BMC Public Health

RESEARCH

Open Access

Effectiveness of catch-up vaccination from 2009 to 2011 on incidence of hepatitis B in Guangzhou, China: a time series analysis

Bo-Wen Ming[1†], Wen-Hui Liu[1,2†], Li Li[1†], Jin-Lun Zhang[1], Jing Liu[1], Jia-Jun Ma[1], Hao-Neng Huang[1], Zhou-Bin Zhang[2*] and Chun-Quan Ou[1*]

Abstract

Background The high prevalence of hepatitis B weighs heavily on public health in China. In 2009, a catch-up vaccination program for children aged 8–15y was implemented to curb hepatitis B, while the effectiveness of this intervention has not been investigated. We aimed to evaluate the effectiveness of catch-up vaccination on the incidence of hepatitis B in Guangzhou, China.

Methods We obtained individual data of all hepatitis B cases from 2005 to 2019 in Guangzhou from Guangzhou Center for Diseases Control and Prevention. Based on daily reported number of cases, we constructed generalized linear models to estimate the effectiveness of the intervention on the incidence of hepatitis B in each age group from 11 to 25 years. We further estimated the age-standardized effectiveness. Finally, we examined the effectiveness in different subgroups by sex and clinical types of hepatitis B.

Results A total of 58,204 hepatitis B cases among individuals aged 11–25y were reported in Guangzhou from 2005 to 2019, with an average annual age-standardized incidence of 117.30 cases per 100,000 individuals. The catch-up vaccination contributed to an age-standardized 20.02% (95% confidence interval: 15.97%, 23.87%) decrease in the hepatitis B incidence among individuals aged 11–25y and prevented an annual age-standardized average of 17.40 (95% empirical confidence interval [eCI]: 9.24, 23.78) cases per 100,000 individuals from hepatitis B during the study period. The intervention could better protect males (excess incidence rate [EIR]: -21.82 [95% eCI: -30.51, -10.15] cases per 100,000 individuals), and prevent chronic cases (EIR: -24.27 [95% eCI: -30.62, -16.09] cases per 100,000 individuals).

Conclusions The massive catch-up vaccination against hepatitis B among children plays an important role in alleviating the burden of hepatitis B.

Keywords Hepatitis B, Incidence, National program on immunization, Catch-up vaccination, China

†Bo-Wen Ming, Wen-Hui Liu and Li Li contributed equally to this work.

*Correspondence:
Zhou-Bin Zhang
gzcdczzb@gzcdc.org.cn
Chun-Quan Ou
ouchunquan@hotmail.com

Background

Hepatitis B is a common liver disease caused by the Hepatitis B virus (HBV) and can be spread mainly through sexual, vertical, and blood transmission [1–4]. Acute HBV infection in healthy persons is commonly self-limiting [1, 5]. However, HBV can give rise to lifelong infections and hepatocellular injuries, especially in the neonatal period and childhood [2, 5]. Untreated individuals with chronic HBV infection are prone to hepatitis B, liver fibrosis, cirrhosis, and hepatocellular carcinoma [2, 3]. In newborns and children, hepatitis B virus (HBV) infection is usually asymptomatic [6]. In adults, chronic hepatitis B is usually asymptomatic or presents with symptoms such as fatigue, or right upper abdominal pain [6]. These characteristics render early diagnosis and treatment of hepatitis B a considerable challenge. Globally, even though the incident cases of HBV-related liver diseases have dipped from 84.45 million cases (i.e., 1552.21 cases per 100,000 individuals) in 1990 to 80.65 million cases (i.e., 1009.96 cases per 100,000 individuals) in 2019, it was estimated that about 296 million people were still living with chronic hepatitis B infection in 2019, with 1.5 million new infections each year [7]. Moreover, hepatitis B brought about an estimated 0.82 million deaths worldwide, mostly from cirrhosis and liver cancer, which have taken a heavy toll on public health [8]. Considering the heavy burden, the World Health Organization (WHO) developed a global target to eliminate hepatitis B as a public threat that, by 2030, the incidence and mortality of hepatitis B will have been reduced by 90% and 65%, respectively [9].

