Key outcomes and addressing remaining challenges—Perspectives from a final evaluation of the China GAVI project

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\textbf{A B S T R A C T}

During the China GAVI project, implemented between 2002 and 2010, more than 25 million children received hepatitis B vaccine with the support of project, and the vaccine proved to be safe and effective. With careful consideration for project savings, China and GAVI continually adjusted the budget, additionally allowing the project to spend operational funds to support demonstration projects to improve timely birth dose (TBD), conduct training of EPI staff, and to monitor the project impact. Results from the final evaluation indicated the achievement of key outcomes. As a result of government co-investment, human resources at county level engaged in hepatitis B vaccination increased from 29 per county on average in 2002 to 66 in 2009. All project counties funded by the GAVI project use auto-disable syringes for hepatitis B vaccination and other vaccines. Surveyed hepatitis B vaccine coverage increased from 71% in 2002 to 93% in 2009 among infants. The HBsAg prevalence declined from 9.67% in 1992 to 0.96% in 2006 among children under 5 years of age. However, several important issues remain: (1) China still accounts for the largest annual number of perinatal HBV infections (estimated 84,121) in the WHO WPR region; (2) China still lacks a clear national policy for safe injection of vaccines; (3) vaccination of high risk adults and protection of health care workers are still not implemented; (4) hepatitis B surveillance needs to be refined to more accurately monitor acute hepatitis B; and (5) a program for treatment of persons with chronic HBV infection is needed. Recommendations for future hepatitis B control include: using the lessons learned from the China GAVI project for future introductions of new vaccines; addressing unmet needs with a second generation hepatitis B program to reach every infant, including screening mothers, and providing HBIG for infants born to HBsAg positive mothers; expanding vaccination to high risk adults; addressing remaining unsafe injection issues; and improving monitoring of acute hepatitis B. This paper describes findings and discusses perspectives from a final project evaluation, a national stratified validated cross-sectional survey done in October 2010.

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1. Introduction

China received GAVI support in 2001 because of the high disease burden of hepatitis B and a strong government commitment to protect infants at risk. The Ministry of Health/Global Alliance for Vaccines and Immunization Project on hepatitis B immunization (China GAVI project) implemented from 2002 in 22 of the 31 provinces was designed to (a) increase coverage of hepatitis B vaccine through a pro-poor approach targeting all counties of the 12 Western provinces and poverty counties of the 10 Central provinces, (b) accelerate integration of hepatitis B vaccine into routine immunization, and (c) assure immunization injection safety \cite{1}. The central and sub-national levels shared a common responsibility and complemented each other's functions.

In collaboration with GAVI, the government of China implemented a number of activities, including (1) increasing awareness of the importance of a timely birth dose (TBD) of hepatitis B vaccine among providers and parents, (2) intensifying training for
health care workers (HCWs), (3) monitoring and supervision of vaccination activities, (4) improving hospital delivery rates through provisions of subsidies to parents to encourage hospital delivery of infants, (5) building collaborative bridges between delivery services (maternal and child health, MCH) and vaccination service (EPI), and (6) subsidizing providers as a incentive for providing timely birth dose and three doses of hepatitis B vaccine along with other EPI vaccines [1].

Initially, GAVI project funds were only used to procure vaccine and safe injection equipment. However, provision of insufficient operational costs in some provinces was identified as a bottleneck for implementation. Hence, from 2007 onwards, China GAVI project savings were assigned to support operational costs in low performing areas, with flexibility given for expenditures so that human resources could also be covered. This paper describes findings and perspectives from a final project evaluation which included a national stratified, validated cross-sectional survey conducted in October 2010.

2. Final evaluation process

We used the methods recommended by WHO to select a cluster sample of 244 health care facilities for the purpose of injection safety assessments [2]. The design of this assessment, which included both vaccine coverage and injection safety assessments, is described in other papers in this supplement [1,3].

2.1. Key outcomes

Results of China GAVI project final evaluation suggest that in 2010, the project goal of 85% coverage of three doses was reached in 98% of China GAVI project counties that together accounted for 99% of the target population [3]. The 75% timely birth dose (TBD) project goal was reached in 80% of counties that together accounted for 79% of the target population. Auto-disable (AD) syringes were successfully introduced in all GAVI-supported areas, although standard disposable syringes remained in use in non-GAVI supported areas in Central and Eastern provinces [4].

