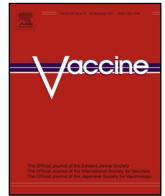




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Evaluation of policies and practices to prevent mother to child transmission of hepatitis B virus in China: Results from China GAVI project final evaluation

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ABSTRACT

Background: Mother to Child Transmission (MTCT) has remained a leading cause of HBV infection in China, accounting for 40% of total infections. Providing hepatitis B vaccine (HepB) to all infants within 24 h of birth (Timely Birth Dose, TBD), and subsequent completion of at least 3 vaccine doses is key to preventing perinatal HBV infection. In 2002, with the financial support of the Global Alliance on Vaccine and Immunization (GAVI) targeted to Western region and 223 poverty-affected counties in Central region, hepatitis B vaccine was provided for free. In 2010, we evaluated the China GAVI project in terms of its activities to prevent perinatal infections.

Objective: The objectives of the evaluation were to (1) measure achievements in the China GAVI project in terms of TBD coverage, and (2) describe practices for HBsAg screening of pregnant women and HBIG use outside the GAVI China project.

Methods: We used the methods recommended by WHO to select a cluster sample of health care facilities for the purpose of an injection safety assessment. We stratified China into three regions based on economic criteria, and selected eight counties with a probability proportional to population size in each region. 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. In each hospital, we abstracted 2002 through 2009 records to collect information regarding birth cohorts, hospitals deliveries, vaccine management, hepatitis B vaccination delivery, HBsAg screening practices and results, and HBIG administration. In addition, in all hospitals, we abstracted records regarding the delivery of TBD.

Results: We visited 244 facilities in the three regions, including 24 county hospitals and 220 township hospitals. We reviewed 837,409 birth summary records, 699,249 for infants born at county or township hospitals. Hospital delivery rates increased from 58% in 2002 to 93% in 2009. Surveyed TBD coverage increased from 60% in 2002 to 91% in 2009 (+31%). Surveyed TBD coverage among children born in hospitals increased from 73% in 2002 to 98% in 2009. Between 2002 and 2009, the proportion of pregnant women screened for HBsAg increased from 64% in 2002 to 85% in 2009. In 2009, the proportion of infants born to women screened and found to be HBsAg positive who did not receive any immunization within 24 h after birth ranged from 0% to 0.7% across regions.

Conclusions: 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. Screening for HBsAg to guide HBIG administration has begun, but with heterogeneous immuno-prophylaxis practices and a poor system for follow up.

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1. Background

Perinatal transmission is a major source of hepatitis B virus (HBV) infection in many countries, especially in highly endemic regions [1]. Perinatal HBV infections occur in infants of mothers with chronic HBV infection (positive for the HBV surface antigen (HBsAg)). The earlier the HBV infection occurs in a child the higher the probability of developing chronic infection [2]. In addition, the risk of perinatal transmission is higher when the mother's HBV DNA level is high, correlating with the presence of hepatitis B e antigen (HBeAg) in the maternal serum. In the absence of immunoprophylaxis, 70% to 90% of children born to HBeAg-positive mothers develop chronic HBV infection by six months of age [3]. Among those born to HBsAg positive, HBeAg-negative mothers, less than 10% develop chronic infection [3]. Providing hepatitis B vaccine (HepB) to all infants within 24 h of birth (Timely Birth Dose, TBD), and subsequent completion of at least 3 vaccine doses is key to preventing perinatal HBV infection. Overall, published studies report a 90% efficacy of hepatitis B vaccine for the prevention of perinatally acquired HBV carriage in infants of carrier mothers. Among infants born to HBsAg and HBeAg positive mothers, efficacy is lower (70%–90%) [4]. Adding human Hepatitis B Immunoglobulin (HBIG) to vaccination at birth increases efficacy to 95% [4]. 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 a TBD to prevent perinatal HBV infection [5]. In addition to this, many industrialized countries also include screening of pregnant women to provide vaccination plus HBIG within 12 h after birth to children born to HBsAg positive mothers [6]. A smaller number of countries, including the United Kingdom and Japan, screen pregnant women for HBsAg, in order to provide selective immunoprophylaxis in the absence of universal hepatitis B vaccine immunization of newborns. In 2009, 177 counties had integrated hepatitis B vaccine into routine immunization [5].