Timely vaccination in newborns and children is the most important strategy against hepatitis B. A phase III clinical trial found that hepatitis B vaccines provide effective immunogenicity (i.e., hepatitis B surface antigen, HBsAg) [10]. A meta-analysis of clinical trials indicated the high seroprotection of hepatitis B vaccines in infants and individuals aged 10–20 years [11]. A 15-year cohort study confirmed the long-term protection (i.e., lower HBsAg and lower hepatitis B core antibody) of hepatitis B vaccines [12]. The effect of hepatitis B vaccination was also evaluated through serological investigations and ecological studies. A series of studies in China utilized multiple serosurveys to determine the decrease of the HBsAg prevalence due to hepatitis B vaccines [13–17]. Another review also reported a beneficial change in the prevalence of hepatitis B due to hepatitis B vaccines [18]. Most of the serological studies were carried out before 2016 with long intervals between two surveys due to the huge workload and cost of the investigation. Socioeconomic and other factors during intervals can affect the prevalence of hepatitis B. A modelling study used mathematical simulation to estimate the vaccination impact [19]. Mathematical simulation was generally performed based on some parameters from previous literature instead of real data, which may lead to imprecise estimate. An ecological study used quasi-Poisson regression models to capture the effect of hepatitis B vaccination on the incidence of hepatitis B among neonataes and whole people in China based on yearly data [20]. However, the aforementioned modeling studies failed to explore the effectiveness of hepatitis B vaccines on the incidence of hepatitis B in different subgroups (e.g., by sex and clinical types of hepatitis B).

China bore the brunt of hepatitis B all over the world [21, 22]. In 1992, HBV was highly endemic in China with approximately 10.1% of people under the age of 30 carrying the prevalence of HBsAg, 20 million people suffering from chronic hepatitis B, and almost 0.30 million deaths [14]. The Chinese government has adopted a series of preventive measures to stem the tide of hepatitis B infection (Fig. S1). The National Ministry of Health integrated hepatitis B vaccines into the National Immunization Program (NIP) in 2002 [21, 23, 24]. From 2009 to 2011, a national-wide, catch-up vaccination project was strictly carried out for all children under the age of 15 who were not systematically vaccinated at birth [23]. Previous literature has demonstrated the beneficial impact of the NIP in 2002 on the prevalence of hepatitis B [19, 20]. It remained unknown about the effectiveness of the mass hepatitis B catch-up vaccination in 2009 on the incidence of hepatitis B.

Guangzhou is one of the most developed cities in China with about 18.74 million inhabitants in 2020 [25]. The HBsAg prevalence in the resident population in Guangzhou (12.5% in 2008) was higher than the average level in the Chinese mainland (7.2% in 2006) [14, 26], indicating more infected persons and possibly heavier disease burden in Guangzhou. It merits a deeper investigation of the catch-up vaccination effect in 2009 on the burden of hepatitis B in Guangzhou. Herein, based on individual data of hepatitis B cases, we aimed to evaluate the effectiveness of the catch-up vaccination on the hepatitis B incidence, which could provide valuable insights for accelerating the elimination of hepatitis B, such as the expansion of the catch-up population in the future and a favorable paradigm of mass hepatitis B catch-up vaccination for other countries and regions with the heavy burden of hepatitis B.

Methods

Data collection

We collected individual data on hepatitis B cases occurring in Guangzhou from 2005 to 2019 from the National Infectious Disease Monitoring Information System, as compiled by the Guangzhou Center for Disease Control

and Prevention (CDC). The information on each case included date of birth, date of onset, sex, occupation, residence address, and classification of hepatitis B (i.e., acute hepatitis B, chronic hepatitis B, and unclassified hepatitis B cases). A diagnosis of hepatitis B can be made when an individual presents with significant gastrointestinal symptoms (e.g., hepatomegaly), elevated alanine aminotransferase, and HBsAg positive [27]. The corresponding diagnosis criteria are shown in detail in Table S1. All newly confirmed hepatitis B cases must be reported to the Chinese Information System for Disease Control and Prevention within 24 h. Subsequently, local CDC staff will verify the information of diagnosed cases to ensure data quality, such as excluding hepatitis B cases that have already been reported.

