

**Scaling up hepatitis B vaccination with the support of GAVI in China:
Lessons learned for introduction of new vaccines and for the future of
hepatitis B control**

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Summary

Background: Hepatitis B virus (HBV) infection is a leading cause of illness and death in China. In 1992, 60% of the population had a history of HBV infection and 9.8% were chronically infected with HBV. Each year, an estimated 263,000 persons died from HBV-related hepatocellular carcinoma or cirrhosis, accounting for 37%-50% of HBV-related deaths worldwide before 1992. In 1992, the Ministry of Health introduced hepatitis B vaccine into the management system of the Expanded Programme on Immunization (EPI) as a cost-effective way to prevent HBV infection. The schedule included a timely birth dose (within 24 hours of birth, to prevent perinatal infections that are most strongly associated with long term chronic infections and adverse outcomes) and subsequent doses at one month and six months. However, this introduction into the EPI management system only meant that the Government took responsibility over administration and coverage monitoring, but not funding support: The cost of vaccination was covered out of pocket. As a result, coverage was lower in rural areas, in Western provinces (low economic status) and among females. In 2002, the Ministry of Health fully integrated free hepatitis B vaccine into EPI with funding from the Global Alliance for Vaccines and Immunization (GAVI). The GAVI China project financially supported vaccine and auto-disable syringes in Western provinces and poverty-affected counties of Central provinces (Chapter 1). As the GAVI China project was completed in 2010, we compiled all evaluation work conducted to understand how input and process lead to output and outcomes that impacted the heavy HBV associated burden in China.

Methods: We compiled data from GAVI China project areas between 2002 and 2009, reviewed cross-sectional studies conducted in 2004 and 2006 and conducted a final evaluation survey in 2010. These investigations covered input (funds invested into the project

for vaccine and AD syringes), process (integration of the vaccine in EPI, increase in institutional births, introduction of auto-disable syringes for vaccination and training), output (immunization coverage for third dose and timely birth dose, use of auto-disable syringes for immunization), outcome (immunity in the population, safe injection practices) and impact (prevalence of HBV surface antigen among children included in the vaccination cohort).

Results: With respect to **hepatitis B immunization**, input included 27 million USD provided by the GAVI China project to fund hepatitis B vaccine between 2002 and 2007. These funds came from the international GAVI Alliance (50%) and the Government of China (50%). In addition, the Chinese government provided an additional 21.5 million USD in government co-funding of subsidies from central to provincial to health care workers in provinces between 2007 and 2009 so that the vaccine could be administered without user fees. The health system efficiently processed these resources. First, in GAVI-supported areas, the increase in the HepB3/DPT3 ratio (increased from 57% in 2002 to 94% in 2009), indicated that EPI absorbed well the new vaccine. Second, institutionalized deliveries increased to reach 96% nationwide in 2009, indicating that maternal and child health services created conditions to maximize coverage of the timely birth dose. As a result, from 2002 to 2009, the national three-dose hepatitis B vaccine coverage progressed from 71% to 93% (Chapter 5) and the timely birth dose coverage progressed from 60% to 91% (Chapter 7) with a reduction of inequities between Eastern and Western areas. Both of these resulted in immunity among vaccinated cohorts (85% of anti-HBs among children 12 to 23 months of age in the national 2006 serological survey) (Chapter 2). One key factor strongly associated with being HBsAg negative is receiving timely birth dose of hepatitis B vaccine as early as possible (Chapter 4).

With respect to **injection safety**, input included 14 million USD of GAVI funds to supply auto-disable syringes, safety boxes and needle cutters. In 2009, auto-disable syringes and safety boxes were used in 78% and 79% facilities in GAVI supported areas of the Western areas, respectively (Chapter 6). In terms of output, sterilizable injection devices disappeared and attempts to re-use disposable injection equipment became rare (0% in the 2010 final evaluation). 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 those were not directly funded by GAVI China. These funds were provided by the Government because of the leverage effect of the GAVI China project. These were used in 28,753 training workshops for health care workers that resulted in better knowledge among health care workers (In 2010, 98% of them knew that hepatitis B virus can be transmitted from mother to child) and guardians (In 2010, 89% of them knew that the first dose of hepatitis B vaccine had to be given in the first 24 hours of life). This higher level of knowledge also contributed to higher immunization coverage and safer injections.

Ultimately, the elements of the GAVI China project combined at the **impact** level to prevent HBV infections. The 2006 national serological survey documented these achievements and pointed to 1% prevalence of HBsAg among children under five years of age, a decrease of 90% from the 9.8% prevalence in the same age group in 1992 (Chapter 3). These infections prevented will lead to the future prevention of cirrhosis, hepatocellular carcinoma. Those should result in early deaths prevented and benefits in terms of disability-adjusted life years (DALYs). However, in 2010, it was too early to measure these longer term effects and the final impact of the project on HBsAg prevalence had not yet been quantified.

Conclusion: The introduction of hepatitis B vaccine into the national immunization programme was successful and the strategies and policy used for the GAVI China project provided a successful case study for the introduction of other new vaccines in China. The determinants of the success of the GAVI China included (1) a well documented disease burden, (2) a good collaboration between the government of China and the international GAVI Alliance that resulted in a strong national GAVI China project, (3) local production of vaccine and AD syringes, (4) solid processes for implementation and (5) leverage of additional support through national and provincial levels co-funding. Remaining challenges include (1) the persistence of an estimated 80,000 perinatal HBV infections each year in China, (2) the lack of homogeneous regulations to harmonize injection practices, (3) the absence of a scaled implementation for the national policy that recommends vaccination of health care workers, (4) the weak specificity and sensitivity of acute hepatitis B surveillance and (5) the absence of policy and plans for the management of chronic hepatitis B infection. We recommended that China (1) maintain universal hepatitis B infant vaccination, with a high priority to reach all infants, especially for those living in remote, mountain areas (2) make additional efforts to strengthen the health system and further improve hospital delivery rates to increase timely birth dose coverage and decrease perinatal HBV transmission, (3) develop clear surveillance guidelines to monitor acute hepatitis B rates (4) immunize health care workers, with an emphasis on pre-service delivery (5) collect manage sharps waste in a way that is safe for the health care workers, the community and the environment, and (6) screen pregnant women to administer adapted immuno-prophylaxis (including hepatitis B immune globulin, HBIG) for children born to those HBsAg positive. These should prepare the country for the next phase of a policy for the prevention and control of hepatitis B, which should ultimately include screening and treatment of patients with chronic infections,

particularly those of older age cohorts who were born before the era of universal immunization.

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General Introduction

1. Hepatitis B in the world and in Asia

1.1 HBV, its transmission and burden of disease

Hepatitis B is a liver disease that results from infection with the Hepatitis B virus (HBV). It can range in severity from asymptomatic infection, to mild illness lasting several weeks, to a serious, lifelong illness. HBV is usually spread when blood, semen, or another body fluid from an infected enters the body of someone who is uninfected and susceptible. This can happen through sexual contact, blood transfusion and unsafe percutaneous exposures, including sharing of needles, syringes, or other drug-injection equipment. HBV can also be passed from an infected mother to her baby at birth ^[1] and through long-term close contacts among younger children. HBV is not spread by contaminated food or water, and cannot be spread through casual contacts in the workplace. HBV may be detected in the blood of the subject 30 to 60 days after initial infection and may persist for a variable period of time.

HBV was discovered in 1965 and by 1970, diagnostic tests were available for routine screening of blood donors to prevent transfusion-transmitted hepatitis ^[2]. Antigens and antibodies associated with HBV infection include hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), antibody to the HBV core antigen (Anti HBc, including IgG and IgM), hepatitis B e antigen (HBeAg), and antibody to HBeAg (anti-HBe). The presence of a positive HBsAg result indicates current, active HBV infection. HBV DNA can be detected in all persons who are HBsAg positive and indicates active viral replication. All HBsAg-positive persons should be considered infectious. Anti-HBc antibodies appear at the onset of symptoms or liver test abnormalities in acute HBV infection and persist for life. Recently acquired infections, among which acute infections, can be distinguished by the presence of the IgM class of anti-HBc. They are detected at the onset of the new HBV infection and persist for up to 6 months. In patients who develop chronic hepatitis B,

IgManti-HBc can persist at low levels during viral replication (However, this is uncommon). The presence of anti-HBs typically indicates immunity resulting from naturally resolved HBV infection or from vaccination. In addition, anti-HBs can be detected for several months after hepatitis B immune globulin (HBIG) administration. Persons who recover from natural infection will typically be positive for both anti-HBs and anti-HBc, whereas persons who respond to hepatitis B vaccine develop only anti-HBs. HBV DNA has been detected in the blood of 5% of persons with isolated anti-HBc, suggesting that this marker profile can be associated with some level of viral replication. HBeAg can be detected in the serum of persons with acute or chronic HBV infection. The presence of HBeAg correlates with high levels of viral replication.

All persons who do not acquire immunity are susceptible to HBV. Individual responses to HBV infection varies with age. Fewer than 10% of infected children under age 5 have initial clinical signs or symptoms of disease (i.e., acute hepatitis B), compared with 30% to 50% of older children and adults. The risk of developing chronic HBV infection also varies with age: approximately 90% of infants infected during the first year of life develop chronic infection, compared with 30% of children infected between ages 1 and 4 years and 5% of persons infected as adults^[3]. Male, cellular immune dysfunction, poor nutritional status are also associated with the risk of developing chronic infection.

Hepatitis B can be either acute or chronic. Acute hepatitis B virus infection is a short-term illness that occurs within the first 6 months of exposure. The case fatality of acute hepatitis B is around 0.5%^[4]. Acute infection rarely leads to chronic infection. Chronic Hepatitis B virus infection is a long-term illness and is a serious disease that can result in long-term morbidity, including cirrhosis, liver cancer (hepatocellular carcinoma), and even death. USA studies suggested that 90%-95% of newborns progressed towards chronic infections after being infected with HBV, and that of those, 15%-25% of persons with

chronic HBV infection were at risk for premature death from cirrhosis and liver cancer ^[5, 6]. Chronic hepatitis B infection is a lifelong condition for most patients. Hepatitis B is difficult to treat. Response rate ranges from 20% to 60% for those receiving anti-viral treatment such as lamivudine, adefovir, entecavir, tenofovir or pegylated interferon. The cost of treatment of chronic hepatitis B is high, ranging from 4,907-12,450 RMB per year in China. Patients suffering from cirrhosis face much higher expenses ^[7]. While hepatitis B is difficult to treat, it is preventable. Options include preventing exposures to the virus through safe sex, safe and appropriate use of blood, safe and appropriate use of injections, implementation of universal precautions and risk reduction among injection drug users. However, the most effective prevention measure for the entire population is active immunization through vaccination ^[8].

In the year 2000, Goldstein used a model to estimate that 620,000 persons died each year worldwide from HBV-related causes. This included 580,000 (94%) deaths from chronic infection-related complications (i.e., cirrhosis and HCC) and 40,000 (6%) deaths from acute hepatitis B ^[7,9]. In 2010, WHO endorsed these estimate as a basis for worldwide estimates ^[9, 10].

In 2001, a WHO report classified the world into three levels of endemicity based on HBsAg prevalence ^[11]. In areas of high endemicity (>8% HBsAg prevalence in the general population) such as Asia and Africa, the lifetime risk for HBV infection is 60% or higher and most infections are acquired at birth or early in life. In the absence of any preventive measures, more than 70%~90% of infants born to HBsAg and HBeAg positive mothers will be infected and develop chronic infections within one year after birth. When the mother is HBsAg positive and HBeAg negative, 10% infants will be HBsAg positive within one year after birth. Therefore, perinatal transmission is an important mode of transmission in Asia, and Africa. Aside from perinatal transmission, horizontal transmission between young children, particularly siblings, has been reported. Such transmission within family circles

probably occurs through repeated exposures to small quantities of blood (e.g., cuts, bruises, abrasions) or sharing of skin-piercing instruments (e.g., razors, "family syringe"). However, there is no evidence that casual contacts (e.g., in schools) leads to transmission of HBV. Most of these infections in early childhood are asymptomatic. However, rates of chronic liver disease and liver cancer are high ^[10]. In areas of intermediate endemicity (2%-8% HBsAg prevalence in the general population), the lifetime risk for HBV infection ranges from 20% to 60%, and infections occur in all age groups. Acute hepatitis B is common because many infections occur in adolescents and adults. However, high rates of chronic HBV infection are maintained primarily because of infections occurring in infants and children ^[12]. In areas of low endemicity (<2% HBsAg in the general population), the lifetime risk for HBV infection is less than 20%. For example, in 1999, the prevalence of chronic HBV infection in the United States was approximately 0.35% and approximately 5% of the general population had serologic evidence of HBV infection ^[12]. Most HBV infections in areas of low endemicity occur among adults engaging in high risk behaviours, but a high proportion of chronic infections may also occur as a consequence of perinatal and early childhood exposures ^[13]. Among global HBV associated deaths, 21% of were infected at birth, 48% in early childhood (<5 years old), and 31% were infected after the age of five. Overall, in 2009, a World Health Organization position paper reported that >2 billion people worldwide had been infected with HBV. Among those, 360 million people had current chronic HBV infection (6% of the global population, of which 2/3 lived in Asia, and 1/3 in China ^[10, 14].

In the WHO Western Pacific Region, HBV is often acquired at birth. It can also be contracted later in life through exposure during childhood or adulthood. The Western Pacific Region, home to 28% of the global population, suffers disproportionately from hepatitis B, containing around 45% of all infected individuals. Of the approximately 278,000 deaths

attributed to hepatitis B in the region, the greatest proportion is from the consequences of chronic liver disease - either cirrhosis or hepatocellular carcinoma.

1.2 Global milestones in vaccine development

The first vaccines to prevent hepatitis B were developed in the mid 1970's. Clinical trials conducted in the late 1970's reported efficacy greater than 90% in preventing chronic infection, and in 1981, hepatitis B vaccine was first licensed in the United States.

Since 1982, safe and effective hepatitis B vaccines have been commercially available. The first available vaccines were produced by harvesting HBsAg from the plasma of persons with chronic HBV infection. Subsequently, in 1986, the development of recombinant DNA technology to express HBsAg in other organisms offered the potential to produce unlimited supplies of vaccine. Recombinant DNA vaccines are now predominantly used in all countries. Hepatitis B vaccines are formulated to contain 3 μ g to 40 μ g of HBsAg per milliliter with an aluminum phosphate or aluminum hydroxide adjuvant. In 2010, there were 9 international manufacturers of hepatitis B vaccine and 6 domestic manufacturers in China (Table 1, Table 2).

Table 1: Hepatitis B vaccines available internationally (WHO pre-qualified) and in China, 2010

International market ^[15]			
Manufacturer	Brand name[†]	Country	Type
Berna Biotech Korea	Hepavax-Gene	South Korea	Recombinant DNA
Bio Farma	Vaksin Hepatitis B	Indonesia	Recombinant DNA
Center for Genetic Engineering and Biotechnology	Enivac-HB	Cuba	Recombinant DNA
GlaxoSmithKline	Engerix-B	Belgium	Recombinant DNA
	Tritanrix-HB	Belgium	Combined DTPwP and recombinant DNA
	Tritanrix-HB-Hib	Belgium	Combined DTPwP-Hib and recombinant DNA
LG Life Sciences	Euvac B	South Korea	Recombinant DNA
Merck Sharp &Dohme	Recombivax HB	United States	Recombinant DNA
Panacea Biotech	Enivac B	India	Recombinant DNA
Serum Institute of India	Genevac-B	India	Recombinant DNA
ShanthaBiotechnics	Shanevac-B	India	Recombinant DNA
China market			
Manufacturer	Brand name and Type		
GlaxoSmithKline	Engerix-B , Recombinant DNA		
Shenzhenkangtai	Hepatitis B vaccine made by recombinant DNA techniques in yeast		
Beijing Tiantan	Hepatitis B vaccine made by recombinant DNA techniques in yeast		
HuabeiZhiyao	Hepatitis B vaccine made by recombinant DNA techniques in Chinese Hamster Ovary cell		
Dalian Hanxun	Hepatitis B vaccine made by recombinant DNA techniques in HansenulaPolymorpha yeast		
Changchun Shengwu	Hepatitis B vaccine made by recombinant DNA techniques in Chinese Hamster Ovary Cell		
Lanzhou Shengwu	Hepatitis B vaccine made by recombinant DNA techniques in Chinese Hamster Ovary Cell		

1.3 Global milestones in programme development

Universal childhood immunization with three doses of hepatitis B vaccine in the first year of life is the most effective strategy to control hepatitis B. HBV vaccine became part of the recommended immunization schedule in the United States in 1991. There, it had been first recommended for use among high risk individuals, then scaled up for universal vaccination. In 1992, The World Health Assembly (WHA) set a goal for all countries to integrate hepatitis B vaccination into their routine childhood immunization programmes by 1997^[16]. In 1995, WHO suggested that countries and regions with HBsAg prevalence over 5% in population should implement the vaccination of all newborns with hepatitis B vaccine^[8]. Economic analyses on vaccination against hepatitis B in different populations in the USA^[17], Canada^[18] and other countries have confirmed the cost-effectiveness of this approach^[19-24]. In 2004, WHO recommended that countries opt for vaccination schedules including a birth-dose. In some cases, this monovalent first dose given at birth comes in addition of three doses given later in the form of combination vaccine^[25]. In 2009, 177 countries had integrated hepatitis B vaccine into routine immunization, and the coverage of timely hepatitis B vaccine birth dose (that is, given within 24 hours of birth) was recommended as a performance indicator for all immunization programmes^[14].

In the Western Pacific Region, South Korea was one of the first countries to begin manufacturing hepatitis B vaccine. Several nations/areas including Brunei Darussalam and Hong Kong introduced the vaccine in 1983^[26]. Most Pacific countries began using the vaccine by 1992, by which time the price had dropped significantly from 150 USD in 1980s to 15 USD in 1990s. In 2005, of the 25 of 37 countries in WPR reporting coverage data, 15 reported coverage greater than 85%. Only 4 of these 25 countries (Philippines, Papua New Guinea, Vanuatu and Vietnam) reported coverage of less than 70%. Of the remaining 11 countries/areas, one has chosen not to use the vaccine; four did not report progress and three

had only recently begun giving the vaccine. However, in 2005, WHO estimated that there were still around 3,824,000 infants in the Western Pacific Region each year not receiving full hepatitis B immunization, with nearly 66% of them living in China. In September 2005, Western Pacific became the first WHO Region to set a time-bound control goal for the reduction of chronic hepatitis B infection, hoping to reduce its prevalence to less than 2% among five-year-old children by 2012^[27]. In 2010, WHO estimated that there were only 0.956 million children not receiving hepatitis B vaccination in Western Pacific Region, with only 9% in China, indicating an impressive change (WPRO, unpublished data)^[27].

Table 2: Milestones in prevention and control hepatitis B in China and in the world, 1975-2010

Timeline		Chinese milestones			Key international milestones
		Burden of disease documentation	Vaccine development and production	Programme development and implementation	
Pre GAVI China years	1975		Clinical trial of vaccine		Clinical trials of vaccines
	1979	First national sero-survey			Clinical trials of vaccines
	1981				Hepatitis B vaccines become available
	1982				Hepatitis B vaccine used in the United States
	1985		Plasma derived vaccine licensed		
	1986			Pilot vaccination in partial counties	Recombinant hepatitis B vaccine available
	1991	Hepatitis B reported by type in the national disease reporting system			EPI Global Advisory Board recommends inclusion of hepatitis B vaccine in national immunization programmes in high endemicity countries by 1995 and in all countries by 1997 U.S. recommends universal vaccination of infants in 1991.
	1992	Second national serosurvey	Chinese Hamster Ovary vaccine licensed	Universal vaccination recommended, but with cost incurred by parents	World Health Assembly endorses EPI recommendation
	1993		Merck helps organizing a hepatitis B production line in China through technology transfer		
	1994				World Health Organization sets goal of 80% reduction in the incidence of new HBV chronic infections among children by the year 2001
	1996		Yeast-derived vaccine available		First regional conference on prevention and control of hepatitis B in Central and Eastern Europe
	1997		Hansenula Polymorpha technology available in Dalian		
	1998		Plasma derived vaccine production stopped		
	2000		Plasma derived vaccine use stopped		GAVI alliance established to help improve delivery of traditional childhood vaccines and introduce new ones
2001			China applied for GAVI support	World Health Assembly resolution sets new goal of 90% coverage with three-dose regimen of hepatitis B vaccine for all children by 2015	

Table 2: Milestones in prevention and control hepatitis B in China, 1975-2010 (Continued)

Timeline		Chinese milestones			Key international milestones
		Burden of disease documentation	Vaccine development and production	Programme development and implementation	
GAVI China years	2002			GAVI China project launched, auto-disable syringes used	
	2004			National EPI review	Third regional conference on prevention and control of hepatitis B in Central and Eastern Europe
	2005	Surveillance project in 18 counties		Free vaccination policy started	Hepatitis B control goal voted by the WHO WPR regional committee
	2006	Third national sero-survey		National hepatitis B action plan	
	2007			EPI enlarged to include a total of 14 vaccines (8 new antigens)	
Extension of GAVI China	2008			Extension of the GAVI China project, savings used for support to activities in under-performing areas	
	2009			Last year of the GAVI China project, catch-up campaign for children under 15	
After GAVI China	2010			Final evaluation of the GAVI China project	New WHO resolution on comprehensive approaches to prevention and control of viral hepatitis

2. Hepatitis B and its prevention in China

2.1 Progress in burden of disease documentation

In 1979, China conducted a national serosurvey. Results indicated that the prevalence of HBsAg was 8.9% among persons 1-59 years of age. Prevalence of HBsAg was 9.2% among children under 5 and peaked among children 5-9 (10.6%). HBsAg prevalence clustered among families. Families with more than one case of HBsAg infection accounted for 27.3% of the total. Within families, the HBsAg status of the parents, especially the mother, was strongly associated with the status of the children. The prevalence of HBsAg among children was higher in mother-positive families than that in mother-negative families^[28]. Although the HBsAg test used lacked sensitivity, HBsAg prevalence was higher in men than in women (10.3% among males versus 7.3% among females)^[29]. Overall, this suggested that hepatitis B was widely endemic in China, with most infections occurring among the youngest age groups. Furthermore, perinatal transmission was a major mode of transmission, and the high prevalence of HBsAg among children also contributed to the high burden of disease^[30,31].

In 1992, a second sero-epidemiological investigation of viral hepatitis in the whole country reported that 57.6% of the population had evidence of past or present HBV infection (Anti-HBc). The prevalence of HBsAg was 9.8% in the general population^[32]. The prevalence of HBsAg among children under 5 was as high as among persons above 15. This suggested a high frequency of perinatal transmission, in agreement with the results of the 1979 sero-survey. Based on these prevalence estimates, China CDC estimated that 690 million people had been infected with HBV in the country, and that among those, 120 million people were chronically infected^[32]. HBsAg prevalence was higher in men than in women (11.3% among males versus 8.2% among female in 1992) ($P < 0.01$). The prevalence of anti-HBs was also higher among men than among women (28.9% versus 27.5%, $p < 0.01$)^[29].

In 2005, a study documented the rates of progression from chronic hepatitis B towards cirrhosis and from cirrhosis towards hepatocellular carcinoma among chronic HBV infection. These rates at five year were 9% and 5%, respectively. In addition, the study suggested that 260,000 people died of hepatitis B related diseases each year in China ^[33], accounting for a third of global HBV-related deaths. Chinese studies also estimated that there were 30 million chronic hepatitis patients in the country, and about 250,000-300,000 persons dying of HBV infection-associated consequences each year. Among chronically infected patients in China, only a small number (0.6%-6.6% per year) become HBsAg negative each year ^[34]. Therefore, newborns constitute the priority group for hepatitis B prevention.

In 2005, a study conducted by the Chinese Foundation for Hepatitis Prevention and Control estimated that the cost of outpatient and hospitalized patients was 17,988 RMB (USD 2,500) each year for each case of chronic hepatitis B. Based on the estimated 20 million hepatitis patients in the country, the direct economic loss from hepatitis B is 360 billion USD each year, while Chen estimates the direct medial loss caused by hepatitis is up to 900 billion RMB (USD 128 billion) each year in China ^[35].

2.2 Progress in vaccine development

2.2.1 The development of hepatitis B vaccine

In 1975, China began the development of hepatitis B vaccines. In 1985, domestic plasma derived hepatitis B vaccine was licensed. In 1992, recombinant Chinese Hamster Ovary (CHO) cell Hepatitis B vaccine was developed and China imported a recombinant yeast hepatitis B production line from American Corporation Merck. In 1993, middle term testing was completed and in 1995, the State Food and Drug Administration (SFDA) allowed production for a yeast derived, recombination hepatitis B vaccine. In 1995, German Rheinland limited company developed the recombinant HansenulaPolymorpha Hepatitis B

vaccine, which improved the production capacity of vaccines. In 1996, China began producing hepatitis B vaccine using the technology transferred from Merck, and the production capacity rose to 60 million doses each year. In 1997, China developed and licensed recombinant *Hansenula* yeast engineered bacteria vaccine. Since then, recombinant *Hansenula* yeast engineering has been used widely in eastern China. In 1998, the Ministry of Health (MoH) stopped the production of haematogenous hepatitis B vaccine and in 2000, the MoH stopped using this plasma derived Hepatitis B vaccine. In 2010, Chinese hepatitis B vaccines produced in China included the recombinant hepatitis B vaccine from beer yeast, *Hansenula Polymorpha* and CHO cells ^[36].

2.2.2 Progress of hepatitis B vaccine introduction in China

In 1978, China began the expanded programme on immunization (EPI), and provided bacillus Calmette-Guerin (BCG), oral poliomyelitis vaccine (OPV), diphtheria, tetanus, and pertussis vaccine (DTP) and measles vaccine (MV). When plasma-derived hepatitis B vaccine became available in 1986, vaccination was only implemented among high risk populations in urban areas. No recommendations from the MoH framed this use. Vaccination took place on a voluntary basis and was paid for by users. Its price included the cost of the vaccine, the syringes and the administration fee.

In 1992, the China MoH recommended the introduction of Hepatitis B vaccine into routine immunization management. Although the national policy encouraged infant vaccination and timely birth dose, parents had to pay for the cost of the vaccine, which the government could not afford at that time. Because of the high cost, hepatitis B vaccination was only implemented among children living in rich and urban areas ^[37-39]. Coverage of three dose of hepatitis B vaccine reached 30% in 1992 ^[40,41]. Seven years later, in 1999, China conducted a national EPI review, which included a coverage survey. The EPI review also

addressed injection practices. Result indicated that hepatitis B coverage had increased to 70.7% overall (88.5% in urban areas and 62.7% in rural areas). The timely birth dose (TBD, the first dose given within 24 hours of birth) coverage was only 29% ^[42]. Coverage remained low overall, especially among children in the Western region and the poverty-affected counties of the Central region. Studies suggested that cost was one of the important factors that constrained vaccination. With respect to injection safety, grass root level clinics had comparatively high rates of unsafe injection practice. Disposable syringes were re-used and the level of knowledge about safe injection was poor ^[43]. Therefore, the Chinese government was eager to obtain funds to integrate hepatitis B vaccine into routine immunization and to improve injection safety. In 2002, following a Chinese application, the GAVI alliance provided the funds to pay for hepatitis B vaccine and injection devices in Western areas and in poverty-affected counties in the Central region. This provided the resources that were missing in China to fully integrate hepatitis B vaccine into routine immunization national wide.

3. The GAVI China project

3.1 Origins of the project

Since most chronic HBV infections were acquired early in life, universal vaccination for infants and children was a priority for China. In 2002, with support from the GAVI alliance, the central government fully integrated hepatitis B vaccine into routine immunization and provided free vaccine and syringes for all infants in the Western region and in poverty-affected counties in the Central region. China received GAVI support because of (1) high prevalence of HBsAg, (2) low vaccine coverage in areas where economic status was poor, (3) a gross domestic product (GDP) per capita < \$1,000 with a government that could not afford universal free vaccination and (4) political commitment to protect infants at risk.

3.2 The introduction of the GAVI China project

According to memorandum of understanding (MOU) that framed the GAVI China project, GAVI China supported the 12 Western project provinces (2002 population: 367 million). In addition, in the 10 middle provinces (2002 population: 507 million), GAVI China also supported 223 poverty-affected counties (2002 population: 107 million, 21% of the population of the middle provinces) (Table 3).

Table 3: GAVI China project support by region, 2002

Eastern (No GAVI fund)	Central (Partially funded)	Western (Fully funded)
Beijing, Fujian, Guangdong, Jiangsu, Liaoning, Shandong, Shanghai, Tianjin, and Zhejiang.	Anhui, Hainan, Hebei, Heilongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, and Shanxi.	Chongqing, Gansu, Guangxi, Guizhou, Neimenggu (Inner Mongolia), Ningxia, Qinghai, Shaanxi, Sichuan, Tibet, Yunnan, and Xinjiang

Source: China GAVI MOU

In GAVI supported areas, the project supported provinces through provision of hepatitis B vaccine and auto-disable (AD) syringes for all childhood vaccinations. The project covered 1,301 counties in 22 provinces for a total population of 470 million persons and an average birth cohort of 5.6 million each year. The goal of the project was to achieve universal infant hepatitis vaccination in GAVI project areas, reaching 85% coverage for three dose of hepatitis B vaccine and 75% for TBD at the county level. In addition, the project planned to introduce AD syringes to improve the safety of injection in all counties by the end of project.

GAVI alliance and the Chinese government shared funding responsibilities for the GAVI China project. Of the total GAVI China project funds of 76 million USD, 50% came from the international GAVI alliance and 50% came from the Chinese government. The GAVI China project funds covered 100% of the cost of the hepatitis B vaccine itself and 100%

of the cost of the AD syringes used for hepatitis B vaccination. In addition, with respect to the cost of AD syringes for other vaccines included in the national immunization programme, it funded (1) 70% of the cost in Western areas and in the poverty-affected counties of 6 Central provinces and (2) 50% of the cost in the poverty-affected counties of 4 other Central provinces. This additional support for injection safety over and beyond what was strictly necessary for hepatitis B vaccine was designed to facilitate transition from sterilizable syringes to AD syringes in the whole EPI system.

The MoH took the responsibility making arrangements with the Ministry of Finance for the flow and the management of funds. MoH also took responsibility for centrally-managed procurement, and for the coordination and monitoring of the procurement conducted by the provinces. Activities supported by the government at all levels included the routine EPI work, including logistics, health care workers, and surveillance. Aside from GAVI China project funds, additional government funding contributed to support new training needs, information and communication, project management, supervision and monitoring. The government also agreed to work towards improving the EPI reporting system at the county level to improve monitoring. At the central level, MoH and GAVI alliance created a project office, which was a unique model for project management. The national manager and an international project co-manager/consultant ran the project office, were responsible for routine work and developed the project indicator: the HepB3/DTP3 ratio and the DTP1/HepB1OT (Hepatitis B first dose on time) ratio. Since children who received DTP3 should also received three dose of hepatitis B vaccine and since children receiving DTP1 should also receive hepatitis B first dose on time, GAVI China was able to use these ratios as process indicators of the progressive introduction of hepatitis B vaccine into the EPI system. An Operational Advisory Group (OAG) of the project was constituted of the MoH, China CDC, GAVI alliance representatives, UNICEF, and WHO. The OAG met every year and made all key decisions

relevant to the GAVI project. Overall, the managerial structure of the GAVI project provided a conduit for policy dialogue and technical exchanges while the Chinese Government had full responsibilities over the implementation.

The government also ensured that the following inputs were available to the project:

(a) Local counterpart professional staff and other services, including national counterparts to operational experts;

(b) Land, buildings, training and other facilities available or produced within the country;

(c) Equipment, materials and supplies available or produced within the country.

3.3 The main project years (2002-2007)

3.3.1 Implementation

The investment: The scheduled investment of the GAVI China project amounted to 76 million USD, paid 50% by GAVI alliance and 50% by the government of China (300 million RMB). The central and sub-national levels shared a common responsibility, provided the co-funding to the project, including cost for AD syringes and operational cost of training, supervision, surveillance and management. Between 2002 and 2007, during project years, the central government invested 180 million RMB each year for hepatitis B vaccine and AD syringes in GAVI China project areas. Aside from the GAVI China contribution, the government invested a total of 227 million RMB for cold chain, surveillance, operational costs and Information, Education and Communication (IEC) costs during the project. The provincial governments in the Western and Central areas invested 96 million RMB for (1) co-funding for AD syringes and (2) operational cost of training, supervision, surveillance and management. Overall, from 2002 to 2007, the Chinese government invested an additional 203 million RMB in the GAVI China project in addition to the original 300 million given as the

50% contribution of China to the GAVI China project. Using the GAVI China funds, between 2002 and 2007, the GAVI China project provided 29,282,364 person doses of hepatitis B vaccine (one person-dose=three doses, enough to fully vaccinate one person), 206,649,679 auto-disable (AD) syringes, and 150,154 safety boxes (Table 4).

Strategies: In collaboration with GAVI China, the Government of China implemented a number of activities, including (1) increasing awareness of the importance of TBD 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 for hospital deliveries, (5) building bridges between delivery service (maternal and child health, MCH) and vaccination service (EPI) and (6) subsidizing providers.

Social mobilization: The GAVI China project developed IEC material and conducted social mobilization activities in 22 provinces. Data from 22 provinces between 2002 and 2009 indicated that provinces invested 4.45 million RMB, 200 prefectures invested 8.28 million RMB, and 1,301 counties invested 55.62 million RMB for social advocacy, media, posters, and banners to deliver information to the public.

Training: Between 2002 and 2009, the GAVI China project office at the national level conducted 5 workshops and trained 540 participants from 22 provinces. 22 provinces conducted 328 workshops and trained 36,610 professionals. 200 prefectures conducted 2,754 workshops, and trained 119,122 professionals. 1,301 counties conducted 25,671 workshops and trained 991,542 professionals. Finally, 23,047 townships conducted 114,358 workshops, and trained 5,350,879 village doctors. All HCWs at each level received at least one training during the project period (Table 5 and Table 6).

During 8 years of project implementation, 193,000 health care workers in 118,316 health care facilities participated in the project, mostly at the township hospitals level (55,051)

and in health community centers (104,547). In each county of the Western region, as a result of Government co-investment in EPI, EPI staff increased from an average 29 in 2002 to 66 in 2009 number of workers. GAVI China project areas also benefitted from training, supervision and capacity building.

Table 4: Inputs of GAVI China project, from the GAVI Alliance and the Government of China, data are shown in RMB (2002-2007)

	Items	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total
Funds disbursements in RMB	Vaccine	56,103,663	45,198,130	35,999,817	36,000,000	20,780,322	1,241,600				195,323,532
	AD syringes	10,890,337	26,471,593	12,910,952	13,381,463	9,678,134	24,047,643				97,380,123
	Serosurvey					4,440,000					4,440,000
	Catch-up campaign and Demonstration project to improve TBD							50,332,459		56,300,000	106,632,459
	Information system									53,550,000	53,550,000
Commodities procured	Vaccine*	7,099,340	6,325,925	5,038,488	5,142,858	5,355,753	320,000				29,282,364
	AD syringes	21,298,022	49,419,810	24,958,904	31,718,178	18,258,244	60,996,521				206,649,679
	Safety boxes		150,154								150,154
	Needle cutters										0
Input per live birth	GAVI China project Birth cohort	5,843,662	5,680,529	5,481,887	5,406,975	5,422,372					27,835,425
	Vaccine doses/birth	1.21	1.11	0.92	0.95	0.99					-
	AD syringes/birth	3.64	8.70	4.55	5.87	3.37					-
Government co-funding	Province level	100,000	5,766,000	11,505,000	14,108,100	18,236,400	22,492,300	6,821,600	16,831,700		95,861,100
	National level			17,260,000	24,610,000	40,400,000	25,970,000	43,921,213.2	37,414,366.8	37,414,366.8	226,989,947

* 1 person dose= 3 doses

In 2002, AD syringes were procured for hepatitis B vaccine only, in 2003, AD were procured for two years.

1 USD=7.28-8.28 RMB (2002-2007)

Table 5: Summary of the training sessions conducted during the implementation of the GAVI China project, 2002-2009

Year	Provincial		Prefecture		County		Township	
	# Training sessions	# persons trained						
2002	28	1,760	128	3,210	1,197	34,338	5,357	116,446
2003	31	13,988	292	9,671	2,789	104,741	12,924	677,504
2004	46	3,118	314	10,370	2,969	99,186	13,097	660,238
2005	49	3,743	335	13,593	2,862	109,728	16,919	676,713
2006	55	3,120	391	14,286	3,828	130,591	16,607	756,633
2007	31	3,108	360	15,401	3,716	142,498	15,647	754,459
2008	39	3,274	436	20,236	3,957	174,832	18,293	824,583
2009	49	4,499	498	32,355	4,353	195,628	15,515	884,303
Total	328	36,610	2,754	119,122	25,671	991,542	114,359	5,350,879

Table 6: Content of the training sessions and targeted participants, GAVI China project implementation, 2002-2009

Year	Training material	Targeted participants
2002	1. Project implementation and management 2. Vaccine and AD management	Project managers of provinces
2003	1. Injection safety and improving training for use of AD syringes 2. Hepatitis B vaccination and data reporting	National training for provincial project managers and enhanced training in Tibet, Qinghai , Ningxia and Chongqing
2004	1. Evaluation of training on hepatitis B and injection safety 2. Training of the Trainers (TOT) to improve skills on immunization with hepatitis B vaccine and safe injections	Provincial staff from CDC and health bureau
2005	1. Training to update the knowledge of safe injection and to improve the practice of AD syringe use 2. Meeting to exchange experiences 3. Middle term evaluation	Provincial staff
2006	1. Safe injection training courses to update knowledge and improve the practice of AD syringe use. 2. Data management	Provincial staff
2007	1. Experience regarding improving timely birth dose 2. Data auditing and programme monitoring	Provincial staff
2008	Guideline for GAVI China savings utilization and evaluation	Provincial staff
2009	Guideline for GAVI China savings utilization and evaluation	Provincial staff

3.3.2 Policy decisions

In 2002, hepatitis B vaccine was integrated into China's national immunization programme. Since then, hepatitis B vaccine and AD syringes for infants have been provided for free either through GAVI China project in Western region and poverty-affected counties in Central region, or by the provincial government in other counties in the Central region and Eastern regions. However, user fees (around 1 USD for three doses) were still charged until 2005. The regulation on "Vaccine Circulation and Vaccination Management" issued in 2005 by the Ministry of Health recommended recombinant yeast hepatitis B vaccine or recombinant CHO hepatitis B vaccine for use in China with an immunization schedule of '0, 1, 6', which required immunization of infants 24 hours after birth, 1 month after birth and 6 months after birth, respectively.