The China GAVI project final evaluation went further than a review of the initial goals and examined all the components of the China GAVI project as per the logic model to understand the causes of the success and identify remaining issues (Box 1). With respect to hepatitis B immunization, inputs included 76 million USD provided by the China GAVI project to fund hepatitis B vaccine between 2002 and 2007, and 21.5 million USD of additional China government subsidies to health care workers between 2007 and 2009. The health system efficiently utilized these resources. First, the increase in the HepB3/DPT3 ratio (reaching 94% in 2009) indicated that EPI effectively implemented hepatitis B immunization. Second, the increase in the proportion of institutionalized deliveries (reaching 96% in 2009) indicated that Maternal and Child Services created conditions that maximized TBD coverage. As a result, from 2002 to 2009, three doses of hepatitis B vaccine coverage increased from 71% to 93% and TBD coverage increased from 60% to 91% based on national survey data [3]. Both of these factors resulted in immunity among vaccinated cohorts as 85% of children 12–23 months of age were anti-HBs+ in the 2006 serological survey [5].

With respect to injection safety, inputs included 14 million USD of China GAVI funds to supply AD syringes, safety boxes and needle cutters. In 2009, AD syringes and safety boxes were used in 78% and 79% facilities in the GAVI-supported areas of the Western areas, respectively. In terms of output, sterilizable injection devices disappeared and attempts to re-use disposable injection equipment became rare (0% in the 2010 final evaluation) [4]. However, no data regarding the incidence of injection-associated infections were available to evaluate the outcome of the progress in injection safety.

With respect to social mobilization and training, 10 million USD were assigned to training between 2002 and 2009. Most of these funds were not directly funded by GAVI alliance but by the government, through a leverage effect of the China GAVI project support. Funding was used in 28,753 workshops to train health care workers resulting in better knowledge among health care workers (in 2010, 98% knew that hepatitis B virus can be transmitted from mother to child) and guardians (in 2010, 89% knew that the first dose of hepatitis B vaccine had to be given in the first 24 h of life). This also contributed to higher immunization coverage and safer injections.

Ultimately, the elements of the China GAVI project combined at the impact level to prevent HBV infections. The 2006 national serological survey documented these achievements and pointed to a 0.96% prevalence of HBsAg among children under five years

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<th>Box 1: Summary of key indicators of input, process, output, outcome and impact for the GAVI project, China, 2002–2010.</th>
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of age in China (a decrease of 90% from the 9.67% prevalence in the same age group in 1992), and a 1.26% prevalence among children under five years of age in GAVI-supported areas [5,6]. These improvements will lead to the future prevention of cirrhosis and hepatocellular carcinoma which should result in the prevention of early deaths and morbidity from chronic hepatitis B, cirrhosis, and liver cancer.

3. The benefit of vaccination: impact

3.1. The effectiveness of hepatitis B vaccine

The results from the 2006 serosurvey indicated that the prevalence of HBsAg was 7.18% overall. However, there were large variations in prevalence by age, ranging from 0.96% among children 1–4 years of age, to 2.42% among children 5–14, and 8.57% among persons 15–59. This age-specific prevalence profile showing low prevalence among children and high prevalence among adults is new for China. The 1979 and 1992 surveys showed little variation in the prevalence by age, with a slight decrease in prevalence among older age groups (probably reflecting selective higher mortality in HBsAg positive persons). In contrast with these earlier profiles, the age-specific prevalence of HBsAg from the 2006 survey featured a marked reduction among younger age groups who were exposed to the immunization program (Fig. 1) [5–7].

Overall, the HBsAg prevalence was 7.18% in 2006, compared with 9.75% in 1992 (a decrease of 26%). The classification criteria of the World Health Organization (WHO) specify that a prevalence of HBsAg >8% indicated high endemicity, 2–8% intermediate endemicity and <2% low endemicity areas. Hence, China should now be listed as an intermediate prevalence area [8]. The prevalence of HBsAg among children under 5 has already reached the WPRO goal (less than 2% by 2012), allowing for China to be verified as reaching the WHO goals [9]. Based on the results of the 1992 and 2006 sero-epidemiological studies, we estimated that since 1992, nearly 80 million children under the age of 15 had averted an HBV infection, and that 19 million had averted a chronic HBV infection [5].