The ambient meteorological information on daily temperature, relative humidity, wind speed, and total precipitation in Guangzhou was derived from the China Meteorological Data Sharing Service System. We collected the overall and age group-specific resident population size by the end of every year from 2000 to 2020 from the Guangzhou Statistics Bureau. The daily resident population was derived from linear interpolation.

Data analysis

We included confirmed cases reported to the Chinese infectious diseases reporting system from 1 January 2005 to 31 December 2019 and currently residing in Guangzhou in the study. For children under the age of 15, a series of rigorous, nationwide, hepatitis B catch-up vaccination procedure was implemented in 2009 (Fig. S1). After that, all children were timely vaccinated. It was estimated that the childhood hepatitis B vaccine coverage (three-dose coverage) and the birth-dose coverage reached 99.08% and 96.92% in Guangzhou in 2012, respectively [28]. We removed data from 2009 to 2011 because those were the years of catch-up implementation.

First, we modeled the whole population. The whole population incorporates the catch-up population after 2009. Therefore, the intervention term was set to 1 after 2009. We removed data during the catch-up implementation period from 2009 to 2011. The formula of the whole-population model was specified as follows:

$$log[E(Y_t)] = offset(log(Population_t)) + \alpha + \beta_1 Intervention_t + \beta_2 t + \gamma Dow_t + \delta Holiday_t + \zeta Temperature_t \quad (1)$$

where Y_t is the reported number of hepatitis B cases among the whole population in the day t (t = 1, 2, …, 1460, 2556, 2557,…, 5478); the logarithm of the whole population size for the day t is used as an offset; $Intervention_t$ is a dummy variable with 0 and 1 indicating the pre-intervention (from 1 January 2005 to 31 December 2008) and post-intervention period (from 1 January 2012 to 31 December 2019), respectively; Dow_t is a categorical variable of the day of the week; $Holiday_t$ is a categorical variable of the public holiday (i.e., 2: the spring festival; 1: other statutory holidays; 0: other days); $Temperature_t$ is the 7-day moving average of temperature. We found that catch-up vaccination is not significantly associated with the decrease in the incidence of hepatitis B among the whole population (Table S2).

Second, we modeled separately each age group for children aged 11–25y in consideration of the fact that different age groups were affected by the catch-up vaccination at different times (Fig. S2). In 2009, the catch-up vaccination was initiated targeting children born between 1994 and 2001, who, at that time, were between 8 and 15 years of age. Subsequently, there was a shift in the affected population to children aged between 9 and 16 years of age. By analogy, in 2019, the population affected by the intervention was adults aged 18–25y. The whole population was divided into two categories based on their intervention status: the catch-up population, which consisted of individuals aged between 8 and 25 years of age, and others. We did not include the children aged 8–10y in the model due to the removal of data from 2009 to 2011 from the modelling. Consequently, the study population was individuals aged 11–25y.

We calculated the cumulative cases, crude incidence and corresponding 95% confidence intervals (CI), and age-standardized incidence to represent the burden of hepatitis B. For lack of data regarding the prevalence and seroprevalence of hepatitis B, the number of the resident population was used as the denominator for the calculation of the incidence. We used the Poisson Exact equation to estimate 95% CI of the incidence rate [29]. The formula of the age-standardized incidence is as follows:

$$Incidence_{age-standardized} = \sum w_a Incidence_a = \frac{\sum Population_a \times Incidence_a}{\sum Population_a}, \quad (2)$$

where $\boldsymbol{a}$ is the $\boldsymbol{a^{th}}$ age group, depending on the selected population (i.e., the whole, catch-up, or study population); $Population_a$ and $Incidence_a$ are the population size and the incidence in the a^{th} age group, respectively; w_a is the weight of the a^{th} age group.

We used a wavelet analysis to detect the seasonality of hepatitis B incidence among the study population. We

constructed quasi-Poisson regression models to evaluate the effectiveness of the hepatitis B vaccination on the incidence of hepatitis B among the study population after adjusting for covariates (Fig. S2). The formula was specified as follows:

$$log[E(Y_{t,a})] = offset(log(Population_{t,a})) + \alpha_a + \beta_{1,a}Intervention_{t,a} + \beta_{2,a}t \\ \gamma_a Dow_t + \delta_a Holiday_t + \zeta_a Temperature_t \quad (3)$$

where $Y_{t,a}$ is the reported number of hepatitis B cases in the age group a ($a = 11, 12, 13,\ldots, 25$ years old) on the day t ($t = 1, 2, \ldots, 1460, 2556, 2557,\ldots, 5478$); the logarithm of the population size in the a^{th} age group on the day t was used as an offset; $Intervention_{t,a}$ is a dummy variable with 0 and 1, which was assigned as demonstrated in Fig. S2. Dark and light colors were assigned a value of 1 and 0 for the corresponding year, respectively. For instance, in the model for 11-year-old children, the intervention term was set to 0 in 2012 and 1 in other years.