In 2005, the State Council issued the regulation on "Vaccine Circulation and Vaccination Management," which required implementers to give all vaccines integrated into routine immunization at no cost^[44]. Since June 1, 2005, a national policy banned the user fee and all hepatitis B vaccination has been provided to all newborns for free. This important document assured the sustainability of EPI and indicated that hepatitis B vaccination of infants was the responsibility of the government^[45, 46].

In 2006, to strengthen the prevention and treatment of hepatitis B, the MoH classified hepatitis B as one of the four key diseases (the others being AIDS, TB and schistosomiasis) and issued the 2006-2010 National Plan on Hepatitis B Prevention and Control (January 2006)^[47]. The objectives of the plan were to (1) preferentially protect the neonates and the most susceptible populations through prevention, (2) reduce the incidence of hepatitis B, (3) decrease HBsAg prevalence in China and (4) reduce the mortality caused by cirrhosis and/or cancer of the liver resulting from hepatitis B by 2010. Multiple year guidelines were issued between 2006 and 2010.

Since 2006, in collaboration with the Ministry of Education, the MoH carried out regular school entrance immunization checks to provide a second opportunity for those who had missed vaccination at an earlier age.

In 2007, the government of China integrated 14 vaccines into its national immunization programme and provided funding for all vaccines (including hepatitis B vaccine) and AD syringes for all provinces.

In 2007, GAVI China planned a catch-up campaign for children under 5 years (born after GAVI China project) starting in 22 provinces, and completing it in 2008, immunizing 1 million children (Table 7).

3.3.3 Remaining problems: Need for programme activity funds

According to the project memorandum of understanding, the GAVI China funds only paid for the cost of hepatitis B vaccine and the cost for AD syringes during the years of the project (i.e., equipment and supplies). However, because of imbalances in economic situations in the various areas of China, there was often a shortage of operational funds at the prefecture and county level that affected training, supervision and monitoring. The local health bureaus did not fully pay subsidies to HCWs and as a result, HCW did not have incentives to work on vaccination. Thus, limitations on the use of GAVI China funds for activities became a bottleneck for vaccination. Health departments needed enough program activity funds to ensure universal hepatitis B vaccination.

During the project implementation, several reasons resulted in GAVI savings. Those included (1) smaller birth cohorts than originally estimated, (2) lower price of vaccine and AD syringes, and (3) the national government paying its full share from beginning. This left GAVI China funds unspent. Hence, from 2006 onwards, GAVI China savings were assigned to support operational costs in low performing areas with flexibility given for expenditure so

that human resources could also be covered. In 2006, as part of this GAVI China saving expenditure plan, 4.44 million RMB was used to conduct a national wide serosurvey to monitor the HBsAg prevalence among the population aged 1-59, and to evaluate the impact of vaccination for children born after 1992 (when hepatitis B vaccine was integrated into EPI management). The results of this serological survey are reported in Chapter 2, 3 and 4.

3.4 The extension years (2008-2009)

The original project duration was 5 years from 2002 to 2007, but because of savings accumulated during implementation, GAVI alliance and MoH made an agreement to expand the project to the end of 2009, which allowed China to spend all savings while focusing on strengthening programme activities. As a result, China went through four stages of hepatitis B vaccine integration into routine immunization.

First, between 1992 and 2001, parents were charged the vaccine and the user fee.

Second, between 2002 and 2005, parents were only charged the user fee.

Third, between 2005 and 2007, all vaccination was provided for free. Policy support from the national government assured sustainable funding for hepatitis B vaccination, which not only provided for the cost of vaccines and syringes, but also the cost of the subsidies to the health care providers

Fourth, from 2008 onwards, the Central government took over the cost of vaccine and AD syringes in the whole country. Hence, GAVI China project savings allowed the provision of operational funding to improve timely birth dose, catch-up campaign, and support hepatitis B vaccination relevant activities such as training and social mobilization(Box 1).

In addition, GAVI China project office monitored immunization coverage by county using the indicators of HepB3/DTP3 and HepB1OT/DTP1, and provided specific activities in low performance prefectures and poverty-affected counties, including training, supervision,

and demonstration projects. In 2008, the GAVI China project allocated 50 million RMB in savings to all 666 national poverty-affected counties. This enhanced training and supervision for better performance in counties and provided special support to those low performance prefectures where it provided funds to improve the timely birth dose, train health professionals, conduct supervisions, and implement social mobilization. In addition, GAVI China provided 28 million in 666 poverty-affected counties to conduct the campaign among children born after 2002 (Table 7).

In 2009, the national government started to conduct catch-up immunization for children under 15 years of age, and GAVI China provided savings for operational costs in 22 provinces. Altogether, 62 million children were targeted for vaccination in 2009, 2010 and 2011 (Table 7). The costs for the vaccine and injection equipment were entirely covered by the MoH.

3.5 The final extension year (2010)

At the end of 2009, funds remained in the GAVI China account because (1) the Chinese government decided to cover the main costs of the catch up vaccination for children under 15 years of age and because (2) the H1N1 pandemic slowed down use of the GAVI China funds in 2009. Hence, in 2010, another calendar year of extension was negotiated between GAVI alliance and MoH to spend left over funds. This allowed MoH to have one last year to use the GAVI China savings. A major component of the use of the GAVI China savings for the last year was an investment in the Chinese information management system (53.55 million RMB, 43% of the final savings). In addition, other activities included project evaluation and other activities to facilitate a smooth closure of GAVI China and to spend the last of GAVI China project savings. Those included (1) pilot projects for timely birth dose administration, (2) IEC activities, and (3) operational funds for the catch up campaign in poor areas. These GAVI

China project savings also provided 32.7 million RMB to fund programme operations for the catch-up campaigns in 22 provinces (there was no need for vaccine and AD syringe funding since the Chinese government already paid these costs) and provided 23.6 million RMB for improving timely birth dose in 29 prefectures with timely birth dose <75% (Table 8).

Table 7: Summary of the hepatitis B catch up vaccination activities among children in China, 2008-2011

Year	Location	Objective	Implementation strategy	Target population	Children reached	Funding
2002-7	16 provinces	Improve coverage	School entrance and routine immunization	Children under five years of age	8 million	Government funds and cost recovery
2008	666 poverty-affected counties in Western and Central areas (GAVI-supported areas)	Immunize children born after project launch who had missed vaccination	Catch-up campaign	Children born between 2002 and 2004 (Under five years of age)	1 million	GAVI China (Vaccine, AD and subsidies)
2009-11	Nationwide	Immunize all children under 15	Catch-up campaign	Children born between 1994 and 2001	62 million	Government of China (Vaccine and AD) GAVI China savings (Operational costs in GAVI supported areas)

Box 1: Policy decisions relevant to hepatitis B vaccine introduction, China, 1992-2008

Year	Key decisions	Subsequent situation	
		Progress	Remaining issues
1992	Hepatitis B vaccine included in EPI management	China government takes responsibility for administration of the vaccine and monitors coverage	Parents charged the vaccine, the syringe and the user fee
2002	Hepatitis B vaccine fully integrated into EPI, with vaccine and syringes free of charge	Vaccine and syringes provided for free	Parents still charged a user fee
2005	Users fee abolished through provision of subsidies to vaccinators by the central government	All vaccination provided for free	Hepatitis B vaccine and syringes still funded though GAVI China in GAVI-supported areas
2008-	Central government took over the cost of vaccine and AD syringes in the whole country, provided operational funding and subsidies	Sustainability ensured	Additional efforts needed to reach the unreached (e.g., remote, rural areas, migrant)

Table 8: Funding envelopes from the GAVI China savings approved for use by the OAG (million RMB)

	Sero-survey	IEC	Training and supervision	Activities for the catch up campaigns	Birth dose pilot project	Final evaluation	End of project activities	Information system	Total
2006	4.44	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.44
2007	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2008	0.00	1.38	11.07	27.89	10.00	0.00	0.00	0.00	50.34
2009	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2010	0.00	6.80	0.00	32.70	23.60	3.70	4.78	53.55	125.13
Total	4.44	8.18	11.07	60.59	33.60	3.70	4.78	53.55	179.91

3.6 Wrapping up the GAVI China project

In 2010, GAVI China office started to implement a package of activities to ensure a smooth closure of the project, according to the agreed upon goals. These activities included:

- ✓ Conducting a final evaluation to evaluate the input, process, the output, outcome and impact of the GAVI China project.
- ✓ Conducting a scientific review, bringing back the various stakeholders of the project to document achievements and provide vision in terms of the next challenges in viral hepatitis prevention and control in China.
- ✓ Developing an advocacy package on the success of the GAVI China project, including a movie, calendar posters, and media advertisement.
- ✓ Auditing the financial management of the project
- ✓ Conducting an external evaluation before project closure.
- ✓ Organizing a high level summary meeting for the project closure.
- ✓

3.7 Need of an evaluation

A high quality evaluation of the GAVI China project was important for a number of reasons. First, GAVI China received a large investment from the GAVI alliance and from the Government. Second, the GAVI Alliance and the Government of China needed a good understanding of the relations between input, process, output, outcome and impact. This information regarding returns on investment could impact future commitment in the field of immunization. Third, documentation of the work in promoting timely birth dose could help WHO and other partners regaining support from the GAVI Alliance (As global support to this area of work has been minimal in the recent years). Fourth, China evaluations on timely birth dose and equity in immunization are relevant to many countries in the Western Pacific region that struggle to meet immunization targets largely due to challenges with reaching their

impoverished populations. Fifth, the Government of China wanted to seize the opportunity to generate a comprehensive evaluation for this large-scale programme. Such comprehensive evaluation for large-scale programmes are often not undertaken because of a lack of resources, a lack of time, or simply because interventions are assumed to be effective. However, the complexity and multiple simultaneous factors influencing outcome should not deter public health stakeholders from trying to document these situations in the best possible way.

The various evaluation elements of the China GAVI project were brought together as a single piece of work. While some components of the GAVI evaluation were conducted in 2006 (the serological survey), others were conducted in 2010 using the last portion of the GAVI savings. The overall objectives of the evaluation work were to measure the progress and to learn the achievements and challenges of the project. The evaluation included reviewing the project documents (including GAVI annual project reports), conducting field investigations, interviewing HCWs and parents and analyzing the vaccine coverage data available. This evaluation was organized according to a logic model (Box 2).

Structural elements that were essential to the project included (1) its integration with the National Immunization Programme (NIP), (2) its cooperative management based on a national and international co-manager and an Operational Advisory Group (OAG) that made all the key decisions, (3) the domestic procurement and (4) the decentralized implementation at the provincial level and below.

Elements of the GAVI China project included (1) hepatitis B immunization, including timely birth dose, (2) injection safety and (3) social mobilization and training.

With respect to **hepatitis B immunization**, input included the GAVI China project funds to supply vaccine and the subsidies to the health care workers after 2005. These were used by the immunization services (process) to obtain programmatic outputs that included

timely administration of the first dose within 24 hours and completion of the three-dose series. The national immunization programme schedule was shown in box 3. Both of these resulted in immunity in the population (outcome).

With respect to **injection safety**, input included the GAVI China project funds to supply auto-disable syringes, safety boxes and needle cutters. These were used by the immunization services (process) to administer safe injections (output), which resulted in the reduction of injection-associated infections (outcome).

With respect to **social mobilization and training**, input included the resources assigned locally for Information, Education and Communication (IEC). Most of those were not directly funded by GAVI alliance but leveraged during the implementation of the project. These were used to train health care workers and produce material (process) that resulted in better knowledge but also in higher immunization coverage and safer injections (output).

Ultimately, the output of the elements of the GAVI China project combined at the **impact** level to prevent HBV infections, which led to prevention of cirrhosis and hepatocellular carcinoma and ultimately to the prevention of early deaths and benefit in terms of disability-adjusted life years (DALYs).

While the introduction of this dissertation reviews the input into the GAVI China project, chapters 1 to 7 will examine process, output and impact. In the report, we describe what the GAVI China project has done with respect to immunization, injection safety and social mobilization and the input, process, the output, outcome and impact of the GAVI China project to hepatitis B vaccination and safety injection in China (Box 2).

Box 2: Logic model of the GAVI China project, 2002-2009

Structure	<ul style="list-style-type: none"> - Integration within the National Immunization Programme - Management structure (Advisory Operational Group), national and international co-managers - National procurement - Decentralized management 		
Elements	Immunization against hepatitis B	Social mobilization and training	Injection safety
Input	<ul style="list-style-type: none"> - Funds for hepatitis B vaccine - Subsidies to health care workers (from 2005) 	<ul style="list-style-type: none"> - IEC material - Funds disbursed 	<ul style="list-style-type: none"> - Funds for AD syringes - Funds for safety boxes
Process	<ul style="list-style-type: none"> - Immunization services - Hospital deliveries 	<ul style="list-style-type: none"> - People trained 	<ul style="list-style-type: none"> - Use of AD in EPI - Use of safety boxes in EPI - Use of needle-cutters
Output	<ul style="list-style-type: none"> - Timely birth dose - Completion of three dose hepatitis B vaccine schedule 	<ul style="list-style-type: none"> - Knowledge 	<ul style="list-style-type: none"> - Safe injections
Outcome	<ul style="list-style-type: none"> - Immunity in the population 	<ul style="list-style-type: none"> - No injection associated infections 	
Impact	<ul style="list-style-type: none"> - Infections prevented - Cirrhosis/Hepatocellular carcinoma cases prevented - Deaths prevented - DALY averted 		

4. Goals and objectives

The goal of this work was to review the process of hepatitis B introduction, develop an evidence base upon which countries could make decisions regarding national policies for the new vaccine introduction. The specific objectives included:

1. Describe the progress in hepatitis B prevention through universal infant vaccination- China, 1997-2006 (Chapter 1)

2. Evaluate the impact of hepatitis B vaccination among children born during 1992–2005 in China (Chapter 2)

3. Describe the prevalence of hepatitis B among general population aged 1-59, to describe the strength of the association between HBV prevalence and Hepatitis B vaccination (Chapter 3)

4. Determine the factors associated with effectiveness of the first dose of hepatitis B vaccine in China -1992-2005 (Chapter 4)

5. Evaluate the inequities in hepatitis B prevention: results from final evaluation of the GAVI China project (Chapter 5)

6. Assess the immunization injection safety in China, 2010: progress and residual challenges (Chapter 6)

7. Examine the status of progress towards the elimination of mother to child transmission of hepatitis B virus in China (Chapter 7)

Box 3: Vaccination schedule for the National Immunization Programme, China, 2007

Vaccine	Age of Targets	Number of doses	Site of vaccination	Vaccination route	Dosage /dose	Remark
Hepatitis B vaccine	0, 1, 6 month	3	Upper arm deltoid	Intramuscular injection	Yeast vaccine 5µg/0.5ml, CHO vaccine 10µg/1ml, 20µg/1ml	The first dose should be immunized within 24 hours after birth, the interval between the first dose and the second dose is not less than 28 days (Figure1)
BCG	At birth	1	Lower part of the middle in upper arm deltoid	Intra-dermal injection	0.1ml	
Poliovirus vaccine	2, 3, 4 months, 4 years old	4		oral	1 granule	The interval between the first and the second dose, the second and the third dose is not less than 28 days
Diphtheria-Tetanus -Pertussis-Vaccine (DTaP)	3, 4, 5 months 18-24 months	4	Deltoid in the lateral side of upper arm	Intramuscular injection	0.5ml	The interval between the first and the second dose, the second and the third dose is not less than 28 days
Diphtheria Tetanus vaccine	6 years	1	Upper arm deltoid	Intramuscular injection	0.5ml	
Measles Rubella vaccine (MR)	8 months	1	Attachment site of the lower border of lateral deltoid in upper arm	Subcutaneous injection	0.5ml	
Measles Mumps and Rubella vaccine(MMR)	18-24 months	1	Attachment site of the lower border of lateral deltoid in upper arm	Subcutaneous injection	0.5ml	

Box 3: Vaccination schedule for the National Immunization Programme, China, 2007 (Continued)

Vaccine	Age of Targets	Number of doses	Site of vaccination	Vaccination route	Dosage /dose	Remark
Japanese encephalitis live attenuated vaccine	8 months, 2 years	2	Attachment site of the lower border of lateral deltoid in upper arm	Subcutaneous injection	0.5ml	
Inactivated Japanese B encephalitis vaccine	8 months (2 doses, 2 years, 6 years	4	Attachment site of the lower border of lateral deltoid in upper arm	Subcutaneous injection	0.5ml	The interval between the first and the second dose is 7-10 days
Epidemic cerebrospinal meningitis group A vaccine	6-18 months	2	Attachment site of lateral deltoid in upper arm	Subcutaneous injection	30µg/0.5ml	The interval between the first and the second dose is 3 months
Epidemic cerebrospinal meningitis group A plus C vaccine	3 years, 6 years	2	Attachment site of lateral deltoid in upper arm	Subcutaneous injection	100µg/0.5ml	The interval of the two doses is not less than 3 years, the interval between the first and the second dose of epidemic cerebrospinal meningitis group A vaccine is not less than 12 years
Live attenuated hepatitis A vaccine	18 months	1	Attachment site of lateral deltoid in upper arm	Subcutaneous injection	1ml	
Inactivated hepatitis A vaccine	18 months, 24-30 months	2	Attachment site of deltoid in upper arm	Intramuscular injection	0.5ml	The interval between 2 doses is not less than 6 months

Note: 1. The dosage of CHO vaccine used to prevent mother to child transmission is 20µg/ml.

2. The vaccination site, route and dosage of vaccines which are not in pharmacopeia refer to the instructions of vaccines.



Figure 1: Healthcare provider vaccinating a new born against hepatitis B within 24 hours after birth, Gansu, 2005

Methods

Methods used to achieve the objectives at each chapter:

1. A review of national EPI reviews conducted in 1997, 1999 and 2004 and the present data to evaluate progress on hepatitis B introduction (Chapter 1);
2. National serosurvey to evaluate the prevalence of HBV and the association between prevalence of HBsAg and hepatitis B vaccination (Chapter 2 and 3);
3. Sub-group analysis of the serosurvey to evaluate the factors associated with effectiveness of timely birth dose (Chapter 4);
4. A national evaluation to examine the equity of hepatitis B vaccination, the progress of safety injection and progress towards the elimination of mother to child transmission of hepatitis B virus in China (Chapter 5, Chapter 6, Chapter 7).

Box 4: Data collection methods, GAVI China project evaluation, 2002-2009

	Indicators	Data collection methods
Input	- Funding support	- Annual reports from the provinces - Field supervision
Process	- Birth cohort - People trained - Vaccine allocated - AD syringes allocated	- Birth Registration - Annual report from the provincial GAVI China office - Final project report from the provincial GAVI China office - MoH/GAVI office
Output	- Vaccine coverage - HepB3 and TBD	- Reported: GAVI China office - Estimated: GAVI China office - Surveyed: Final evaluation
	- AD syringes used	- Final evaluation survey
Outcome	- Anti-HBs Prevalence - HBsAg prevalence	- National serological survey (2006)
Impact	- HBsAg prevalence - Morbidity from cirrhosis and HCC	- National serological survey (2006) - Published data from China

Results

1. Chapter 1: Progress in Hepatitis B Prevention Through Universal Infant Vaccination- China, 1997-2006.
2. Chapter 2: Evaluation of the Impact of Hepatitis B Vaccination among Children Born during 1992–2005 in China
3. Chapter 3: Epidemiological Serosurvey of Hepatitis B in China - Declining HBV Prevalence due to Hepatitis B Vaccination
4. Chapter 4: Factors Associated with Effectiveness of the First Dose of Hepatitis B Vaccine in China -1992-2005
5. Chapter 5: Reducing inequities in hepatitis B prevention: A final evaluation of the GAVI China Project
6. Chapter 6: Immunization injection safety in China, 2010: Progress and residual challenges
7. Chapter 7: Progress towards the elimination of mother to child transmission of hepatitis B virus in China: Results from GAVI China project Final evaluation (Table 9)

Table 9: Presentation of the results as per the larger evaluation plans

Chapters	Content	Relevance to evaluation plans	
		Level of the logic model	Intervention elements
Chapter 1	Mid-term progress in coverage	- Structure - Process - Output	- Hepatitis B immunization
Chapter 2	Serological survey among children targeted by vaccination	- Outcome - Impact	- Hepatitis B immunization
Chapter 3	Serological survey in the whole population	- Outcome - Impact	- Hepatitis B immunization
Chapter 4	Factors associated with effectiveness of birth dose	- Process - Output - Outcome - Impact	- Hepatitis B immunization, more specifically, prevention perinatal infections
Chapter 5	Coverage progress in terms of equity	- Output	- Hepatitis B immunization - Social mobilization and training
Chapter 6	Injection safety assessment	- Output	- Injection safety
Chapter 7	Progress in prevention of perinatal infections	- Output	- Hepatitis B immunization, more specifically, prevention perinatal infections - Social mobilization and training

1. Chapter 1: Progress in Hepatitis B Prevention through Universal Infant Vaccination-

China, 1997-2006*

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Contribution statement:

Cui Fuqiang led the data collection, data analysis and drafted the manuscript. Wang Xiaojun participated in the design of the vaccination project, Cao Lei analyzed the data, Liang Xiaofeng reviewed the manuscript, Lu Yong and Hu Yuansheng coordinated the data collection, Stephen Hadler analyzed the data and guided the writing. Craig Shapiro, John ward and Steve Wiersma reviewed the manuscript.

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Hepatitis B virus (HBV) infection is a leading cause of illness and death in China. Approximately 60% of the population has a history of HBV infection, and 9.8% of persons in China are chronically infected with HBV and at risk for premature death from liver disease^[32]. Each year, an estimated 263,000 persons in China die from HBV-related liver cancer or cirrhosis, accounting for 37%–50% of HBV-related deaths worldwide^[48]. Because most HBV infections occur during infancy or early childhood, when HBV infection is most likely to become chronic, vaccination of infants beginning at birth is the key strategy for preventing chronic HBV infection. This report describes China's progress in increasing coverage among infants with hepatitis B vaccine and timely administration of the hepatitis B vaccine birth dose (i.e., within 24 hours of birth). Infant vaccination coverage with both the timely birth dose and the complete vaccine series was substantially higher among children born during 2003 than among those born during 1997; timely birth-dose coverage increased from 29.1% to 75.8%, and HepB series completion increased from 70.7% to 89.8%. Furthermore, in economically disadvantaged populations in western and middle provinces[†] targeted by the China-Global Alliance for Vaccines and Immunization (China-GAVI) project, reported coverage with timely HepB birth dose increased from 64% in 2004 to 81% in 2006, and coverage with the complete HepB series increased from 52% in 2001 to 92% in 2006. China has established a goal to reduce chronic HBV infection among children aged <5 years to <1% by 2010^[49]. Achieving this goal will require continued commitment to increasing vaccination coverage in impoverished regions and ensuring that infants born at home are vaccinated within 24 hours of birth.

[†] China-GAVI-funded western provinces: Chongqing, Gansu, Guangxi, Guizhou, Neimenggu (Inner Mongolia), Ningxia, Qinghai, Shaanxi, Sichuan, Tibet, Yunnan, and Xinjiang; middle provinces with GAVI funding in government-designated poor counties: Anhui, Hainan, Hebei, Heilongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, and Shanxi.

Hepatitis B Immunization Program

HepB was first recommended for routine vaccination of infants in China in 1992, with the first dose to be administered within 24 hours of birth and subsequent doses at ages 1 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.[‡] Beginning in 2002, infant hepatitis B vaccination was added to China's National Immunization Programme. Also in 2002, the China Ministry of Health began a project with the GAVI Alliance[§] (formerly known as the Global Alliance for Vaccines and Immunization) to ensure HepB availability in China's poorest provinces and counties. The 5-year China-GAVI project provides free HepB, 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. In 2005, a new vaccination regulation abolished all charges and user fees for all nationally recommended vaccines, including hepatitis B; the vaccine is now free to all children in China. To estimate national 3-dose HepB coverage and timely (i.e., within 24 hours of birth) HepB birth-dose coverage and to describe the effects of province and location of birth (e.g., home versus hospital) on vaccination coverage levels, data from two national vaccination coverage surveys conducted by the China Ministry of Health in 1999 and 2004 were reviewed. In both 1999 and 2004, parents were interviewed in house-to-house surveys regarding the vaccination status of eligible children born during the study periods. Sampling of households in each province was conducted using the probability proportional to size (PPS)

[‡] Eastern provinces: Beijing, Fujian, Guangdong, Jiangsu, Liaoning, Shandong, Shanghai, Tianjin, and Zhejiang.
[§] Additional information regarding the GAVI Alliance is available at <http://www.gavialliance.org>.

method. In the 1999 survey, counties in each province were divided into four economic strata, and PPS sampling was conducted within each strata. In 2,173 counties in 31 provinces, parents of 25,878 children born during 1997 were interviewed ^[50]. In the 2004 survey, 273 counties were selected randomly from all counties throughout the country, including at least three counties in each province, and PPS sampling was conducted in each county; parents of 171,188 children born during 2001–2003 were interviewed ^[51]. For both surveys, 3-dose HepB and timely HepB birth-dose coverage were measured by dividing the number of children receiving 3-dose HepB and timely HepB birth dose, respectively, by the number of children surveyed, taking into account the PPS sampling design. To examine in more detail the impact of the China-GAVI project, routine immunization-reporting-system data from 2001 through 2006 for China-GAVI-funded provinces were reviewed. In this national reporting system, the numbers of children targeted for and receiving each dose of routinely recommended vaccines are compiled by each immunization clinic and reported monthly to provincial and national immunization programs. For this analysis, 3-dose HepB and timely HepB birth-dose coverage in China-GAVI-funded provinces were measured by comparing the ratio of the number of children receiving doses of HepB to the number of children targeted to receive doses of diphtheria, tetanus, pertussis (DTP) vaccine, because the latter represents the most accurate local estimate of the number of children requiring routine childhood vaccination. Timely HepB birth-dose coverage could only be analyzed from 2004 through 2006 since reporting of HepB birth-dose timing was not required by the China Ministry of Health until 2004. A mathematical model was used to calculate hepatitis B disease burden before inception of the vaccination program and to estimate the number of deaths prevented through vaccination ^[32, 48].

National Vaccination Coverage Survey

Comparison of the two national vaccination coverage surveys indicated that estimated 3-dose HepB coverage increased substantially overall, from 70.7% among children born in 1997 to 89.8% among children born in 2003 (Figure 2). Timely HepB birth-dose coverage also increased, from 29.1% among children born in 1997 to 75.8% among children born in 2003 (Figure 1). During 1997–2003, estimated national 3-dose DTP coverage remained level (93%). The difference between 3-dose HepB coverage and 3-dose DTP coverage was reduced from 20% in 1997 to 3% in 2003.

In the 2004 survey, estimated coverage was substantially lower in western provinces (68.0% for 3 doses of HepB and 49.5% for timely birth dose) than in middle provinces (91.8% for 3 doses of HepB and 72.7% for timely birth dose) or eastern provinces (94.1% for 3 doses of HepB and 81.9% for timely birth dose) (Figure 3). Timely birth-dose coverage among infants born at home during 2001–2003 was less than half that of those born in hospitals. Among children born in 2004, timely birth-dose coverage for infants born in township hospitals was only two thirds that of those born in county, provincial, or national hospitals.

China-GAVI Project

For the period 2003–2006, 3-dose HepB coverage and timely HepB birth-dose coverage increased in the 12 western provinces and in the counties in 10 middle provinces supported by the China-GAVI project. In 2006, the ratios of 3-dose HepB/3-dose DTP coverage and timely HepB birth dose/first-dose DTP coverage were 92% and 81%, respectively (Figure 4). During 2003–2006, approximately 15.4 million children in China-GAVI project counties received the 3-dose HepB series, preventing an estimated 1.47 million chronic HBV infections in children

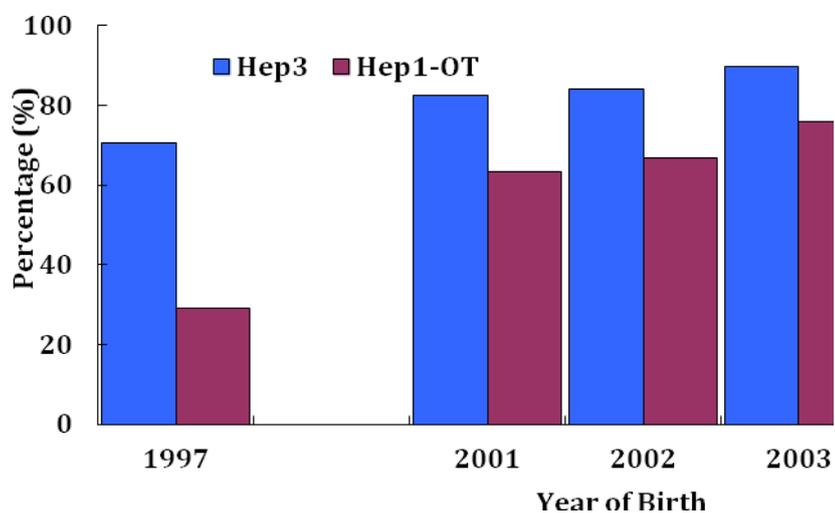
and 265,000 future deaths attributable to chronic HBV infection.

China has made substantial progress in implementing universal, timely hepatitis B vaccination for infants and in reducing disparities in coverage between the poorest and wealthiest parts of the country. The support from the China-GAVI project has improved vaccination coverage and helped prevent chronic HBV infection in children. During 2003–2006, approximately 15 million children in China-GAVI-funded provinces and approximately 42 million children nationwide received HepB. Since 2002, implementation of universal infant hepatitis B vaccination in China has focused particularly on improving timely administration of the birth dose. Approaches used to increase timely birth-dose coverage have included 1) increasing the percentage of births that occur in hospitals; 2) improving vaccine availability in hospitals and township health facilities; 3) building collaboration among delivery services (i.e., maternal and child health programs and obstetrics) and between vaccination services (i.e., immunization programs and pediatrics) in hospitals and township health centers; 4) increasing the awareness of the importance of timely birth dose administration among providers and parents; 5) intensifying training, supervision, and monitoring of county, township, and village health workers; and 6) providing subsidies to village doctors to provide vaccines. Disparities in vaccination coverage continue to exist by region and by location of birth. Despite the China-GAVI activities, during 1997–2006, children from eastern provinces had substantially higher coverage than those from middle or western provinces, as did children born in hospitals versus those born at home. Income levels continue to be highest in China's eastern provinces and lowest in the western provinces; residents in eastern provinces generally have greater access to and ability to pay for health care, including hospital care for childbirth. Children born

in hospitals generally have better access to immunization services and can be vaccinated more easily within 24 hours of birth. In western China, children are more likely to live in remote, mountainous areas and have less access to hospital delivery and immunization services. The China Ministry of Health is implementing programs to increase births in hospitals nationwide by expanding and improving obstetric care in health-care facilities throughout China and providing incentives to give birth in hospitals. Prevention of chronic HBV infection in China is integral to global initiatives to reduce the burden of HBV infection. In 1992, the World Health Assembly passed resolution 45.17, which called for all World Health Organization (WHO) member states to integrate cost-effective new vaccines, including HepB, into national immunization programs where feasible. The same year, WHO recommended that HepB be included in routine vaccination schedules for all children in all countries^[52]. During 2000–2006, the GAVI Alliance has provided support for HepB introduction to 51 less developed member states (i.e., countries with less than \$1,000 per capita gross national income), and these countries have made substantial progress in introducing HepB into their vaccination schedules^[53]. As of 2005, a total of 154 (80%) of 192 WHO member states reported having integrated HepB into their routine infant vaccination schedules; global coverage with 3-dose HepB had increased from 32% in 2001 to 55% in 2005, with 2005 coverage varying by WHO region (South-East Asia: 27%; Africa: 39%; Eastern Mediterranean: 74%; Europe: 76%; Americas: 85%; Western Pacific: 87%)^[54]. The advances in hepatitis B vaccination have led countries and WHO regions to set goals for the elimination of HBV transmission. The WHO Western Pacific Region has committed to reducing chronic HBV infection in children aged <5 years to <2% by 2012. The findings in this report are subject to at least two limitations. First, the design

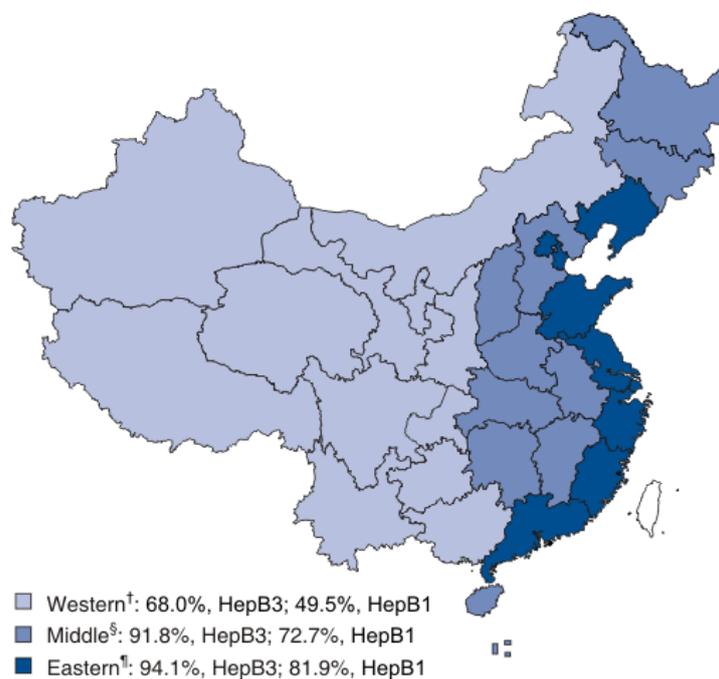
of the national surveys conducted in 1999 and 2004 differed in how counties were stratified before PPS sampling, which might limit comparability of the two surveys. Second, for the analyses using data from the routine immunization reporting system, the precise number of children requiring vaccination at local levels is not known because some children might not be registered; hence, the use of children targeted to receive DTP vaccine as a surrogate for total number of children might result in overestimation of reported vaccination coverage. Despite China's progress in increasing hepatitis B vaccination coverage and timely administration of the birth dose, challenges remain to reaching the national goal of <1% chronic HBV infection among children aged <5 years by 2010. Achieving this goal will require increasing 3-dose HepB coverage to the same level as 3-dose DTP coverage and increasing timely HepB birth-dose coverage to 90% in all provinces. The greatest challenge is to increase administration of the birth dose among children born at home. Three provinces (Guizhou, Tibet, and Yunnan) and 42% of China-GAVI project counties still have timely birth-dose coverage levels of <75% and are most in need of targeted interventions. Although most hospitals now are achieving >95% timely birth-dose coverage for infants born in hospitals, strategies are needed to ensure that false contraindications to vaccination, including low birth weight and unstable medical condition at birth ^[55], do not delay administration of the birth dose. Innovative measures also are needed to reach infants born at home, particularly through linking prenatal care and birthing-care providers with immunization program staff at township and village levels. With these improvements, China can reduce substantially the burden of hepatitis B.

Figure 2: Estimated infant vaccination coverage with 3 doses of hepatitis B vaccine (HepB3) and timely* administration of the HepB birth dose (HepB1), by year of birth- China, 1997 and 2001-2003



SOURCE: China Ministry of Health national vaccination coverage surveys, 1999 and 2004.

Figure 3: Estimated infant vaccination coverage with 3 doses of hepatitis B vaccine (HepB3) and timely* administration of the HepB birth dose (HepB1), by region — China, 2001–2003

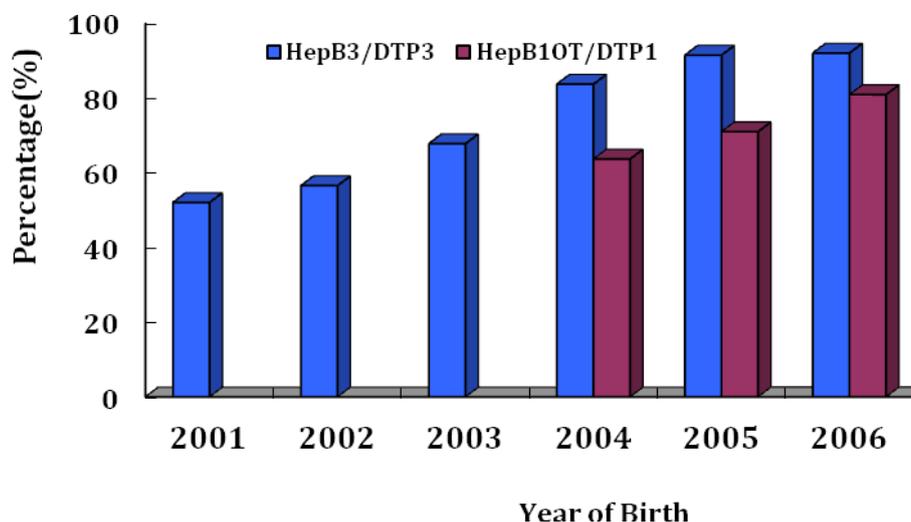


SOURCE: China Ministry of Health national vaccination coverage survey, 2004.