3.2. Safety of hepatitis B vaccination

In 2005, China established a system to monitor Adverse Events Following Immunization (AEFI) in 10 provinces, and expanded it to 16 provinces in 2008. The monitoring data from 16 provinces indicated that 252 AEFI following hepatitis B vaccine were reported between 2005 and 2008. This accounted for 5.16% of the total number of reported AEIs. The reported incidence was 2.28/100,000, including allergic rash, allergic purpura, vascular edema, Arthus reaction and thrombocytopenic purpura. The incidence of adverse events with hepatitis B vaccine in China was lower than the global incidence worldwide as reported by WHO [10].

During January 2006 to March 2007, the monitoring system of sudden public health events in China reported 10 cases of infant death after vaccination with hepatitis B vaccine. They were comprehensively analyzed by on-site investigation, clinical examination and/or autopsy. Among 6 cases that were subject to autopsy, one case was attributed to acute allergic shock induced by vaccination with hepatitis B vaccine, while five were attributed to coincidence. Among 4 cases that were not subject to autopsy, one was possibly due to acute allergic shock induced by vaccination [10–12]. While the AEFI monitoring system in China did not allow a formal relation to a denominator expressed in terms of doses used, we used approximations to estimate a rate based on the birth cohort (16 million) and vaccine coverage in a year. Using these calculations, the death rate following AEFIs associated with hepatitis B vaccine (2/16 million) was 0.1/million, lower than the one quoted by UNICEF [13]. All these data suggested that hepatitis B vaccine is very safe. Reactions usually include minor local pain and/or mild fever, and recovery occurs without any treatment [14,15].

3.3. Maintaining hepatitis B vaccination (2011 onwards)

Since 2007, the China/GAVI project has not made additional investments for hepatitis B vaccine and AD syringes because the China central government has assumed financial responsibility for hepatitis B vaccination and injection safety for all newborns in China. Hepatitis B vaccine became one of the vaccines integrated into the national immunization program, with all costs fully funded by the government of China including vaccine, syringes, subsidy for vaccination, salaries of HCWs, cold chain and operational funds.

4. Challenges and remaining issues after China GAVI project

4.1. Persistence of perinatal HBV infections

Despite great achievements in terms of the elimination of perinatal HBV infection, in 2010, China still accounted for the largest annual number of perinatal HBV infections (estimated 84,121) in the WHO WPR region. Two factors explain the difficulties that China is facing when trying to eliminate remaining perinatal HBV transmission. First, the efficacy of hepatitis B vaccine alone for prevention of perinatal HBV transmission ranges from 85% to 95% [16] overall but there will still be some infants infected by HBsAg positive mothers despite receiving a TBD. The inclusion of HBlg into the protocol of immune-prophylaxis increases vaccine effectiveness to 95% [16]. Second, challenges remain in the field of TBD administration among certain rural, remote, and poorer populations. Vaccination coverage was lower among children born at home, especially in remote areas [17]. Thus, in the future, China must identify mechanisms to address these two issues and reach more children with more effective prophylactic regimens. This will require increasing TBD through increased births in hospitals or delivering a timely birth dose to those born at home, and increasing HBsAg screening of pregnant women so that HBlg can be provided to infants of HBV carrier mothers along with the TBD.

4.2. Remaining unsafe injection issues

Despite the large scale introduction of AD syringes in China because of the China GAVI project and development of an industry in China to produce them, the Eastern region and some non-project areas in the Central areas still do not use AD syringes [4]. This leaves a risk of reuse of injection equipment in the absence of sterilization. Management of sharps waste has made progress in China.
However, some grassroots level (village clinic) facilities and private hospitals still engage in unsafe sharps waste management that may (1) expose the community to sharps injuries or (2) generate toxic fumes. In addition, sharps waste collection and management suffers from lack of standardization, which exposes health care workers and the community to needle-stick injuries. Finally, some health care workers remain unprotected with the hepatitis B vaccine. Without a clear national policy that includes a regulatory framework, technical guidelines and implementation funds, this situation will not change.

