatment for chronic hepatitis B (2010 version) issued by the Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association, the Technical Guide for Adult Hepatitis B Immunization proposed that the HBV vaccine should be recommended for high-risk populations. High-risk populations include on-the-job health care workers, college students (especially the students of Medical College), rescue workers (policemen, firemen, emergency rescue persons), patients receiving hemodialysis, blood transfusion and organ transplantation, the spouses or partners of hepatitis B virus infected individuals, sexually active persons who are not in a long-term, mutually monogamous relationships, homosexuality, injection-drug users, immunodeficiency or immune compromised individuals, and HIV positive individuals. Three doses of 20 µg HBV vaccines at 0, 1, and 6 months are required to be given to high-risk populations. Four doses of 60 µg HBV vaccines at 0, 1, 2, and 6 months are recommended to patients with hemodialysis and organ transplantation.¹⁴

After routine vaccination, in individuals who respond adequately, the protective response usually lasts for at least 12 years,¹⁶ So periodic anti-HBs testing is not recommended nor are booster doses of vaccine in the general population. In high-risk groups, anti-HBs monitoring is significant and a booster dose of vaccine should be given if anti-HBs are lower than 10 mIU/ml.¹⁷

In Beijing, local governments or medical facilities have granted HBV immunization of health care workers.¹⁸ However,

in most areas in China, the expenses of HBV vaccine immunization of high-risk populations should be covered by personal payment.

Immunization strategies for non-response to HBV vaccines

Age, gender, number of doses and dose levels have been shown to influence antibody titers following hepatitis B vaccination.¹⁹⁻²⁷ Studies suggest that higher HBsAg formulation of HBV vaccines may be associated with faster seroconversion rates and higher peak antibody levels, as well as improved sero-protection rates in populations difficult to immunize.²⁸⁻³⁰ Since 2012, Chinese authorities abolished 5 µg HBV vaccines and defined 10 µg HBV vaccines for use in neonates, infants, and children up to and including 15 years of age. The 20 µg dose of HBV vaccine was intended for use in subjects 16 years of age and older.

For non-responders to the HBV vaccine, the dose and frequency of the HBV vaccine injections should be increased. If there is no response after completing the 3-dose primary series of the HBV vaccine, an additional 3-dose series should be administered, and the recipients should be detected for anti-HBs level 12 months after completing the second 3-dose HBV vaccine series. One dose of 60 µg HBV vaccines should be immunized if the recipients also cannot induce anti-HBs level higher than 10 mIU/ml.¹⁴

Immunization strategies for population with anti-HBc alone

Currently, there are no recommendations for individuals with positive anti-HBc alone and waned anti-HBs concentrations to receive the HBV vaccination. According to the study results of Su et al., a single booster dose of HBV vaccine was recommended for participants with isolated positive anti-HBc who had been fully vaccinated with a HBV vaccine as infants.³¹ A study on the HBV immunization strategy for college students found that 3 doses of HBV vaccines could induce a higher protection rate and anti-HBs concentrations compared with one dose of the HBV vaccine, in students with isolated positive anti-HBc.³²

Immunization strategies for accidental exposure prevention

The following procedures should be followed in the event of accidental exposure. Serologic testing of HBsAg, anti-HBs, and ALT levels should be checked immediately after exposure and rechecked within 3–6 months. There is no need for treatment for those who have been vaccinated and have anti-HBs ≥ 10 mIU/ml. For those who have not been previously vaccinated or have been vaccinated but with anti-HBs < 10 mIU/ml or the anti-HBs level unknown, HBIG 200–400 IU should be injected immediately after exposure and, at the same time, a 20 µg HBV vaccine should be administered at another site. The second and third doses of 20 µg HBV vaccine should be given one and 6 months later.¹⁴

Challenges and outlook of HBV immunization strategies in China

The primary 3-dose HBV vaccine series induces protective antibody concentrations in more than 95% of healthy infants, children and young adults.³³⁻³⁵ As pointed out in the WHO's

position paper, perinatal or early childhood transmission was the main cause of chronic HBV infection throughout the world. Thus, the first dose of hepatitis B vaccine should be administered after birth as soon as possible (within 24 hours of birth). Delay in the birth dose resulted in an increased risk of HBV infection.³⁶

