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Impact evaluation of the routine hepatitis B vaccination program of infants in China

Mei Sun[1,2†], Chengyue Li[1,2†], Dan Wu[1,2,3], Pingping Li[1,2,4], Jun Lu[1,2], Ying Wang[1,2], Fengshui Chang[1,2], Xiaohong Li[1,2], Mo Hao[1,2]

[1]Research Institute of Health Development Strategies, Fudan University, 177 box, 130 Dong'an Road, Shanghai 200032, China
[2]Collaborative Innovation Center of Social Risks Governance in Health, Fudan University, Shanghai 200032, China
[3]Current address: Shanghai Health Education Institution, Shanghai 200000, China
[4]Current address: Shanghai Children's Medical Center, Shanghai 200127, China
Address correspondence to Mo Hao, E-mail: haomo03@fudan.edu.cn

ABSTRACT

Background To evaluate the impact of the routine hepatitis B vaccination program of infants in China.

Methods The incidence of new hepatitis B infection and coverage with three doses of the vaccines by age groups and provinces were derived from the National Network Direct Report System of Infectious Disease during 2004–10. Chi square test and Pearson correlation analysis were used to analyze differences in incidence according to vaccination coverage and the relationship between the coverage with three doses and the incidence in different provinces.

Results The incidence of new infection was 8.96/100 000 among children with complete coverage (0–15 years old), which was significantly lower than that with partial or no coverage. Among 0–9-year-old children in 2010, the incidence of new infection was 6.36/100 000, which was significantly lower than 2004. Considering the impact of vaccination on cumulative incidence among 0–5-year-old children, a 2.2-fold greater incidence of new infection was observed in provinces with the lowest to the highest vaccination rate.

Conclusion The impact of the routine hepatitis B vaccination program of infants in China has become more apparent over time. Program implementation and regional disequilibrium should be payed attention to as well as the expanded program.

Keywords coverage with three doses of the vaccine, hepatitis B vaccination program of infants, impact evaluation, incidence of new hepatitis B infection, public policy

Introduction

Infection with the hepatitis B virus (HBV) is a serious infectious disease that is widely prevalent throughout the world.[1] The World Health Organization (WHO) has reported that, in 2015, ~257 million people have been infected with chronic HBV. Unfortunately, ~887 000 people died due to HBV-associated liver cirrhosis or hepatocellular carcinoma.[2,3] Furthermore, although there are several effective antiviral drugs for chronic HBV infection, it is hard to radically treat it currently.[4] Thus, actively promoting hepatitis B vaccine (HepB vaccine) is considered an effective prevention and control approach,[5] which has generally been accepted.[6] For example, researchers have demonstrated that HBV morbidity and mortality rates have been effectively reduced after HBV vaccination in various countries, including the USA,[7] Australia[8] and Taiwan.[9] In addition, the WHO has reported that at least 85–90% of all HBV-related deaths can be prevented via HepB vaccine.[10]

†These authors contributed equally to this work.
Mei Sun, Associate Professor
Chengyue Li, Associate Professor
Dan Wu, Research Assistant
Pingping Li, Research Assistant
Jun Lu, Professor
Ying Wang, Associate Professor
Fengshui Chang, Lecturer
Xiaohong Li, Associate Professor
Mo Hao, Professor

In 1992, the WHO suggested that HepB vaccine should be integrated before 1995 into the universal vaccination programs of countries with a high risk of HBV infection, and that every country should integrate this measure before 1997.[11] By late 2015, 185 WHO member countries (185/194) had implemented hepatitis B vaccine in the Expanded Program on Immunization (EPI), and the coverage of hepatitis B immunization at birth dose increased and reached 39% worldwide.[12] However, HBV infection remains a prominent public health concern in China. Based on the WHO classification criteria,[13] China is a region with a high prevalence of HBV.[14] The average incidence of HBV infection is 50–100/100 000, with the hepatitis B surface antigen (HBsAg) having a prevalence of 10–15%, an infection rate of 60–70%[15] and 300 000 annual deaths due to HBV-related cancers.[16]

Although various Chinese regions had implemented HBV vaccination in 1987, detailed HBV vaccination strategies and implementation schemes were not established until 1990.[17] Given that mother-to-infant transmission is a major route for HBV transmission, the Chinese Ministry of Health (MOH) began promoting this program throughout China on 1 January 1992. But the parents should pay for the vaccine.