*Within 24 hours of birth.

[†]China-GAVI-funded western provinces: Chongqing, Gansu, Guangxi, Guizhou, Neimenggu (Inner Mongolia), Ningxia, Qinghai, Shaanxi, Sichuan, Tibet, Yunnan, and Xinjiang. (GAVI was formerly known as Global Alliance for Vaccines and Immunisation.) [§]Middle provinces with GAVI funding in government-designated poor counties: Anhui, Hainan, Hebei, Heilongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, and Shanxi. [¶]Eastern provinces: Beijing, Fujian, Guangdong, Jiangsu, Liaoning, Shandong, Shanghai, Tianjin, and Zhejiang.

Figure 4: Estimated infant vaccination coverage with 3 doses of hepatitis B vaccine (HepB3)/3 doses of DTP* vaccine (DTP3) and timely† administration of the HepB birth dose (HepB1)/first dose of DTP vaccine (DTP1), by year of birth — China-GAVI §–funded provinces and counties, ¶ China, 2001–2006



SOURCE: Routine Immunization Reporting System, China Center for Disease Control and Prevention.

* Diphtheria, tetanus, pertussis.

† Within 24 hours of birth.

§ Formerly known as Global Alliance for Vaccines and Immunisation.

¶ China-GAVI–funded western provinces: Chongqing, Gansu, Guangxi, Guizhou, Neimenggu (Inner Mongolia), Ningxia, Qinghai, Shaanxi, Sichuan, Tibet, Yunnan, and Xinjiang; middle provinces with GAVI funding in government-designated poor counties: Anhui, Hainan, Hebei, Heilongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, and Shanxi.

2. Chapter 2: Evaluation of the Impact of Hepatitis B Vaccination among Children Born during 1992–2005 in China[#]

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Contribution statement:

Xiaofeng Liang organized the survey, Shengli Bi guided the laboratory testing for the survey, Weizhong Yang coordinated the analysis and linked the data from epidemiology investigation and with the results of the laboratory testing. Longde Wang organized the review of the manuscript. Gang Cui contributed to the designing of study, identified funds, Fuqiang Cui contributed to design, pilot study, data collection, data analysis. He drafted the manuscript and was responsible for the revisions on the paper. Yong Zhang, Feng Wang, Zhiyuan Jia and Jingchen Ma tested the specimens. Jianhua Liu, Jing Guo and Shuigao Jin analyzed the data. Xiaohong Gong, Fuzhen Wang, Huizheng, Yuansheng Chen contributed to the pilot study, data collection and reporting. Huaqing Wang, Huiming Luo and Li Li reviewed the manuscript. Stephen Hadler helped designing the study and revised the manuscript. Yu Wang supervised the drafting, reviewing and revising of the manuscript.

[#] This manuscript has been published in *J Infect Disease: Evaluation of the Impact of Hepatitis B Vaccination among Children Born Between 1992 and 2005 in China*. *Journal of Infectious disease*, 2009,200(1):39-47.

Abstract

Background: Endemic hepatitis B virus (HBV) infection is a serious health problem in China. Hepatitis B vaccination of infants was introduced in 1992 and was progressively expanded during the subsequent 15 years.

Methods: We conducted a national serosurvey, with participants selected by multiple-stage random sampling. Demographic characteristics and hepatitis B vaccination history were collected by a questionnaire and a review of vaccination records, and serum specimens were tested for hepatitis B surface antigen, antibody to hepatitis B core antigen, and hepatitis B surface antibody by enzyme-linked immunosorbent assay.

Results: Hepatitis B vaccine coverage (3 doses) increased from 30.0% for children born in 1992 to 93.4% for children born in 2005. Receipt of a timely birth dose increased from 22.2% to 82.6% for children born during this interval. Multivariate analysis showed that older age, western and rural residence, birth at home, and certain ethnicities were risk factors for under vaccination with both full vaccine series and timely birth dose. The prevalence of hepatitis B surface antigen was reduced to 2.1% among all children and 1.0% among children born after 1999. The efficacy of hepatitis B vaccination with a timely birth dose was 88.3%.

Conclusions: Hepatitis B vaccine has been successfully integrated into routine infant immunization in China, now reaching most infants within 24 h after birth, and the prevalence of hepatitis B surface antigen has been greatly reduced among children born after 1992.

Background

Endemic hepatitis B virus (HBV) infection is a serious health problem in China, causing a substantial burden of acute and chronic liver disease ^[33]. A national serosurvey from 1992 revealed that the prevalence of hepatitis B surface antigen (HBsAg) was 9.8% in the general population, and that 9%–12% of children aged <5 years carried HBV ^[32]. The duration of hepatitis B carriage is almost lifelong, and current antiviral treatment is costly and has limited effectiveness in resolving chronic HBV infection ^[56-58]. Perinatal transmission is a major mode of HBV transmission in China. Therefore, China has made strong efforts to establish universal infant immunization. The recommended schedule involves administration of the first dose within 24 h after birth and administration of subsequent doses at ages 1 and 6 months—a schedule shown to be 70%–95% effective in preventing transmission from mother to infant ^[50]. In 1992, the Ministry of Health recommended routine immunization with the hepatitis B vaccine for routine immunization of infants. At this time, parents could be charged for the cost of hepatitis B vaccine and its administration. Data from national Expanded Programme on Immunization reviews showed that the rate of immunization coverage with the 3-dose series was 70.7% for children born in 1997 and was highest in urban and eastern areas ^[59]. In 2002, China fully integrated hepatitis B vaccine into the routine immunization program, providing free vaccine, although parents could still be charged a user fee. A collaborative project between the China Ministry of Health and the Global Alliance for Vaccines and Immunization assured that free vaccine would be available for all children born in poorer western provinces and impoverished areas of the central provinces beginning in 2003 ^[50]. In 2004, a review by the National Expanded Programme on Immunization reported that, for children born during 2001–

2003, the rate of 3-dose vaccine coverage reached 85.5% nationally; the rate was 94.1% in the eastern provinces but only 68.0% in western provinces^[51]. In 2005, the State Council issued the “Regulation on Vaccine Circulation and Immunization Management,” which eliminated all vaccination-associated charges, so that infants born after 1 June 2005 would be provided with hepatitis B vaccine for free^[49].

In 2006, the Chinese government conducted a national serosurvey to evaluate the progress in the prevention of hepatitis B. This article describes the immunization coverage for children who were born after hepatitis B vaccine had been integrated into routine immunization, identifies risk factors for under-immunization, and evaluates the impact of hepatitis B vaccination on the seroprevalence of HBV markers among children born during 1992–2005.

Methods

Study population. The target population was children born during the period 1 January 1992 through 31 December 2005 in each of 160 national Disease Surveillance Points (DSP) in 31 provinces, which were selected by the Chinese Center for Disease Control and Prevention (CDC) to be representative of the population of China. Each DSP consists of 1 county; in total, 73 million persons live in these counties, with a birth rate of 12.09 births per thousand inhabitants. Demographic characteristics and economic conditions in these points are not statistically different from those for whole country^[60-62].

These sites were divided into 6 major regional groups (eastern urban, eastern rural, central urban, central rural, western urban, and western rural) for sampling. Western provinces included Chongqing, Gansu, Guangxi, Guizhou, Inner Mongolia, Ningxia, Qinghai, Shaanxi, Sichuan, Tibet, Yunnan, and Xinjiang. Central provinces included Anhui, Hainan, Hebei,

Heilongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, and Shanxi. Eastern provinces included Beijing, Fujian, Guangdong, Jiangsu, Liaoning, Shandong, Shanghai, Tianjin, and Zhejiang. Children aged 1–14 years and adults aged 15–59 years who had resided in the DSP for 16 months at the survey visit were selected for the study; the complete selection methods are described elsewhere^[40].

Sampling method. With use of the expected prevalence of HBsAg for different age groups in the study (1% for age 1–4 years, 4% for age 5–14 years, and 9% for age 15–59 years), the desired sample size was 79,129 children, including 15,213 children aged <5 years and 23,416 children aged 5–14 years. First, 369 townships were identified from 160 counties (1–4 townships per county) by simple random selection; second, one village was randomly selected from each township; and third, the populations of children aged 1–4 and 5–14 years were enumerated and selected on the basis of systematic interval from a list of village residents. Average sampling proportions for each age group at village were 1:1 for children aged <5 years and 1:7 for children aged 5–14 years.

Investigation. A house-to-house investigation was completed by trained staff on the basis of the sampled name list. Basic information, including sex, birth date, ethnicity, place of birth, and immunization history, was compiled through parent interview. Immunization status was recorded from the child's home immunization certificate or, if not available, by a review of the child's immunization card at the township immunization clinic; if neither was available, the village doctor's registry was reviewed. Otherwise, the immunization information was recorded as unvaccinated or unknown. Full vaccination was defined as receipt of 3 doses of hepatitis B

vaccine within 12 months, as documented by any immunization record. Timely birth-dose coverage was defined as receipt of the first dose of hepatitis B vaccine within 1 day after birth.

Specimen collection. Blood samples were obtained from each study participant (4 ml for children aged ≥ 2 years and 2 ml for children aged < 2 years). Serum was separated in county laboratories, transported, and stored at $-20\text{ }^{\circ}\text{C}$, initially at provincial laboratories and subsequently at the National Hepatitis Laboratory, Chinese CDC (Beijing).

Laboratory testing. All serum specimens were tested in the National Hepatitis Laboratory, Institute for Viral Disease Control and Prevention (IVDC) at the Chinese CDC. A detailed laboratory testing protocol was used that included retesting of specimens with inconsistent results. Testing reagents were selected on the basis of an evaluation of available enzyme-linked immunosorbent assay (ELISA) kits in China and were compared with use of Abbott enzyme immunoassay reagents using a panel of 153 reference serum specimens. ELISA reagents for HBsAg and hepatitis B surface antibody (anti-HBs) testing were purchased from Xiamen Xinchuang Production Company, utilizing a single lot of each test kit (batch number 2006071301 for HBsAg, 2006071401 for anti-HBs, and 20060705 for hepatitis B core antigen (anti-HBc)). Anti-HBc detection reagents were purchased from the Shanghai Kehua Company. For specimens with inconsistent results, Abbott radioimmunoassay or ELISA reagents were used for reconfirmation testing, with neutralization method for final HBsAg confirmation. Data analysis. All data were double-inputted using EPI Data software, version 3.02 (The EpiData Association), and were checked for consistency. After verification of the accuracy of the data set, it was analyzed at the Chinese CDC with SAS software, version 9.13 (SAS Institute).

Appropriate sampling weights were constructed for national sample data set. The weight for person i can be expressed as follows:

$$w_{kji} = w_k \times w_{jk} \times w_{i|k,j} \times w_{adj}$$

where,

w_k is the reciprocal of the inclusion probability of township k ;

w_{jk} is the reciprocal of the conditional inclusion probability of village j within the selected township k ;

$w_{i|k,j}$ is the reciprocal of the conditional inclusion probability of person i within the selected village j ;

w_{adj} is an adjustment factor for person i such that the sum of the weights equals the actual size of the Chinese population.

The Taylor series linearization methods were applied for variance estimation. We used survey freq procedure of SAS software for computation. The weighted prevalence rates of hepatitis B vaccination and HBV biomarkers include the point estimates and their estimated 95% CIs^[63-67]. Multivariable logistic regression (forward method) was used to identify the predictors for high risk of under-vaccination. Vaccine effectiveness was calculated using the formula $VE = (AR_{uv} - AR_v) / AR_{uv}$, where AR_{uv} is prevalence in unvaccinated and AR_v is prevalence in vaccinated children.

7. Quality control: National specialist groups were convened to guide statistical design, epidemiological investigation, laboratory testing and logistic services, training and data analysis. Two field pilots were conducted before the survey. Appropriate visiting time was

considered to ensure high response rate. Trained County CDC staffs were responsible for administering the questionnaire, and collecting, storing and transporting the blood specimens.

8. Ethical Issues: The survey was approved by the China CDC Ethics Committee, and all study work done according to the national Ethics regulations. Study participants were informed of the study purpose and their right to keep information confidential.

Results

1. Characteristics of study population

During the investigation, 87,454 persons (1~59 years old) were enumerated; among these, 5,376 were excluded due to absence or refusal, 82,078 interviewed, and 82,008 blood samples were taken. Overall, 40,129 children born between 1992 and 2005 participated. The study population was predominantly Han (86.4%), balanced by sex and among regions and urban/rural status; 40.8% were 1-4 years while 59.2% were 5-14 years; 75% had been born in county or above (47.7%) or township (28.1%) hospitals, while 21.5% were born at home.

2. Immunization coverage of HepB for children born between 1992 and 2005

Among the study population, 32,732 (81.6%) had received hepatitis B vaccination (any doses), 3,755 (9.4%) had not received HepB vaccine, and 3,642 (9.1%) had unknown vaccination history.

For children born between 1992 and 2001, weighted 3 dose and timely birth dose coverage of HepB were 50.6% and 35.1%. For children born between 2002 and 2005, weighted 3 dose and timely birth dose coverage of HepB had increased to 89.4% and 73.4%, respectively, and reached 93.4% and 82.6%, respectively, for children born in 2005 (Table 10).

In both time periods, weighted coverage for 3 dose and timely birth dose of HepB were significantly higher among Han, Mongolian, and Hui children than among all other ethnic groups (Table 10). Vaccine coverage did not differ by gender.

3. Hepatitis B immunization coverage trends in different regions

For children born between 1992 and 2001, both 3 dose and timely birth dose HepB coverage were highest in the eastern region, intermediate in central region, and lowest in the western region, and were significantly higher in urban than rural areas in each region (Table 11, Figures 5, Figure 6). For children born between 2002 and 2005, regional and urban/rural vaccine coverage differences had decreased but remained significant. Increases in coverage were seen in all 6 sub-regions, and were most dramatic in areas that had lowest coverage in 1992-2001 birth cohorts (western urban and all rural areas). Timely birth dose coverage in Western rural regions, however, reached only 58% in 2002-2005.

4. Relationship of birth place and hepatitis B Immunization coverage

The proportion of births occurring in hospitals increased substantially during the study period. Among children born between 1992 and 2001, 70.9% of were delivered at hospitals, and 27.4% were delivered at home, while among children born between 2002 and 2005, 85.1% were delivered at hospitals, and only 13.9% were delivered at home ($p < 0.05$).

Timely birth dose coverage increased substantially among children born in 2002-2005 compared to those born between 1992-2001 in all settings (Table 10). Coverage was highest among children born in county hospital and above (84% in 2002-2005), and was slightly lower among children born in township hospitals. Coverage among children born at home improved, but remained low (31.4%) for children born between 2002 and 2005.

5. Prevalence of HBV among children born between 1992 and 2005 by year

Weighted prevalence of HBsAg for children born between 1992 and 2005 was 2.1%, with highest prevalence in oldest children and decreasing steadily with decreasing age (Table 12). Among children born in 1992, the HBsAg prevalence was 5.5%, decreasing to 1.8% among children born between 1993 and 1998. Among children born after 1998, HBsAg prevalence was approximately 1%. Prevalence of anti-HBc, also decreased monotonically with age, from 16.5% in the oldest to 3.3% in the youngest children. Conversely, the weighted prevalence of anti-HBs decreased steadily with earlier birth year, reaching a plateau of about 55% for children born before 2002 (Table 12).

6. Weighted prevalence of HBsAg and other HBV markers and immunization history

Weighted prevalence of HBsAg was significantly lower among children who were fully vaccinated than among unvaccinated children and those with unknown immunization status. HBsAg prevalence among children who received the full 3 dose immunization series and timely birth dose were 1.0% and 0.7% among children born between 1992-2001 and 2002-2005, respectively (Table 13). HBsAg prevalence among children receiving a birth dose between 2 and 7 days after birth was 0.4-0.5%, lower than that of children receiving a birth dose on time, but this difference was not statistically significant. However, children receiving the birth dose after 1 week of age had higher HBsAg prevalence (1.3-1.8%), significant for children born 2002-2005. Among children with no immunization, HBsAg prevalence was 5.5-5.6%, approximately 60% that observed among children in this age group in the 1992 hepatitis B serosurvey². Based on these results, the effectiveness of HepB for full and on-time immunized infants compared with non-immunized infants is estimated to be 88%. The weighted prevalence

of anti-HBs was higher among fully immunized children (63.2% and 74.3% in children born in 1992-2001 and 2002-2005, respectively) than among not immunized (34.8% and 21.1%) children in both time periods. Anti-HBc prevalence was significantly lower for fully immunized children (3.7-5.6%) than in unimmunized children (10.6-17.8%).

7. Multivariable regression analysis on risk of low immunization coverage

Multivariable analysis was used to examine risk factors for not being fully immunized for HepB, with vaccination status as the dependent variable, and age, gender, ethnicity, type of residence, region, and birthplace as covariates. Risk factors for low 3 dose immunization coverage included being born before 2001; Tibetan, Uigur, and other ethnicity compared to Han ethnicity; and living in western region and rural location. In addition, full immunization was lower among children born at home or in other settings than for children born at hospital (Table 14).

Results for low timely birth dose coverage were almost identical to those for full immunization series, although odds ratios were higher for most factors. Thus birth before 2001; Tibetan, Uigur, Zhuang, and other ethnicity; living in western region and rural location; and birth in township hospital or at home, were strong predictors of low timely birth dose (Table 15).

Discussion

Before wide availability of hepatitis B vaccination in China, HBV infection was acquired rapidly by perinatal and infant transmission among children aged 1-4 years, with the HBsAg prevalence reaching 9.8%, and remaining consistently high in older age groups. Among the global deaths attributed to hepatitis B, about 40% occur in China ^[10]. Therefore, control of

hepatitis B is among the highest priorities in China. Policies currently being implemented to control hepatitis B include universal infant immunization, HBsAg screening of blood for transfusion, control of blood exposure in medical settings, and management and treatment of hepatitis B infected persons^[68].

Vaccination is considered the most cost-effective way to control hepatitis B, and immunization of newborns is necessary to prevent perinatal HBV transmission^[50,69]. HepB was fully integrated into the National Immunization Program in 2002, and since 2005, all vaccination of infants has been provided for free, providing equal opportunity for all socioeconomic classes. Since 2002, multiple approaches have been implemented to increase timely birth doses, with strongest emphasis on increasing the proportion of births in hospitals, building collaboration between Maternal Child Health (MCH) and EPI departments, and assuring timely birth doses for children born in hospitals. Assuring safe childbirth has been a national priority since 2000; in addition to training and upgrading hospital facilities, the government provides subsidies to pregnant women to deliver in hospitals, through national rural health reform cooperation policy, reducing or eliminating the hospital charges. This has increased the percentage of births that occur in hospitals to over 85% nationally. Regular communication between MCH and EPI has been mandated by provincial and local Health Bureaus to ensure collaboration to deliver vaccination. In 2002, national guidelines were established to require obstetrical nurses who deliver the baby to give the hepB birth dose within 24 hours after birth; with strong training, systematic recordkeeping, and regular monitoring, the policy has been well implemented^[70], with coverage now exceeding 90% in most hospitals. Timely birth doses for births at home may be provided by village doctors, who coordinate with

MCH staff/midwives to track pregnancies and to facilitate having hepB vaccine available in village at time of childbirth.

The successful introduction of HepB into the national immunization program has brought great impact in reducing the prevalence of HBsAg among population aged 1 to 14 years. The results affirm that universal vaccination of infants contributed directly to the reduction of HBsAg prevalence; vaccination with full series and timely birth dose was 88% effective compared to unvaccinated children among both recently born and older children. Interestingly, un-immunized children tested in 2006 had lower HBsAg prevalence compared with same age group tested in the 1992 serosurvey (5.6% vs. 9.8%)^[32]. This is likely due to several factors: a modest decrease in HBsAg prevalence among women (15~59 yrs), from 8.1% in 1992 to 6.7% in 2006; reduced size of families due to the one-child per family policy and therefore reduced transmission risk among children; improvement of safe injection practices^[50, 59], and herd immunity due to high rates of vaccination.

Hepatitis B vaccination of infants and children has been demonstrated to reduce the prevalence of HBsAg in many different populations that previously experienced high HBV endemicity^[71]. Previous studies have shown marked reduction in prevalence in both urban and rural areas of China (Shanghai, LongAn County, Beijing, etc), Africa (eg. Gambia and Senegal), and all other populations with high HBV endemicity^[72-79]. This study reaffirms the effectiveness of infant vaccination for the national Chinese population, and demonstrates the importance of timely birth doses for greatest reduction of risk. Delayed delivery of timely birth dose, but within one week, also appeared to reduce the prevalence of infection in infants. This is reassuring for programs where challenges remain to achieving timely birth doses within 24

hours. However, this finding is based on observations in a relatively small number of infected infants, and will require confirmation in a larger study to be sufficient to consider modifying current HepB birth dose recommendations. Available controlled trials show that timely birth dose within 24 hours is highly effective for hepB prevention among children born to highly infectious HBsAg, HBeAg positive mothers or those with high HBV DNA, and it is strongly recommended that hepB vaccination programs provide the birth dose within 24 hours if possible.

Although China has greatly improved infant hepatitis B vaccination coverage and reduced HBsAg prevalence in young children, this study shows that certain groups remain at high risk of not receiving timely birth dose or full immunization. Due to uneven development among regions, immunization coverage remains low in rural areas and in the western region, and among several ethnic minority groups. Finally, children born at home remain at very high risk of not receiving timely birth dose or full immunization. Because a high proportion of women of child-bearing age remain HBsAg and HBeAg positive (6.7% HBsAg +; 30% of these HBeAg positive), to achieve further gains in reducing hepatitis B risk among children, the national program must continue to improve immunization, and particularly timely birth doses, in these risk groups ^[80].

In addition, efforts still need to focus on assuring high timely birth dose coverage (>95%) among children born in hospitals. Field studies in China indicate that birth doses are often delayed due to false contraindications, including low birth weight (< 2500 gms), prematurity, and unstable infant condition ^[70]. HepB vaccine has been shown to be safe when given to

infants of any age, and prematurity or low birth weight should not delay the administration of timely birth doses ^[81].

This study has several limitations. First, because the target population was children living in village more than 6 months, some floating (migrant) children as well as children born outside the birth control plan (unregistered children) were excluded from the study. Therefore, this study may overestimate immunization coverage. The floating population represents only a small proportion in this age group (3%), but the number of unregistered children is not known. Secondly, effectiveness of timely birth dose vaccination may be overestimated, since in urban areas, many pregnant women are screened for HBsAg and infants born to HBsAg positive mothers given not only HepB but also HBIG at birth. In this survey, the proportion of infants who were reported by parents to have received HBIG was relatively small (<1%), and exclusion from the analysis did not change the results. One other limitation is that because all children were tested during 2006, the children who were less than 5 years (born 2002-2005) may still be at risk for horizontal transmission of HBV.

China has made great achievement in integrating HepB into routine immunization programs, achieving very high full immunization coverage and timely birth dose, and has demonstrated dramatic impact in reducing the prevalence of HBsAg among young children. In particular, the collaborative approach to achieve uniform vaccination of infants at birth should serve as a guide to other countries with high HBV endemicity to achieve rapid reduction in perinatal HBV transmission. Prevalence of HBsAg for children under 7 years is now about 1% indicating achievement of the national goal of 1% HBsAg prevalence among children by 2010, and of the WHO Western Pacific Regional Office (WPRO) hepatitis B reduction goal. WPRO

is the first WHO region to set a time-bound goal of reducing chronic HBV infection rates to less than 2% among five-year-old children by 2012. To further reduce the prevalence of HBsAg, accelerate progress toward further reducing hepatitis B transmission, and assure high levels of protection for the Chinese population, the national program will need to focus strongest efforts on improving timely birth doses among disadvantaged minority populations and the Western rural areas where many births still occur at home, and among floating and unregistered children. In addition, China should continue to focus on protecting all children through providing vaccination to previously unvaccinated children < age 5 years, and to expanding coverage to all children < 15 years, and to high risk populations.

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Table 10: Immunization coverage of hepatitis B vaccine for children born during the period 1992–2005.

Year	No. Investigated	3 dose		Timely Birth dose	
		Weighted Coverage (%)	95% <i>CI</i>	Weighted Coverage (%)	95% <i>CI</i>
1992	1,724	30.0	22.7~37.2	22.2	14.7~29.7
1993	2,285	34.3	29.4~39.2	23.7	19.2~28.2
1994	2,415	38.1	33.3~43.0	22.5	19.2~25.7
1995	2,773	39.7	35.8~43.6	27.1	21.2~32.9
1996	2,647	45.2	40.8~49.6	28.2	24.7~31.8
1997	2,578	55.9	47.4~64.4	39.4	31.6~47.3
1998	2,434	56.8	52.2~61.3	39.1	34.1~44.0
1999	2,326	61.2	57.3~65.1	43.7	39.8~47.6
2000	2,356	76.6	71.3~82.0	54.1	49.9~58.2
2001	2,215	83.0	78.7~87.3	64.4	59.8~68.9
2002	4,175	84.3	82.0~86.5	66.1	62.7~69.6
2003	4,412	87.7	86.3~89.2	68.9	65.9~71.9
2004	4,153	92.4	90.9~93.9	76.8	74.5~79.1
2005	3,636	93.4	92.1~94.7	82.6	80.2~85.0
Total	40,129	59.6	57.3~61.8	43.9	41.6~46.2

Table 11: Weighted hepatitis B immunization coverage among children born between 1992 and 2005 by characteristics of study population

	Category	Frequency	1992~2001		2002~2005	
			3 doses	Timely	3 doses	Timely
Gender	Male ^a	20,960	51.8	35.5	89.6	73.2
	Female	19,169	49.2	34.6	89.2	73.6
Ethnicity	Han ^a	34,668	53.6	37.7	92.9	78.0
	Mongolian	336	70.2*	26.2*	97.1	75.3
	Tibetan	1,138	6.4**	3.9**	38.5**	8.4**
	Uigur	599	2.0**	2.0**	55.7**	15.1**
	Zhuang	244	19.0**	11.3**	65.6**	37.4**
	Hui (Muslim)	583	50.6	45.5	79.6	70.5
	Others	2,561	25.0**	13.2**	61.8**	41.0**
Urban/Rural	Urban ^a	19,999	68.6	58.7	93.4	81.5
	Rural	20,130	45.5**	28.4**	88.0**	69.5**
Region	Eastern ^a	13,530	64.2	45.2	96.8	85.5
	Central	13,336	60.7*	41.9	91.9**	75.9**
	Western	13,263	33.5**	22.8**	78.8**	57.7**
Birth Place	County Hospital ^a	19,156	60.6	49.5	94.9	84.5
	Township Hospital	11,266	72.7	41.2*	94.4	78.0**
	At home	8,631	27.0**	11.6**	62.5**	31.4**
	Others	1,076	35.1**	18.4**	91.1	64.5**

^aReference * P<0.05 ** P<0.01

Table 12: HBV markers among children born between 1992 and 2005 by birth year

Year	No. Investigated	HBsAg		Anti-HBc		Anti-HBs	
		Weighted	95%CI	Weighted	95%CI	Weighted	95%CI
1992	1,724	5.5	3.7~7.4	16.5	13.7~19.2	50.5	46.8~54.1
1993	2,285	3.4	2.5~4.2	13.3	10.8~15.7	57.9	54.2~61.7
1994	2,415	2.9	1.9~4.0	10.5	8.3~12.7	53.4	46.1~60.8
1995	2,773	3.0	1.8~4.1	8.7	6.6~10.9	61.6	56.4~66.9
1996	2,647	2.1	1.1~3.1	7.1	5.4~8.7	60.5	57.1~63.9
1997	2,578	2.3	1.8~2.9	7.5	5.9~9.1	55.7	50.8~60.5
1998	2,434	1.8	1.4~2.1	6.1	4.8~7.5	54.2	49.8~58.6
1999	2,326	1.0	0.4~1.6	5.3	3.5~7.1	54.8	51.0~58.5
2000	2,356	0.9	0.4~1.5	3.7	2.0~5.4	56.9	50.4~63.5
2001	2,215	1.1	0.4~1.8	4.8	3.3~6.4	55.8	45.6~65.9
2002	4,175	1.2	0.8~1.6	4.2	3.3~5.1	63.5	60.9~66.0
2003	4,412	0.9	0.5~1.3	4.5	3.4~5.6	65.7	63.4~67.9
2004	4,153	0.9	0.4~1.3	4.2	3.1~5.4	72.9	70.6~75.1
2005	3,636	0.9	0.4~1.3	3.3	2.3~4.4	84.5	82.4~86.7
Total	40,129	2.1	1.78~2.38	7.4	6.8~8.0	60.0	58.4~61.5

Table 13: Immunization status and prevalence of HBsAg

Status of Immunization	1992-2001			2002-2005		
	Investigated	Weighted prevalence (%)	95% <i>CI</i>	Investigated	Weighted prevalence (%)	95% <i>CI</i>
Full,-Birth dose	11,103	1.0	0.7~1.4	12,024	0.7	0.5~0.8
Full,-BD within 1 week	887	0.4	0~0.8	671	0.5	0.1~1.0
Full, BD after 1 week	5,026	1.8	1.2~2.3	2,614	1.3	0.7~1.8
Not immunized	3,274	5.5	3.4~7.7	481	5.6	3.5~7.6
Unknown	3,222	3.7	2.9~4.5	420	3.2	1.6~4.8

Legend:

Full, Birth Dose OT: Full HepB series with birth dose within 24 hours of birth

Full, BD within one week: Full series, with birth dose given between 2-7 days after birth

Full, BD after 1 week: Full series with birth dose given > 7 days after birth

Table 14: Multivariable regression analysis on risk of low full immunization coverage (HepB3)

	Category	Frequency	OR	95.0% CI	P value
Age	1~4*	16,376	1.0		
	5~14	23,753	10.0	8.6~11.8	<0.01
Sex	Male*	20,960	1.0		
	Female	19,169	1.1	0.8~1.5	0.5
Ethnicity#	Han*	34,668	1.0		
	Mongolian	336	0.3	0.1~0.8	<0.05
	Tibetan	1,138	5.9	3.5~9.9	<0.01
	Uigur	599	5.3	3.7~7.5	<0.01
	Zhuang	244	1.5	0.9~2.5	0.09
	Hui	583	1.1	0.7~1.8	0.67
	Others	2,561	2.2	1.6~3.1	<0.01
Urban/Rural	Urban*	19,999	1.0		
	Rural	20,130	1.9	1.4~2.6	<0.01
Region	Eastern*	13,530	1.0		
	Central	13,336	1.0	0.7~1.5	0.85
	Western	13,263	3.1	2.2~4.3	<0.01
Birth Place	County Hospital*	19,156	1.0		
	Township Hospital	11,266	1.2	1~1.5	0.15
	Home	8,631	4.4	3.5~5.7	<0.01
	Others	1,076	3.2	1.7~6.0	<0.01

* Reference

Table 15: Multivariable regression analysis on high risk of low timely birth dose coverage

	Category	Frequency	OR	95.0% CI	P value
Age	1~4*	16,376	1.0		
	5~14	23,753	5.5	4.8~6.3	<0.01
Sex	Male*	20,960	1.0		
	Female	19,169	1.0	0.9~1.2	0.79
Ethnicity#	Han*	34,668	1.0		
	Mongolian	336	1.2	0.5~3.0	0.69
	Tibetan	1,138	9.1	5.2~16.2	<0.01
	Uigur	599	7.7	4.3~13.6	<0.01
	Zhuang	244	1.7	1.2~2.6	<0.01
	Hui	583	0.9	0.6~1.3	0.53
	Others	2,561	2.3	1.8~2.8	<0.01
Urban/Rural	Urban*	19,999	1.0		
	Rural	20,130	2.6	2.1~3.3	<0.01
Region	Eastern*	13,530	1.0		
	Central	13,336	1.1	0.8~1.4	0.66
	Western	13,263	2.4	1.8~3.1	<0.01
Birth Place	County Hospital*	19,156	1.0		
	Township Hospital	11,266	1.7	1.3~2.1	<0.01
	Home	8,631	7.6	5.7~10.2	<0.01
	Others	1,076	4.3	2.5~7.5	<0.01

* Reference

Figure 5: Hepatitis B Immunization coverage of 3 doses for children born between 1992 and 2005 in different regions

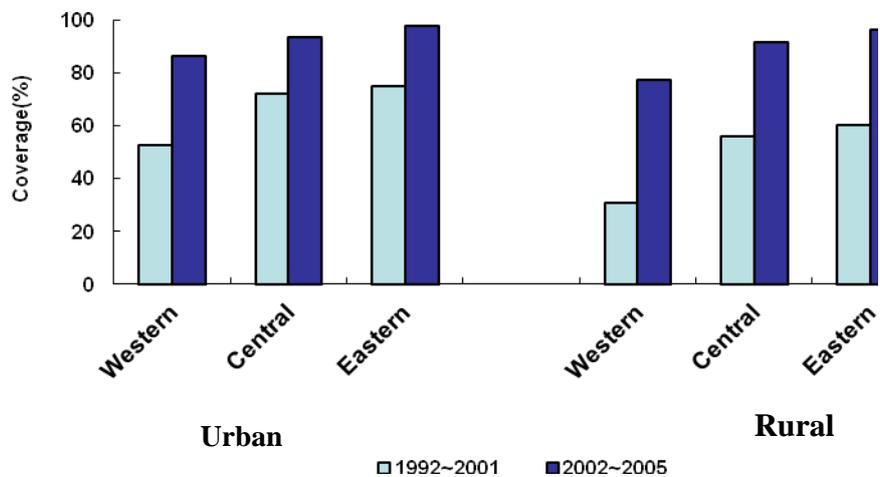
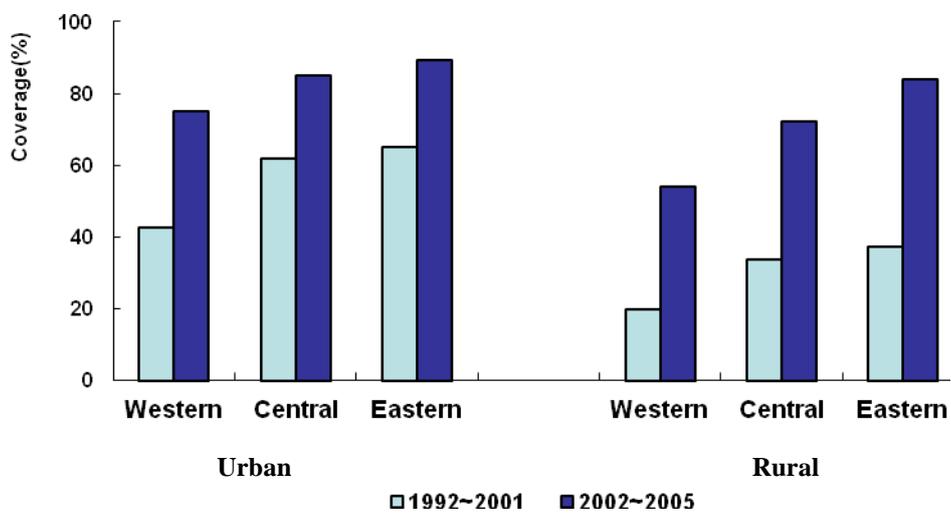


Figure 6: Timely birth dose coverage for children born between 1992 and 2005 by different regions



3. Chapter 3: Epidemiological Serosurvey of Hepatitis B in China - Declining HBV

Prevalence due to Hepatitis B Vaccination[§]

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Contribution statement:

Xiaofeng Liang organized the survey, Shengli Bi guided the laboratory testing for the survey, Weizhong Yang coordinated the analysis and linked the data from epidemiology investigation and with the results of the laboratory testing. Longde Wang organized the review of the manuscript. Gang Cui contributed to the designing of study, identified funds, Fuqiang Cui contributed to design, pilot study, data collection, data analysis. He drafted the manuscript and was responsible for the revisions on the paper. Yong Zhang, Feng Wang, Zhiyuan Jia and Jingchen Ma tested the specimens. Jianhua Liu, Jing Guo and Shuigao Jin analyzed the data. Xiaohong Gong, Fuzhen Wang, Huizheng, Yuansheng Chen contributed to the pilot study, data collection and reporting. Huaqing Wang, Huiming Luo and Li Li reviewed the manuscript. Stephen Hadler helped designing the study and revised the manuscript. Yu Wang supervised the drafting, reviewing and revising of the manuscript.

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Abstract

Objective: To determine the prevalence of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core anti-body (anti-HBc) in a representative population in China fourteen years after introduction of hepatitis B vaccination of infants.

Methods: National serosurvey, with participants selected by multi-stage random sampling. Demographics and hepatitis B vaccination history collected by questionnaire and review of vaccination records, and serum tested for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc) and hepatitis B surface antibody (anti-HBs) by ELISA.

Findings: The weighted prevalence of HBsAg, anti-HBs and anti-HBc for Chinese population aged 1-59 years were 7.2%, 50.1%, 34.1% respectively. HBsAg prevalence was greatly diminished among those age < 15 years compared to that found in the 1992 national serosurvey, and among children age < 5 years was only 1.0% (90% reduction). Reduced HBsAg prevalence was strongly associated with vaccination among all age groups. HBsAg risk in adults was associated with male sex, Western region, and certain ethnic groups and occupations while risk in children included birth at home or smaller hospitals, older age, and certain ethnic groups (Zhuang and other).

Conclusions: China has already reached the national goal of reducing HBsAg prevalence to less than 1% among children under 5 years and has prevented an estimated 16-20 million HBV chronic infections through hepatitis B vaccination of infants. Immunization program should be further strengthened to reach those remaining at highest risk.