4.3. Vaccination of high risk adults and protection of health care workers

China has successfully completed a catch-up campaign to vaccinate children under 15 years of age who previously had not received the hepatitis B vaccine. The next phase in China could consider vaccinating high-risk adults. Health care workers are universally at high risk for HBV infection. Two WHO resolutions in 2007 [18] and 2010 [19] recommended vaccinating health care workers against hepatitis B. Aside from health care workers, WPRO has a guideline for hepatitis B vaccination of high-risk adults [9]. These resolutions and recommendations provide general guidance to China. However, the WPRO guidelines recommend using national data to identify high-risk populations so that the national guidelines for the vaccination of high-risk adults are based upon evidence. Thus, a sound surveillance system is needed to identify risk factors for infection and frame the groups that could benefit from immunization.

4.4. Surveillance challenges for incident disease

The Chinese National Notifiable Disease Reporting System (NNDRS) offers a solid foundation for good hepatitis surveillance. Viral hepatitis has been a national notifiable disease since 1959, with reporting by type since 1990. Health care workers use a national case definition system to report cases through the electronic NNDRS. The basic demographic and epidemiological characteristics are routinely compiled. The system is implemented nationally in a uniform manner, is Internet-based and person centered. All diagnosed hepatitis B cases are entered into system, and then county, prefecture, province and national level staff can access the data.

However, both acute and chronic hepatitis B cases are included in the system and are not differentiated. This hides potential new risks and does not accurately reflect the occurrence of new infections. Therefore, China should refine the surveillance system, according to appropriate case definitions, so that acute and chronic infections can be separated. This will need to take into consideration the field aspects of disease diagnosis, laboratory diagnosis, epidemiologic case investigation and data collection and transmission.

4.5. Burden of chronic infections among adults

China, having managed the most pressing problem of incident perinatal and early childhood infections, is now faced with tackling the prevalent burden of HBV-infected patients among adults (8.57% of the population). Since the burden of chronic infections is large, the approach to case management needs to address cost effectiveness and willingness to pay. In addition to economic issues, standards of care, evidence-based treatment guidelines, availability of appropriate and affordable drugs needs to be addressed as well. Pilot population-based projects in selected settings may provide useful guidance on the way to proceed. In addition, China is developing a new reformed health system for treatment, but due to the varying funding capacity of provinces [20], this is not universally implemented and inequity remains. Although safe and effective anti-viral drugs are now available and widely used in China, costs are directly charged to patients and not subsidized by the government. Therefore, China should have eligible medicines integrated into the national health insurance system, which will benefit many patients with chronic infections and increase equities in access to care in the long run. A national guideline should frame screening, case management, counseling, medical treatment, and follow-up.

5. Recommendations for future hepatitis B control

5.1. Transferring knowledge for introduction of new vaccines

The success of the introduction of hepatitis B vaccine into China’s EPI was based upon careful preparation that addressed all critical points. In the future, to ensure the successful introduction of new vaccines into China’s EPI, preparatory work should address (1) burden of disease, (2) cost-effectiveness, (3) financing and (4) local production of the vaccine. In view of its developing economy, China is no longer eligible for GAVI alliance support. Therefore, in the future, if a new, locally produced, cost-effective vaccine for a disease with a high burden is considered for introduction in the EPI, the cost of the new vaccine should be funded using domestic funds. With domestic production in mind, the experience from the China GAVI project could be used to generate delivery and financing mechanisms that will ensure equitable coverage (Table 1).

The China GAVI project provides a model for how to scale up the introduction of a new vaccine into routine immunization in collaboration with the GAVI alliance. The China GAVI experience with respect to hepatitis B vaccine in recent years can be compared to the current situation of other new vaccines in China (Table 1). For hepatitis B vaccine, documentation of a large burden of disease, demonstration of cost effectiveness, and the presence of large-scale domestic vaccine production led to a strong government commitment. This government commitment progressively led to universal, equitable financing. This experience is similar to the Chinese experience with Japanese encephalitis [21,22], for which information on burden of disease [5,6] and cost effectiveness [23,24] combined with the availability of a good national vaccine [25] triggered national introduction into the EPI in 2007. Overall, these experiences point to a number of criteria with respect to introduction of new vaccines that could be of use to National Immunization Technical Advisory Groups (NITAGs) in China and other countries. These NITAGs should consider epidemiologic, economic and other issues to assist Ministries of Health with the decision-making process around new vaccine introduction. When a new vaccine is ready to be introduced, NITAGs may benefit from collaboration with international partners, including the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, the WHO group on New and Under-utilized Vaccines Implementation (NUVI), the SIVAC initiative (i.e., Supporting National Independent Immunization and Vaccine Advisory Committees and the GAVI in eligible countries) NITAGs can then consider these elements to recommend a mechanism for equitable and sustainable financing for universal introduction when the right conditions are met.