In 2002, the HepB vaccine was formally integrated into the EPI, and targeted all newborns. The HepB vaccine was currently free, although a service fee approximately equal to 1.10 US dollars was charged.

In 2007, the MOH stated that the government should support the administration of all vaccines in the EPI, and that all eligible children should receive the HepB vaccine and services for free. This policy was designed to promote the sustainable development of the vaccination program.

Furthermore, to effectively prevent adolescents from acquiring HBV infection, the MOH screened for children who had not received the vaccination, especially those who were not covered by that the free program. Between 2006 and 2008, the Global Alliance for Vaccines and Immunization (GAVI) estimated that 1 million children from 22 provinces, who were born after 2002, had missed their hepatitis B vaccination. Two key documents raised important concerns regarding this issue ('Opinions of the Central Committee of the Communist Party of China and the State Council on Deepening the Health Care System Reform' and 'the Plan on Recent Priorities in Carrying Out the Reform of Health Care System (2009–11)'). Therefore, 'the HBV revaccination program for children who are <15 years old' was developed as a major public health priority by the MOH, and free HBV revaccination was performed for children who were born between 1 January 1994 and 31 December 2001.

Now the HBV vaccination program has been implemented with routine vaccinations for more than 20 years and integrated into the EPI for more than 10 years in China. What about the impact of this program? This study is aiming to evaluate the impact of the infant vaccination program, according to the nationwide data of vaccination coverage and incidence of new hepatitis B infection.

Methods

Coverage with three doses of the vaccine

The coverage with three doses of the vaccine (C) was defined as the number of inoculated children (N_i) who correctly received three doses within 12-month old, divided by the number of children who should receive the vaccination (N). A timely birth dose is not restricted; the interval between the first and second doses should be no less than 1 month, and no <2 months between the second and third doses; and the third vaccination must be completed within 12 months. C is calculated as follows:

$$C = (N_i \div N) \times 100\%$$

Incidence of new hepatitis B infection

The incidence of new hepatitis B infection (I_{N-Hb}) was defined as the frequency of new hepatitis B cases within a certain period (usually a year) and a specific population. N_n is the number of new hepatitis B cases, and N_o is the number of observed population within the corresponding period. The new hepatitis B infection should be diagnosed following the 'Guidelines of HepB Diagnosis (WS299-2008)', based on the serology data of IgM anti-HBc, HBsAg, etc., as well as the physician's professional judgment. I_{N-Hb} is calculated as follows:

$$I_{N-Hb} = (N_n \div N_0) \times 100\%$$

Cumulative incidence among 0–5-year-old children

Given the large and stable population, the cumulative incidence of hepatitis B was calculated using the population size at the initial observation as the denominator and the number of hepatitis B cases during the observation period (age of 0–5 years) as the numerator. This incidence is calculated as follows:

$$CI_{HB} = \frac{\sum_{t}^{t+5} N_n}{N_0} \times 100\%$$

Data collection and analysis

Data in this study were derived from the National Network Direct Report System of Infectious Disease (NNDRSID) database, which included the coverage with three doses of the vaccines and incidences of new hepatitis B infection among different age groups (grouped nationally and according to province), during 2004–10. Coverage data of the vaccines were reported from community health service centers who were in charge of giving vaccination; incidences data of new hepatitis B infection were reported from hospitals. According to the 'Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases', the responsible reporters of all hospitals should immediately record the infectious disease card after experimental and medical diagnosis. The staff from CDCs of corresponding regions will check the cards and then input the information into the NNDRSID. However, four provinces did not record single-year age-specific incidences for hepatitis B. Thus, data from 27 provinces were used to calculate the cumulative incidence among 0–5-year-old children. Data for the various age groups during 2004–10 were derived from the Population Database of China's National Bureau of Statistics.