Key Words: Hepatitis B, Serosurvey, immunization

Background

In 1992, the China national hepatitis seroepidemiological survey found that the prevalence of HBsAg for population aged 1-59 years was 9.8%. Based on this survey, it has been estimated that in China, 120 million people carry HBsAg^[32, 82, 83], 20 million suffer from chronic hepatitis B, and almost 300,000 die annually from chronic consequences of HBV infection. Both liver cancer and cirrhosis are among the 10 most common causes of mortality in China; for both, hepatitis B virus causes the majority of deaths^[33, 84, 85].

To control hepatitis B, the Chinese government has implemented infant vaccination with hepatitis B vaccine as the highest priority. In 1992, the Ministry of Health recommended hepatitis B vaccine for routine immunization of infants but parents had to pay for the vaccine, therefore vaccine coverage was higher in urban and high socioeconomic areas and lower in rural and lower socioeconomic areas. In 1999, a National Expanded Programme on Immunization (EPI) review showed that, the immunization coverage with 3 doses of hepatitis B vaccine was 70.7%, but varied from 99% in Beijing to only 7.8% in Tibet^[42]. A follow-up survey showed immunization coverage among children born in 2001 had reached 82.4 %, but with continued disparities in western provinces and rural counties^[51]. In 2002, China integrated hepatitis B vaccine into EPI, with emphasis on providing a timely birth dose (within 24 hours of birth). The cost of vaccine was paid by the government, but vaccine administration fees of up to \$1.10 per dose were still allowed as a charge to parents. In addition, the China/Global Alliance on Vaccine and Immunization (GAVI) project provided \$76 million funding to purchase hepatitis B vaccine and autodisable syringes for all children born in western provinces

and poverty counties in middle provinces^[50]. In May 2005, the government required that all infant vaccinations be given at no charge to parents.

To accelerate the control of hepatitis B, the Ministry of Health developed the "2006 ~ 2010 National guidelines for hepatitis B prevention and treatment", establishing national goals of achieving HBsAg prevalence less than 7% by 2010 for whole population and less than 1% for children under five years^[86].

The vaccination program in China has been regarded as a success story in preventing hepatitis B through universal infant vaccination^[53]. To measure the prevalence of hepatitis B markers among population aged 1-59 years, ongoing risk factors for hepatitis B infection, and to evaluate the impact of the hepatitis B vaccination programme since 1992, the China government conducted the national hepatitis serosurvey in 2006.

Methods

Planning for this study was started in December 2005 and data analysis completed in December 2007. All field work was conducted between September and October 2006.

1. Study population: The target population was local residents aged 1 to 59 years living in 160 disease surveillance points (DSP) in 31 provinces which have been selected by Chinese Center for Disease Control and Prevention (China CDC) to be representative of the population of China. Demographic, economic conditions and the situation of the population in these sites are not statistically different compared to whole country^[60, 61, 87]. For the serosurvey, these sites were divided into 6 major regional groups -- urban eastern, rural eastern, central urban, central

rural, western urban and western rural -- for further sampling^{**}. Persons aged 1-59 years resident for more than 6 months at the survey visit were selected.

2. Sampling Method: Using the expected HBsAg prevalence for different age groups in the study (1% for age 1-4 yrs., 4% for age 5-14 yrs., 9% for age 15-59 yrs), the desired sample size was 79129, and included 15,213 children < 5 yrs and 23,416 children 5-14 years.

First, 369 townships were identified from 160 counties (1-4 per county) by simple random selection; secondly, one village was randomly selected from each township; third, the population aged 1-4, 5-14, and 15-59 years, respectively, were enumerated and selected based on the systematic interval from a list of village residents. Average sampling proportions for each age group at village were 1:1 for children < 5 years, 1:7 for children 5-14 years, and 1:8 for population aged 15-59 years.

3. Investigation: House to house investigation was completed by trained staff based on the sampled name list. A standard questionnaire was used to compile the basic information including gender, birth date, education, occupation, ethnicity, place of birth, and immunization history through face to face interview with the study subject or parent (if child < 15 years). For children under 15 years, immunization status was recorded from the child's immunization certificate kept by the parents or by review of the child's immunization card kept at the township hospital immunization clinic; if neither were available, the village doctor's registry was reviewed. If none of these sources were available, the vaccination status was recorded as unvaccinated (if parent denied vaccination) or as unknown. Because there are no personal

^{**} Western provinces include: Chongqing, Gansu, Guangxi, Guizhou, Inner Mongolia, Ningxia, Qinghai, Shaanxi, Sichuan, Tibet, Yunnan, and Xinjiang. Central provinces include: Anhui, Hainan, Hebei, Heilongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, and Shanxi. Eastern provinces include: Beijing, Fujian, Guangdong, Jiangsu, Liaoning, Shandong, Shanghai, Tianjin, and Zhejiang. Urban counties are defined as that counties which are capital in prefecture; rural counties are those counties which are not capital of the prefecture.

immunization records for adults, the immunization information for adults was based on memory (vaccinated, unvaccinated, unknown). Definitions of education and occupation are according to the Chinese social classification criteria, and only applicable to population aged 15~59 years. Occupation of public service worker is defined as a person who works in hotel, hospital, barber, transportation center, etc, and who has high frequency of contact with the public.

4. Specimen collection: Blood samples collected for each study participant included 4ml for population above 2 years, and 2ml for children age 2 years or less. Serum was separated in county laboratories, transported and stored at -20°C at provincial laboratories, and submitted to National Hepatitis laboratory of Institute for Viral Disease Control and Prevention (IVDC) at China CDC in Beijing.

5. Laboratory testing: All serum specimens were tested in the National Hepatitis laboratory at IVDC, China CDC. A detailed laboratory testing protocol was established before testing, including retesting of specimens with inconsistent results. Testing reagents were selected based on evaluation of available ELISA kits from 5 companies in China compared to Abbott EIA reagents using a panel of 153 standard reference sera. ELISA reagents for HBsAg, anti-HBs, HBeAg and anti-HBe testing were purchased from Xiamen Xinchuang Production Company, utilizing a single lot of each test kit for all specimens^{††}. Anti-HBc detection reagents were purchased from the Shanghai Kehua company. For specimens with inconsistent

^{††} Batch number 2006071301 for HBsAg, 2006071401 for anti-HBs, 2006095312 for HBeAg, 2006071801 for anti-HBe; anti-HBc batch number 20060705

results, Abbott EIA reagents were used for reconfirmation testing, with neutralization method for final confirmation of HBsAg.

6. Statistical analysis: All data was double inputted into an EPI Data 3.02 software database, and checked for consistency with provinces. After verifying accuracy, the data was analyzed at China CDC, with SAS 9.13 software.

Appropriate sampling weights were constructed for national sample data set. The weight components computed for this design, which involves 160 county strata, 369 township and village clusters and 81,775 persons, consisted of factors reflecting township selection probability, village selection probability within the selected township, age-specific person selection probability within the selected village and post-stratification adjustments to adjust to the sex and age of the entire Chinese population. The weight for each person i can be expressed as follows:

$$w_{kji} = w_k \times w_{j|k} \times w_{i|k,j} \times w_{adj}$$

where,

w_k is the reciprocal of the inclusion probability of township k ;

$w_{j|k}$ is the reciprocal of the conditional inclusion probability of village j within the selected township k ;

$w_{i|k,j}$ is the reciprocal of the conditional inclusion probability of person i within the selected village j ;

w_{adj} is an adjustment factor for person i such that the sum of the weights equals the actual size of the Chinese population.

The Taylor series linearization methods were applied for variance estimation. The prevalence rates of HBV sero-markers include the point estimates and their estimated 95% CIs [10, 63-67]. 95%

confidence intervals (95% CI) were compared for HBV marker prevalence of each variable; 95% CI which did not overlap were considered as statistically significant. Multivariate analysis (forward multinomial logistic regression analysis) of weighted data was used to identify the predictors for high risk of prevalence of HBsAg among the study population.

7. Comparison with 1992 national serosurvey

The prevalence of HBsAg found in the 2006 national survey was compared with that of the 1992 national serosurvey, standardized to national census data in 2000. The target population of the 1992 serosurvey was persons aged 1 to 59 years residing in the same disease surveillance points (counties) in 31 provinces^[32]. Based on the desired sample sizes, first, 3 villages were identified from each county by systematic random selection; secondly, families were randomly selected according the sample size for each village; thirdly, all family members in selected families were investigated and blood were taken for testing for hepatitis B markers.

The mathematical model developed by Goldstein^[10] was used to estimate hepatitis B disease outcomes in China, and HBV chronic infections and deaths prevented by vaccination, using data from the 1992 and 2006 national serosurveys. Key data inputs included birth cohorts (from China national census data and projections), HBsAg and HBeAg prevalence among women of childbearing age, anti-HBc prevalence at 5 and 30 years of age, and proportions of children completing the three-dose vaccination series.

8. Quality control: National specialist groups were convened to guide statistical design, epidemiological investigation, laboratory testing, training and analysis. Two field pilots were conducted before the survey. All the villages were selected at the national level. Appropriate visiting time was considered to ensure high response rate. Trained County CDC staffs were

responsible for administering the questionnaire, collecting the blood specimens, and separating, storing and transporting the serum specimens. 227 of 378 inconsistent laboratory results were confirmed by testing with Abbott reagents, and 151 were tested by neutralization method for final confirmation.

9. Ethical Issues: The survey was approved by the China CDC Ethics Committee, and all study components done according the national ethics regulations. Study participants were informed of the study purpose and the right to keep information confidential.

Results

Overall, the survey investigated 82,078 persons, from whom 82,008 blood samples were collected, and 81,963 with both investigation and blood sample available. Among houses visited, in 93.5% the occupants participated in the survey. Among these, 81,775 (99.6%) were eligible for data analysis; 178 persons were excluded due to being outside the study age range, and for 10 persons serum samples were insufficient.

1. Characteristics of study population

The characteristics of study population are shown in table 16. Among the study population, 20.0% were age 1-4 years, 29.1% age 5-14 years and 50.9% age 15-59 years. The male to female ratio is 0.91:1, and 86.6% were Han ethnicity. The proportions of persons reporting any hepatitis B vaccination were 13.8% among persons age 15-59 years; 72.7% among children age 5-14 years, and 94.5% among children <5 years old (Table 16).

2. Results of HBV testing and distribution of HBV serological markers by age

Among the eligible study population, 4,150 persons were positive for HBsAg (5.1%); 44,928 positive for anti-HBs (54.9%) and 20,163 positive for anti-HBc (24.7%). The weighted

prevalence adjusted to represent the Chinese population age 1-59 years were HBsAg 7.2%; anti-HBs 50.1%, and anti-HBc 34.1%. The major differences between unweighted and weighted prevalences were due to age standardization.

Prevalence of HBsAg varied markedly by age group, increasing steadily from 0.96% among children age 1-4 years, to 8-12% among persons age 20 years and older (Table 17). Differences in prevalence were highly significant for each 5 year age group through age 20 years, after which they did not vary significantly. The trend of prevalence of anti-HBc was similar to that of HBsAg, but continued to increase among adults to reach 50.0% among those age 50-59 years. The prevalence of anti-HBs was inverse to that of HBsAg, decreasing with increasing age from 72% among children age < 5 years, to 45-50% among 15-59 year olds (Table 17).

3. Prevalence of HBsAg by other demographic characteristics

HBsAg prevalence was significantly higher for males (8.6%) than females (5.7%, $p < 0.01$) (Table 18). Persons of the Zhuang minority had the highest weighted HBsAg prevalence (13.4%), followed by Uigur (8.2%) and Han (7.2%) ethnic groups. HBsAg prevalence was significantly lower among Mongolian (2.1%), Hui (3.1%) and Tibetan (5.0%) ethnic groups. Among persons >15 years, the HBsAg prevalence decreased with increasing education level. The highest prevalence was in the illiterate population (9.7%), and was significantly lower in persons with undergraduate degrees (3.1%). Among occupation groups, HBsAg prevalence was lowest in health care workers and students, and highest in public service workers (22.9%) (Table 18).

The HBsAg prevalence among persons living in western regions (8.3%) was higher than the eastern region (6.5%, $p < 0.05$). The prevalence of anti-HBs was slightly higher in urban (52.6%) than in rural areas (49.3%, $p < 0.05$), and in the western region (53.0%) than eastern region (46.8%, $p < 0.05$).

4. Relationship between hepatitis B immunization and prevalence of HBsAg

The prevalence of HBsAg among vaccinated persons was only 2.1%, compared to 9.4% among unvaccinated persons ($p < 0.001$). Similarly, prevalence of anti-HBc was lower among vaccinated (8.5%) than unvaccinated persons (41.1%), while the prevalence of anti-HBs was higher among vaccinated persons (68.2% vs. 42.6% respectively). Among all age groups, the immunized population had a much lower prevalence of HBsAg than un-immunized population; this difference was proportionally greatest in children < 5 years (Figure 7).

5. Comparison with results of the 1992 national hepatitis serosurvey

Compared with the national serosurvey conducted in 1992, the prevalence of HBsAg among children age 1-14 years born after hepatitis B vaccine was recommended for routine childhood immunization was much lower than same age groups in 1992 (Figure 8). In particular, among children < 5 years, prevalence was only 1.0%, 90% lower than in 1992 (9.8%). For persons age 15-19 years, HBsAg prevalence was also moderately lower ($P < 0.05$), but for population aged 20 to 59 years, the prevalence of HBsAg was high in both surveys. In the 2006 survey, the prevalence of anti-HBc was consistently lower than in the 1992 survey, especially in younger age groups (Figure 9).

Among children age 1-14 years, assuming that the force of infection remained the same as in 1992, and using the mathematical model to estimate hepatitis B disease outcomes, an

estimated 16-20 million HBV chronic infections and 2.8-3.5 million future HBV related deaths have been prevented ^[10].

6. HBeAg status among HBsAg positive persons

Among HBsAg positive children <15 yrs, the proportion positive for HBeAg was high (>68%). HBeAg decreased with age to 15% among persons age 40-59 years. The prevalence of HBeAg among HBsAg positive childbearing women was 30.0%, similar to that measured in 1992 (Table 19).

7. Multivariable analysis of HBsAg status for adults and children

To identify factors that affected the prevalence of HBsAg for population aged 15 to 59 years, a multivariable logistic regression was used, the dependent variable being the weighted prevalence of HBsAg; independent variables included gender, location of community (urban vs. rural), region, ethnicity, occupation, education, and immunization history. Results show that male sex (O.R= 1.7), living in the western region (O.R. 1.2), and unvaccinated persons or with vaccination status unknown (OR=2.5, 2.3) had higher likelihood of HBsAg positivity than females, persons living in Eastern region and vaccinated populations, respectively (p<0.01) (Table 20). Among the different ethnic groups, Inner Mongolian, Tibetan and Hui had lower HBsAg prevalence than Han (p<0.05), while Zhuang had borderline significantly higher prevalence. Public workers and others were found to have higher HBsAg prevalence than farmers, while students were found to have lower HBsAg prevalence (P<0.01).

Among children aged 1 to 14 years, multivariate analysis showed the strongest predictors of HBsAg status were vaccination status (unvaccinated or vaccination status unknown, OR=2.5, 2.0), and place of birth (Table 21). Children born in hospital had the lowest prevalence, while

those born in smaller township hospitals or at home had successively higher risk. Children aged 10 to 14 years have higher prevalence than children aged 1 to 4 years (OR=1.9) ($P<0.01$). Among the different ethnic groups, Zhuang (OR=3.5, $p<0.01$) have higher prevalence than Han ethnicity, and other ethnic groups (mainly from southern China) had borderline significant higher risk (O.R = 1.5, $p=0.08$).

Discussion

Hepatitis B is among the most important infectious diseases in China. Based on the national serosurvey in 1992, Chinese population's prevalence of HBsAg was about 10% for all age groups, including young children. The national serosurvey in 2006 shows that for population aged 1 to 59 years, the prevalence of HBsAg has decreased from 9.8% to 7.2%, and for children under 5 years is now only 1.0%. The findings from this survey indicate that the HBsAg prevalence in the whole population is now close to the national goal (less than 7% by 2010), and that the prevalence for children under 5 has already reached both the national goal of less than 1% by 2010, and the WHO Western Pacific Regional goal of less than 2% by 2012.

The most dramatic finding is the decrease in HBV infection risk and HBsAg prevalence among children born after hepatitis B vaccine was recommended for infant routine immunization in 1992, and especially for children born after hepatitis B vaccine was fully integrated into infant routine immunization in 2002. The HBsAg prevalence among children aged 1-4 years has decreased by 90%; in addition, HBsAg prevalence among children aged 5-9 and 10-14 years have decreased by 86% and 72%, respectively. In these cohorts, an estimated 16-20 million HBV chronic infections and 2.8-3.5 million future HBV related deaths have been prevented^[10].

Conversely, the prevalence of anti-HBs for population aged 1-59 years has increased from 27.4% in 1992 before hepatitis B vaccine was recommended, to 50.1% in 2006, with a four fold increase among children 1 to 4 years (from 15.8% to 72.3%).

These data are consistent with many studies globally and in China which show that after introduction of hepatitis B vaccination programs, the prevalence of HBsAg has declined significantly [73, 74, 76-79, 88]. The decline of HBsAg among children in China can be attributed primarily to impact of hepatitis B vaccination [40], and will not only bring the decreased prevalence of HBsAg, but will decrease the future incidence of cirrhosis and hepatocellular carcinoma [71]. Other factors such as the single child policy which reduces horizontal (child to child) transmission in the home, and possibly safer injection practices that reduce nosocomial transmission may have also contributed to this decline, but their precise impact cannot be evaluated in this survey.

The multivariate analysis provided useful insights into risk factors for HBsAg positivity among both the adult and child population, in addition to showing the clear effect of hepatitis B immunization. Among adults, risk factors included male sex, living in Western provinces, belonging to specific ethnic groups (Zhuang), and certain work professions. We found a relatively low HBsAg prevalence among health care workers, but also that public service workers had a high prevalence of HBsAg. Health care workers are in high socio-economic status, have better access to public health services, and some are already protected by vaccination, but high prevalence of HBsAg for social workers in public places is of concern, particularly for risk of long term disease and of discrimination. On detailed review, the high prevalence for public service workers was found in a single cluster of workers with high

prevalence of HBsAg in one large community; outside of this community prevalence among public workers was similar to that of other workers.

Among children, the main risk factors for HBsAg positivity, in addition to lack of vaccination, included birthplace – a predictor of health care and immunization access; age, region and ethnicity. Infants born in hospitals are much more likely to receive a birth dose of HepB than those born at home; in addition, in larger hospitals mothers may be screened for HBsAg, and infants of those found positive may also be given HBIG (1.9% of infants born in larger hospitals between 2002-2005 were given HBIG). The reason for low risk in the western region may be greater recent improvement in vaccination status. While certain northern China groups (Mongolian, Hui) consistently have lower risk, risk is consistently elevated in the Zhuang and others mainly in southern China^[32]. For these groups, particularly the Zhuang, the risk of developing chronic HBV infection remains high among children, in part due to lower accessibility to hepatitis B vaccine before incorporation in routine EPI and removal of financial barriers to infant immunization.

Despite the substantial progress in preventing hepatitis B infection in children, this study confirms the ongoing high prevalence of active HBV infection among adults, and its consequent high risks of HBV transmission and chronic sequelae. The continued high prevalence of HBsAg and HBeAg positive women of child bearing age -- who have a 90% chance of infecting their newborns unless the newborns are treated with vaccine or vaccine plus HBIG soon after birth -- reaffirms the need to further strengthen infant immunization programs, including assuring timely birth doses are given to all children in the poorest areas and to underserved ethnic groups. In addition, expanded vaccination is needed to prevent HBV

infection in older children and adults, among whom 40%-50% remain susceptible to HBV infection. Catch-up vaccination is now planned for children less than 15 years, and immunization is recommended for adults at high risk. Finally, programs to prevent the long-term consequences of HBV infection, through screening and antiviral drug treatment, need to be developed and expanded to reach those at risk of developing cirrhosis and liver cancer. The China government has greatly expanded funding to evaluate strategies for prevention of hepatitis B, and for identifying and treating those persons at highest risk for developing cirrhosis and liver cancer^[86].

One study limitation is that study participation was limited to persons resident in the villages for 6 months or more, and excluded the short-term floating population, who are estimated to comprise 3% of the total population in China (higher in some urban areas)^[68], and unregistered children born outside of family planning. As the majority of these persons come from poorer, rural areas, they may have a relatively high prevalence of HBsAg and lower likelihood of hepatitis B vaccination, therefore, underestimating overall HBsAg prevalence. In addition, 6.5% of the interviewees were not present during the visits.

In conclusion, China has successfully integrated hepatitis B vaccine into routine immunization programs and has achieved very significant impact on decreasing the HBV chronic infection rate among children born after 1992. The national goal of reducing HBsAg prevalence to less than 1% by 2010 among children less than 5 years old will certainly be reached if current immunization programs can be sustained. To achieve the national goal for whole population in decreasing the prevalence of HBsAg to less than 7%, free immunization of infants should be maintained and timely birth dose should be targeted to reach all newborn

infants in the coming years. In addition, expanded vaccination is needed to prevent HBV infection in older children and adults.

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Table 16: Characteristics of study population

Category		Frequency	Proportion (%)	
Age (years)	1~4	16,376	20.0	
	5~14	23,753	29.1	
	15~59	41,646	50.9	
Gender	Male	38,895	47.6	
	Female	42,880	52.4	
Education (15~59 years)	Illiterate	3,993	9.6	
	Primary school	10,125	24.3	
	Middle school	16,615	39.9	
	High school	7,581	18.2	
	Junior College	2,248	5.4	
	Undergraduate Degree	1,068	2.6	
Occupation (15~59 years)	Student	2,232	5.4	
	Farmer	24,144	58.0	
	Worker	5,352	12.9	
	Cadre	2,443	5.9	
	Health care worker	640	1.5	
	Public place	1,336	3.2	
	Others	5,499	13.2	
Ethnicity	Han	70,815	86.6	
	Mongolian	566	0.7	
	Tibetan	1,211	1.5	
	Uigur	1,165	1.4	
	Zhuang	525	0.6	
	Hui	2,441	3.0	
	Others	5,052	6.2	
Urban/Rural	Urban	40,840	49.9	
	Rural	40,935	50.1	
Region	Eastern	27,457	33.6	
	Central	27,218	33.3	
	Western	27,100	33.1	
Immunization	Yes	5,744	13.8	
	15~59 years	No	28,642	68.8
		Unknown	7,260	17.4
		Yes	17,257	72.7
	5~14 years	No	3,274	13.8
		Unknown	3,222	13.6
		Yes	15,475	94.5
	1-4 years	No	481	2.9

Unknown

420

2.6

Table 17: Age Distribution of HBV markers among population aged 1-59 years

Age Group (Year)	Sample Tested	HBsAg		Anti-HBs		Anti-HBc	
		Prevalence*	95%CI	Prevalence*	95%CI	Prevalence*	95%CI
		(%)		(%)		(%)	
1~	16,376	1.0	0.8~1.2	71.2	69.8~72.7	4.1	3.5~4.7
5~	11,909	1.4	1.2~1.7	55.5	52.4~58.5	5.5	4.7~6.3
10~	11,844	3.2	2.6~3.8	57.5	55.4~59.5	10.7	9.7~11.7
15~	2,942	5.4	4.4~6.4	50.3	44.4~56.2	25.0	22.3~27.7
20~	6,778	10.5	8.2~12.7	45.6	42.9~48.4	38.9	36.6~41.3
30~	13,164	8.6	7.5~9.6	46.4	44.1~48.7	41.8	39.3~44.3
40~	10,477	8.5	7.4~9.6	46.0	43.5~48.5	45.1	42.7~47.5
50~59	8,285	8.9	7.1~10.7	50.3	47.2~53.5	50.0	46.6~53.4
Total	81,775	7.2	6.7~7.7	50.1	48.8~51.3	34.1	32.8~35.5

* Weighted prevalence – see text

Table 18: Prevalence of HBsAg by gender, occupation, education, nationality, geographic, vaccine status

		Investigated	Prevalence* %	95% CI
Gender	Male	38,895	8.6	7.8~9.4
	Female	42,880	5.7	4.9~6.6
Education (15~59)	Illiterate	3,993	9.7	7.6~11.7
	Primary school	10,125	8.8	7.9~9.7
	Middle school	16,615	9.1	8.1~10.1
	High school	7,581	8.3	7.2~9.3
	Junior college	2,248	5.9	4.2~7.7
	Undergraduate	1,068	3.1	1.4~4.9
	Occupation (15~59)	Student	2,232	4.0
Farmer		24,144	8.5	7.8~9.3
Worker		5,352	8.9	7.7~10.1
Cadre		2,443	6.5	2.2~10.8
Health care worker		640	2.7	1.2~4.2
Public worker		1,336	22.9	17.4~28.4
Others		5,499	10.0	8.1~12.0
Ethnicity	Han	70,815	7.2	6.9~7.8
	Mongolian	566	2.1	0.8~3.3
	Tibetan	1,211	5.0	4.1~6.0
	Uigur	1,165	8.2	6.0~10.5
	Zhuang	525	13.4	7.4~19.4
	Hui	2,441	3.1	1.2~5.1
	Others	5,052	7.0	5.6~8.4
Region	Eastern	27,457	6.5	5.7~7.3
	Middle	27,218	6.7	5.6~7.8
	Western	27,100	8.3	7.6~8.9
City	Urban	40,840	6.8	5.8~7.8
	Rural	40,935	7.3	6.7~7.9
Vaccinated	Yes	38,476	2.1	1.8~2.4
	No	32,397	9.4	8.4~10.3
	Unknown	10,902	7.8	5.0~10.6

* Weighted prevalence – see text

Table 19: Proportion of HBeAg among HBsAg positive person by gender

Age Groups (Year)	Male			Female		
	HBsAg Positive	Prevalence* (%)	95% <i>CI</i>	HBsAg Positive	Prevalence* (%)	95% <i>CI</i>
	1~4	106	76.4	65.5~87.2	71	74.1
5~14	341	69.4	61.4~77.4	249	67.6	56.4~78.7
15~39	962	38.4	29.6~47.2	874	30.0	25.9~34.1
40~59	814	15.7	11.8~19.6	733	15.0	11.4~18.5

* Weighted prevalence – see text

Table 20: Multinomial logistic regression analysis of HBsAg prevalence among population aged 15 to 59 years

Variable	Category	Frequency	OR	95.0% C.I. for OR		P value
				Lower	Upper	
Gender	Female*	23,637	1.0			
	Male	17,883	1.7	1.5	2.0	<0.01
Urban	Urban *	20,785	1.0			
	Rural	20,735	1.0	0.8	1.2	0.96
Region	Eastern*	13,887	1.0			
	Central	13,833	1.1	0.8	1.3	0.70
	Western	13,800	1.4	1.2	1.6	<0.01
Ethnicity	Han*	36,041	1.0			
	Mongolian	230	0.3	0.2	0.6	<0.01
	Tibetan	1,296	0.5	0.3	0.7	<0.01
	Uigur	608	0.7	0.3	1.6	0.38
	Zhuang	281	1.5	0.9	2.5	0.08
	Hui	580	0.4	0.2	0.7	<0.01
	Others	2,480	0.9	0.7	1.1	0.32
Occupation	Student	2,117	0.6	0.5	0.9	<0.01
	Farmer*	24,136	1.0			
	Worker	5,352	1.1	0.9	1.3	0.36
	Cadre	2,442	1.2	0.4	3.7	0.71
	Health worker	639	0.5	0.2	1.2	0.12
	Public worker	1,335	3.8	2.9	4.8	<0.001
	Others	5,499	1.4	1.1	1.8	<0.01
Education	Illiterate	3,972	2.8	0.9	8.7	0.07
	Primary School	10,097	2.4	0.8	6.3	0.11
	Middle School	16,574	2.4	0.9	5.6	0.08
	High School	7,564	2.2	0.9	4.6	0.76
	Junior College	2,246	1.4	0.8	2.5	0.21
	Undergraduate *	1,067	1.0			
Immunization History	Yes*	5,730	1.0			
	No	28,557	2.5	1.9	3.2	<0.01
	Unknown	7,233	2.3	1.5	3.6	<0.01

*Reference category

Table 21: Multinomial logistic regression analysis of HBsAg prevalence among population aged 1 to 14 years

Variable	Category	Frequency	OR	95% C.I. for OR		P value
				Lower	Upper	
Gender	Female *	19,169	1.0			
	Male	20,960	1.3	0.9	1.9	0.20
City	Urban *	19,999	1.0			
	Rural	20,130	1.1	0.8	1.4	0.65
Region	Eastern*	13,530	1.0			
	Central	13,336	1.0	0.7	1.3	0.23
	Western	13,263	0.6	0.4	0.8	<0.01
Age group (yrs)	1-4*	16,376	1.0			
	5-9	11,909	1.1	0.9	1.4	0.41
	10-14	11,844	1.9	1.3	2.7	<0.01
Ethnicity	Han*	34,668	1.0			
	Inn Mongolia	336	0.2	0.0	1.2	0.08
	Tibetan	1,138	1.0	0.6	1.7	0.98
	Uigur	599	1.9	0.5	7.4	0.35
	Zhuang	244	3.5	1.8	6.9	<0.01
	Muslim	583	0.9	0.3	2.5	0.89
	Others	2,561	1.5	0.9	2.4	0.08
Immunization History	Yes*	32,732	1.0			
	No	3,755	2.5	1.5	4.1	<0.01
	Unknown	3,642	2.0	1.4	3.0	<0.01
Birth Place	County Hospital	19,156	1.0			
	Township hospital	11,266	2.1	1.5	3.5	<0.01
	Home	8,631	4.0	2.7	6.0	<0.01
	Others	1,076	3.5	2.0	6.3	<0.01

*Reference category

Figure 7: Relationship between immunization and prevalence of HBsAg, by age

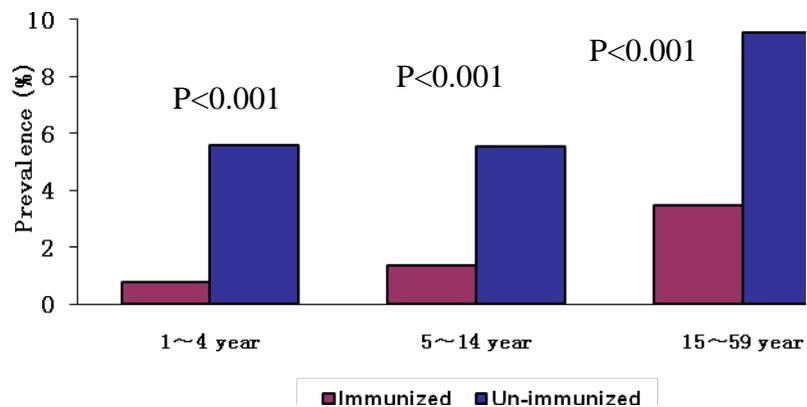


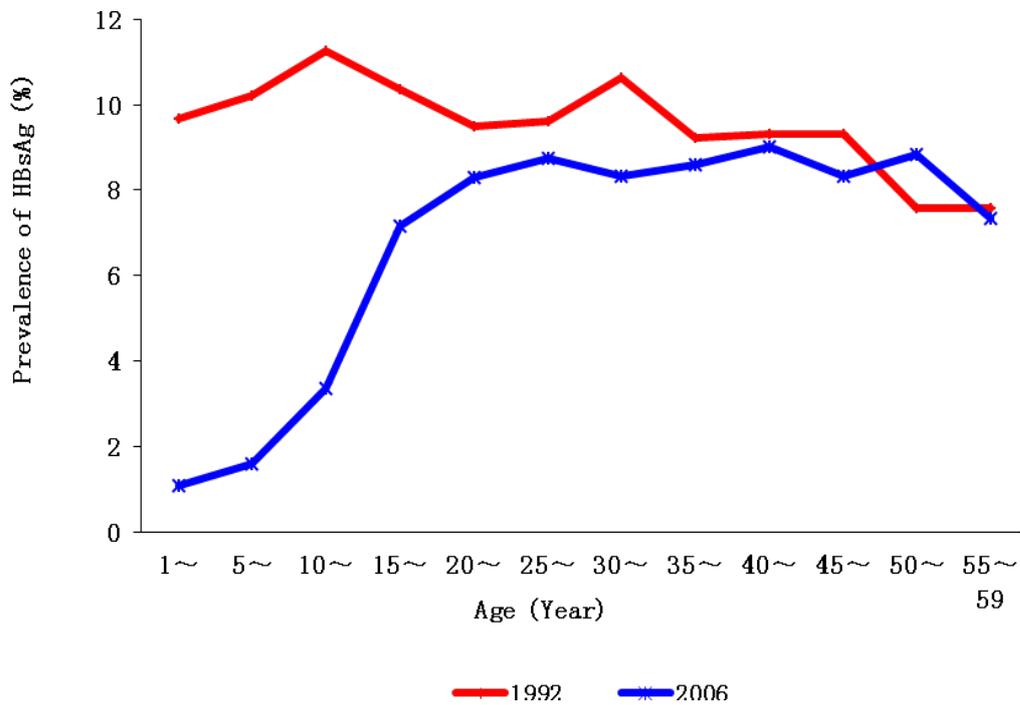
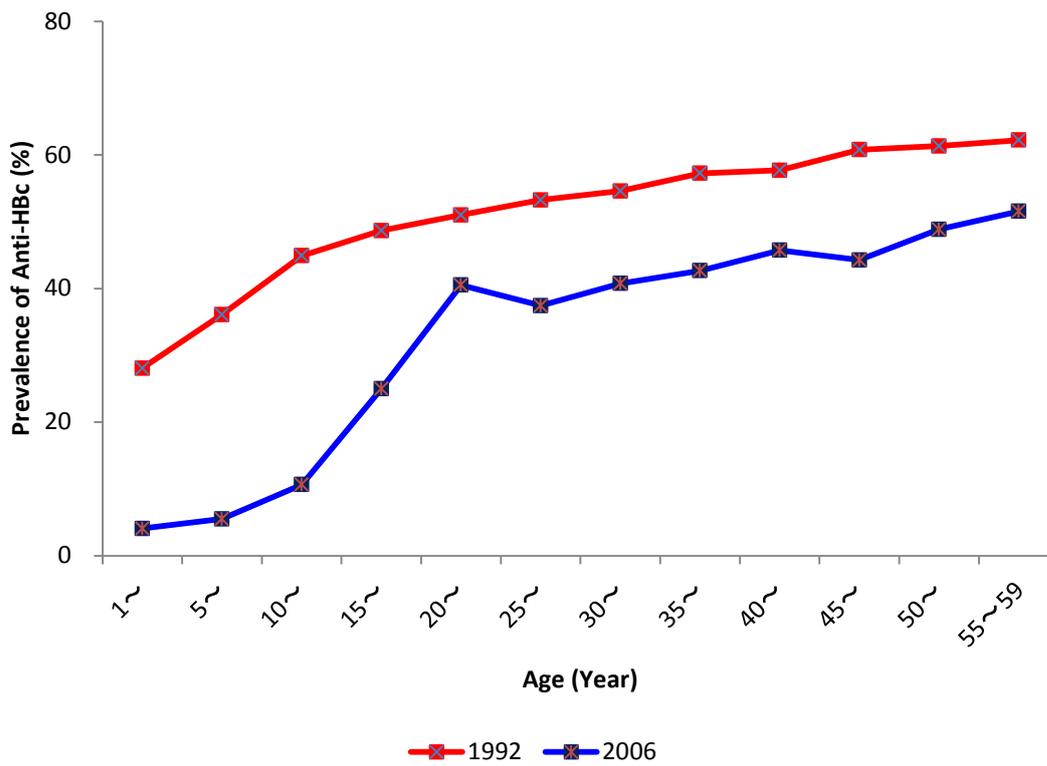
Figure 8: Comparison of Prevalence of HBsAg in 1992 and 2006

Figure 9: Comparison of Prevalence of anti-HBc in 1992 and 2006

4. Chapter 4: Factors Associated with Effectiveness of the First Dose of Hepatitis B

Vaccine in China -1992-2005[£]

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Contribution statement:

Fuqiang Cui was responsible for designing the study, collecting of data, training the investigators, analyzing the data and reporting. Li Li contributed to the data analysis, data collection in the field, reporting and supervision. Stephen C. Hadler provided guidance to the survey and contributed to data analysis and manuscript reviewing. Fuzhen Wang, HuiZheng, Yuansheng Chen and Xiaohong Gong participated in the design of the survey and supervised data collection. Yvan J. Hutin contributed to data analysis and to manuscript revisions. K.Lisa Cairns reviewed the manuscript. Xiaofeng Liang provided the guidance to the survey and contributed to the data analysis. Weizhong Yang organized the survey, supervised the data analysis and reporting.

Note: This study consist is supplemental analysis of the serological survey reported in Chapter 3 .Hence, details about the sampling methods may be obtained from Chapter 3.

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Background: In China, the prevalence of chronic hepatitis B infection was high because of perinatal and early childhood transmission. A three-dose hepatitis B vaccine schedule with a first dose as soon as possible after birth was introduced in 1992 and generalized in 2002 in the Expanded Programme of Immunization (EPI). In 2006, a serological survey evaluated the effectiveness of vaccination.

Methods: We conducted a restricted analysis of the national serological survey that sampled children and collected information on demographic characteristics, birth history, hepatitis B vaccination and hepatitis B surface antigen (HBsAg) status as determined by ELISA testing. We compared children who received the first dose in a timely way (i.e., within 24 hours of birth) with others in terms of HBsAg status, stratified by birth cohort and place of birth.