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 [7]. Among HBsAg positive women aged 15–39 years, 30% were HBeAg positive, indicating a high risk of perinatal infection [8]. In 2002, with the financial support of the Global Alliance on Vaccine and Immunization (GAVI), targeted to Western Provinces and 223 poverty-affected counties in Central Provinces, hepatitis B vaccine became free throughout although parents were still charged a small user fee. One of the goals of the China GAVI project was to reach 75% TBD coverage among infants born in GAVI-supported areas [9]. In 2005, the government provided free hepatitis B vaccination services to all infants with 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 [10].

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 identified the best operational approaches to timely birth dose delivery [11]. Second, use of hepatitis B vaccine out of cold chain was studied [12]. 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 gave birth in hospitals. Fourth, in 2007, China GAVI project funds were allocated to support low performing prefectures in Western poverty-affected counties so that they could reach the China GAVI project targets [11]. These resulted in increased hospital delivery rates and in 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 h after birth. However, strategies to implement this new recommendation are in the process of being developed. Before this 2010 recommendation, and unrelated to the China GAVI project, many hospitals were already implementing HBsAg screening and HBIG delivery at the expense of the pregnant women.

In 2010, we evaluated the China GAVI project impact in preventing perinatal HBV infections. The objectives of the evaluation were to (1) measure achievements in the China GAVI project in terms of TBD coverage, (2) describe HBsAg screening practices for pregnant women and HBIG use outside the China GAVI project and before the official 2010 recommendation, and (3) propose recommendations for the future prevention of perinatal HBV infection in China.

2. Methods

2.1. 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 conducting injection safety assessments, which was an important component of the final China GAVI project evaluation [13,14]. First, we stratified China into three regions (Eastern, Central and Western) based on economic criteria [8]. 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 [13], which for the whole country totaled 240 facilities. In addition, we reviewed each of the township hospitals for TBD 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.

2.2. Data collection

In each hospital visited, we abstracted all summary records between 2002 and 2009 to collect information regarding birth cohorts, hospital deliveries, vaccine management, hepatitis B vaccination delivery, HBsAg screening practices and results, and HBIG administration. In each township, we randomly selected 10 parents in the general population who had a child born between 2002 and 2009 from the lists presented in township hospitals. We interviewed parents to collect information about knowledge, attitudes and practices with respect to hepatitis B and its prevention. Data were compiled and analyzed in Excel spreadsheets.

2.3. 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 in 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 vaccine delivery after birth) with the progress of three dose hepatitis B vaccine coverage, reflecting the availability of the vaccine and its integration in EPI.

Table 1
Coverage for hepatitis B timely birth dose among all infants, China 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	No. Live birth	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	3543	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

2.4. Model to estimate the number of perinatal HBV infections

We used the formula proposed by Goldstein [15] 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) [10], the HBeAg prevalence among HBsAg-positive women (a_e : 30% in China) [10], 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 infections that would remain chronic [14]. 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 calculated the proportion of infants born to infected mothers who received HBIG,

but neglected the effect of HBIG in the calculations for perinatal HBV infection since the vaccination coverage is very high.

3. Results

3.1. Coverage survey

We visited 244 facilities in the three regions, including 24 county hospitals and 220 township hospitals (for counties with less than 10 townships all townships and facilities were selected). We reviewed 837,409 birth records, including 699,249 for children born at county or township hospitals. The hospital delivery rate increased from 58% in 2002 to 93% in 2009.

3.2. General population

Overall, surveyed TBD coverage increased from 60% in 2002 to 91% in 2009 (+31%). Surveyed TBD coverage increased from 82% in 2002 to 96% in 2009 (+14%) in the Eastern region, from 51% to 86% in 2009 (+35%) in Central region, and from 26% to 86% in 2009 (+61%, Table 1) in Western region. 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, from 0.78 in 2002 to 0.89 in 2009, and in the Western region, from 0.55 to 0.96 in 2009 (Fig. 1).