All data were analyzed using SPSS software (version 16.0; SPSS Inc., Chicago, IL). *K*-means clustering was used to cluster the data of coverage with three doses of the vaccine (*C*) from 27 provinces. Pearson correlation analysis was used to evaluate the relationship between the coverage with three doses of the vaccines in different provinces and the incidences of hepatitis B. Chi square test was used to analyze the incidence differences between the age groups with different program coverages.

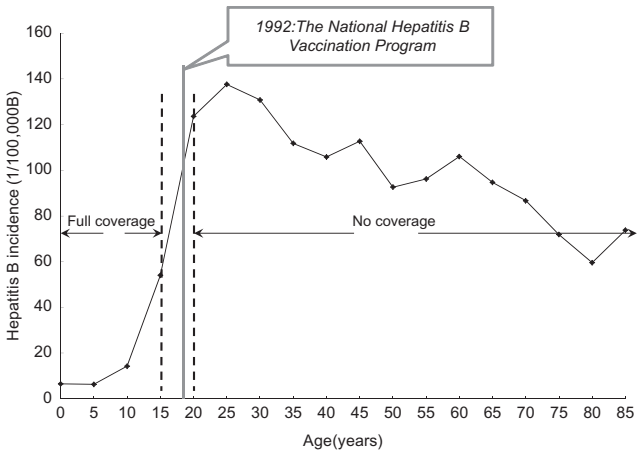

Fig. 1 The incidence of new hepatitis B infection in 2010 by different age groups.

Results

Overall impact of the HBV vaccination program in China

Since the national neonatal HBV vaccination program was proposed in 1992, it has provided variable levels of coverage to children who were born before 2010. Therefore, we grouped children according to their level of coverage: complete coverage (age: 0–15 years), partial coverage (age: 15–20 years) and no coverage (age: >20 years). Our analysis revealed that children with complete coverage (0–15 years old) had a significantly lower incidence of hepatitis B, and that children who were under 10 years old exhibited a morbidity rate of <10/100 000 (Fig. 1).

The incidences of hepatitis B in 2010 were 8.96/100 000 among children under 15 years old (complete coverage), 53.99/100 000 among children ages 15–20 years old (partial coverage), and 110.32/100 000 among children over 20 years old (no coverage). These differences were statistically significant ($\chi^2 = 24.770$, $P < 0.001$). We assumed that population with partial coverage and no coverage would have the same incidence rate of HBV with those under 15 years old children when they are inoculated at birth and projected that expanding coverage to the general population would decrease the number of HBV infections by 47 800 among patients who are 18–20 years old. Furthermore, we projected that expanding the coverage would decrease the number of HBV infections by 995 400 among individuals who are over 20 years old. Thus, it appears that expanding the HBV vaccination program to the general population could provide meaningful benefits (Table 1).

Differences of incidences for populations that were covered in 2004 and 2010

Among all children who were 0–9 years old in 2004, the incidence of hepatitis B was 15.86/100 000, and this incidence decreased to 6.36/100 000 in 2010. This difference was statistically significant ($\chi^2 = 6897.915$, $P < 0.001$). Thus, it appears that promoting the neonatal HBV vaccination program has had significant effects among children who are 0–9 years old.

We also compared the age-specific incidences of hepatitis B among children who were 0–9 years old in 2004 and 2010. Although the incidence among children who were under 1 year old in 2010 was 10.39/100 000, which was slightly higher than the corresponding incidence in 2004 (Fig. 2); for the ages of 1–9 years, the incidences were significantly lower in 2010, compared to those in 2004. Thus, it appears that the increasing promotion of neonatal HepB vaccine has had a preventative effect.