Results: Three-dose hepatitis B vaccine coverage increased from 60.8% for children born in 1992 -1997 to 93.2% for children born in 2002 - 2005. Meanwhile, timely birth dose coverage increased from 38.7% to 74.4%. Among 29,410 children born in 1992-2005 who had received three vaccine doses and no hepatitis B immune globulin, factors associated with being HBsAg negative in multivariate analysis included receiving a timely birth dose ($p=0.04$), birth after 1998 ($p<0.001$), living in an urban setting ($p=0.008$) and hospital birth ($p=0.001$). The relative prevalence of HBsAg among children receiving the timely birth dose was lower for children born in county or larger hospitals (0.39), intermediate in township hospitals (0.73) and highest at home (0.87).

Conclusions: Hospital birth and receiving a timely birth dose are the main determinants of the field effectiveness of the first dose of hepatitis B vaccine. Efforts to increase the proportion of hospital deliveries are key to increasing timely birth dose coverage and its effectiveness.

Key Words: Hepatitis B, Vaccine, Birth dose, HBsAg

Background

Hepatitis B virus (HBV) infection is more likely to become chronic among persons infected as infants or young children^[89] leading to a substantial burden of chronic liver disease in settings where perinatal transmission is common^[32]. HBV is most efficiently transmitted from the mother to the child during delivery, but also is frequently transmitted among young children in low socioeconomic or poor hygienic conditions. Chronically infected persons are at increased lifetime risk for cirrhosis and hepatocellular carcinoma (HCC) and serve as the main reservoir for continued HBV transmission. Current anti-viral treatment is costly and has limited effectiveness in resolving chronic HBV infection^[33, 83]. Thus, hepatitis B vaccination of infants is the most effective measure to prevent HBV infection and its consequences^[14, 90]. Recommendations advise that vaccination should occur as soon as possible after birth^[14]. In practice, a "timely" birth dose of hepatitis B vaccine is one that is administered in the first 24 hours of life. WHO recommends improving the system to deliver the timely birth dose of hepatitis B vaccine as a priority to eliminate hepatitis B virus transmission in high endemicity regions. However, availability of epidemiological data on the actual field effectiveness of the timely birth dose in the Expanded Programme of Immunization (EPI) is limited.

China has made strong efforts to establish hepatitis B immunization with universal infant immunization^[42, 50]. The recommended schedule includes a first dose within 24 hours of birth and subsequent doses at one and six months of age. This schedule was reported to be 70-95%

effective in preventing transmission from mother to infant. In 1992, the Ministry of Health (MOH) recommended routine immunization of infants against hepatitis B. In 2002, China fully integrated Hepatitis B vaccine into the routine immunization program with support from the Global Alliance on Vaccines and Immunization (GAVI). As a result, three-dose immunization coverage reached high levels (93.4% in 2005) in all areas, including Western provinces ^[50]. In 2006, a serological survey documented the impact of the introduction of hepatitis B vaccine on the prevalence of chronic infection among Chinese children ^[80].

In remote areas, giving hepatitis B vaccine within 24 hours of birth can be difficult logistically, particularly for home deliveries as cold-chain infrastructure is limited in villages ^[91]. Children born at home represented 14% of the birth cohort, or 2.2 million children, in 2005. In 1999 a survey indicated that the coverage of the timely birth dose among these children was only 17% ^[42]. These findings resulted in the development and implementation of a strategy to improve timely birth dose coverage. The strategy included (1) increasing the percentage of hospital births, (2) improving vaccine availability in health facilities, (3) promoting a hospital policy by which “whoever delivers the infant gives the hepatitis B birth dose”, and (4) increasing awareness among providers and parents. Following the implementation of this strategy, the coverage of the timely birth dose increased from 35% among children born in 1992–2001 to 83% among children born in 2005 ^[50]. However, the actual health impact of improved coverage has not been estimated. Hence, we conducted a restricted analysis of the 2006 serological survey to examine in detail the association between the circumstances of administration of the first dose of hepatitis B vaccine and hepatitis B surface antigen (HBsAg) prevalence in infants ^[40].

Methods

1. Study population and design: The study population consisted of children born between 1992 and 2005 who were included in the 2006 national serological survey in 160 national Disease Surveillance Points (DSP) in 31 provinces. These were selected by China Center for Disease Control and Prevention (CDC) to be representative of the population of China. We restricted our study sample to children who had received three doses of hepatitis B vaccine. Among those, we compared the HBsAg prevalence among those with and without timely birth dose. To adjust for confounders, we stratified by birth cohort and place of delivery. In addition, we excluded the small proportion (1.3%) of children who had received hepatitis B immune globulin (HBIG) at birth. Although the national programme does not finance HBsAg screening of pregnant women and HBIG delivery in those who are HBsAg positive, this practice occurs in selected settings, particularly larger, urban hospitals. Information was not available for this study about whether the mother had been screened for HBsAg; however, information was available regarding whether the infant received HBIG. Because of concerns that these children might not be comparable to those who received hepatitis B vaccine alone, we excluded children who received both HBIG and hepatitis B vaccine from our study.

2. Sampling method: The detailed sampling methods are reported elsewhere ^[40, 80]. Briefly, 369 townships were first identified from 160 counties by simple random selection. Second, one village was randomly selected from each township. Third, the population aged 1-4 and 5-14 years was enumerated and selected with a systematic interval from a list of village residents.

3. Investigations: House to house investigations were conducted by trained staff based on the sampled name list. Basic information including gender, birth date, ethnicity, place of birth and immunization history was compiled through parent interview. Immunization status was recorded from the child's home immunization certificate or, if not available, through a review of the child's immunization card at the township immunization clinic. If neither were available, the village doctor's registry was reviewed. In the absence of any information, the child's immunization status was recorded as "unvaccinated" or "unknown". "Full vaccination" was defined as having received three doses of hepatitis B vaccine within 12 months, documented by any immunization record. Timely birth dose vaccination was defined as receiving the first dose of hepatitis B vaccine within 24 hours of birth.

4. Specimen collection and testing: Blood specimens were collected for each study participant, and serum tested at the National Hepatitis Laboratory at the Chinese Centers for Disease Control and Prevention in Beijing. The laboratory used a single lot^{‡‡} of Enzyme-linked immunosorbent assay (ELISA) reagents for HBsAg and antibody to the hepatitis B surface antigen (anti-HBs) testing from Xinchuang Production Company (Xiamen). Reagents to detect antibodies against hepatitis B core antigen (Anti-HBc) were procured from the Kehua Company (Shanghai). For specimens with inconsistent results, ELISA reagents (Abbott) were used for reconfirmation testing. The neutralization method was used for final HBsAg confirmation.

5. Data analysis: All data were entered twice in the computer using EPI Data 3.02 software. After consistency check and accuracy verification, the data was analyzed with SAS

^{‡‡} Batch numbers 2006071301 (HBsAg), 2006071401(anti-HBs), and 20060705(anti-HBc)

9.13 software. The weighted prevalence rates of hepatitis B vaccination and hepatitis B virus (HBV) serological markers included the point estimates and their estimated 95% confidence intervals (CI) ^[63, 80]. Multivariate forward logistic regression was used to identify the factors independently associated with positive HBsAg status.

6. Quality control: National specialist groups were convened to guide statistical design, epidemiological investigations, laboratory testing, logistic services, training plans and data analysis. Two field pilot studies were conducted before the survey. Appropriate time was allotted to visit houses on multiple occasions at different times to ensure a high response proportion. Trained county CDC staff conducted all aspects of the local field work.

7. Ethical issues: Study participants were informed of the study purpose and their right to keep information confidential. The survey was approved by the China CDC Ethical Committee. All procedures were conducted according to the national ethics regulations.

Results

1. Vaccination status and HBsAg prevalence among children born in 1992-2005

Three-dose hepatitis B coverage increased from 60.8% among the 11,844 children born in 1992-1997 to 79.8% among the 11,909 children born in 1998-2001 and to 93.2% among the 16,376 children born in 2002-2005. Meanwhile, timely birth dose coverage increased from 38.7% to 56.8% and 74.4% in these cohorts. HBIG use was reported to be 0.4%, 0.7% and 1.4% of children born in 1992-1997, 1998-2001 and 2002-2005, respectively. Among the 352 children who received HBIG, 266 (75.6%) were born at hospitals at the county level or above, 70 (19.9%) were born at township hospitals, 14 (4.0%) were born at home, and 2 (0.5%) were born in other settings. Among children born between 1992 and 2005, the prevalence of HBsAg

was 1.3% among fully immunized children, 2.9% for children receiving an incomplete vaccine series and 5.0% for children not immunized. The prevalence of HBsAg was lower among children who received a timely birth dose or were born in hospital (Table 22). The remainder of the analysis was based upon the 29,420 children born in 1992-2005 who had received three hepatitis B vaccine doses without HBIG. These accounted for 55.9% of children born in 1992-1997 (N=6,624), 73.7% of children born in 1998-2001 (N=8,780) and 85.6% of children born in 2002-2005 (N=14,016)

2. Timely birth dose and prevalence of HBsAg among fully immunized children with no HBIG

Among children fully vaccinated but who did not receive HBIG, 73% of infants received a timely birth dose. Others received hepatitis B vaccine 2 -7 days after birth (4.7%), and 8 -27 days after birth (4.3%), and more than 27 days after birth (18%). The prevalence of HBsAg was 0.97% among children fully vaccinated with a timely birth dose, 0.41% for children fully vaccinated who received the first dose after 24 hours but before seven days and 1.4%-2.7% among children fully vaccinated who received the first dose eight days or later (Table 23).

3. Timely birth dose and prevalence of HBsAg among fully immunized children with no HBIG, by birth cohort

For all birth cohorts of children fully vaccinated without HBIG, the HBsAg prevalence tended to be lower among those who had received a timely birth dose. Overall, the later the birth dose, the higher the prevalence of HBsAg. However, a delay of seven days after birth was not associated with higher HBsAg prevalence (Table 24).

4. Timely birth dose and prevalence of HBsAg among fully immunized children with no HBIG, by birth place

Among children born between 1992 and 2005 fully immunized without HBIG, 73% had received the first dose on time and 55% were born at a hospital at the county level or above (Table 25). Regardless of birth setting, the prevalence of HBsAg was significantly lower among children who had received a timely birth dose. However, there was a trend for this difference to be larger in hospitals at the county level or above (prevalence ratio: 0.39), intermediate in the township hospital (prevalence ratio: 0.73) and less marked in homes and other settings, (prevalence ratio: 0.87 and 0.84, respectively). A global chi-square test suggested that these prevalences were heterogeneous ($\chi^2=27.78$, $p<0.001$).

5. Multivariate regression analysis

The multiple logistic regression examined the effect of the timing of first dose (within one day, after one day but within seven days, eight-14 days, 15-27 days, 28-180 days, 181 days above) stratified stepwise by ethnicity (Han versus others), region (East, Central, West), setting (urban versus rural) and birthplace. Overall, the most important factor was the location of birth, with the lowest prevalence of HBsAg among children born in hospitals at the county level or above and the highest among those born at home. Residing in an urban setting was also independently associated with lower HBsAg prevalence. Children who had received the first dose within seven days of birth had an HBsAg prevalence that was lower than those who had received it within 24 hours. However, this difference was not statistically significant. Children who had received the birth dose after seven days had higher HBsAg prevalence, but this difference was significant only for those who received the birth dose after 181 days (Table 26).

Discussion

With respect to the factors associated with HBsAg prevalence among children fully vaccinated but who did not receive HBIG, the timing of the first dose of vaccine and the birthplace played the greatest roles. In addition, the effect of the timing of the birth dose varied according to birthplace.

Children born in hospitals had a lower HBsAg prevalence than those born at home. In China, mothers who give birth in hospitals usually have more education and higher family income than mothers who give birth at home. They may have better acceptance of medical and preventive health care^[92, 93], and thus be more willing for their babies to be vaccinated early. In addition, it is logistically easier to give a child born in hospital a timely first dose of hepatitis vaccine as opposed to a child born at home. Taking these factors into account, it is not surprising that timely birth dose coverage was higher among children born in hospitals. However, our data suggested that birth in hospital per se was associated with lower HBsAg status independently of the higher birth dose coverage in hospitals.

The HBsAg prevalence was lower among children who received the first dose within 24 hours than among those who received it more than 7 days after birth. This suggests that providing the first dose of hepatitis B vaccine within 24 hours of delivery provides additional protection. Published studies suggest that hepatitis B vaccine should be given within 24 hours after birth^[94, 95] to provide early protection^[1]. Most countries have strategies to deliver timely birth doses^[77, 96].

While vaccine delivered more than seven days after birth resulted in a higher prevalence of HBsAg, in our study we failed to detect a major difference of HBsAg prevalence between

children who received the first dose within 24 hours and those who received it within seven days of birth. Delays of the birth dose within seven days did not seem to be associated with substantially lower protection in each birth cohort. A number of factors may explain this finding. First, vaccine given within one week may still be effective since the incubation period of the virus may be six months or longer^[14, 89, 97]. Second, as a result of the sustained efforts for hepatitis B control in China, the prevalence of HBsAg among childbearing women was lower in 2006 (6.7%) than in 1992 (9.8%)^[80]. Therefore, vertical transmission may play less of a role than in the past^[32, 96].

The results of our analysis also indicate that the effectiveness of the birth dose differed by birth setting. Four factors may have had an impact. First, caliber of staff and equipment may be better at larger hospitals (county and above). In these settings, professionals may be better trained and more skilled, resulting in better vaccination technique. The quality of cold chain equipment may have been better in larger hospitals. At peripheral levels in China, cold chain equipment is limited and the vaccine could have been exposed to freezing which could have affected potency^[88]. Second, the quality of data at lower levels may be less good. As a result, some children recorded as being vaccinated within 24 hours after birth may in fact have been vaccinated later than this. Third, screening mothers for HBsAg to provide HBIG to infants is a practice that is more common in larger, better equipped, urban hospitals. We excluded children who received HBIG from our study, and may thus have decreased the risk of perinatal transmission in the hospital-born babies included in the study relative to those born in lower level facilities. Finally, while doctors are instructed to give both hospital and home-born

children a dose of vaccine at the first opportunity, this opportunity may occur later for children born at home.

This study was subject to some limitations. First, as already discussed, some children may have been misreported as being vaccinated with 24 hours when they were not. Second, we had no data on pre-natal screening. Babies of mothers identified as HBsAg positive may have preferentially received timely birth doses leaving a pool of babies of HBsAg-negative mothers who would be less affected in terms of HBsAg status by delays in receiving the first dose of vaccine. Third, we excluded children who had received HBIG. This exclusion of some children at high risk of perinatal transmission may have led to an underestimation of the relative effect of the timely birth dose in this population.

In conclusion, controlled trials indicate that receiving a dose of vaccine within 24 hours of birth is highly effective for hepatitis B prevention among children born to infectious HBsAg-positive, and HBeAg-positive mothers. Hence, this remains the gold standard, and hepatitis B vaccination programmes should provide the birth dose as soon as possible, within 24 hours if feasible. While our field data suggest that delayed delivery of the first dose within one week is not associated with high HBsAg prevalence, these findings should be confirmed by further studies before forming the basis of programmatic recommendations. However, these findings do support that there is still a benefit in administering the first dose as soon as possible if the first 24 hour deadline has passed. Finally, our data suggest that, in China, pregnant women should give birth in hospital. In these settings (1) the birth dose coverage is at its highest and (2) the birth dose has maximum effectiveness. Increasing hospital births is not only the most effective programmatic way to increase the coverage of the hepatitis B birth dose, it

also results in reduction of neonatal and maternal mortality and promotion of neonatal tetanus elimination.

Table 22: Prevalence of HBsAg according to selected characteristics, 1992-2005 birth cohorts, China

Factors	No. tested	HBsAg prevalence				
		Un-weighted		Weighted		
		No.	%	%	95% CI	
Birth cohort						
1992-1997	11,844	399	3.4	3.69	3.68-3.71	
1998-2001	11,909	191	1.6	1.63	1.62-1.65	
2002-2005	16,376	177	1.1	0.95	0.94-0.96	
Number of vaccine doses						
0	7,397	393	5.3	4.98	4.96-5.01	
1-2	759	16	2.1	2.94	2.88-3.00	
3	31,973	358	1.1	1.29	1.28-1.30	
HBIG received						
Yes	352	8	2.3	1.34	1.24-1.44	
No	36,330	667	1.8	2.19	2.19-2.20	
Unknown	2,929	62	2.1	2.75	2.71-2.79	
Timely birth dose						
Yes	23,535	212	0.9	1.01	1.00-1.02	
No	16,594	555	3.3	3.33	3.32-3.35	
Place of birth						
County hospital	19,156	178	0.9	1.09	1.08-1.10	
Township hospital	11,266	184	1.6	1.75	1.73-1.76	
Home	8,631	356	4.1	4.52	4.49-4.54	
Other	603	22	3.6	3.62	3.53-3.70	

Table 23: Prevalence of HBsAg among children fully vaccinated against hepatitis B according to the timing of the first dose, 1992-2005 birth cohorts, China*

First dose of hepatitis B vaccine	No. Tested	HBsAg Un-weighted		HBsAg weighted	
		No. positive	%	%	95% CI
Within 1 day	21,529	193	0.90	0.97	0.96-0.98
1-7 days	1,375	8	0.58	0.41	0.39-0.43
8-14 days	547	10	1.83	2.33	2.25-2.41
15-27 days	722	12	1.66	1.40	1.35-1.45
28-180 days	3,220	57	1.77	1.50	1.43-1.62
181 Days+	2,027	49	2.53	2.71	2.68-2.74
Total	29,420	329	1.12	1.31	1.30-1.32

*Excluding infants who received HBIG

Table 24: Prevalence of HBsAg among children fully vaccinated against hepatitis B according to the timing of the first dose, by age cohorts, 1992-2005 birth cohorts, China

Birth Cohort	Timing of first dose	No. tested	HBsAg Prevalence			
			Un-weighted		Weighted	
			No.	%	%	95% CI
1992-1997	Within 1 day	4,164	67	1.61	2.18	2.15-2.21
	1-7 days	314	2	0.64	0.37	0.33-0.41
	8-14 days	146	3	2.05	1.29	1.19-1.40
	15-27 days	185	5	2.7	2.77	2.64-2.91
	28-180 days	879	11	1.25	1.27	1.23-1.31
	181 days+	936	35	3.74	3.95	3.91-4.00
	Total	6,624	123	1.86	2.46	2.44-2.48
1998-2001	Within 1 day	6,194	43	0.69	0.60	0.59-0.61
	1-7 days	480	2	0.42	0.36	0.33-0.38
	8-14 days	176	6	3.41	4.41	4.24-4.58
	15-27 days	215	1	0.47	0.24	0.21-0.28
	28-180 days	1,074	20	1.86	1.65	1.59-1.67
	181 days+	641	8	1.25	0.94	0.91-0.97
	Total	8,780	80	0.91	0.85	0.85-0.86
2002-2005	Within 1 day	11,171	83	0.74	0.65	0.64-0.67
	1-7 days	581	4	0.69	0.56	0.51-0.62
	8-14 days	225	1	0.44	0.14	0.10-0.18
	15-27 days	322	6	1.86	1.53	1.43-1.64
	28-180 days	1,267	26	2.05	1.57	1.51-1.62
	181 days+	450	6	1.33	1.32	1.24-1.40
	Total	14,016	126	0.90	0.77	0.76-0.79

Table 25: Prevalence of HBsAg among children fully vaccinated against hepatitis B according to the timing of the first dose, by birth place, 1992-2005 birth cohorts, China

Place of birth	Timing of first dose	No. tested	HBsAg					Relative prevalence* (95% CI)
			Crude		Weighted			
			No. positive	%	%	95% CI		
County above	Within 24 hours	13,531	94	0.69	0.65	0.64-0.66	0.39 (0.36-0.39)	
	After 24 hours	2,692	21	0.78	1.70	1.68-1.73		
Township	Within 24 hours	6,381	68	1.07	1.19	1.17-1.20	0.73 (0.71-0.75)	
	After 24 hours	2,564	44	1.72	1.62	1.60-1.65		
Home	Within 24 hours	1,472	29	1.97	1.99	1.95-2.03	0.87 (0.84-0.90)	
	After 24 hours	2,482	69	2.78	2.28	2.25-2.32		
Others	Within 24 hours	141	2	1.42	2.30	2.15-2.44	0.84 (0.75-0.95)	
	After 24 hours	147	2	1.36	2.71	2.58-2.85		
Total	Within 24 hours	21,525	193	0.90	0.97	0.96-0.98	0.52 (0.51-0.53)	
	After 24 hours	7,885	136	1.72	1.86	1.85-1.88		

*Relative prevalence is ratio of weighted HBsAg among infants receiving birth dose within 24 hours to that among after 24 hours

Table 26: Factors associated with HBsAg positive status in multivariable regression analysis, 1992-2005 birth cohorts, China

Variables	Categories	Frequency	Odds ratio	95% CI	P value
Timing of the first dose	Within 1 day*	21,525	1.00		
	2-7 days	1,371	0.54	0.27-1.11	0.093
	8-14 days	545	1.53	0.80-2.92	0.200
	15-27 days	722	1.26	0.69-2.30	0.445
	28-180 days	3,220	1.31	0.95-1.81	0.102
	181 days+	2,027	1.54	1.10-2.20	0.017
Birth cohort	1992-1997*	6,624	1.00		
	1998-2001	8,771	0.52	0.39-0.70	<0.001
	2002-2005	14,015	0.55	0.42-0.72	<0.001
Ethnicity	Han*	26,689	1.00		
	Others	2,721	0.95	0.65-1.39	0.781
Setting	Urban	15,707	1.00		
	Rural	13,703	1.39	1.09-1.77	0.008
Region	Eastern*	10,533	1.00		
	Central	10,599	1.23	0.95-1.60	0.124
	Western	8,278	1.06	0.79-1.43	0.698
Place of birth	County*	16,223	1.00		
	Township	8,945	1.54	1.17-2.03	0.002
	At home	3,954	2.52	1.86-3.43	<0.001
	Others	288	1.51	0.55-4.14	0.427
Constant		-4.731	-		

* Reference categories

5. Chapter 5: Preventing Hepatitis B through universal vaccination: Reduction of inequities through the GAVI China Project[※]

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Contribution statement:

Fuqiang Cui was responsible designing the evaluation, training the investigators, analyzing the data and reporting. Xiaofeng Liang and Xiaohong Gong participated in the design of the survey and supervised data collection. Yuansheng Chen, Fuzhen Wang, HuiZheng, Zhenhua Wu, and Ning Miao contributed to data collection and data analysis. Stephen C. Hadler and Yvan J. Hutin helped designing the survey, provided guidance for the implementation of the survey and contributed to the data analysis, reporting and manuscript reviewing. Huiming Luo supervised the implementation of the survey and the field supervision. WeiZhong Yang organized the survey and reviewed the manuscript.

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Background

In 1992, a World Health Assembly resolution called for all countries to integrate hepatitis B vaccination into their routine childhood immunization programmes by 1997^[16]. In 2010, WHO estimated that each year, 500,000-700,000 deaths were caused by hepatitis B^[98], many of those in Asia^[98]. Use of hepatitis B vaccine in routine immunization has been shown to be cost effective^[14]. However, it may represent an investment that is too large for national governments to pay. The risk then is of selective introduction among those who can afford it, which results in inequities^[99]. Inequities in viral hepatitis burden and poverty mutually aggravate each other while equity in preventive health services breaks this cycle^[100,101-103]. Thus, immunization must be accessible to all^[104]. Donors, lenders and partners, including the Global Alliance for Vaccine and Immunization (GAVI), invest funds to help national governments introduce new vaccines free of cost in the entire population. Overall, immunization services, including mass immunization campaigns have a documented track record of working against inequities^[101, 105,106]. Studying these inequities in disease burden or access to vaccine may help reducing them through adapted intervention, including free, universal immunization.

In 1985, Chinese manufacturers initiated domestic production of hepatitis B vaccine which resulted in local introduction on the Chinese market. In 1992, use of the vaccine in the absence of any national guidelines already resulted in a three-dose vaccine coverage of 30% among infants, while hepatitis B timely birth dose (TBD: within 24 hours of birth) coverage reached 22%^[40]. The same year, the Ministry of Health first recommended hepatitis B vaccine for routine vaccination of infants because of the high prevalence of hepatitis B virus infection and

the large disease burden. However, local health departments charged parents for the vaccine and administrative costs. As a result, infant vaccination occurred primarily in large cities of wealthier Eastern provinces^[107]. In 1999, three-dose coverage of hepatitis B vaccine reached 71%^[42], but was 26% higher in urban than in rural populations^[108] and 1.5 higher in males than in females^[109, 110]. Moreover, surveys indicated that the TBD coverage was only 44%. Two years later, in 2002, the three dose coverage had increased to 84% but remained 38% higher among children of higher socio-economic status than among others^[68, 111]. The cost of vaccination was one of the reasons of the slow progress^[112,113]. Thus, identifying a financial mechanism to reach all infants became a priority^[32].

In 2002, China collaborated with GAVI to implement a five-year project to provide free hepatitis B vaccine and Auto-Disable syringes (AD) for all infants in China^[107]. This was planned through GAVI support of the Western region and 223 poverty-affected counties of the Central region. China received GAVI support because of (1) high prevalence of hepatitis B, (2) low vaccine coverage in poorer areas, (3) a national annual Gross Domestic Product (GDP) per capita < \$1,000 with a government that could not afford universal, free vaccination and (4) political commitment to protect infants at risk. The 76 million USD project was funded 50% by GAVI and 50% by the Government of China. Central and sub-national levels shared a common responsibility and clarified each other role and responsibilities. GAVI support was used for the purchase of vaccine and injection devices. In addition, the government of China implemented a strategy that included (1) increasing awareness of the importance of TBD among providers and parents, (2) intensifying training for health care worker (HCW), (3) improving hospital delivery rate through provisions of subsidies, (4) building bridges between maternal and child health

(MCH) and immunization services and (5) subsidizing providers. Monitoring and supervision mechanisms were also built into the project. A national coverage survey in 2004 already showed progress, with a three-dose hepatitis B coverage of 94% in the East, 92% in the Centre and 68% in the West ^[51]. In 2005, the Government decided to abolish user's fees and all hepatitis B vaccination were provided for free. Overall, from 2002 to 2007, the GAVI China project provided doses of hepatitis B vaccine for 29,282,364 children, along with 206,649,679 AD syringes. In 2008, the project was extended for two years. In 2010, we conducted a final evaluation to measure hepatitis B coverage and progress in equity with respect to protection against hepatitis B.

Methods

We reviewed routinely reported coverage data and conducted a national stratified, validation, cross-sectional survey in October 2010.

Definitions

We defined a timely birth dose of hepatitis B vaccine (TBD) as a dose of hepatitis B vaccine received by a surviving infant within 24 hours after birth. The targets of the GAVI project were to increase (1) three dose coverage of hepatitis B vaccine (HepB3) in children under 12 months to 85% and (2) to increase TBD coverage to 75%. These two targets had to be achieved at the county level. We defined the urban and rural setting according to the geographic location and the national statistical bureau definition. We defined regions as Eastern (Beijing, Tianjin, Liaoning, Shandong, Jiangsu, Shanghai, Zhejiang, Fujian, and Guangdong), Central (Hebei, Shanxi, Heilongjiang, Jilin, Henan, Anhui, Hubei, Hunan, Jiangxi, and Hainan) and Western (Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet,

Shaanxi, Gansu, Ningxia, Qinghai, and Xinjiang,) according to national classification by geographic location and economic status^[80, 107].

Sampling methodology

We used the methods recommended by WHO to select a cluster sample of health care facilities for the purpose of injection safety assessments (The final GAVI evaluation included an injection safety assessment, see chapter 6)^[114]. The injection safety assessment component of the final evaluation of the GAVI project was used to design the sampling strategy as its required confidence intervals that needed to be calculated using the WHO reference guidelines. First, we stratified the country into Eastern, Central and Western regions. Second, in each region, we selected eight counties using the probability proportional to population size (PPS) methods. Third, in each selected county, we selected 10 townships at random from the list and the county-level hospital. Fourth, in each selected township, we investigated the township hospital that maintained all immunization records. In each region, the sample size was eight clusters of 10 facilities, for a total of 80 facilities as per the WHO guidelines^[114].

In addition, we reviewed each of the county hospitals, for timely birth dose evaluation. Finally, we collected timely birth dose data from the county level hospital that accounted for a large proportion of the deliveries in each county.

Data collection

We constituted a national team by recruiting 40 health professional working in EPI from national and provincial CDCs, trained them using the same standard protocol for data collection, and then divided eight groups who each visited 24 counties from 12th to 30th October 2010. Provincial staff recruited did not go to their own provinces. Teams collected birth cohort, DTP

and hepatitis B vaccine coverage data, including TBD and full series, in each township hospital.

Data analysis

Coverage

Ratios: We calculated the ratio of the number of three doses of hepatitis B vaccine administered/the number of infants targeted for DTP3 as an indicator of the progressive introduction of hepatitis B vaccine into routine EPI. We calculated the ratio of TBD administered/infants targeted for DTP1 as an indicator of the progress in TBD coverage from 2004 onwards (TBD coverage was not routinely reported before 2004). These indicators were only calculated in the GAVI supported areas.

Reported coverage: Each calendar year, the various level of the CDC system (county, prefecture, provincial and national) reported coverage calculated by dividing the number of doses administered by the number of children registered for vaccination in health care facilities. This data was available for the whole of China.

Estimated coverage: Because the number of children registered for vaccination differed from the National Bureau of Statistics figures, we calculated estimated coverage using denominators from the National Statistical Yearbook^[115]. As studies reported that the some townships that did not report vaccination status of children to county level^[116], we adjusted numerators to take this underreporting into consideration, according to China-specific WHO recommendations^[117, 118]. In this adjustment, the numerator consisted of those recorded as vaccinated plus half of the difference between the estimated National Bureau of Statistics birth cohort as drawn from the National Statistical Yearbook and the birth cohort as estimated by the

EPI. Since 2005, China has used this adjustment method to officially report vaccine coverage estimates through the WHO and UNICEF Joint Reporting Form (JRF). Estimated coverage data were available for the whole of China.

Surveyed coverage: We calculated survey coverage estimates by dividing the number of doses administered by the number of children registered on the birth cohort at the township level hospital. This data was available for the sample of townships investigated as part of the 2010 final evaluation.

Equity indicators

We used coverage and ratios to measure inequities and gaps. We compared coverage among males and females, as well as among urban and rural area. We obtained data regarding the 2009 GDP per capita for each county (which was estimated based on the reported data of previous year) from in our sample from the Internet site of the county government. We compared the ratio of vaccine coverage across counties regrouped in GDP quintiles. We used the Contraction Index (CI) to measure the equity of coverage among regions, we considered $CI < 0$ as pro-rich, 0 was equity, > 0 was considered as pro-poor ^[106]. CI was defined as the following:

$$S = \frac{1}{2} \sum_{i=0}^{n-1} (Y_i + Y_{i+1})(X_{i+1} - X_i), \quad CI = 2 \times (0.5 - S)$$

Where, X was proportion of accumulated population by GDP rank, Y was the accumulated coverage by the rank, $Y_0=0$, $X_0=0$ ^[119].

We used SPSS and Excel software for data analysis.

Results

1. Vaccine coverage by year

Progress in hepatitis B vaccine introduction in GAVI supported areas: Overall, in the GAVI supported areas, the HepB3/DTP3 ratio increased from 57% in 2002 to 94% in 2009; a 37% increase in seven years; with the most dramatic increase between 2002 and 2005. The TBD/DTP1 ratio increased from 64% in 2004 to 88% in 2009; a 25% increase in five years (Figure 10).

National surveyed coverage: We visited 244 townships as part of the final evaluation (71 in the East, 86 in the Centre and 87 in the West). Overall, in these 244 townships, surveyed TBD coverage increased from 60% in 2002 to 91% in 2009 and surveyed three dose of hepatitis B vaccine coverage increased from 71% in 2002 to 93% in 2009 (Table 27, Figure 11).

2. Regional and gender differences

Three dose of hepatitis B vaccine: In Eastern areas, surveyed coverage of three dose hepatitis B vaccine increased from 89% in 2002 to 92% in 2009 (+3%). In Central areas, during the same time, it increased from 65% to 96% (+31%), bringing the Central/Eastern coverage ratio from 0.73 to 1.04. In Western areas, it increased from 47% to 90% (+43%), bringing the Western/Eastern coverage ratio from 0.53 to 0.98 (Table 27).

TBD: In Eastern areas, surveyed TBD coverage increased from 82% in 2002 to 96% in 2009 (+14%). In Central areas, it increased from 51% to 86% (+35%), bringing the Central /

Eastern coverage ratio from 0.63 to 0.90. In Western areas, it increased from 26% to 86% (+60%), bringing the Western/ Eastern coverage ratio from 0.3 to 0.9.

On the basis of the 2010 survey data, the concentration index for three dose of hepatitis B vaccine decreased from 0.12 in 2002, to 0.02 in 2005 and to 0 in 2008 and 2009.

3. Vaccination coverage according to GDP per capital

From 2002 to 2009, the surveyed three dose of hepatitis B vaccine coverage increased from 71% to 93% overall. In the 1st quintile, it increased from 80% to 98% while in the 5th quintile, it increased from 53% to 93%. The ratio of 5th to 1st quintile coverage increased from 0.66 in 2002 to 0.95 in 2009 (Table 28). Reported coverage and estimated coverage showed less progress in terms of the 5th to 1st quintile coverage ratio from 2002 to 2009, from 0.95 to 1, and from 0.85 to 0.97, respectively (The baseline 2002 values were already higher). Although the ratio was higher between 2nd and 4th quintile than ration between 5th and 1st in 2002, but all ratios reached up to 1 in 2009.

From 2002 to 2009, the surveyed TBD coverage increased from 60% to 91% overall. In the 1st quintile, it increased from 76% to 97% while in the 5th quintile, it increased from 27% to 85%, for as ratio of 5th to 1st quintile coverage ratio that increased from 0.35 in 2002 to 0.88 in 2009 (Table 29). Reported coverage and estimated coverage showed less progress in terms of the 5th to 1st quintile coverage ratio from 0.62 in 2004 to 0.90 in 2009, from 0.72 in 2002 to 0.94 in 2009, respectively. The ratio trends were similar as trend of three dose of hepatitis B vaccine.

4. Proportion of counties having reached GAVI targets (Reported coverage)

As of 2009, with respect to the three doses of hepatitis B vaccine criteria (hepB3/DTP3 ratio), among 22 GAVI project provinces, 16 provinces had reached the GAVI China target in all counties and five additional provinces had reached it in 85% of counties. One province, Tibet had only reached the target in 76% of counties. Overall, 98% of the GAVI-supported counties reached the three dose of hepatitis B vaccine goal. These accounted for 99% of the population in the GAVI-supported areas.

As of 2009, with respect to the TBD criteria, among 22 GAVI project provinces, 11 provinces met the target in all counties, six provinces had met the target 85% of counties, and only five (Tibet, Gansu, Yunnan, Guizhou, and Sichuan) had reached target in less than 85% of counties (Figure 12). Overall, 80% of the GAVI-supported counties reached the TBD goal. These accounted for 79% of the population in the GAVI-supported areas.

In terms of both targets, 80% of the GAVI-supported counties reached both the three dose of hepatitis B vaccine and TBD goals. These accounted for 79% of the population of the GAVI-supported areas.

5. Validation of reported and estimated coverage

Overall, the reported three dose of hepatitis B vaccine coverage increased minimally from 95% in 2002 to 99% in 2009 (+4% in 7 years). According to these reported data, the Western/Eastern coverage ratio only progressed from 0.92 to 0.99 between 2002 and 2009. Estimated three dose of hepatitis B vaccine coverage increased more from 74% in 2002 to 96% in 2009 (+22% in 7 years). The Western/Eastern estimated coverage ratio progressed more from 0.85 to 0.94 between 2002 and 2009. Surveyed three dose of hepatitis B vaccine coverage showed the

largest increase, from 71% in 2002 to 93% in 2009 (+22% in 7 years). Surveyed coverage showed the largest progress in terms of the Western/Eastern coverage ratio, from 0.53 to 0.98 between 2002 and 2009.

Discussion

From 2002 to 2009, following GAVI support to the hepatitis B vaccination programme, the national coverage of three dose of hepatitis B vaccine increased dramatically, from 71% to 93% as per survey data. Overall, the 2002 coverage gap that affected Western and Central provinces was closed in 2009, with West/East coverage ratio that increased from 0.53 to 0.98 and a Centre/East coverage ratio that increased from 0.74 to 1.0. Several factors may explain this improvement. First, GAVI provided the hepatitis B vaccine and AD syringes to Western provinces and national poverty counties in the Central region, lifting the cost barrier to infant vaccination. The evolution of the estimated ratios of three dose of hepatitis B vaccine expressed in dose administered/DTP3 targeted indicated that in GAVI-supported areas, the project was effective at integrating hepatitis B vaccine in routine EPI. Second, government of China support of new policy was a major co-factor. In 2002, the HepB3/Targeted DTP3 ratio was 0.72 when the vaccine was free but with user-fees; by 2005, it had increased to 0.91 when services fees were abolished. Third, the government of China trained health care providers to increase their awareness. Fourth, social mobilization and supervision in 2002-2009 improved awareness of parents, who sought vaccination more actively. Finally, the government of China allocated funds to each province to improve universal vaccination among infant^[117].