5.2. Implementation of a second generation hepatitis B program

5.2.1. Immunization

Immunization system. The future of hepatitis B immunization in China must include maintaining high levels of universal infant vaccination. Vaccinating all infants in a timely manner remains the highest priority, especially for those living in remote, mountain areas. To this effect, the program must (1) regularly analyze data
to identify the difficult to reach, (2) make vaccines available in all villages or townships (which could have implications in terms of cold chain), (3) assign the responsibility to vaccinate to the village health care worker (instead of relying on the township hospitals), (4) conduct regular supervision and (5) provide hands on training for health care workers.

**Perinatal infections.** With respect to the prevention of the transmission from mother to children, China first should conduct additional efforts to strengthen the health system and further improve hospital delivery rates. This increases TBD coverage and decreases perinatal HBV transmission, which results in reduction of disease burden. Tibet, Guizhou and Yunnan should be the priority areas. Screening for HBsAg in pregnant mothers and provision of HBIG for those born to HBsAg positive mothers would be the second step, which will further decrease new infections among susceptible infants. As screening and HBIG to infants of carrier mothers is already done in many provinces, at cost to parents, China needs a national guidance to support and promote this policy.

**Catch-up campaigns.** As China has already completed catch-up vaccination for children under 15 years old (birth cohorts since 1994), the strategy will now evolve toward routine activities through school entry checks in primary school or middle school, plus provision of routine vaccination in all vaccination sites. Raising the target age for catch-up campaigns would lead to smaller returns in terms of cost-effectiveness [26].

**Health care worker protection.** In addition to the routine immunization of infants, catch-up campaigns for children and vaccination for high-risk adults, pre-service vaccination for students in medical, nursing and other health care related schools and university should be addressed[27,28]. Hence, health care workers would be protected before exposure. This is a cost-effective way to protect health care workers [29,30].

5.2.2. **Addressing remaining unsafe injection issues**

**Injection practices.** China needs to have clear safe injection guidelines that would be mandatory for all injections. For vaccination, use of AD syringes should be generalized. This could be achieved through training, supervision, national legislation, regulation or law making. A Chinese expert committee could review the WHO best practices and the recent national evidence to define best practices for China. China should develop national guidelines for safe injections that require that all vaccinations to be given using AD syringes.

**Waste management.** Management of waste could be achieved through national legislation, regulation or law making, which should be implemented in the entire country, and cover all health units. As heterogeneity of solutions facilitates the adoption of substandard choices, precise guidance should define what is acceptable and what is not.

5.2.3. **Surveillance for acute HBV disease**

China should develop clear guidelines for the surveillance of hepatitis B including clear differentiation of acute and chronic hepatitis B. Key aspects to address include (1) guiding hospital professionals to make the right diagnosis and report according to the right case definition, (2) testing specimens appropriately in the laboratory, (3) case investigation and effective data management. Reliable reporting of acute hepatitis B will allow identification of risk factors for use in policy making. Such work should be done in pilot projects first, before expanding to a national scale. Evidence generated could guide vaccination of high-risk adults.

5.2.4. **Toward screening and treatment**

As time will progressively unveil the impact of hepatitis B immunization on the incidence of cirrhosis/hepatocellular carcinoma cases, China will need to set up a system that will be able to measure these health events to calculate the number of deaths prevented and Disability Adjusted Life Years (DALYs) averted.

In the meantime, China will have to address the issue of the current burden of chronic infections among older age groups. These chronically infected persons have not benefited from the immunization of newborns. A China CDC study already monitors morbidity and mortality outcomes among HBV-infected patients identified during the 2006 serological survey [5]. This is a first documentation step for future programs of management. In the future, developing pilot approaches for population-based screening for management could be an easy first step to identify how China could provide long term care and support for the large population already infected. It is through these kinds of small-scale pilot projects that the first chapters of the great hepatitis B immunization success story were written some thirty years ago in China.

**Conflict of interest statement**

The authors state that there is no conflict of interest.
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