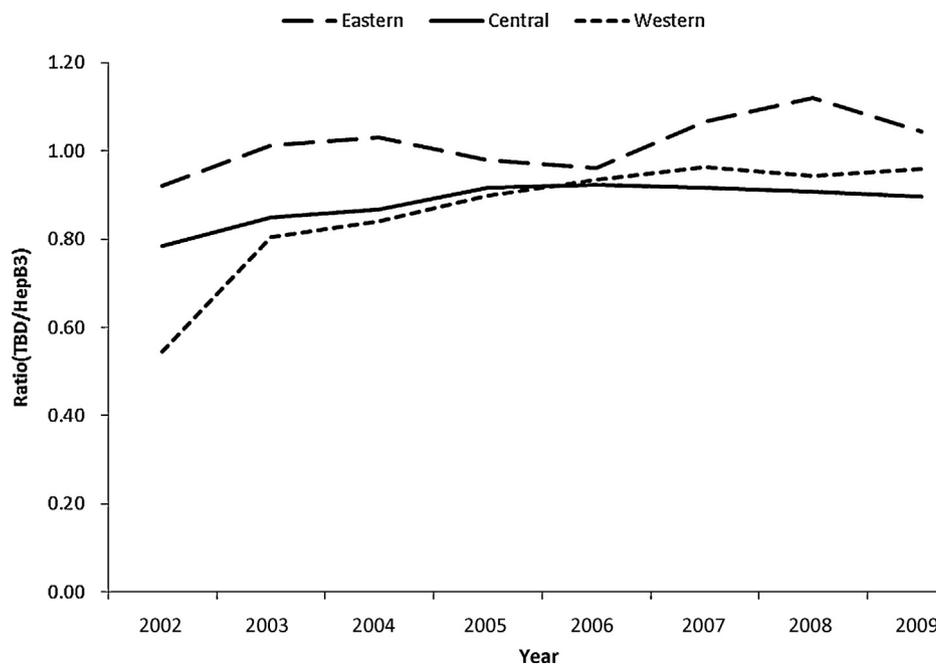


Fig. 1. Ratio of the surveyed TBD/HepB3 coverage by region in China, China GAVI final evaluation, China, 2002–2009.

Table 2
Hepatitis B timely birth dose coverage among infants born in health care facilities, China 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	7982	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	3582	8652	15,554	14,474	16,418	18,554	21,609	23,306
	No. TBD	2120	7599	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

3.3. 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 levels 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 2). 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 [16], greatly enhancing the impact of TBD delivery in hospitals.

3.4. 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 (Fig. 2). Between 2002 and 2009, the prevalence of HBsAg among pregnant

women recorded in hospitals 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 h after birth ranged from 0% to 0.7% across regions (Fig. 3). 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 who received HBIG and hepatitis B vaccine (N=980) followed by the West (N=584) and the Centre (N=350, Fig. 3).

3.5. Knowledge of parents

We interviewed 2323 parents in the three regions. Of these, 1899 (82%) were younger than 40 years of age. The male to female ratio was 1.4:1. Among these parents, 1937 (83%) knew that hepatitis B vaccine was the first vaccine to be administered after birth