Table 1 The incidence of new hepatitis B infection according to degree of vaccination coverage in 2010

Program coverage	*Age (years)*	*Population (10 000s)* ①	*Incidence (1/100 000)* ②	*Cases (10 000s)* ③	*Number of cases when an incidence of complete coverage was achieved (10 000s)* ④	D-*value (10 000 s)* ⑤*
Complete coverage	0-	24 655.04	8.96	2.21	2.21	0
Partial coverage	15-	10 609.96	53.99	5.73	0.95	4.78
No coverage	20-	98 209.00	110.32	108.34	8.80	99.54
Total		133 474.00	87.12	116.28	11.96	104.32

*⑤ = ③ − ④; ④ = ① ∗ 8.96/100 000 (incidence of complete coverage).

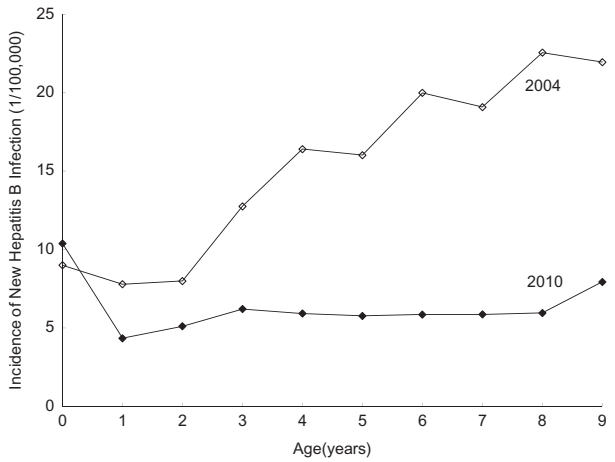

Fig. 2 The incidences of new hepatitis B infection for 0–9-year-old children in 2004 and 2010.

Relationship between CI and coverage of different provinces

To examine the program's effects in the different provinces, we observed the cumulative incidences among 0–5-year-old children during 2004–09 in 27 provinces. Using *K*-means clustering, three different groups were clustered according to the coverage with three doses of the vaccine in 2004: low (96.27%), moderate (97.51%) and high (99.19%). The cumulative incidences among 0–5-year-old children were 80.93/100 000, 44.70/100 000 and 36.51/100 000, respectively, which revealed a gradually decreasing trend. The cumulative incidence in the provinces with the lowest vaccination rate was 2.2-fold higher than that in the provinces with the highest vaccination rate (Table 2).

Pearson correlation analysis revealed the correlation coefficient for the relationship between the coverage with three doses of the vaccine and the cumulative incidence among 0–5-year-old children was $-0.447 (P = 0.020)$. Thus, although the program was effective for populations with full program coverage, the program's effect varies according to province, and the execution of the program appears to have a significant effect on the program's outcomes.

Discussion

Main finding of this study

The results of this study indicate that HBV vaccination program is effective, with a significant benefit for the population with full coverage. With the implementation of the national program, children who were 0–15 years old had a significantly lower incidence of hepatitis B, compared to individuals who were over 20 years old in 2010. These findings suggest that infant HBV vaccination is effective and that the infant incidence of new hepatitis B infection has been controlled, which are in agreement with the results of other studies in the USA, Malaysia and other countries.[18,19]

The impact that we observed may be related to the strong promotional efforts that the Chinese government have dedicated to the HBV vaccination program. The coverage with three doses of the vaccine has persistently increased since the nationwide promotion of the HBV vaccination program in 1992, and particularly since HepB vaccine was integrated into EPI in 2002. Furthermore, the Chinese government has increased the financial support for this program, with a nominal service charge of ~1.1 US dollars from 2002 to 2005, and no fee after 2005. During 2003–06, the China-GAVI project invested ~76 million US dollars to subsidize the HBV vaccination program for 15 million children from 12 provinces in west China and 10 provinces in central China.[20,21]