The final evaluation survey provided the most reliable estimates of coverage. Even though our survey may have suffered from biases, it generated the best estimate available. The 2004

national population-based EPI coverage survey validated our final survey estimates for children born in 2003 (89.8% three dose of hepatitis B vaccine coverage in the 2004 survey versus 84.0% in our survey). The 2006 national population-based serological survey also validated our final survey estimates for children born in 2005 (93.4% three dose of hepatitis B vaccine coverage in the 2006 serological survey versus 90.28% in our survey). In contrast, reported and estimated coverage differed from those obtained from the final evaluation survey. According to the reported three dose of hepatitis B vaccine coverage, coverage ratio between West and the 1st quintile only progressed from 0.95 to 1.0. A number of factors may explain this difference. First, the reported coverage is based upon a list of registered children that may not represent the real target population^[120]. For example, migrant children and children born out of plan may not be registered on the target lists. This could underestimate the denominator. Second, local CDCs may overestimate their performance while reporting coverage data. This could over-estimate the numerator. Third, grass root level may make mistakes when handling and reporting data through the reporting system. This could under or over-estimate the reported coverage. As a result, the reported coverage is consistently higher than surveyed coverage and tends to over-estimate performance^[118]. More specifically, this misrepresentation may hide inequities. Hence, reported coverage data need validations before they can be used to guide efforts to reduce inequities^[120]. Estimated coverage provided a somewhat intermediate figure that still suffered from limitations since it was based upon ad-hoc adjustments in the numerators and denominators. China used this adjustments method since 2004 to report vaccination coverage but the methods used have not been validated or evaluated using sensitivity analyses. Although there was a difference among reported, estimated and surveyed data, the surveyed data that

were more reliable pointed to the largest coverage increase and inequities reductions between 2002 and 2009.

In China, between 1992 and 2009, the GDP per capita increased from 2,311(USD 419)[121]to 25,575 RMB (USD 3,744)^[122], (a 8.94 times increase, 4.6 times if corrected for the value of the currency). In the same time interval, surveyed TBD coverage increased from 22% to 91% (4.1 times) while surveyed three dose of hepatitis B vaccine coverage increased from 30% to 96% (3.2 times). Thus, increasing coverage, follows the same trend as GDP. From 2004 to 2009, the Western/Eastern three dose of hepatitis B vaccine coverage ratios improved from 0.72 to 0.98 while the Rural to Urban coverage ratio improved from 0.91 to 1.0^[123,40]. This indicated that once free hepatitis B vaccine was provided, children in Western and rural areas received the same opportunity to receive the vaccine without paying out of pocket. As a result, the 2009 three dose of hepatitis B vaccine coverage reached universally high levels. The 2006 national serological survey also documented the absence of difference in the three dose of hepatitis B vaccine coverage in terms of gender and urban /rural residence. The concentration index that reached 0 in 2009 also suggested that equity had been reached. Experience from other countries also suggests that immunization systems can decrease inequities when designed with this objective. Approaches used in immunization to improve equity also include supplemental immunization activities^[106] and specific strategies to reach every district^[124].

Our study suffered from some limitations. First, as this was an internal EPI evaluation, hepatitis B vaccination coverage could be overestimated. However, we used staff that was external to each province for data collection so that this source of bias could be minimized. Second, while we audited data during the evaluation, recall bias or misreporting may have

existed. This, however, is unlikely to have affected the trends observed. Third, the increase of coverage observed can be attributed to not only to the GAVI China project, but also to the general improvement of the Chinese immunization system. Fourth, although we sampled health care facilities to measure coverage, we did not use statistical analysis because our objectives were limited to documenting progress in reductions of inequities and did not include any reference to testing differences in coverage across different strata. Finally, this data analysis used an ecological approach conducted with the objective of evaluating a programme. Hence, it cannot be used to draw inferences regarding causality.

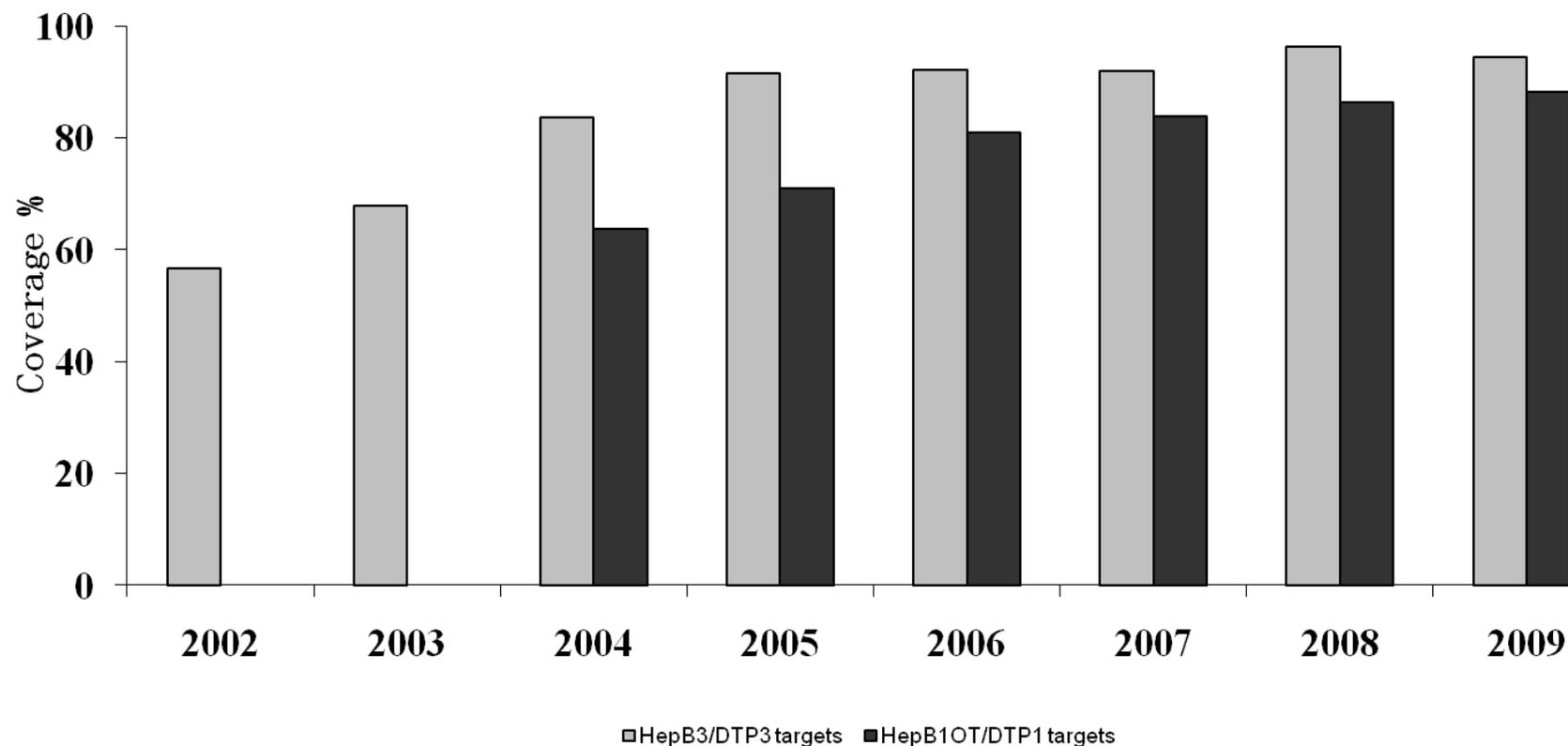
On the basis of this evaluation, we formulated a number of conclusions. First, the pro-poor GAVI approach was an effective way to reduce inequity among children through provision of free vaccination. When vaccine and AD syringes were provided for free, they closed the gap between Eastern and Western regions and between the rich and the poor. Second, reported and estimated data only partially reflected inequities in immunization coverage. Third, pockets of low coverage persisted in the population living in GAVI-supported areas. In 2009, one percent infants lived in counties that had not reached the 85% three dose of hepatitis B vaccine coverage target and 21% lived in counties that had not reached the 75% TBD coverage target. On the basis of these conclusions, we formulated a number of recommendations. First, new vaccines should be introduced in China in a way that takes into account the lessons learned from the introduction of hepatitis B vaccine and the GAVI China collaboration project. Hence, this should consider (1) burden of disease, (2) cost-effectiveness, (3) willingness to pay, (4) availability of operational funds, (5) improved delivery system (human resource and technical capacity) and (6) equitable financing. Availability of domestically-produced vaccines will be

key issue because of the lower price and convenient transportation. Second, we must conduct regular surveys to validate reported and estimated coverage estimates so that inequities can be measured and addressed. Third, persisting pockets of low coverage need to be subject to more focused plans. As reduction of inequities is a key function of the government, the government must show leadership by introducing new vaccines in a comprehensive, equitable approach. Through GAVI, China benefited from externally funded, pro-poor mechanisms to reduce inequities with respect to hepatitis B. In 2011, newer vaccines, such as those against rotavirus, Hib and pneumococcal diseases were still used in China with an inequitable cost recovery system but were being considered for introduction into free, government-supported routine immunization services. As the China annual GDP per capita now exceeds 1,000 USD, China is no longer eligible for GAVI support. Hence, China could consider developing its own, national financial mechanism to support new vaccine introduction and reduce inequities with respect to other diseases in the same way it did for hepatitis B. To this effect, a mechanism based on individual social economic status (e.g., demand-side subsidies, conditional cash transfer) rather than geographic area of residence, may be more adapted to the China's heterogeneity. Such inequity-reduction strategies may be more effective at increasing vaccine access for the poor wherever they live, including migrants in larger cities of the East. However, policy dialogue with GAVI and international partners will remain instrumental so that creative equitable solutions are identified.

Acknowledgements

We would like to thank all EPI staff at all levels for their contribution in the reduction of inequities through the GAVI project and for their assistance to the universal vaccination of infants.

Figure 10: Coverage of the hepatitis B third dose⁸ and timely birth dose expressed as a ratio of the target populations,^{9,10} GAVI China project counties, 2002-2009



⁸ Calculated by dividing HepB3 doses administered by the size of the target groups for DTP3 vaccination

⁹ Calculated by dividing HepBOT doses administered by the size of the target groups for DTP1 vaccination

¹⁰ Reported TBD data was only available since 2004

Figure 11: Coverage of hepatitis B timely birth dose in the Western, Central and Eastern areas as per the 2010 final evaluation survey, by Region, China, 2002-2009

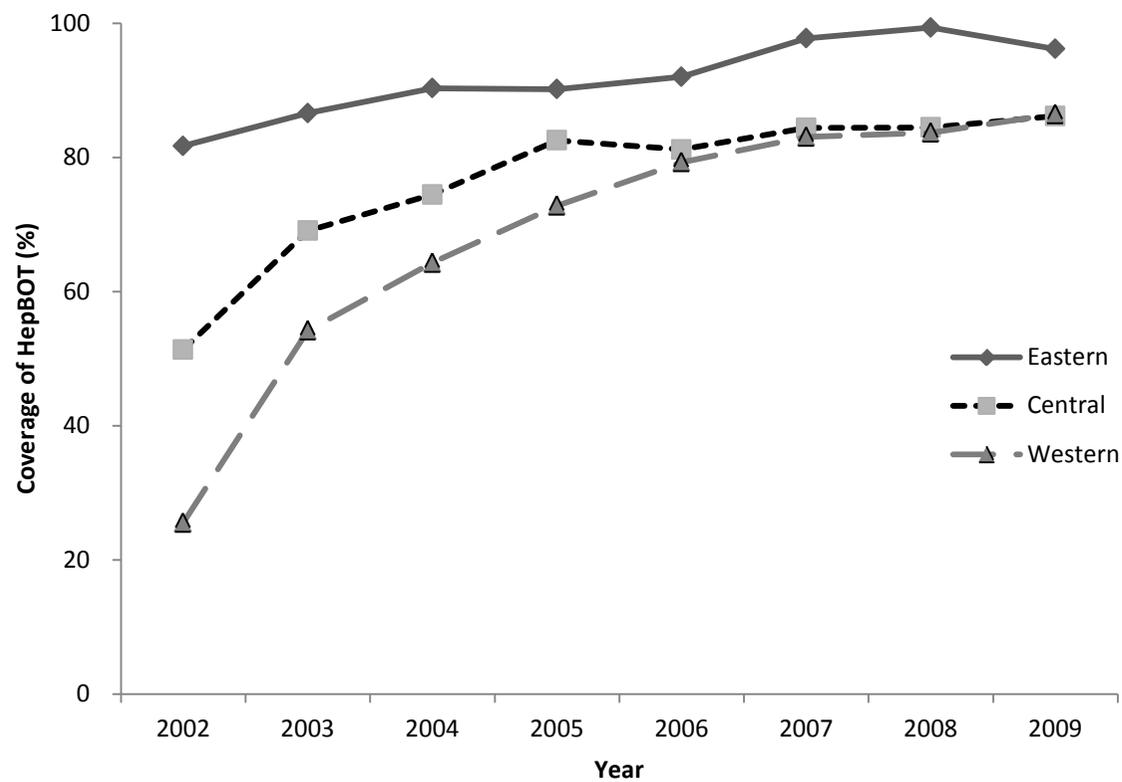


Figure 12: Proportion of counties having reached the GAVI targets (HepB3 > 85% and HepBOT > 75), reported coverage, by province, China, 2009

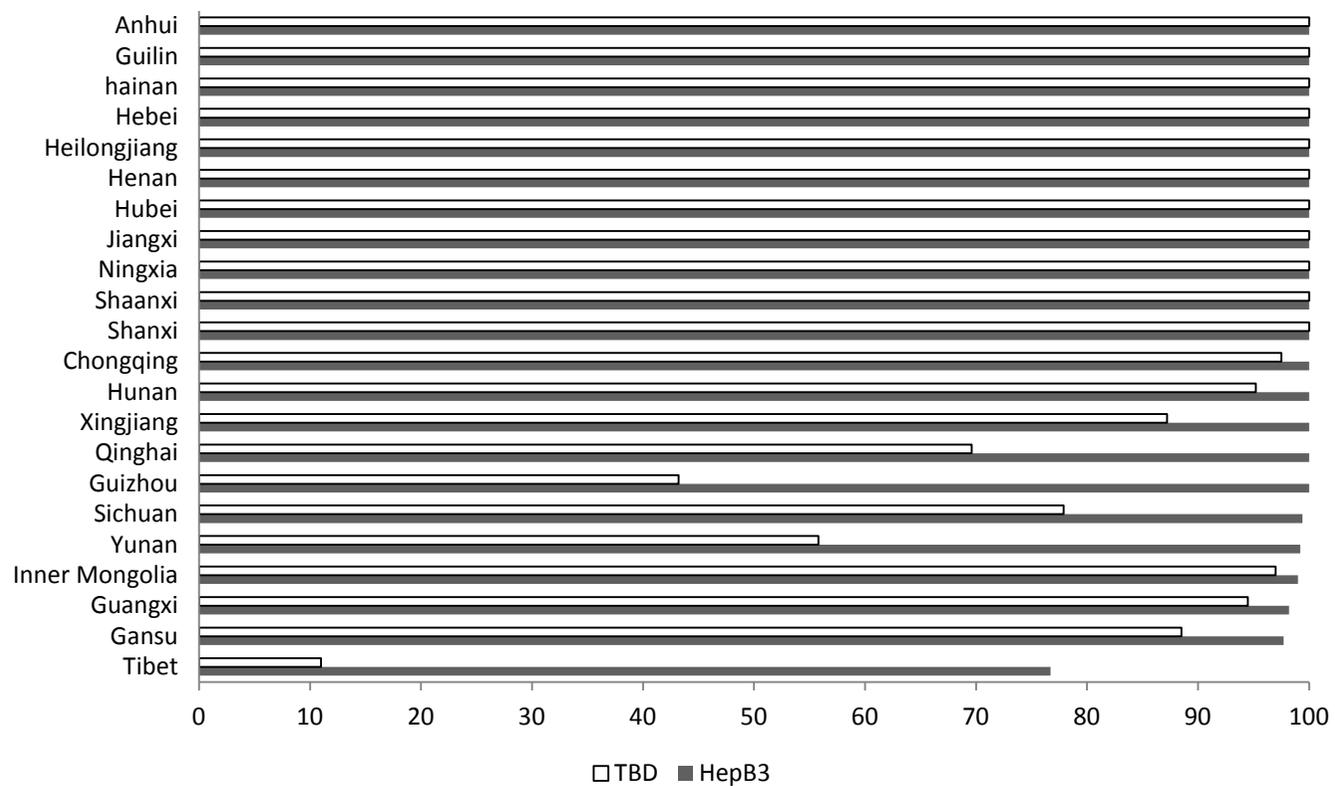


Table 27: Hepatitis B third dose coverage by region, China, 2002-2009

	Region	Year							
		2002	2003	2004	2005	2006	2007	2008	2009
Reported ¹¹	Eastern	98.54	99.11	98.86	98.92	98.64	98.92	99.00	99.19
	Central	96.08	97.47	98.91	99.24	99.26	99.27	99.34	99.40
	Western	91.06	93.24	96.79	97.16	97.12	97.69	98.32	98.66
	Overall	95.61	96.68	98.23	98.89	98.47	98.77	98.95	99.13
	Western/Eastern Ratio	0.92	0.94	0.98	0.98	0.98	0.99	0.99	0.99
Estimated ¹²	Eastern	81.88	82.76	86.56	90.95	92.98	96.53	97.64	99.17
	Central	75.66	80.92	76.67	85.43	89.28	90.65	95.27	96.25
	Western	69.55	73.39	77.40	82.80	84.68	87.27	91.31	93.40
	Overall	74.11	78.78	78.07	85.20	89.05	91.46	94.82	96.30
	Western/Eastern Ratio	0.85	0.89	0.89	0.91	0.91	0.90	0.94	0.94
Surveyed ¹³	Eastern	88.80	85.51	87.59	92.19	95.80	91.72	88.69	92.09
	Central	65.51	81.27	85.85	90.02	87.96	92.03	93.21	96.27
	Western	46.89	67.39	76.45	80.96	84.81	86.19	88.75	90.21
	Overall	71.73	84.01	86.75	90.18	91.36	91.39	91.35	93.19
	Western/Eastern Ratio	0.53	0.79	0.87	0.88	0.89	0.94	1.00	0.98

¹¹National data as reported by the CDC system¹² National data adjusted by denominator according to the methods used for official reports to WHO and UNICEF¹³Data from the 244 counties surveyed in 2010

Table 28: HepB3 coverage by quintile of county 2009 GDP per capita, China, 2002-2009

GDP (per capital)* Quintile		Year							
		2002	2003	2004	2005	2006	2007	2008	2009
Reported ¹⁴	1st Quintile	97.80	98.98	98.48	98.56	98.16	98.59	98.69	98.92
	2nd Quintile	99.07	99.29	99.44	99.5	99.52	99.57	99.53	99.55
	3rd Quintile	97.35	98.10	98.42	99.08	99.12	99.10	99.25	99.38
	4th Quintile	88.86	91.51	97.89	97.98	98.10	98.68	98.85	99.14
	5th Quintile	93.39	94.54	96.76	97.19	97.23	97.49	98.24	98.51
	Overall	95.61	96.68	98.24	98.89	98.47	98.77	98.95	99.13
	5th /1st Quintile ratio	0.95	0.96	0.98	0.99	0.99	0.99	1.0	1.0
Estimated ¹⁵	1st Quintile	90.16	96.03	95.50	97.60	96.96	97.34	99.20	99.19
	2nd Quintile	88.65	95.22	97.18	94.75	96.72	96.05	97.67	98.10
	3rd Quintile	88.38	90.25	91.18	92.33	94.14	94.19	94.95	96.27
	4th Quintile	75.22	81.10	90.08	93.51	92.56	95.30	96.19	98.80
	5th Quintile	76.56	90.64	93.16	94.57	95.53	99.52	98.00	96.71
	Overall	85.86	92.01	93.88	95.09	95.68	96.70	97.68	98.10
	5th /1st Quintile ratio	0.85	0.94	0.98	0.97	0.99	1.02	0.99	0.97
Surveyed ¹⁶	1st Quintile	80.33	92.06	91	95.19	93.92	94.68	98.4	98.39
	2nd Quintile	77.30	90.45	94.35	89.49	93.43	92.1	95.35	96.2
	3rd Quintile	76.77	80.49	82.37	84.67	88.28	88.38	89.91	92.53
	4th Quintile	50.44	62.21	80.16	87.03	85.11	90.61	90.38	92.60
	5th Quintile	53.12	81.29	86.33	89.15	91.05	99.05	95.99	93.42
	Overall	71.73	84.01	86.75	90.18	91.36	91.39	91.35	93.19
	5th /1st Quintile ratio	0.66	0.88	0.95	0.94	0.97	1.05	0.98	0.95

¹⁴National data as reported by the CDC system¹⁵ National data adjusted by denominator according to the methods used for official reports to WHO and UNICEF¹⁶Data from the 244 counties surveyed in 2010

Table 29: TBD coverage by quintile of county 2009 GDP per capita, China, 2002-2009

	GDP (per capita)* Quintile	Year							
		2002	2003	2004	2005	2006	2007	2008	2009
<u>Reported</u> ¹⁷	1 st Quintile			86.26	88.26	89.42	91.69	92.94	93.48
	2 nd Quintile			81.26	95.63	96.18	96.88	97.33	97.66
	3 rd Quintile			79.39	88.84	91.76	94.35	95.03	95.80
	4 th Quintile			82.71	98.34	80.17	90.35	91.56	92.35
	5 th Quintile			53.35	64.79	74.00	76.28	81.93	84.22
	Overall			75.91	86.95	86.84	90.79	92.07	92.95
	5 th /1 st Quintile	0.72	0.86	0.62	0.73	0.83	0.83	0.88	0.90
<u>Estimated</u> ¹⁸	1 st Quintile	87.86	92.60	93.60	94.72	97.61	96.05	97.84	98.64
	2 nd Quintile	85.41	92.27	93.40	93.21	93.98	93.79	93.98	94.69
	3 rd Quintile	84.23	88.42	90.07	94.62	95.38	95.48	96.55	96.49
	4 th Quintile	65.88	77.12	81.33	86.76	88.23	90.22	91.23	91.41
	5 th Quintile	63.26	80.04	89.76	89.97	89.92	91.82	93.45	92.63
	Overall	80.54	87.55	90.73	92.72	94.29	94.28	95.56	95.87
	5 th /1 st Quintile			0.96	0.95	0.92	0.96	0.96	0.94
<u>Surveyed</u> ¹⁹	1 st Quintile	75.72	85.19	87.19	89.43	95.22	92.10	95.69	97.28
	2 nd Quintile	70.82	84.53	86.79	86.42	87.96	87.58	87.96	89.38
	3 rd Quintile	68.45	76.83	80.14	89.23	90.76	90.96	93.10	92.99
	4 th Quintile	31.75	54.24	62.66	73.53	76.46	80.45	82.45	82.81
	5 th Quintile	26.52	60.09	79.53	79.94	79.84	83.63	86.90	85.26
	Overall	60.41	73.43	78.95	83.64	85.98	90.46	91.40	91.18
	5 th /1 st Quintile	0.35	0.71	0.91	0.89	0.84	0.91	0.91	0.88

¹⁷National data as reported by the CDC system, available since 2004¹⁸ National data adjusted by denominator according to the methods used for official reports to WHO and UNICEF¹⁹Data from the 244 counties surveyed in 2010

6. Chapter 6: Evaluation of immunization injection safety in China, 2010: achievements, future sustainability^γ

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Contribution statement:

Zhenghua Wu was responsible for training, data collection, data analysis and reporting and drafting of the manuscript. Fuqiang Cui contributed to the design, the training; he guided data collection, data analysis and manuscript editing. Yuansheng Chen, Ning Miao, Xiaohong Gong, Huiming Luo, Fuzhen Wang and Hui Zheng participated in data collection and data analysis. Mark Kane and Stephen C. Hadler provided guidance to the survey and contributed to data analysis and manuscript reviewing. Yvan J. Hutin helped in the design of the survey, provided guidance for the survey implementation and reviewed the manuscript. Xiaofeng Liang and WeiZhong Yang supervised the survey and participated in the design and in the data analysis. They also reviewed the manuscript to provide critical comments.

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Introduction

Vaccines prevent diseases, avoiding human suffering and disability ^[125]. As vaccine-preventable diseases are less and less common, immunization safety becomes more and more important. Immunization safety includes quality of vaccine production, circumstances of shipment, delivery system, cold-chain and administration. As most vaccines are still administered through the percutaneous route, immunization injections need to be safe. A safe injection is defined as one that does not harm the recipient, the health care worker, or the community ^[126, 127]. In 2000, WHO estimated that of the 16 billion injections given annually worldwide in developing and transitional countries, 39.3% were given with syringes and/or needles reused in the absence of sterilization^[128]. Even though immunization activities account for a minority of injections worldwide, the safety of immunization injections is a high priority to vaccine recipients, immunization providers, communities and policy makers in charge of the Expanded Programme on Immunization (EPI). In the late 1990s, a number of determinants led to poor injection practices in the specific context of immunization services. Those included short supplies of injection devices, challenges in ensuring adequate re-sterilization procedures for sterilizable devices, lack of knowledge among health care workers and community, and lack of systems to manage sharps waste ^[129]. In 1999, to eliminate unsafe administration of immunization injections, WHO, UNICEF and UNFPA called for the exclusive use of auto-disable (AD) syringes (disposable syringes that inactivate themselves automatically after one use to prevent re-use) in immunization services by 2003. In addition, the statement called for donors and lenders to include the cost of auto-disable

injection equipment and safety boxes when providing financial assistance to supply vaccines [130].

In 1995, the Chinese World Bank VII infectious disease control project introduced the "one needle, one syringe, one shot" policy for the first time in China. However, the choice of type of injection devices to be used in EPI was left to the provinces. Between 1999 and 2000, China, conducted a number of injection safety assessments [131-133]. The proportion of health care facilities using glass syringes ranged between 43% and 55%. The proportion of health care facilities reusing syringes and/or needles without sterilization ranged between 5% and 51%. In 2000, China passed a regulation banning the reuse of medical devices labeled for single use. In 2003 another regulation required health institutions to sort health care waste and to collect sharps waste in puncture- and leak-proof containers. In 2002-2007, the implementation of the China project of the Global Alliance for Vaccine and Immunization (GAVI) provided support to immunization injections safety. In Western areas and in national poverty-affected counties of the Central areas (223 of the 1,087 counties in Central areas, 20% of the population), GAVI provided funds for auto-disable (AD) syringes for all hepatitis B vaccine and for 50%-70% of other EPI vaccines (provinces paid for the differences)^[44]. For these GAVI supported areas, financing and procurement took place at central level. For areas not supported by GAVI in the Central and Eastern areas, procurement and financing took place at provincial level. In 2005, the Chinese Medical Association published clinical guidelines for injections and other skin-piercing procedures. In 2006, the Ministry of Health hepatitis B control plan called for exclusive use of disposable syringes in health services and for use of AD syringes for EPI. In 2007, this requirement for AD syringes in immunization

was taken into account for the national budget and currently in 2011, the price difference between AD and disposable syringes is minimal.

In 2007, the GAVI project stopped providing financial support for injection equipment before it finally closed in 2010. By that time, injection safety interventions in China had largely introduced AD syringes in immunization services. A pilot injection safety assessment conducted in 2009 by the Chinese Field Epidemiology Training Programme (CFETP) pointed to major improvements in injection practices ^[134]. We decided to gather more evidence to quantify progress and document the current national situation. In October 2010, three years after the discontinuation of the GAVI financial support, we assessed immunization injection safety in three different areas of China (Western, Central and Eastern). The results of the evaluation describes injection practices in China in the post GAVI project era and can guide policy makers to update national standard for injection practices and further improve vaccination services.

Methods

Type of evaluation

We conducted a cross-sectional evaluation in health care facilities using a tool adapted on the basis of the Tool C–Revised of the World Health Organization (WHO) ^[135]. This was based upon the WHO definition of a safe injection ^[128] and included (1) observations of health care facilities, (2) observations of practices from injection providers and (3) interviews of injection providers.

Sampling method

We used the WHO recommended methods to select a cluster sample of health care facilities^[135]. First, we stratified the country into three regions (Eastern, Central and Western) reflecting three levels of socio-economic development level in China^[115]. Second, in each region, we selected eight counties using a probability proportional to population size (PPS) method. Third, in each selected county, we selected 10 townships at random among the list of townships of the county. Fourth, in each selected township we investigated one immunization delivery site. If all immunizations were given at the township hospital, we investigated the township hospital. If immunizations were given at the township hospital and in village clinics, we selected one vaccine delivery site at random. In each of the three regions, the sample size was eight clusters of 10 facilities (80) as per the WHO guidelines^[135], for a total of 240 for the country.

Data collection

EPI staff from China CDC (central level) or other provinces coordinated data collection in collaboration with the local EPI staff. We first conducted structured observations using a standardized instrument to collect information on the facility. Second, we observed providers while giving vaccination injections using a checklist. Third, we interviewed vaccination injection providers using a standardized questionnaire to collect information regarding knowledge regarding diseases acquired from unsafe injections, training experiences and occurrence of needle-stick injuries.

Data analysis

For each stratum, we estimated the frequency of specific findings through calculation of proportions using the relevant sample size as denominator. Then, we calculated China national

estimates through an average of the regional values weighted for the population size. For each of the indicators we calculated, the best estimate and a 95% of confidence interval (CI) generated by software of Statistical Package for the Social Sciences (Version 13) that took into account the complex sampling design (Clustering and weighting).

Quality assurance

We designed and adapted the instruments through consultation of the WHO guidelines and experience recovery from two 2009 CFETP injection safety assessments ^[134]. We then pilot tested the instruments in the Banyan county of Guizhou province in July 2010 and subsequently revised the tools. We finally conducted a training workshop for all national assessment teams prior to the evaluation.

Results

Overall, we visited 231 facilities in the three regions. In the Western region, we visited 80 facilities that benefited from the GAVI China project. In the Central region, we visited 77 facilities (Three could not be visited as two counties had less than 10 townships). Of these 77 facilities, 20 (26%) benefited from GAVI support. In the Eastern region, we visited 74 facilities, none of which received GAVI support (Six could not be visited as three counties had less than 10 townships).

Risks observed through structured observations of health care facilities

With respect to the risk to the patient (Table 30), we never observed open injection equipment lying around or needles left in the septum of multi-dose vials. The proportion of facilities missing first aid medicine for anaphylaxis ranged from 1% to 5%. One facility presented evidence of attempts to re-sterilize disposable injection equipment in the Eastern

region. Six to eight percent of facilities prepared handmade cotton balls. The proportion of facilities that did not have water and soap for hand washing was 24% in the Eastern region, 46% in the Western region and 55% in the Central region.

With respect to the risk to health care workers, the proportion of health care facilities without sharps containers was 15% in Eastern areas, 21% in Western areas and 44% percent in Central areas. Only two facilities presented evidence of overfilled or pierced containers in Central areas. The proportion of sharps in open containers was 8% in Eastern areas, 10% in Western areas and 18% in Central areas.

With respect to the risk to the community, presence of sharps around health care facilities was uncommon, but highest (6%) in Western areas (Table 30).

Safe practices observed through structured observations of injections

We never observed sterilizable injection devices syringes in any of the facilities (Table 30). The proportion of facilities using AD syringes was 78% in Western areas, 73% in Central areas and 25% in Eastern areas. Standard disposable syringes were still in use, but more in the East (90%) than in the Centre (49%) and in the West (39%).

With respect to practices before injection, almost all providers took out injection devices from a new, sterile package. 92% to 99% of providers prepared injection in a clean, dedicated area. 97% of providers prepared the skin with antiseptic in all regions. The proportion of providers who did not touch the injection site after disinfection ranged from 90% to 95%.

With respect to practices after giving injections, most providers (82% to 88%) abstained from removing the needle by hand and from two-hand recapping (81% to 89%). The proportion of providers who placed used devices directly into a sharp container was 29% in

the West, 36% in the Centre and 50% in the East. One provider presented evidence of attempts to re-sterilize disposable devices in Central areas (Table 31).

Waste collection and management

The proportion of facilities using sharps containers was highest in the East (85%), intermediate in the West (79%) and lowest in the Centre (56 %). 21% to 39% of facilities used needle cutters or destroyers. The proportion of facilities using open containers to collect sharps ranged from eight percent in the East to 10% in the West and 18% in the Centre.

With respect to methods used to manage waste, only one facility in Central area dumped sharps waste in the open field. Burying waste shallowly was uncommon, highest (4%) in the West. The proportion of facilities that burnt and buried sharps waste ranged from 31% in the east to 69% in the centre. 14% to 25% of facilities disinfected sharps waste before further management. Three percent to 10% of facilities had small-scale incinerators. 26% to 53% of facilities transported the waste to the referral centers (Table 32).

Health care workers interviews

With respect to health care workers knowledge, the proportion who knew that unsafe injections could transmit viral hepatitis viruses ranged from 80% in the centre to 91% in the East. A lower proportion knew unsafe injections could transmit HIV (66% to 83%) or cause abscesses (61% to 74%). The proportion of health care workers who received at least three doses of hepatitis B vaccine ranged from 80% in the East to 98% in the Centre (three to five percent had never received a dose). 91% to 97% of health care workers reported having attended a training addressing injection safety in the last two years. The proportion of health care workers who self-reported sharp injuries in the last six months ranged from 3% in the

East to 10% in the West, and higher among those who recapped needles (5/35, 14%) than among those who did not (8/198, 4%, $X^2=5.9$, $P<0.05$) (Table 33).

Discussion

Results of our evaluation suggested that in 2010, sterilizable injection equipment has been eliminated in China. Disposable syringes were universally used, with a predominance of AD syringes in areas formerly supported by GAVI. These observations took place three years after the withdrawal of GAVI support, at a time when the central government paid for all AD syringe costs. No national data were available to compare our results with the situation in place before. However, a 2000 survey in Gansu province reported that 82% of facilities used sterilizable syringes ^[132]. In 2002, the final report of the implementation of a World Bank loan indicated that no facilities used AD syringes in the project areas ^[136]. In contrast, in our 2010 assessment, the proportion of facilities using AD syringes was 78% in the West, 73% in the Centre, and 25% in the East. The progress observed in the field of immunization occurred in parallel with progress in the field of curative injections ^[134, 137]. A number of factors may explain these findings. First, GAVI funds provided support necessary to provide AD syringes free of charge through a pro-poor approach focusing on Western regions and poverty-affected counties in the central region. This created a demand that resulted in a national, large-scale production of AD syringes with several manufacturers competing with each other. As a result, the difference of price between AD and disposable syringes fell. Secondly, the implementation of the “one syringe, one needle, and one shot” policy started on a large scale after 2001. As a result, the local governments supplied co-funding for purchase of AD syringes and operational funding for the implementation of the GAVI project. However, despite the progress, a few

unsafe practices persisted in 2010 that could harm injection recipients. First, we still observed attempts of re-use of disposable equipment. Universal implementation of safe injection practices is challenging, even in industrialized countries like the United States ^[138]. These underlined the importance of AD injection devices since these give the highest, provider-independent safety. Other breaks in infection control practices included poor hand hygiene, handmade disinfection-cotton-balls and touching the injection site after disinfection. These should be eliminated through targeted interventions and training.

Our assessment indicated the proportion of facilities using sharps containers was higher in the East (85%) and in the West (79%) than in the Centre (56%). A few factors may explain this heterogeneity. First, GAVI supported provision of safety box and needle cutter. However, this support was only available to Western regions and poverty-affected counties in the Central region. In the Eastern area, local governments purchased sharps container for immunization with their own funds. The Central area was divided in GAVI-supported areas (20 of the 78 visited facilities, 17 (85%) using safety boxes) and non GAVI-supported areas (58 of the 78 visited facilities, 11 (19%) using safety boxes) in which practices differed. These differences of use by area suggested that the cost of the safety boxes could be an obstacle of the use. Second, the GAVI project organized a number of injection safety trainings, as reflected in the interviews of health care workers. Although progress had been achieved, our assessment observed that dangerous practices persisted, especially in Central areas. As a result, needle recapping and needle-stick injuries remain too common. Overall, the national situation is heterogeneous with respect to sharp collection and needle-stick injury prevention.

Standardization of practices and funds to implement policy could address this and further improve the situation.

Our assessment indicated that the main methods used to manage waste were (1) burn and bury, (2) destruction after disinfection (mostly in buckets of bleach) and (3) transport off-site to referral centers. This was comparable to the observations made in the CFETP 2002-2009 assessments in Wulong county, Chongqing municipality and Fumeng county, Liaoning province^[134]. In this CFETP evaluation, the proportion of open dumping decreased from seven percent in 2001 to five percent in 2009 in Fumeng and from 64% in 2001 to 50% in 2009 in Wulong. In contrast to the 2009 situation in Wulong and Fumeng, our survey did not identify open dumping as a common practice. Transport of waste to referral centers differed in frequency, as it was more common in the East (53%) than in the West (29%) and in the centre (26%). Heterogeneity in regional economic situations may explain these differences, as this option is expensive. In our 2010 assessment, poor practices persisted, including burn and bury and small-scale incineration that could generate toxic fumes^[139, 140]. These unsafe waste management practices could still lead to needle-stick injuries in the community and to environmental pollution. They need to be addressed through a more comprehensive health care waste management strategy that aimed at protecting the population and the environment.

Our assessment suffers from two main limitations. First, as the evaluation was conducted internally within EPI, there could have been an observer bias and remaining subjective judgment. While this could lead to a picture more optimistic than reality, the availability of historical comparison supports the hypothesis of a major improvement. In addition, the observed issues, even if underestimated, still allow us to make recommendations. Second, the

Central area is made of a mixture of GAVI project counties and non GAVI project counties. Hence, the situation there is harder to interpret. Particularly in the context of a cluster sampling that strictly specify, does not allow to stratified analysis. However, the western region with GAVI supported had high proportion of AD utilization than eastern region, and high waste management (safety box) within GAVI supported facilities than no GAVI supported facilities within central region.