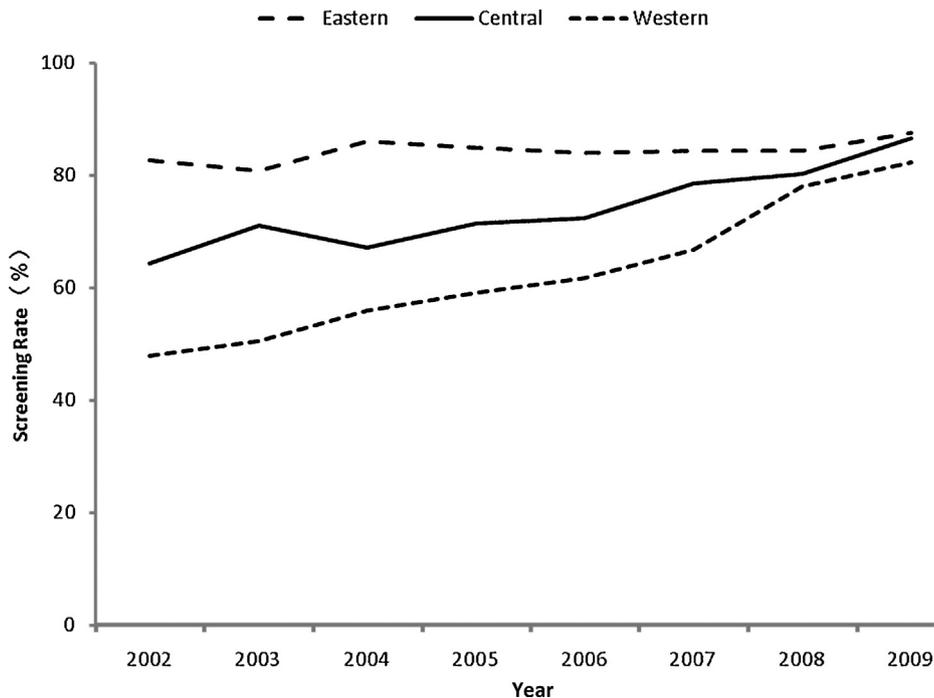


Fig. 2. Frequency of HBsAg screening among pregnant women by region, China GAVI final evaluation survey, China, 2002–2009.

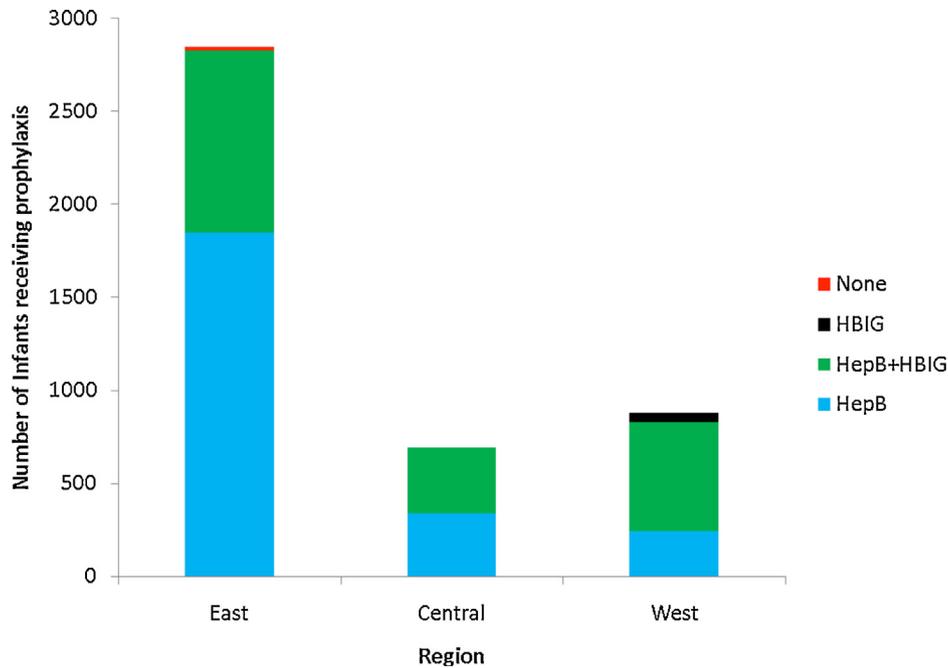


Fig. 3. Frequency of various immuno-prophylaxis practices for children born from HBsAg positive mothers, China GAVI final evaluation survey, by region, China, 2009.

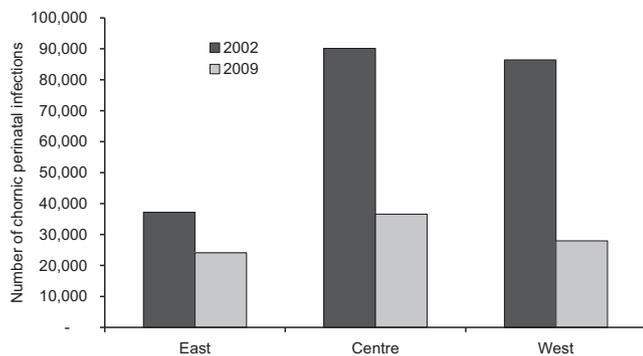


Fig. 4. Estimated number of chronic perinatal HBV infections, China, by region, 2002 and 2009.