The 3-dose HBV vaccination series and the timely delivery of a birth dose of the hepatitis B vaccine (within 24 hours of birth) should be performance measures for HBV immunization programs.³⁷ In China, national 3-dose HBV vaccine coverage and timely (within 24 hours of birth) HBV vaccine birth-dose coverage have gradually improved. Two national vaccination coverage surveys showed that the estimated 3-doses HBV vaccine coverage has increased substantially overall, from 70.7% among children born in 1997 to 89.8% among children born in 2003. Timely HBV vaccine birth dose coverage also increased from 29.1% among children born in 1997 to 75.8% among children born in 2003.^{38,39} Based on the survey results in 2004, the 3-dose HBV vaccine coverage (68.0%) and timely birth dose of HBV vaccine coverage (49.5%) were lower in China's western provinces than middle and eastern provinces.³⁹ The estimated HBV vaccine coverage was also lower in rural compared to urban areas. Lower HBV vaccine coverage mainly resulted from infants born at home, rural families migrating frequently and parents' lack of knowledge on HBV infection and immunization.⁴⁰⁻⁴¹ In order to improve and ensure that all infants receive a dose of hepatitis B vaccine within 24 hours of birth and the 3-dose series requires increasing the number of infants born in a hospital, ensuring that there is coordination between immunization services and maternal health services, expanding vaccine management systems and innovative outreach to provide vaccines for home births, and ensuring that HBV vaccine is available for infants born at home.

The vaccination program in China has been regarded as a success story in preventing hepatitis B through universal infant vaccination. However, HBV vaccine immunization strategies for adults should be improved. The 3-dose vaccine series administered intramuscularly at 0, 1, and 6 months produces a protective antibody response in more than 90% of healthy adults younger than 40 years old after the third dose.⁴⁰ After age 40, the proportion of persons who have a protective antibody response after a 3-dose vaccination regimen declines below 90%, and by age 60, protective levels of antibody develop in only 75% of vaccinated persons.^{43,44} In addition to age, other host factors (e.g., smoking, obesity, genetic factors, and immune suppression) contribute to a decreased HBV vaccine response.^{20,45-47} At present, there are no special recommendations for populations older than 40 years, immune compromised individuals or individuals who have difficulty responding to the HBV vaccine. In order to achieve better effects of the HBV vaccine for these populations, new types of HBV vaccine should be developed, such as a HBV vaccine with higher HBsAg content, 4-dose or more doses schedules or HBV vaccines with new adjuvants. Also for adults, the question on whether HBV vaccine needs booster or revaccination should be further researched. In China, adults have limited knowledge and awareness of the prevention and treatment of hepatitis B. More

healthy education needs to be provided for adults, especially for adults in rural areas.

With the increasing development of communication tools, bias media reporting and the role of new media such as microblog, We-Chat, blogs, have already impacted the implementation of the hepatitis B vaccine immunization strategies in China. During December 2013, the Chinese media reported 18 serious Adverse Events Following Immunization (AEFI) among infants and children that were suspected to be related to the vaccination of the hepatitis B vaccines produced by Shenzhen Biokangtai. Through the field inspection, the detection of product sampling, quality retrospective review and analysis and case investigation, China's Food and Drug Administration and Health and Family Planning Commission announced that there were no quality issues for the hepatitis B vaccines produced by Shenzhen Kangtai Biological Products Co., Ltd on January 17, 2014. However, the events have had a significant impact on public confidence in hepatitis B vaccination, and induced the decline of hepatitis B vaccination coverage rates in China. As the newborns' mortality is very high, at present, how to optimize the hepatitis B vaccination procedure of newborns has become the key consideration for the hepatitis B vaccine immunization strategies in China.

Summary

Although great achievements have been made since planned immunizations of hepatitis B vaccines began, the people of China are still at tremendous risk of hepatitis B virus infection and a large number of people continue to suffer from chronic hepatitis B. Improvements are still needed on the rate of timely (within 24 hours of birth) HBV vaccine birth-dose vaccination and 3-dose HBV vaccine coverage nationwide. Additional resources are needed to increase vaccination coverage for adults and special populations of HBV vaccines with appropriate strategies and corresponding dosages. Based on the features of prevalence of hepatitis B, there is a need to optimize and adjust the hepatitis B vaccine immunization procedure from time to time. It is critical to continue developing high-immunogenicity vaccines and popularizing the knowledge about hepatitis B vaccines to the public and media to further reduce the prevalence rate of hepatitis B in China.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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