On the basis of this evaluation, we formulated three main conclusions. First, use of AD syringe and sharps containers increased in vaccination services in China, especially in GAVI supported area, leading to sustainable progress in terms of elimination of reuse of injection devices. However, risk to patients still existed, including persisting use of standard disposable syringes and attempts to re-use disposable devices. Second, shortage of sharp containers and persisting unsafe practices still lead to needle stick injuries. Third, the absence of standardized approaches to waste management led to heterogeneous practices, some of which could be dangerous for the community or the environment. On the basis of these conclusions, we formulated a number of recommendations. First, remaining unsafe practices must be improved through a regulation implementing a national policy requiring exclusive use of AD syringes in EPI. Targeted training of providers needs to also facilitate the transition to AD syringes and improve residual unsafe practices. Second, the government should supply enough safety boxes or other sharps containers for all facilities, along with the training support to ensure their use. Third, pre-service and catch up vaccination of health care workers against hepatitis B must be generalized, in accordance with the recommendations of the Chinese Liver Study Association, occupational health regulations,^[141, 142] and the 2007 and 2010 World Health Assembly

resolutions^[143] . Fourth, we must frame standardized guidance for sharps waste disposal techniques that would protect communities and the environment. Overall, revised, evidence based, consensus-derived national standard for immunization injection safety could further improve practices, including waste collection and waste management. Political, legislative and financial support from the Ministry of Health should ensure implementation of these revised immunization injection safety standards to build on the 2000-2010 achievements, eliminate persisting unsafe practices and further strengthen public and government confidence in immunization services.

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We would like to thank GAVI which supplied all AD syringes and some of safety boxes free of charge through a pro-poor approach focusing on Western regions and poverty-affected counties in the Central region. We also thank all EPI staff at all level for their contributions to immunization injection safety.

Table 30: Risks identified during structured observations of health care facilities, GAVI project final evaluation survey, China, October 2010

Level of risk	Risk observed	Eastern(N=74)			Middle(N=77)			Western(N=80)			Total ²⁰ (N=231)		
		#	(%)	95% CI ²¹	#	(%)	95% CI	#	(%)	95% CI	#	(%)	95% CI
Overall	Absence of guidelines displayed	15	20	11-29	19	25	15-34	19	24	14-33	53	23	18-29
	Open injection equipment lying around	0	0	-	0	0	-	0	0	-	0	0	-
	Attempts to sterilize disposable devices	1	1	0-7	0	0	-	0	0	-	1	0	0-2
	Needles in septum of multi-dose vials	0	0	-	0	0	-	0	0	-	0	0	-
Patient	Handmade disinfection-cotton-balls	6	8	2-14	5	6	1-12	5	6	1-12	16	7	4-11
	Absence of water and soap for hand washing	18	24	15-34	42	55	43-66	37	46	35-57	97	42	36-48
	Absence of first-aid medicine for anaphylaxis	1	1	0-7	2	3	1-6	4	5	0-10	7	3	1-6
	Absence of sharps containers	11	15	7-23	34	44	33-55	17	21	12-30	62	27	21-33
Provider	Overfilled or pierced sharp containers	0	0	-	2	3	1-6	0	0	-	2	1	0-3
	Sharps in open containers	6	8	2-14	14	18	1-27	8	10	3-17	28	12	8-17
Community	Used sharps outside health care facility	2	3	0-6	1	1	1-4	5	6	1-12	8	3	2-7

²⁰National estimate weighted for the population size of each of the three regions

²¹CI: Confidence interval

Table 31: Frequency of safe practice observed during injections, GAVI project final evaluation survey, China, 2010

Stages	Description	Eastern(N=72)			Middle(N=78)			Western(N=79)			Total(N=229) ²²		
		No	(%)	95% CI ²³	No	(%)	95% CI	No	(%)	95% CI	No	(%)	95% CI
Devices	Sterile syringe	0	0	-	0	0	-	0	0	-	0	0	-
	Disposable syringe	65	90	83-97	38	49	38-60	31	39	28-50	134	59	52-65
	AD ²⁴ syringe	18	25	15-35	57	73	63-83	62	78	69-88	137	60	53-66
Before injection	Syringe / needle from a new, sterile package	69	96	91-100	77	99	96-101	77	97	94-101	223	97	95-99
	Preparation on a clean, dedicated area	71	99	96-101	72	92	86-98	76	96	92-100	219	96	92-98
	Skin preparation with antiseptic	70	97	93-101	76	97	94-101	77	97	94-101	223	97	95-99
	No touch of the injection site after disinfection	65	90	83-97	74	95	90-100	74	94	88-99	213	93	89-96
After injection	No removal of the needle by hand	63	88	80-95	64	82	74-91	68	86	78-94	195	85	80-89
	Absence of two-handed recapping	64	89	82-96	66	85	77-93	64	81	72-90	194	85	80-89
	Collection of sharps into a sharps container	36	50	38-62	28	36	25-47	23	29	19-39	87	38	32-44
	Separate collection of non-sharps	19	26	16-37	17	22	13-31	44	56	45-67	80	35	29-41
	No attempts to re-sterilize disposable devices	72	100	100-100	77	99	96-101	79	100	100-100	228	100	98-100

²² National estimate weighted for the population size of each of the three regions

²³ CI: Confidence interval

²⁴ Auto-Disable syringe and needle set

Table 32: Waste collection and disposal practices, GAVI project final evaluation survey, China, 2010

Levels	Practice	Eastern(N=74)			Middle(N=77)			Western(N=80)			Total (N=231) ²⁵		
		No	(%)	95% CI ²⁶	No	(%)	95% CI	No	(%)	95% CI	No	(%)	95% CI
Waste collection	Open containers	6	8	2-14	14	18	10-27	8	10	3-17	28	12	8-17
	Needle destruction/ removal	29	39	28-50	27	35	24-46	17	21	12-30	73	32	26-38
	Use of sharps containers	63	85	77-93	43	56	45-67	63	79	70-88	169	73	67-79
Waste management	Open dumping	0	0	-	1	1	1-7	0	0	-	1	0	0-2
	Shallow burying	0	0	-	1	1	1-7	3	4	0-8	4	2	0-4
	Burn and bury	23	31	21-42	53	69	58-79	37	46	35-57	113	49	43-55
	Small-scale incinerators	2	3	0-6	8	10	4-17	8	10	3-17	18	8	5-12
	Destruction after disinfection	13	18	9-26	11	14	6-22	20	25	16-34	44	19	14-25
	Transport off-site	39	53	41-64	20	26	16-36	23	29	19-39	82	36	30-42

²⁵ National estimate weighted for the population size of each of the three regions

²⁶ CI: Confidence interval

Table 33: Results of interviews of injection providers, GAVI project final evaluation survey, China, 2010

Indicator	Eastern (N=76)			Middle (N=80)			Western(N=77)			Total(N=233) ²⁷			
	No	(%)	95% CI	No	(%)	95% CI	No	(%)	95% CI	No	(%)	95% CI	
Risk of unsafe injections spontaneously mentioned	Abscess on injection	56	74	64-84	52	65	55-75	47	61	50-72	155	67	60-72
	Transmission of HIV	63	83	74-91	61	76	67-86	51	66	56-77	175	75	69-80
	Transmission of	69	91	84-97	64	80	71-89	63	82	73-90	196	84	79-88
Number of hepatitis B vaccine doses received	0 dose	2	3	0-6	2	3	0-6	4	5	0-10	8	3	2-6
	1 dose	6	8	2-14	0	0	-	7	9	3-16	13	6	3-9
	2 doses	7	9	3-16	0	0	-	4	5	0-10	11	5	3-8
	≥ 3 doses	61	80	71-89	78	98	94-101	62	81	72-89	201	86	81-90
Self reported sharps injuries in last six months	2	3	0-6	3	4	0-8	8	10	4-17	13	6	3-9	
Attendance of an safety injection training in	72	95	90-100	73	91	85-97	75	97	94-101	220	94	91-97	

²⁷ National estimate weighted for the population size of each of the three regions

²⁸ CI: Confidenceinterval

7. Chapter 7: Progress towards the elimination of mother to child transmission of

hepatitis B virus in China: Results from GAVI Final evaluation[§]

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Contribution statement:

Fuqiang Cui was responsible for designing the survey, analyzing the data and reporting the results. Huiming Luo supervised the survey design and the field work. Fuzhen Wang and Hui Zheng trained investigators and contributed to data collection. Xiaohong Gong, Yuansheng Chen, Zhenhua Wu and Ning Miao contributed to data collection and data analysis. Mark Kane, Karen Hennessey and Stephen C. Hadler provided the guidance to the survey design and contributed to the data analysis. They also reviewed the manuscript. Yvan J. Hutin helped the designing survey, provided guidance for the survey implementation and contributed to the data analysis. Xiaofeng Liang supervised the survey design and the field supervision. Weizhong Yang organized the survey, contributed to data analysis. He also reviewed the manuscript to provide critical comments.

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Background

Perinatal transmission is a major source of hepatitis B virus (HBV) infection in many countries, especially in highly endemic region ^[144]. Perinatal HBV infections occur among infants of mothers with chronic HBV infection (positive for the HBV surface antigen (HBsAg)). The earlier the timing of HBV infection in a child, the higher the probability of developing chronic infection^[145]. In addition, the risk of perinatal transmission is higher when the mother's HBV DNA level is high. This correlates with the presence of hepatitis B e antigen (HBeAg) in the serum. In the absence of immuno-prophylaxis, 70% to 90% of children born to HBeAg-positive mothers develop chronic HBV infection by six month of age ^[146]. Among those born to HBeAg-negative mothers, less than 10% develop chronic infection ^[146]. Providing hepatitis B vaccine (HepB) to all infants within 24 hours of birth (Timely Birth Dose, TBD), and subsequently, at one and six month of age is key to preventing perinatal HBV infection. Overall, published studies report a 90% efficacy of hepatitis B vaccine for the prevention of perinatal HBV infection. Among infants born to hepatitis B surface antigen (HBsAg) and HBeAg positive mothers, efficacy is lower (70%-90%) ^[147-150]. Adding Human Hepatitis B Immunoglobulin (HBIG) to vaccination at birth increases efficacy to 95% ^[147]. However, HBIG is much more expensive than hepatitis B vaccine, and appropriate use requires testing of pregnant women to identify HBsAg positive women. WHO recommends universal hepatitis B vaccine immunization of infants with TBD to prevent perinatal HBV infection ^[14]. In addition to this, many industrialized countries also include screening of pregnant women to provide vaccination plus HBIG within 12 hours after birth to children born to HBsAg positive mothers ^[151]. A smaller number of countries, including the United

Kingdom and Japan screen pregnant women for HBsAg for selective immuno-prophylaxis in the absence of universal hepatitis B vaccine immunization of newborns. In 2009, 177 countries had integrated hepatitis B vaccine into routine immunization ^[14].

In 1992, China introduced the hepatitis B vaccine into routine immunization. However, parents had to pay for the vaccine, and there were inequities in coverage. In the early 2000s, Mother to Child Transmission (MTCT) remained a leading cause of HBV infection, accounting for 40% of total infections ^[152]. Among HBsAg positive women aged 15-39 years, 30% of them were HBeAg positive, pointing to a high risk of perinatal infection ^[40]. In 2002, with the financial support of the Global Alliance on Vaccine and Immunization (GAVI) targeted to Western areas and 223 poverty-affected counties in Central areas, hepatitis B vaccine became free throughout China while parents were still charged a small user fee. One of the goals of the GAVI China project was to reach 75% TBD coverage among infants born in GAVI-supported areas ^[44]. In 2005, the government provided free vaccination services to all infants (user fees eliminated). A 2006 serosurvey reported that chronic HBV infection was still common among childbearing age women (HBsAg prevalence: 6.7%), pointing to a persisting risk of perinatal infection ^[80].

Between 2002 and 2010, a number of initiatives in China improved the prevention of perinatal HBV infection. First, successive pilot projects in Qinghai province, Ningxia autonomous region and Gansu province allowed identifying the best operational approach to timely birth dose delivery. Second, use of hepatitis B vaccine out of cold chain was considered in studies. ^[91] This option was not scaled up nationally since the market authorization of the vaccine did not specifically permit this kind of use. Third, the new rural reform policy

reimbursed pregnant women who give birth in hospital. Fourth, in 2007, GAVI funds were assigned to support low performance prefectures in Western poverty-affected counties so that they could reach the GAVI China project targets ^[70]. These resulted in increased hospital delivery rates, and indirectly an increase in TBD coverage. Fifth, in 2010, the Ministry of Health formulated a recommendation that (1) pregnant women should be screened for HBsAg and (2) infants born to HBsAg mothers should receive vaccine and HBIG within 24 hours after birth. However, strategies to implement this new recommendation are in the process of being identified. Before this 2010 recommendation, and aside from the GAVI project, many hospitals were already implementing HBsAg screening and HBIG delivery at the expense of the pregnant women. In 2010, we evaluated the GAVI project in terms of its activities to prevent perinatal infections. The objectives of the evaluation were to (1) measure achievements in China project in terms of TBD coverage, (2) describe practices in terms of HBsAg screening of pregnant women and HBIG use outside the GAVI China project and before the official 2010 recommendation and (3) propose recommendations for the future prevention of perinatal HBV infection in China.

Methods

Sampling methods, evaluation survey, October 2010

We used the methods recommended by WHO to select a cluster sample of health care facilities for the purpose of injection safety assessments ^[135]. The injection safety assessment component of the final evaluation of the GAVI project was used to design the sampling strategy as its required confidence intervals that needed to be calculated using the WHO reference guidelines. First, we stratified China into three regions (Eastern, Central and

Western) based on economic criteria. Second, in each region, we selected eight counties with a probability proportional to population size. Third, in each selected county, we selected (a) 10 townships at random among the list of townships of the county and (b) the one county level hospital. Fourth, in each selected township we investigated the township hospital that maintained immunization records for the whole township. In each of the three regions (Eastern, Central and Western), the sample size was eight clusters of 10 facilities, for a total of 80 facilities, as per the WHO guidelines ^[135] which for the whole country totaled to 240 facilities. In addition, we reviewed each of the county hospitals, for timely birth dose evaluation. Finally, we collected timely birth dose data from the county level hospital that accounted for a large proportion of the deliveries in each county.

Data collection

In each hospital, we abstracted 2002 - 2009 records to collect information regarding birth cohorts, hospitals deliveries, vaccine management, and hepatitis B vaccination delivery, HBsAg screening practices and results, and HBIG administration. In addition, in township level hospitals, we abstracted records regarding the delivery of TBD.

In each township, we randomly selected 10 parents in the general population who had a child born between 2002 and 2009. We interviewed parents to collect information about knowledge, attitude and practice with respect to hepatitis B and its prevention.

Coverage calculation

We calculated survey coverage on the basis of the data collected in the field during the October 2010 survey. We divided the number of doses administered (as for the reported coverage) by the number of children registered on the birth cohort at the township level

hospital. To calculate the surveyed TBD coverage among children born in hospitals, we divided the number of surviving children born in hospitals who received TBD by the number of surviving children born in hospitals. We calculated a ratio of the TBD/HepB3 coverage to compare the progress of TBD coverage (reflecting the system in place to facilitate early delivery after birth) with the progress in terms of three dose of hepatitis B vaccine coverage (reflecting the availability of the vaccine and its integration in EPI).

Model to estimate the number of perinatal HBV infections

We used the formula proposed by Goldstein ^[10] to model the number of perinatal HBV infections that occurred in China.

$$CI_p = [(a_s a_e \cdot 90\% + a_s (1 - a_e) \cdot 10\%)x] \times 90\%$$

This calculation was based on the prevalence of HBsAg among women of child-bearing age (a_s ; 6.7% in China as per the 2006 national serological survey) ^[80], the HBeAg prevalence among HBsAg-positive women (a_e ; 30% in China) ^[80], the risk of perinatal transmission among mothers who are HBsAg and HBeAg positive (90%), the risk of perinatal transmission among mothers who are HBsAg-positive and HBeAg-negative (10%) and the size of the surviving birth cohort (x) obtained from the national yearbook. We multiplied this estimate by 90% to obtain the number of perinatal HBV infection that would remain chronic ^[10]. We estimated the number of chronic perinatal infections prevented assuming (1) 88% vaccine effectiveness for children receiving a timely birth dose and completing the three dose series and (2) independence between receiving a timely birth dose and completing the three doses series. We used the 2002 and 2009 timely birth dose and three-dose coverage from the survey conducted in 2010. We neglected the effect of HBIG in the calculations.

Result

Coverage survey

We visited 244 facilities in the three regions, including 24 county hospitals and 220 township hospitals (among counties with less than 10 townships, then all townships or facilities was selected).

General population

Overall, surveyed TBD coverage increased from 60% in 2002 to 91% in 2009 (+31%). In Eastern areas, surveyed TBD coverage increased from 82% in 2002 to 96% in 2009 (+14%). In Central areas, surveyed TBD coverage increased from 51% in 2002 to 86% in 2009 (+35%). In Western areas, surveyed TBD coverage increased from 26% in 2002 to 86% in 2009 (+61%, Table 34). Overall, the TBD/HepB3 ratio increased from 0.83 in 2002 to 0.98 in 2009. In the Eastern region, it increased from 0.92 in 2002 to 1.04 in 2009. In the Central region, it increased from 0.78 in 2002 to 0.89 in 2009. In the Western region, it increased from 0.55 in 2002 to 0.96 in 2009 (Figure 13).

TBD coverage among hospital births

Overall, surveyed TBD coverage among children born at hospital increased from 73% in 2002 to 98% in 2009. In 2009, all regions had reached high level of coverage for children born in hospitals, although the West had started with much lower coverage in 2002. From 2002 to 2009, coverage increased from 80% to 98% in the East; from 62% to 97% in the Centre and from 59% to 98% in the West (Table 35). Between 2003 and 2008, the proportion of hospital births increased from 92% to 95% in urban areas and from 62% to 87% in rural areas^[153], greatly enhanced the impact of the progress in TBD delivery in hospitals.

Practices in the terms of HBsAg screening and immuno-prophylaxis

Overall, between 2002 and 2009, the proportion of pregnant women screened for HBsAg among women giving birth in hospitals increased from 64% in 2002 to 85% in 2009. The increase was smallest (from 83% to 88%) in the East; intermediate (from 64% to 87%) in the Centre and largest (from 48% to 82%) in the West (Figure 14). Between 2002 and 2009, the prevalence of HBsAg among pregnant women recorded in hospital was highest (ranging between 5% and 6.9%) in the East; intermediate (ranging between 3.9% and 6.5%), in the West and lowest (ranging between 1.9% and 3.2%, in the Centre, data not shown).

Overall, in 2009, the proportion of infants born to women screened and found to be HBsAg positive who did not receive any immunization within 24 hours after birth ranged from 0% to 0.7% across regions (Figure 15). The proportion of children who received hepatitis B vaccine plus HBIG was highest in the West (66%) and lowest in the East (34%). The proportion of children who received only hepatitis B vaccine was lowest in the West (28%) and highest in the East (65%). However, in absolute numbers, in the facilities visited during the 2010 survey, the East had the largest number of children received HBIG and hepatitis B vaccine (N=980) followed by the West (N=584) and the Centre (N=350, Figure 15).

Knowledge of parents

We interviewed 2,323 parents in the three regions. Of these, 1,899 (82%) were less than 40 years of age. The male to female ratio was 1.4:1. 1,937 (83%) of parents knew that hepatitis B vaccine was the first vaccine to be administered after birth (ranging from 77% in the Centre to 88% in West); 2,059 (89%) knew the time schedule of the birth dose (ranging from 82% in the Centre to 92% in the West), and 1,943 (84%) knew that three doses were

needed to complete the series (ranging from 73% in the Centre to 89% in the West). 1,540 (66%) of parents reported they received this information from doctors while 652 (28%) quoted the vaccination certificate as the main source of information.

Modeled number of perinatal HBV infection

Our model projected that in 2002, the annual number of chronic perinatal HBV infections as 37,185 in the East, 90,123 in the Centre and 86,413 in the West (Total: 202,709). In 2009, these numbers decreased to 24,108, 36,593, and 27,954 in the Eastern, Central and Western areas, respectively (Total: 84,121 with vaccination versus 202,709 without vaccination, for an overall 58% reduction between 2002 and 2009) (Figure 16).

Discussion

Our surveyed coverage of the TBD increased from 60% in 2002 to 91% in 2009. A number of factors may explain this improvement. First, GAVI funds provided support necessary to offer hepatitis B vaccine free of charge all over China focusing on Western regions and poverty-affected counties in the Central region. Second, the TBD coverage among facility-based births increased from 73% in 2002 to 98% in 2009. Third, the national hospital delivery rate increased from 78% in 2002 to 96% in 2009 ^[115, 154]. Most of the progress in terms of institutionalized deliveries took place in Western regions where health care reform subsidized pregnant women to give birth in hospitals. The Eastern region already had high level of hospital deliveries in 2002 and did not see much progress in the subsequent seven years. Fourth, we conducted special demonstration projects between 2007 and 2009 in 13 low-performance prefectures in Central and Western areas. 1.4 million USD of the first round of the GAVI saving was invested to support activities that would increase TBD coverage.

Fifth, demand for the vaccine increased in the population. In 2010, in our survey, 83% of guardians knew about the need of the hepatitis B birth dose within 24 hours. Although no national data is available from before, a survey conducted in 2005 in Gansu province reported that only 48% of guardians were aware of this need^[92, 155]. While TBD coverage progressed at the national level, in 2009, 20% of counties accounting for 21% of the birth cohort in GAVI project areas still had not reached the GAVI target of 75% coverage in timely birth dose (China CDC unpublished data). Most of these were rural, isolated and poor counties in Tibet, Guizhou and Yunnan. Since the TBD coverage among institutional births was close to 100% in China, this persisting gap is mostly explained by low coverage among home births. Overall, the increase in TBD coverage prevented many HBV infections among newborns. The 2006 serological survey in China reported a 0.96% prevalence of HBsAg among children less than five years of age, versus 9.8% in the same age group in 1992. In addition, our modeled estimates of the number of perinatal HBV infections suggested a fall of 58% from 202,709 cases in 2002 to 84,121 cases in 2009 in China^[10].

Our evaluation indicated from 2002 to 2009, screening of mothers for HBsAg was already in use and increasing in China. Screening rate in the West were under 50% in 2002, but reached 82% in 2009. Two factors may explain the increase in screening. First, there is high level of awareness of hepatitis B prevention among pregnant women^[156]. Second, some hospitals have included testing of pregnant women for HBsAg among routine procedures^[157]. This occurred in the absence of any support by the GAVI project and before the policy recommendation from the Ministry of Health. HBsAg screening allowed identification of HBsAg status and provision of HBIG immuno-prophylaxis^[158, 159]. Our survey indicated that

overall, the prevalence of HBsAg among women of child bearing area screened in hospital ranged between 4% and 6% between 2002 and 2009. This was lower than the 6.7% prevalence reported among adults between 15 and 59 years of age in the 2006 national serosurvey^[80]. Incomplete recording that is another reason for the lower prevalences. However, these two estimates cannot be compared directly. Unlike the population-based survey of 2006, pregnant women screened in hospital did not constitute a random sample of the general population. Following HBsAg screening, immuno-prophylaxis situations were heterogeneous and hard to interpret. The Eastern region used more of the combined HBIG –hepatitis B vaccine immuno-prophylaxis than in the Central and Western regions, but managed to cover a lower proportion of children. Factors influencing these HBIG utilization patterns may include (1) an ongoing nationwide shortage of HBIG and (2) the smaller population size and lower hospital delivery rate in Central and Western regions. Overall, infants born to HBsAg positive mothers had high proportion of TBD, with or without HBIG, which should prevent most HBV infection. However, screening is not always followed by adapted intervention and there was no system to track children born to HBsAg positive mothers in terms of risk of developing infection^[160]. Almost none of the hospitals visited during the survey had data on the proportion of children born from HBsAg mothers followed up and tested after immuno-prophylaxis.

Our evaluation had limitations. First, surveyed data were based on registered birth cohorts and records of doses administered. Migrant children may not have been well covered in the evaluation. As a result, coverage may be overestimated. Second, the HBsAg prevalence among pregnant women who were not tested remains unknown, and could be higher than in

our survey, alternatively, there could be an incomplete recording of positive HBsAg status. Third, practices in terms of HBIG use depended on parental preferences and on willingness to pay. The government did not mandate those. Therefore, they could have been monitored poorly by the system.

On the basis of this evaluation, we formulated a number of conclusions. First, increased availability of hepatitis B vaccine, along with efforts to improve hospital deliveries, increased TBD coverage in China. This decreased perinatal HBV transmission and will reduce disease burden in the future. However, pockets of unreached children persist in the West, particularly in Tibet, Guizhou and Yunnan - our estimates suggest that China continues to have more than 80,000 perinatal HBV infections each year. Second, screening for HBsAg for HBIG administration has begun, but with heterogeneous immuno-prophylaxis practices and a poor system for follow up.

On the basis of these conclusions, we formulated a number of recommendations. First, China should continue improving hospital delivery rates national wide, with special efforts in provinces such as Tibet, Guizhou and Yunnan. Specific strategies are also need to reach births that continue to occur at home. In 2010, China GAVI project used another three million USD to increase TBD coverage for a new group of 29 low-performance prefectures in Central and Western areas. Among these prefectures, 18 are in Yunnan, Guizhou and Tibet. Second, HBsAg screening must be expanded progressively, beginning with aspects of infrastructure and system so that women are screened and children followed up. Increased HBIG use can then follow with an incremental approach, starting with children born from mothers who are HBsAg positive. However, this has programmatic implications in the management of the test

results for decision making that may require that testing. Ultimately, China could screen all pregnant women, provide HBIG with immunization for all infants born to HBsAg positive mothers, and track the consequences of perinatal exposure among those infants. Other options, such as anti-viral treatment of infection mothers could also be explored. This comprehensive strategy should further reduce the prevalence of HBsAg among children and protect future generations from cirrhosis and hepatocellular carcinoma.

Table 34: Surveyed²⁹ coverage for hepatitis B timely birth dose among all infants, GAVI final evaluation, 2002-2009

Region	Content	2002	2003	2004	2005	2006	2007	2008	2009
Eastern	No. Live birth	33,170	38,179	42,040	46,030	55,032	57,498	59,055	62,516
	No. TBD	27,101	33,055	37,967	41,503	50,635	56,196	58,673	60,106
	Coverage (%)	81.7	86.6	90.3	90.2	92	97.7	99.4	96.1
Central	<i>No. Live birth</i>	24,665	27,432	30,217	30,604	32,631	33,975	35,763	35,700
	No. TBD	12,667	18,948	22,499	25,263	26,484	28,669	30,204	30,755
	Coverage (%)	51.4	69.1	74.5	82.6	81.2	84.4	84.5	86.2
Western	No. Live birth	13,859	19,891	23,325	24,653	26,108	28,696	28,712	27,658
	No. TBD	3,543	10,783	14,998	17,949	20,699	23,835	24,031	23,907
	Coverage (%)	25.6	54.2	64.3	72.8	79.3	83.1	83.7	86.4
Total	No. Live birth	71,694	85,502	95,582	101,287	113,771	120,169	123,530	125,874
	No. TBD	43,311	62,786	75,464	84,715	97,818	108,700	112,908	114,768
	Coverage (%)	60.4	73.4	79	83.6	86	90.5	91.4	91.2

²⁹ GAVI final evaluation survey, October 2010

Table 35: Hepatitis B timely birth dose coverage among infants born in health care facilities, GAVI final evaluation, 2002-2009

Region	Content	2002	2003	2004	2005	2006	2007	2008	2009
Eastern	No. Live birth	25,130	34,205	39,787	45,737	52,551	60,014	59,972	60,322
	No. TBD	20,149	27,920	34,626	38,456	44,195	51,289	58,684	59,005
	Coverage (%)	80.2	81.6	87	84.1	84.1	85.5	97.9	97.8
Central	No. Live birth	12,943	14,994	24,579	25,073	26,706	29,544	31,872	33,671
	No. TBD	7,982	10,760	14,299	15,041	23,887	24,744	29,341	32,578
	Coverage (%)	61.7	71.8	58.2	60	89.4	83.8	92.1	96.8
Western	No. Live birth	3,582	8,652	15,554	14,474	16,418	18,554	21,609	23,306
	No. TBD	2,120	7,599	10,684	13,754	15,786	17,697	21,020	22,932
	Coverage (%)	59.2	87.8	68.7	95	96.2	95.4	97.3	98.4
Total	No. Live birth	41,655	57,851	79,920	85,284	95,675	108,112	113,453	117,299
	No. TBD	30,251	46,279	59,609	67,251	83,868	93,730	109,045	114,515
	Coverage (%)	72.6	80	74.6	78.9	87.7	86.7	96.1	97.6

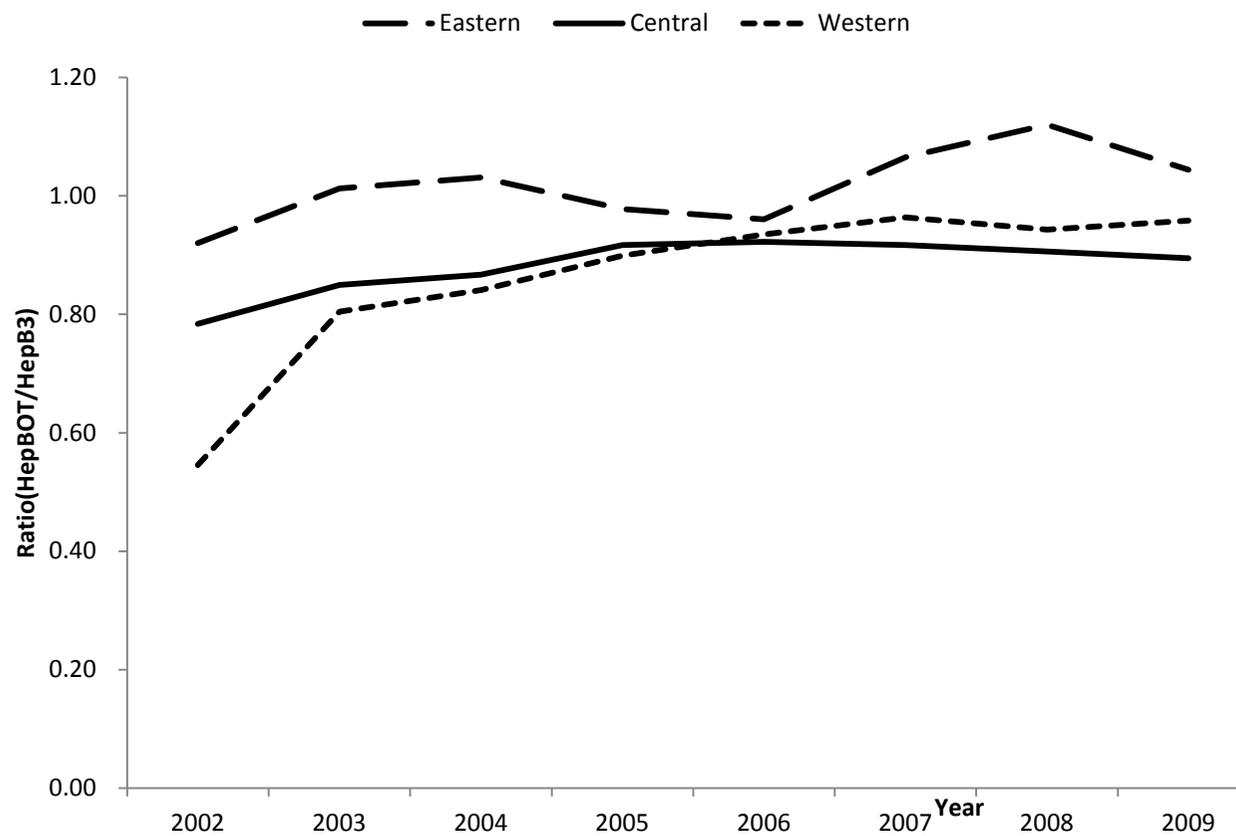
Figure 13: Ratio of the surveyed TBD/HepB3 coverage by region in China, GAVI final evaluation, China, 2002-2009

Figure 14: Frequency of HBsAg screening among pregnant women by region, GAVI final evaluation survey, China, 2002-2009

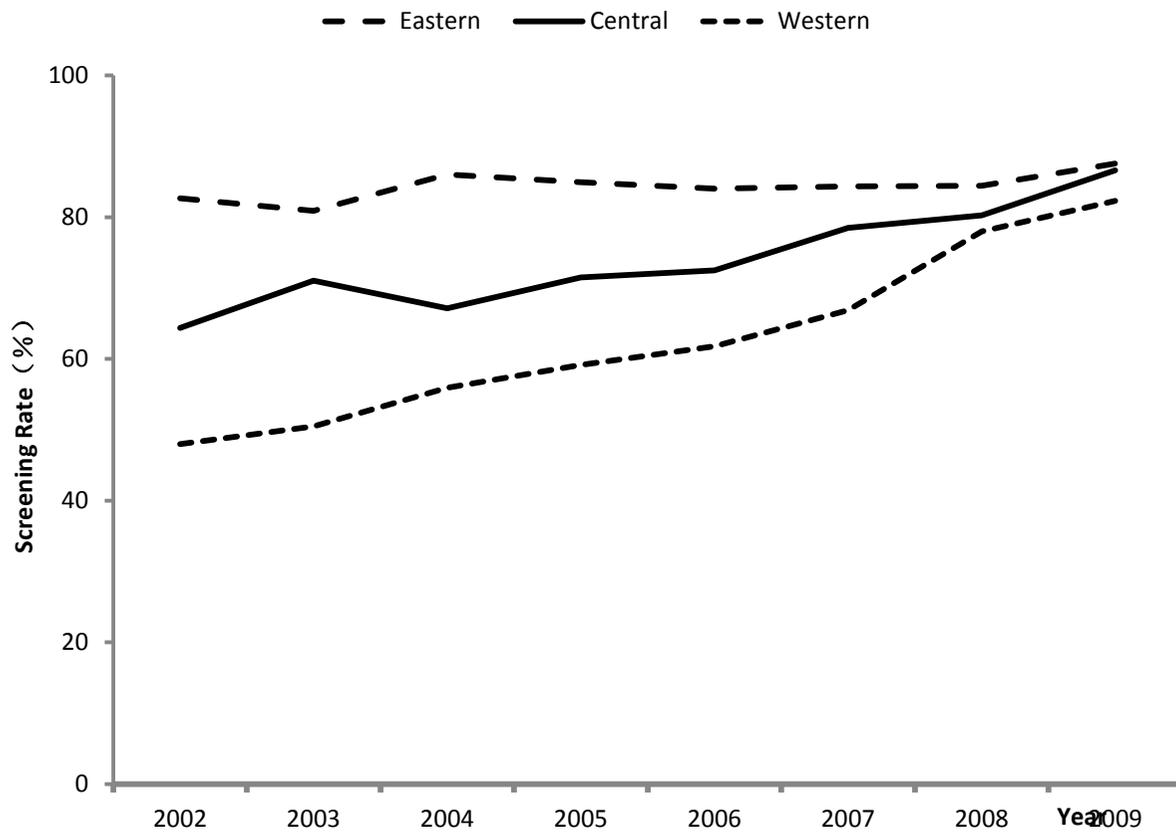


Figure 15: Frequency of various immuno-prophylaxis practices for children born from HBsAg positive mothers, GAVI final evaluation survey, by region, China, 2009

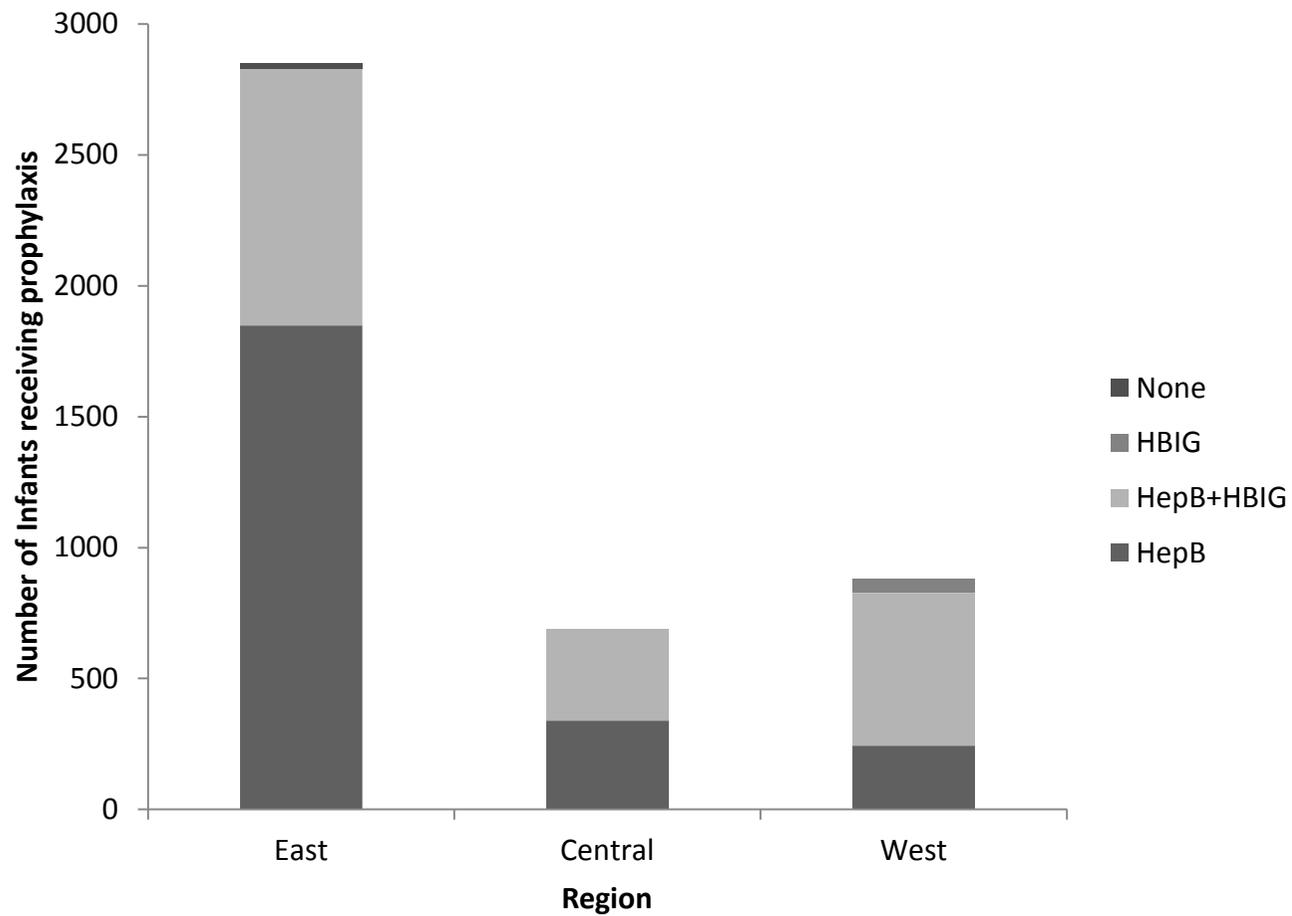
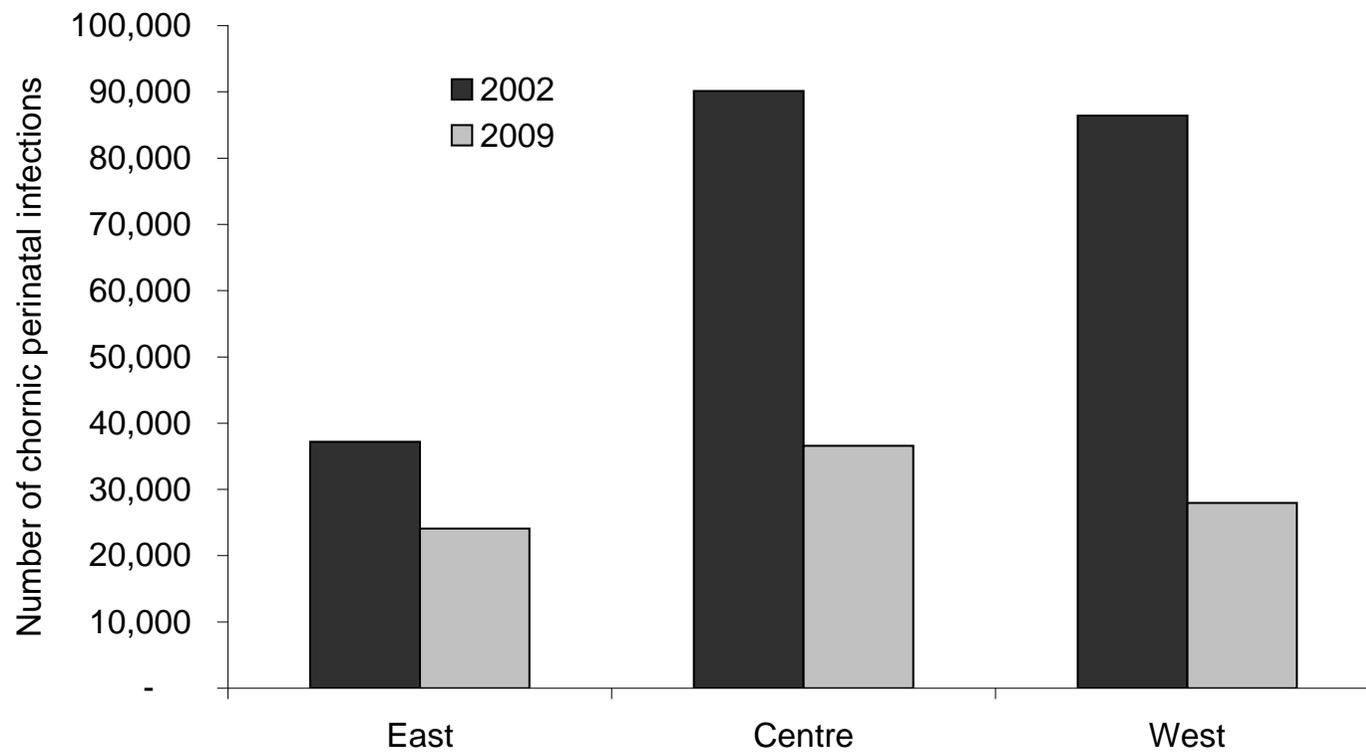


Figure 16: Estimated number of chronic perinatal HBV infections, China, by region, 2002-2009

Conclusions

1. Goals achieved

The initial goals of the GAVI China project were to:

- 1) Reach 85% coverage of three dose of hepatitis B vaccine at the county level;
- 2) Reach 75% coverage of TBD at the county level;
- 3) Introduce AD syringes into immunization services.