(ranging from 77% in the Centre to 88% in West); 2059 (89%) knew the time schedule of the birth dose (ranging from 82% in the Centre to 92% in the West), and 1943 (84%) knew that three doses were needed to complete the series (ranging from 73% in the Centre to 89% in the West). 1540 (66%) parents reported they received this information from doctors while 652 (28%) quoted the vaccination certificate as the main source of information.

3.6. Modeled number of perinatal HBV infections

Our model projected that in 2002, the annual number of chronic perinatal HBV infections was 37,185 in the Eastern, 90,123 in the Central and 86,413 in the Western regions (total: 202,709). In 2009, these decreased to 24,108, 36,593, and 27,954 in the Eastern, Central and Western regions, respectively (total: 84,121) for an overall 58% reduction between 2002 and 2009 (Fig. 4).

4. 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 throughout China, particularly in the highest risk Western region 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 [17,18]. Most of the progress in institutionalized deliveries took place in the Western region where health care reform subsidized pregnant women to give birth in hospitals. The Eastern region already had a 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 provinces. 1.4 million USD from the first round of the China GAVI project saving was invested to support activities to 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 h. Although no previous national data are available, a survey conducted in 2005 in Gansu province reported that only 48% of guardians were aware of this need [19,20]. While TBD coverage progressed at the national level, in 2009, 20% of counties accounting for 21% of the birth cohort in the project areas still had not reached the project target of 75% coverage of timely birth dose [20a]. 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 [8]. In addition, our modeled estimates of the number of perinatal HBV infections suggested a decrease of 58% from 202,709 cases in 2002 to 84,121 cases in 2009 in China, although we may have underestimated the effectiveness of hepatitis B vaccination [15].

Our evaluation indicated that from 2002 to 2009, screening of mothers for HBsAg was already in use and increasing in China. Screening rates in the West were less than 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 [21]. Second, some hospitals have included testing of pregnant women for HBsAg among routine procedures [22]. This occurred in the absence of any support by the China 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 [23,24]. Our survey indicated that overall, the prevalence of HBsAg among women of child bearing age screened in hospitals 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 [10]. However, these two estimates cannot be compared directly. Unlike the population-based survey of 2006, pregnant women screened in hospitals did not constitute a random sample of the general population. Following HBsAg screening, immuno-prophylaxis utilization was heterogeneous and difficult to interpret. The Eastern region used more of the combined HBIG–hepatitis B vaccine immuno-prophylaxis than in the Central and Western regions, but covered a lower proportion of at risk children. Factors influencing these HBIG utilization patterns may include (1) an ongoing nationwide shortage of HBIG and (2) the smaller HBsAg screening rates, lower HBsAg prevalence and lower hospital delivery rate in Central and Western regions. In addition, people in the Western region and poverty counties are poorer and less likely to afford HBIG. Overall, infants born to HBsAg positive mothers had a high proportion of TBD, with or without HBIG, which should prevent most HBV infection. However, screening was not always followed by the appropriate intervention and there was no system to track children born to HBsAg positive mothers for risk of developing infection [25]. Almost none of the hospitals visited during the survey had data on the proportion of children born to HBsAg mothers that were 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 for HBIG use depended on parental preferences and on willingness to pay. Because the government did not mandate screening and HBIG use these practices may 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, and our estimates suggest that China continues to have more than 80,000 perinatal HBV infections each year. Second, screening for HBsAg to guide 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 several recommendations. First, China should continue improving hospital delivery rates nationwide, with special efforts in provinces such as Tibet, Guizhou and Yunnan. Specific strategies are also needed to reach births that continue to occur at home. In 2010, the China GAVI project used three million USD to increase TBD coverage for an additional group of 29 low-performance prefectures in Central and Western regions. Among these prefectures, 18 are in Yunnan, Guizhou and Tibet. Second, HBsAg screening must be expanded progressively, beginning with improvements in infrastructure and development of monitoring systems to ensure that women are screened and children followed up. Increased HBIG use can then

follow in an incremental approach, starting with children born from mothers who are HBsAg and HBeAg positive, if this information is available. However, this has programmatic implications in the management of the test results for decision making. 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 infected mothers to reduce viral load 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, but is most likely to be effective and equitable if costs are supported by the national government.

Contribution statement

Fuqiang Cui was responsible for designing the survey, analysing 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 to design the 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.

Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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