Our results also indicate that the government's increasing promotional efforts have improved the effect of this vaccination program. At the national level, this program has been implemented gradually, with the coverage with three doses of the vaccine increasing from 70.70% in 1999[22] to 98.90% in 2009. This appears to have curbed the incidence of new hepatitis B infection among children, as the incidence among

Table 2 Coverage with three doses of the vaccines and cumulative incidences among 0–5-year-old children from different provinces in 2004

K-means cluster	*Neonatal coverage with three doses of the vaccine (%)*	*Covered children (1 000s)*	*Cumulative incidence among 0–5-year-old children (1/100 000)*
Low	96.27	2 309.16	80.93
Moderate	97.51	1 562.94	44.70
High	99.19	10 229.88	36.51

0–9-year-old children decreased from 15.86/100 000 in 2004 to 6.36/100 000 in 2010. We observed variations in the effect at the provincial level; the coverage with three doses of the vaccine has remained relatively high. However, the cumulative incidence among 0–5-year-old children was higher for provinces with the lowest vaccination rate, and the cumulative incidence exhibited a negative correlation with the coverage with three doses of the vaccine ($r = -0.447$, $P < 0.05$). Even though the cumulative incidence may be correlated with local epidemic status of hepatitis B, findings from recent studies indicate that the coverage with three doses and a timely scheduled birth dose of the vaccine has the greatest effect on the incidence of hepatitis B, which may directly affect this program's effect.[23] Thus, efforts are needed to further strengthen the promotion of the HBV vaccination program, and a balanced approach in different provinces is needed.

In terms of the program's indirect effects, the most vulnerable population must build up their own immunity (e.g. via neonatal vaccination), which will translate into fewer adults being HBV carriers, and ultimately to a lower risk of developing hepatitis B.[24] This indirect effect can also be achieved through further promotion and expansion of the vaccination program.

Although the cumulative incidence among children has significantly decreased since the promotion of the HBV vaccination program, the overall incidence of hepatitis B remains high and has not exhibited a decreasing trend.[25] In contrast, Taiwan implemented an infant HBV vaccination program in 1986, which inoculated all susceptible persons within 10 years (including pre-school children, elementary school students, high school students and adults).[26] Similarly, the American HBV vaccination program has gradually expanded from neonates to the general population.[19]

What is already known on this topic

The early studies mainly focused on the effects of HepB vaccine at an individual level (i.e. for different doses and regimens).[27,28] Additional researches have focused on the effects on other liver-related diseases.[29] Recent studies have evaluated the program's efficacy on a national level, using serological surveys of HBsAg and antibodies to HBV in large population-based samples.[30,31]

What this study adds

It is the first time to evaluate the impact of the infant HBV vaccination program from policy evaluation perspective by analyzing the relationship of nationwide vaccination rates and incidence rates. The relationship between vaccination rates and incidence rates revealed the importance of policy implementation.

Since the introduction of the HBV vaccination program in 1992, the incidence of hepatitis B has decreased among children under 15 years old, and this incidence is significantly lower than that among individuals with no program coverage. Furthermore, it appears that the impact of this program are increasing with time. Moreover, the cumulative incidence was negatively correlated with the coverage with three doses of the vaccine according to provincial disequilibrium. Program implementation including the coverage with three doses of the vaccine and the regional disequilibrium should be paid attention to as well as the expanded program.

Limitations of this study

Nevertheless, it is important to note that our findings are limited by the retrospective use of population-based data, which are not independently verified and cannot account for the patients' immune status, local sanitation conditions, inter-province movements, etc. The coverage data derived from administrative system tend to over-estimate. Timely scheduled birth dose and another crucial indicator, is not considered. Meanwhile, projection analysis did not take into consideration the different effectiveness of HepB vaccine and HBV incident epidemiological characteristics for adults and infants; therefore, the projection results only showed trends rather than absolute figures.

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