Results of our final evaluation suggest that in 2010, goal #1 was reached in 98% of GAVI China project counties that together accounted for 99% of the target population. Goal #2 was reached in 80% of counties that together accounted for 79% of the target population (Chapter 5). 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 (Chapter 6).

Our final evaluation went further than a review of the initial goals and examined all the components of the GAVI China project as per the logic model to understand the causes of the success and identify remaining issues. With respect to **hepatitis B immunization**, input included 76 million USD provided by the GAVI China project to fund hepatitis B vaccine between 2002 and 2007 and 21.5 million USD of additional government subsidies to health care workers between 2007 and 2009 (Introduction). The health system efficiently processed these resources. First, the increase in the HepB3/DPT3 ratio (reaching 94% in 2009) indicated that EPI absorbed the new vaccine well. 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 dose of hepatitis B vaccine coverage progressed from 71% to 93% and TBD coverage progressed from 60% to 91% (Chapter 5). Both of these factors resulted in immunity among vaccinated cohorts as 85% of children 12 to 23 months of age were anti-HBs (+) in the 2006 serological survey (Chapter 2).

With respect to **injection safety**, input included 14 million USD of GAVI China funds to supply AD syringes, safety boxes and needle cutters (Introduction). 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, Chapter 6). 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 (Introduction). Most of these funds were not directly funded by GAVI alliance but by the government, through a leverage effect of the GAVI China project support. Funding was used in 28,753 training 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 hours of life, Chapter 6). This also contributed to higher immunization coverage and safer injections.

Ultimately, the elements of the GAVI China 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 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 (Chapter 2). These improvements will lead to the future prevention of cirrhosis and hepatocellular carcinoma which should result in the prevention of early deaths and health benefits in terms of disability-adjusted life years (DALYs). However, in 2010, these elements had not yet been documented and quantified.

Box 5: Summary of key indicators of input, process, output, outcome and impact for the GAVI project, China, 2002-2010

Elements	Immunization against hepatitis B	Social mobilization and training	Injection safety
Input	<ul style="list-style-type: none"> - 27 million USD disbursed by GAVI for hepatitis B vaccine in 2002-2010 - 21.5 million USD disbursed by the government to subsidize health care workers for vaccination 2007-2009 	<ul style="list-style-type: none"> - 10 million USD disbursed by the government for training activities 	<ul style="list-style-type: none"> - 14 million USD disbursed by GAVI China for AD syringes in 2002-2010 - 100,000 USD disbursed by GAVI China for safety boxes and needle cutters in 2002-2010
Process	<ul style="list-style-type: none"> - HepB3/DTP3 target ratio increased from 57% in 2002 to 94% in 2009 - Hospital delivery rates increased from 78% in 2002 to 96% in 2009 - TBD/DTP1 ratio increased from 0.83 in 2002 to 0.98 in 2009 	<ul style="list-style-type: none"> - 28,753 training workshops held from 2002 to 2009 	<ul style="list-style-type: none"> - 0% of facilities using sterilizable equipment - 78% of facilities using AD syringes in GAVI-supported areas - 79% of facilities using safety boxes in GAVI-supported areas
Output	<ul style="list-style-type: none"> - Surveyed TBD coverage increased from 60% in 2002 to 91% in 2009 - Surveyed HepB3 coverage increased from 71% in 2002 to 93% in 2009 	<ul style="list-style-type: none"> -98% of healthcare workers know about perinatal HBV transmission - 89% of the guardians aware of the need of the first hepatitis B vaccine within 24 hours of life 	<ul style="list-style-type: none"> - 0% of injections for which there is an attempt to reuse syringe and/or needle - Safety boxes used in 79% of facilities
Outcome	<ul style="list-style-type: none"> - Prevalence of Anti-HBs: 85% among children 12-23 months of age in 2006 	<ul style="list-style-type: none"> - No data to determine whether or not injection-associated infections occur 	
Impact	<ul style="list-style-type: none"> - Prevalence of HBsAg decreased from 9.67% in 1992 to 0.96% in 2006 - No data on cirrhosis and hepatocellular carcinoma - No data on mortality reduction - No data on DALY averted 		

2. Reasons why the goals were achieved

2.1 Burden of disease documented

China conducted a national serological survey in 1992 that suggested that chronic hepatitis B infection affected 9.75% of the Chinese population. Children were especially affected (9.67%), with a prevalence as high as adults. The high burden of disease brought it to the attention of the MoH that subsequently recognized hepatitis B as a top priority for control through vaccination.

2.2 Partnership

International: Co-management for the project was a unique model that consisted of the appointment of national and international co-managers who worked under the guidance of an Operational Advisory Group (OAG) comprised of the Ministry of Health, WHO, UNICEF and representatives of the GAVI alliance. This was a creative solution for such a health project (And unique in the world in the way the GAVI alliance implement projects at country level). The national manager was familiar with the domestic vaccination situation while the international co-manager provided insight on international circumstances and global issues. Both worked together, communicated, and ensured good day-to-day management. The OAG made the key decisions during the project years and ensured an objective consensus that was based upon scientific evidence.

National: During the implementation of project, the MoH joined the State Food and Drug Administration (SFDA), the Ministry of Education (MoE), and the Ministry of Finance (MoF) to create a protocol that guaranteed strong cooperation among these

stakeholders. MoH provided strong political support, through (a) development of the national protocol and action plan, (b) allocation of operation funds for vaccination, GAVI China office trained health professionals, regular monitoring, supervision, and social mobilization.

2.3 Local production of vaccine and AD syringes

When China implemented the GAVI project, the country already had national suppliers for hepatitis B vaccines and AD syringes. However, in 2002, these local products were not pre-qualified for purchase by the United Nations agencies. Hence, at the beginning of the project, concerns were raised calling for GAVI China to consider international procurement. Finally, GAVI China opted for domestic procurement. This choice stimulated national vaccine production and ensured a continuity of supply and low prices which were essential elements for sustainability. These low prices contributed to the accumulation of the GAVI China savings that were used for activities in 2007-2010. Throughout the project, there were no incidents regarding the quality of the vaccines and of the AD syringes supplied. In 2011, the Chinese State Food and Drug Administration was declared functional as per the WHO criteria for vaccine regulatory functions^[161]. This milestone event opens the door for Chinese vaccine manufacturers to apply for the WHO pre-qualification process. Hence, in the near future, Chinese vaccine producers will have the opportunity to document that national production has reached international quality standards.

2.4 Solid processes

The Chinese government made strong political commitment to the implementation of the GAVI China project. At the beginning of the project, China designated responsible staff in hospitals and EPI facilities. The project trained health care workers in hospital and rural clinics, encouraged cooperation between MCH and EPI to increase hospital deliveries and TBD coverage, provided subsidies for hepatitis B vaccination and conducted supervision visits to guide activities. As a result, implementation occurred smoothly, as reflected by our process indicators.

The extensive social mobilization campaigns conducted by GAVI China project raised the awareness of vaccination among providers and parents.

The GAVI China project collaborated with a national initiative on health system strengthening (HSS) and an international initiative to eliminate the neonatal tetanus. As a result, a disbursement policy providing incentives for pregnant women to deliver in hospitals increased hospital delivery rates and resulted in increased TBD coverage.

2.5 GAVI China support providing the funding solution that unlocked the situation

Hepatitis B was preventable through cost-effective immunization and the Chinese government recognized it as a priority disease for control. However, in 2002, the Chinese government could not afford to pay for free vaccine in the whole country. Hence, China made a request for support to GAVI alliance and an agreement was reached to provide the funds for hepatitis B vaccination and safe injections in Western provinces and poverty-affected counties of the Central region. The financial support from GAVI alliance

was just the final element that was missing to trigger the implementation of universal immunization against hepatitis B in China.

3. The benefit of vaccination: Impact

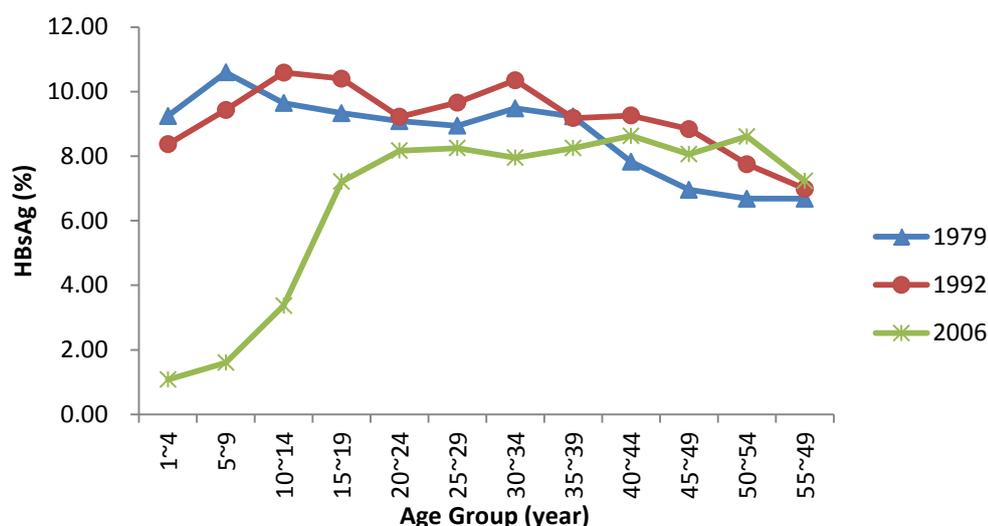
3.1 The effectiveness of hepatitis B vaccine

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 groups, ranging from 0.96% among children 1-4 years of age, to 2.42% among children 5-14 years of age, to 8.57% among persons 15-59 years of age. 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 programme (Figure 17).

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 prevalence of HBsAg > 8% means high endemicity area, prevalence of 2%-8% means intermediate endemicity areas and prevalence < 2% means low endemicity areas. Hence, China should now be listed as an intermediate prevalence area ^[14]. The prevalence of HBsAg among children under 5 has already reached the WPRO goal (less than 2% by 2012), opening the opportunity of China to undergo the formal WHO verification process

[27]. 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 HBV infection, and that 19 million had averted chronic HBV infections [80].

Figure 17: The Prevalence of HBsAg among population aged 1-59 in China 1979, 1992 and 2006



3.2 Economic analysis of hepatitis B vaccination

Although no economic analysis studies on hepatitis B vaccine were conducted during the course of the GAVI project, there is a large body of evidence worldwide on the cost-effectiveness of universal infant vaccination against hepatitis B (Box 6).

Box 6: Economic analysis of hepatitis B vaccination

International	National
<p>Studies in low HBsAg prevalence countries including the USA have indicated that the benefit of vaccination can be obtained through universal hepatitis B vaccination during childhood ^[162].</p> <p>In the Gambia, vaccinating infants against hepatitis B was highly cost-effective. Compared with the absence of intervention, the vaccination programme would cost US\$ 28 per DALY averted from the societal perspective or US\$ 47 per DALY averted from the payers perspective. The programme also has the potential to be affordable, starting at a relatively low budget of US\$ 160,000 per year. Combining the two dimensions of the outcome measure, the probability that vaccinating infants would be both cost-effective and affordable is 40% at an annual programme budget of US\$ 182,000 (the estimated total programme cost from the payers perspective), given a threshold cost-effectiveness value of US\$ 47 per DALY averted ^[163].</p>	<p>In China, the analysis of a study conducted in 2003 in Shanghai indicated that during 10 years of hepatitis B vaccination (between 1992 and 2001), 721,509 infants were vaccinated, and the estimated number of HBV infections, chronic hepatitis B infections, cases of cirrhosis and cancers of the liver would be reduced by 54,864, 4,885, 445 and 48, respectively in the study population in 10 years. An investment of 501,129 RMB can prevent one case of liver cancer, 10 cases of cirrhosis, 100 cases of chronic hepatitis B and 1,000 cases of HBV chronic infections ^[164]. Results of the study and analysis showed that 59,762.55 DALYs were averted for a population of 712,509 by vaccinating against hepatitis B in neonates during these 10 years.</p> <p>Hepatitis B catch-up vaccination for children and adolescents in China is cost-saving across a range of parameters, even for adolescents aged 15 to 19 years old ^[165].</p>

3.3 Safety of hepatitis B vaccination

In 2005, China established 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 numbers of reported AEFIs. 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 ^[166, 167].

During Jan 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 biopsy. Among 6 cases that were subject to biopsy, one case was attributed to acute allergic shock induced by vaccination with hepatitis B vaccine. While among 4 cases that were not subject to biopsy, one was possibly due to acute allergic shock induced by vaccination ^[166-168]. 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 rate based on the birth cohort (16 million) and vaccine coverage in a year. Using these calculations, the death rate of AEFIs induced by hepatitis B (2/16 million) was only 0.1/ million, lower than the one quoted by UNICEF ^[169]. All these data suggested that hepatitis B vaccine is very safe. Reaction usually includes minor local pain and/or mild fever, and recovery occurs without any treatment ^[8, 170]. Because the hepatitis B vaccine has been

shown to be safe and cost-effective, countries worldwide had incorporated it into their routine immunization programmes by 2009^[14]. In WPRO, all countries except Japan have integrated hepatitis B vaccine into routine immunization.

3.4 Maintaining hepatitis B vaccination (2011 onwards)

Since 2007, the China/GAVI project has not made additional investments for hepatitis B vaccine and AD syringes. The China central government has taken over the responsibility for hepatitis B vaccination and injection safety. Hepatitis B vaccine became one of the vaccines integrated into the national immunization programme, with all costs fully funded by the government of China including vaccine, syringe, subsidy of vaccination, salary of HCW, cold chain and operational funds.

4. Remaining issues

4.1 Persistence of perinatal HBV infections

Despite achievements in terms of the elimination of perinatal HBV infection, in 2010, China still accounted for the largest annual number of perinatal HBV infections (84,121) in the WHO WPR region. Two factors explain the difficulties that China is facing when trying to eliminate perinatal HBV transmission. First, the efficacy of hepatitis B vaccine alone ranges from 85% to 95%. Hence, some children present with breakthrough infection despite receiving TBD. 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. Thus, in the future, China must identify

mechanisms to address these two issues and reach more children with more effective prophylaxis regimens. This will require increasing TBD through increased births in hospitals and increasing HBsAg screening of pregnant women so that HBIg can be provided to infants of HBV carrier mothers. The inclusion of HBIg to the protocol of immune-prophylaxis increases effectiveness from about 88% to up to 95%.

4.2 Remaining unsafe injection issues

Despite the large scale introduction of AD syringes in China because of the GAVI China project, the Eastern region and some non-project areas in the Central areas still do not use AD syringes. 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 facilities and private hospitals still engage in unsafe sharps waste management solutions 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 had missed 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 ^[143] and 2010 ^[98] recommended vaccinating health care workers against hepatitis B. Aside from health care workers, WPRO already has a guideline for hepatitis B vaccination of high-risk adults. 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 solid surveillance system is needed to identify risk factors for infection and frame the groups that could benefit from immunization.

4.4 Surveillance problems for incidence 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 sound 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. Pilot population-based project in selected settings may provide useful guidance on the way to proceed. In addition, as China is developing the new reform health system for treatment, but due to the affordable capacity of provinces, this is not universal implemented and inequity remains. Therefore, China should have eligible medicines integrated into national health insurance system, which will benefit many 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.

Recommendations

A. How to use the lessons learned from GAVI China for the future 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 in China's EPI, preparation 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 not longer eligible for GAVI alliance support. Therefore, in the future, if a new, locally produced, cost-effective vaccine for a disease with a heavy burden is considered for introduction in the EPI, the cost of the new vaccine should be afforded using domestic funds. With domestic production in mind, the experience from the GAVI China project could be used to generate a financing mechanism that will ensure equitable coverage (Table 36).

The GAVI China project set up an example to scale up the introduction of a new vaccine into routine immunization in collaboration with the GAVI alliance. The GAVI China experience with respect to hepatitis B vaccine in the recent years can be compared with the current situation of other new vaccines in China (Table 36). For hepatitis B vaccine, documentation of a large burden of disease in view of available information with respect to cost effectiveness and in the presence of large-scale domestic production led to a strong government commitment. This government commitment progressively led a universal, equitable financing. This experience is not so different from the Chinese experience with Japanese encephalitis^[171, 172], for which information on burden of disease^[32, 80] and cost

effectiveness ^[173, 174] combined with the availability of a good national vaccine ^[175] to trigger national introduction in EPI in 2007. Overall, these experiences point to a number of criteria with respect to introduction of new vaccines that could be of use for National Immunization Technical Advisory Groups (NITAGs) in China and other countries. These NITAGs may consider epidemiological, economical 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). NITAGs can then consider these elements to recommend the identification of equitable financing for universal introduction when the right conditions are met.

Table 36: Lessons learned from hepatitis B vaccine introduction in China with respect to the introduction of other new vaccines, GAVI China project evaluation, 2002-9

Elements to consider for introduction of a new vaccine	Hepatitis B vaccine in China	Situation in 2011 with respect to other vaccines		
		H1b	Rotavirus	Pneumococcal conjugate vaccine
Burden of disease documentation	- Extensive documentation using local data - Large burden	- Based on extrapolation of global data - Difficult technically	- Large burden of diarrheal disease - Low mortality	- Based on extrapolation of global data - Difficult technically
Vaccine effectiveness	- Documented in China	- Studies conducted outside of China	- Studies conducted in China	- Studies conducted outside of China
Cost effectiveness	- Documentation on the basis of studies conducted outside of China were sufficient	- Studies conducted outside of China	- Studies conducted outside of China	- Studies conducted outside of China
Local production	- From 1985 - Multiple producers	- Available in 2003 - Two producers - Sufficient supplies	- Available in 2000 - One producer - Insufficient supplies for nationwide use	- Available in 2006 for adult, but not for children
Equitable financing	- Progressively acquired, with key milestones in 1992, 2002, 2005 and 2008	No	No	No

B. How to address unmet needs with a second generation hepatitis B programme

Immunization

Immunization system. The future of hepatitis B immunization in China must be to maintain 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 programme 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.

Catch-up campaigns. As China has already completed catch-up vaccination for children under 15 years old, the strategy will now evolve towards routine activities through school entry checks in primary school or middle school, or provision of routine vaccination in all vaccination sites. Raising the age to conduct catch-up campaigns leads to less and less returns in terms of cost-effectiveness^[165]. However, this strategy could be a useful way to

reach health care workers in the pre-service stage (e.g., nursing students and medical students)^[176, 177].

Health care worker protection. In addition to the routine immunization of infants, catch-up campaigns for children and vaccination for high-risk adults, pre-services vaccination for students in medical school and university should be addressed. Hence, health care workers would be protected before exposure. This is a cost-effective way to protect health care workers^[178, 179].

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 safety injections guideline 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 sub-standard choices, precise guidance should define what is acceptable and what is not.

Surveillance for acute disease

China should develop a clear guideline for the surveillance of 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 and will allow identification of risk factors for use in policy making. Such work should to be done in pilot projects first, before expanding to a national scale. Evidence generated could guide vaccination of high-risk adults.

Towards 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 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 benefitted 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. This is a first documentation step for future programmes 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.

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Appendix

Appendix 1: Counties selected in the sample of the final evaluation, China, 2010

Region	Province	County	Facilities
East	Liaoning	Liaozhong	10
	Shanghai	Chongming	10
	Jiangsu	Sheyang	9
	Zhejiang	Shangyu	10
	Shandong	Zhangqiu	10
		Luxian	9
	Guangdong	Baoshan	8
		Lianshan	8
Central	Hebei	Shenze	11
		Hejian	11
	Jilin	Shuangliao	11
	Anhui	Nanlin	10
		Xuanzhou	11
	Henan	Kaifeng	10
		Ninglong	11
	Hunan	Longhui	11
West	Inner Mongolia	Linhe	11
	Hubei	Macheng	11
	Guangxi	Zhongshan	11
	Sichuan	Fushun	11
		Dazhu	11
	Guizhou	Guiding	11
	Shanxi	Huxian	11
	Gansu	Guanghe	10

Appendix 2: List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AD	Auto-Disable syringes
AEFI	Adverse Events Following Immunization
ALT	Alanine aminotransferase
BCG	Bacillus Calmette–Guérin (vaccine)
CDC	Centers for Disease Control (US)
CFETP	Chinese Field Epidemiology Training Programme
CHO	Chinese Hamster Ovary
CI	Concentration Index
DALYs	Disability-Adjusted Life Years
DSP	Disease Surveillance Points
DTP	Diphtheria, Tetanus, Pertussis Combined Vaccine
ELISA	Enzyme-Linked Immunosorbent Assay
EPI	Expanded Programme on Immunization
GAVI	Global Alliance for Vaccine and Immunization
GDP	Gross Domestic Product
GIVS	Global Immunization Vision and Strategy
GMT	Geometric Mean Titre
HBIG	Human Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBeAg	Hepatitis B e Antigen

HBIG	Hepatitis B Immune Globulin
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCW	Health Care Worker
HepB	Hepatitis B vaccine
HepB3	Three dose of hepatitis B vaccine
IEC	Information, Education and Communication
IVDC	Institute for Viral Disease Control, China CDC
JRF	Joint Reporting Form
KAP	Knowledge, Attitude, Practice
MCH	Maternal and Child Health
MMR	Measles, Mumps and Rubella vaccine
MoH	Ministry of Health
MTCT	Mother to Child Transmission
OAG	Operational Advisory Group
PMTCT	Prevention Mother to Child Transmission
PPS	Probability Proportional to Population Size
RMB	Ren Min Bi (Chinese Yuan)
TBD	Timely Birth Dose
UNICEF	The United Nations Children's Fund
WHO	World Health Organization
WPRO	West Pacific Region Office, WHO

Appendix 3: Curriculum Vitae

Personal information

Name: Cui Given Name: Fuqiang

Gender: Male

Current position

- Secretary, Chinese National Advisory Committee on Immunization Practices
- Director of Hepatitis Division, National Immunization Program, Chinese Center for Disease Control and Prevention
- Manager, Ministry of Health/Global Alliance on Vaccine and Immunization
- Member of Experts committee of Chinese Foundation for Hepatitis B Prevention and Control

Research field

Epidemiology of Vaccine Preventable Diseases, Viral hepatitis prevention and control

Work experience

June 2005 - Present

- Manager, Ministry of Health, China/Global Alliance for Vaccine and Immunization (GAVI) Project
- Director, Division of Hepatitis, National Immunization Program, Chinese Center for Disease Control and Prevention

June 2001- June 2005

- Acting director and Deputy Director, Department of immunization, Gansu Provincial Center for Disease Control and Prevention

June 1995 - June 2001

- Medical officer, Department of immunization, Gansu Provincial Center for Disease Control and Prevention

Education

2010 – Present

- PhD Student on Epidemiology, Swiss Tropical and Public Health Institute, University Basel, Switzerland

2003 – 2004

- School of Public Health, Hebrew University Jerusalem, Israel: Master of Public Health

1990 – 1995

- School of Preventive Medicine, Lanzhou Medical college, Lanzhou University: Bachelor Degree of Medical Doctor

1987-1990

- No 2 high school of Jingyuan, Gansu

The field work records since 2003



Investigation to H1N1 outbreak in June, 2009



TAG Meeting of WPRO in June, 2006



Consultant in Vietnam in Jan, 2010



Technical expert review, in April, 2011



Seminar in WHO China in July, 2009

Publications in English

1. **Cui F**, Luo H, Zhou L, Yin D, Zheng C, Wang D, et al. Transmission of Pandemic Influenza A (H1N1) Virus in a Train in China. *J Epidemiol*, 2011, available on line, 4 June 2011.
2. Yin J, Zhang H, He Y, Xie J, Liu S, Chang W, Tan X, Gu C, Lu W, Wang H, Bi S, **Cui F**, Liang X, Schaefer S, Cao G. Distribution and hepatocellular carcinoma-related viral properties of hepatitis B virus genotypes in Mainland China: a community-based study. *Cancer Epidemiol Biomarkers Prev*. 2010; 19(3):777-86. Epub 2010 Feb 16.
3. **Cui FQ**, Li L, Hadler S, Wang F, Zheng H, Chen Y, et al. Factors associated with Effectiveness of the First Dose of Hepatitis B Vaccine in China -1992-2005. *Vaccine* 28 (2010) 5973–5978.
4. **Cui FQ**, Hadler S, Zheng H, et al. Hepatitis A surveillance and vaccine use in China from 1990 through 2007. *J Epidemiol*, 2009, 19(4):189-195.
5. Liang XF, Bi SL, Yang WZ, Wang LD, Cui G, **Cui FQ**, et al. Evaluation of the Impact of Hepatitis B Vaccination among Children Born Between 1992 and 2005 in China. *Journal of Infectious disease*, 2009, 200(1):39-47.
6. Liang XF, Bi SL, Yang WZ, Wang LD, Cui G, **Cui FQ**, et al. Epidemiological Serosurvey of Hepatitis B in China - Declining HBV Prevalence due to Hepatitis B Vaccination. *Vaccine*, 2009, 27:6550–6557.
7. Yin J, Zhang H, He Y, Xie J, Liu S, Chang W, Tan X, Gu C, Lu W, Wang H, Bi S, **Cui F**, Liang X, Schaefer S, Cao G. Distribution and hepatocellular carcinoma-related viral properties of hepatitis B virus genotypes in Mainland China: a community-based study. *Cancer Epidemiol Biomarkers Prev*, 2010, 19(3):777-86.
8. **Cui F**, Liang X, Cao L, et al. Improving Hepatitis B immunization rates in China. *Journal of Clinical Virology*, 2006, 36(s):237.
9. **Cui FQ**, Wang XJ, Cao L, et al. Progress in Hepatitis B Prevention through Universal Infant Immunization - China, 1997-2006. *MMWR*, 2007; 56(18): 441-445.
10. **Cui FQ**, Wang XJ, Cao L, et al. Progress in Hepatitis B Prevention through Universal Infant Vaccination-China, 1997-2006. *WER*, 2007, 82(24):209-224. (Reprinted)
11. **Cui FQ**, Wang XJ, Cao L, et al. Progress in Hepatitis B Prevention through Universal Infant Vaccination-China, 1997-2006. *JAMA*, 298(5): 506-509. (Reprinted)
12. **Cui FQ**, Gaofin R. Immunization coverage and its determinants in children aged 12–23 months in Gansu, China. *Vaccine*, 2007; 25(4):664-71.

Publications in Chinese

1. Hu YS, **Cui FQ**, Liang XF. Development on timely first dose of hepatitis B vaccine for infants. *ZhongguoJiHuaMian Yi*. 2010,16(2):178-82.
2. Wu ZH, **Cui FQ**, Gong XH. Effect analysis on non-and-low response infants after revaccinated hepatitis B vaccine. *ZhongguoJiHuaMian Yi*, 2010,16(3):207-10.
3. **Cui, FQ**, Miao N, Hu YS, et al. Effect of hepatitis health promotion project in schools of Beijing and Gansu. *Chinese journal of vaccine and immunization*, 2009, 15(5):409-416.
4. **Cui FQ**, Gong X, Chen Y, et al. Evaluation on impact of hepatitis B vaccine integrated into routine immunization in the areas of Ministry of Health/Global Alliance for Vaccine and Immunization (GAVI) Cooperation Project P.R. China. *Chinese journal of vaccine and immunization*, 2009, 15(4):289-293.
5. **Cui FQ**, Bi S, Zhang Y, et al. Combination profiles of hepatitis B marks for Chinese in serosurvey in 2006. *Chinese journal of vaccine and immunization*, 2009, 15(4):294-299.
6. Wang FZ, **Cui FQ**, Liu DW. Analysis on the adverse events following immunization of 10 infants death after hepatitis B vaccination. *ZhongguoJiHuaMian Yi*. 2009,15(1):52-7.
7. Dang R, Zhang S, Zhang W, Liang X, **Cui F**, Zhao F. Assessment for Immune effectiveness of hepatitis B vaccination among infant population in China. *Chinese Journal of public health*, 2009,25(4):
8. **Cui FQ**, Wang FZ, Zheng H, et al. Analysis on Reported Cases of Hepatitis B in China in 2005-2007. *Chinese journal of vaccine and immunization*,2008,14(5):413-417.
9. **Cui FQ**, Gong XH, Chen YS, et al. Chinese Hepatitis B Immunization Strategies and Feasibility of Expanding the Vaccination to Children and High Risk Population among Adult. *Chinese journal of vaccine and immunization* 2008,14(6):553-558.
10. Chen YS, Li FJ, Wang XJ, Wang FZ, **Cui FQ**, Gong XH, et al. Study on the probability of hepatitis B virus infection at public service places. *Zhonghua Liu Xing Bing XueZaZhi*. 2008, 29(7):689-92.
11. Zhang SX, Dang RB, Zhang WD, Liang XF, **Cui FQ**. Analysis on economic efficacy regarding previous strategies and current recommendations for vaccination against hepatitis B virus in China. *Zhonghua Liu Xing Bing XueZaZhi*, 2008, 29(10):1003-8.
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13. **Cui FQ**, Hu YS, Lu Y, et al. Analysis on new born hepatitis B immunization coverage and pregnant women hospital delivery rate in different regions. *Chinese journal of vaccine and immunization*, 2007, 13(4):313-315.
14. Zheng Hui, Wang FZ, **Cui FQ**. Epidemiological Analysis on Hepatitis A in China during 2004-2006. *Chinese journal of vaccine and immunization*, 2007, 13(4):336-340.
15. **Cui FQ**, Li TD, Guo Q. Review on immunization coverage assessment in different studies. *Chinese journal of vaccine and immunization*, 2007, 13(2):170-174.

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17. **Cui FQ**, Lu Y, Wang FZ, Chen YS, Zheng H, Zhang Y, et al. Analysis on the proportion of reported hepatitis B cases through pilot surveillance in China during 2006. Chinese Journal of Epidemiology, 2007, 28(9):872-874.
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19. Sui HT, Liang XF, Yin DP, **Cui FQ**, Wang HQ. Epidemic Characteristics on Hepatitis A in China During 1990~2006. Chinese Journal of Vaccine and Immunization, 2007,13(4):
20. **Cui FQ**, Lu Y, Hu YH, et al. Analysis on Review of Hepatitis B vaccine integrating into National Immunization Programme Chinese journal of vaccine and immunization, 2006,12(4):241-245.
21. **Cui FQ**, Wang XJ, Liang XF. Epidemiology analysis on reported hepatitis B under 15 years in China. Chinese journal of vaccine and immunization, 2006,12(3):206—208.
22. **Cui FQ**, Liang XF, Lu Y, et al. Analysis on Hepatitis B immunization coverage in 12 western provinces. Chinese journal of vaccine and immunization, 2006, 12(2):81-83.
23. Lu Y, **Cui FQ**, Wang XJ, et al. Capacity of laboratory testing for acute hepatitis B in medical setting in 8 provinces in China, Chinese Journal of Epidemiology,2006,9:802-804.
24. **Cui FQ**, Tang Y, Lu XT, et al. Survey on establishing computer based system on cold chain management, Chinese journal of vaccine and immunization, 2003, 9(5):258.
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26. **Cui FQ**, He GS, Li H. Evaluation on elimination project on neonate tetanus, in Gansu, Chinese journal of vaccine and immunization, 2001, 7(3): 152-154.
27. **Cui FQ**. Survey on status of cold chain in Gansu. Chinese Journal of Epidemiology, 1997, 18(1-C): 141-145.

Oral presentations at international conferences

- Progress toward Measles Elimination in China: Achievement and Challenges. WHO Western Pacific Region Technical Advisory Group meeting, 9 August, 2011, Manila, Philippine.
- Experience with measles elimination in high epidemic areas in China. WHO Western Pacific Region Technical Advisory Group meeting, 9 August, 2011, Manila, Philippine.
- Consultation on Best Practices and Tools for Preventing Perinatal Hepatitis B Virus Transmission. Burnet Institute, Melbourne, Australia, 7-8 December 2010.
- Post-marketing surveillance of the live attenuated hepatitis A vaccines in China, Global Advisory Committee on Vaccine Safety, 16-17 June 2010, Geneva.
- Evaluation plans for GAVI project in China, and catch up vaccination in children, Asia and viral hepatitis: Learning from China to enhance prevention and control efforts in Asia. April 28, 2010, Hongkong, China
- Impact of hepatitis A vaccine use on disease incidence in China, Asia and viral hepatitis: Learning from China to enhance prevention and control efforts in Asia. April 28, 2010, Hongkong, China
- Hepatitis B control, Strategies, successes and challenges in China. Scientific seminar on hepatitis B, 26-27 Jan 2010, Hanoi, Vietnam.
- Progress of Measles Control in China, Global Measles Management Meeting, 20 February, 2009, New York, USA.
- Evaluation on Health Promotion Program in China, 11 Feb, 2009. Hong Kong.
- Hepatitis B in China: Example of How to Tackle Discrimination, Asia Summit on Corporate society Responsibility, 3 Nov, 2008, Thailand.
- Achievability of Regional Goal - Strategies, Successes and Challenges, WPRO Technical Advisory Group meeting, 27 June, 2007, Manila, Philippine.
- Operational Features of China - Hepatitis B Immunization Program, WPRO Technical Advisory Group meeting, 20 June, 2006, Manila, Philippine.
- Improving Hepatitis B Immunization Rates in China, 12th International Conference for Hepatitis, 4 July, 2006, Paris, France.
- Hepatitis B Vaccination in China, Annual Meeting of Asian and Pacific Association of Study of Liver, 17 August, 2005, Bali, Indonesia.