The incidence rate ratio (IRR) can be calculated by $e^{\widehat{\beta_1}}$. Excess risk (ER) of the hepatitis B incidence due to the catch-up vaccination (i.e., $[IRR - 1] \times 100\%$) and the corresponding 95% CI were further estimated. In the present study, ER% is interpreted as the relative percentage change in incidence rate during the intervention time period in comparison with that in the absence of the intervention. An ER% of less than 0 indicates that the intervention contributed to a reduction in the incidence of hepatitis B. In addition, the excess incidence rate (EIR) due to the catch-up vaccination was estimated by the difference in the predicted rate under the scenario with and without the intervention. The formula for each age group was specified as:

$$\widehat{EIR} = \frac{\sum_{t=t_0}^{t=t_1}[\widehat{Y}_t|(Intervention_{t=1}) - \widehat{Y}_t|(Intervention_{t=0})]}{Pop \times Year} \times 100{,}000 \quad (4)$$

where $\widehat{Y}_t|(Intervention_t = 1)$ is the predicted number of cases in the post-intervention day t under the factual scenario that the catch-up vaccination was completely implemented in children under the age of 15; $\widehat{Y}_t|(Intervention_t = 0)$ is the predicted number of cases under the counterfactual scenario that the catch-up vaccination was not performed; $\widehat{Y}_t|(Intervention_t = 1) - \widehat{Y}_t|(Intervention_t = 0)$ is the number of excess cases (EC) in the day t; Pop indicates the average population size in the post-intervention stage; $Year$ represents the number of post-intervention years; t_0 and t_1 are the initial points after the completion of the catch-up vaccination and the terminal point of the study period, respectively. The production of analytical formulae for CI of EC and EIR is a challenging endeavour [30]. The most straightforward approach in this context is to rely on the interval estimation obtained empirically through Monte Carlo simulations to estimate the 95% empirical confidence intervals (eCIs) of EC and ER [30–32]. Furthermore, we estimated the age-standardized ER and EIR. The formula for the combined population-weighted ER for different age groups is as follows:

$$ER_{age-standardized} = [exp(\sum_{a=11}^{25} w_a\widehat{\beta}_{1,a}) - 1] \times 100\%. \quad (5)$$

With the assumption that each regression coefficient followed a normal distribution, the combined term also followed a normal distribution, which is as follows:$\sum_{a=11}^{25} w_a\widehat{\beta}_{1,a} = WB \sim N_1(w\mu, w\prime\sigma w)$, where B is a set of normal distributions of $\beta_{1,a}$, with a mean vector of μ and a standard deviation vector ofσ; W is a constant vector representing the proportions of different age groups in the study population to the total study population. The age-standardised excess incidence rate was calculated with the same process as the age-standardised incidence.

Furthermore, we seek to illustrate the effectiveness of the hepatitis B vaccination on the incidence of hepatitis in different subgroups by sex (i.e., males and females), and clinical types of hepatitis B (i.e., acute cases and chronic cases). Each stratum was modeled separately after adjusting for the same covariates in the Model (1) for the whole population. For stratified analyses by sex, the offset terms are the daily number of male and female residents in Guangzhou, respectively, while the offset terms for the clinical type subgroup are the number of all residents in Guangzhou.

We performed sensitivity analyses to examine the robustness of the main results. First, we replaced the 7-day moving average of ambient temperature with a natural cubic spline function with 3 degrees of freedom (dfs). Second, the 7-day moving average of relative humidity, wind speed, and total precipitation were additionally incorporated into the model. Third, we fitted a negative binomial regression model instead of the quasi-Poisson regression model. Finally, we employed a model with monthly data to check the influence of

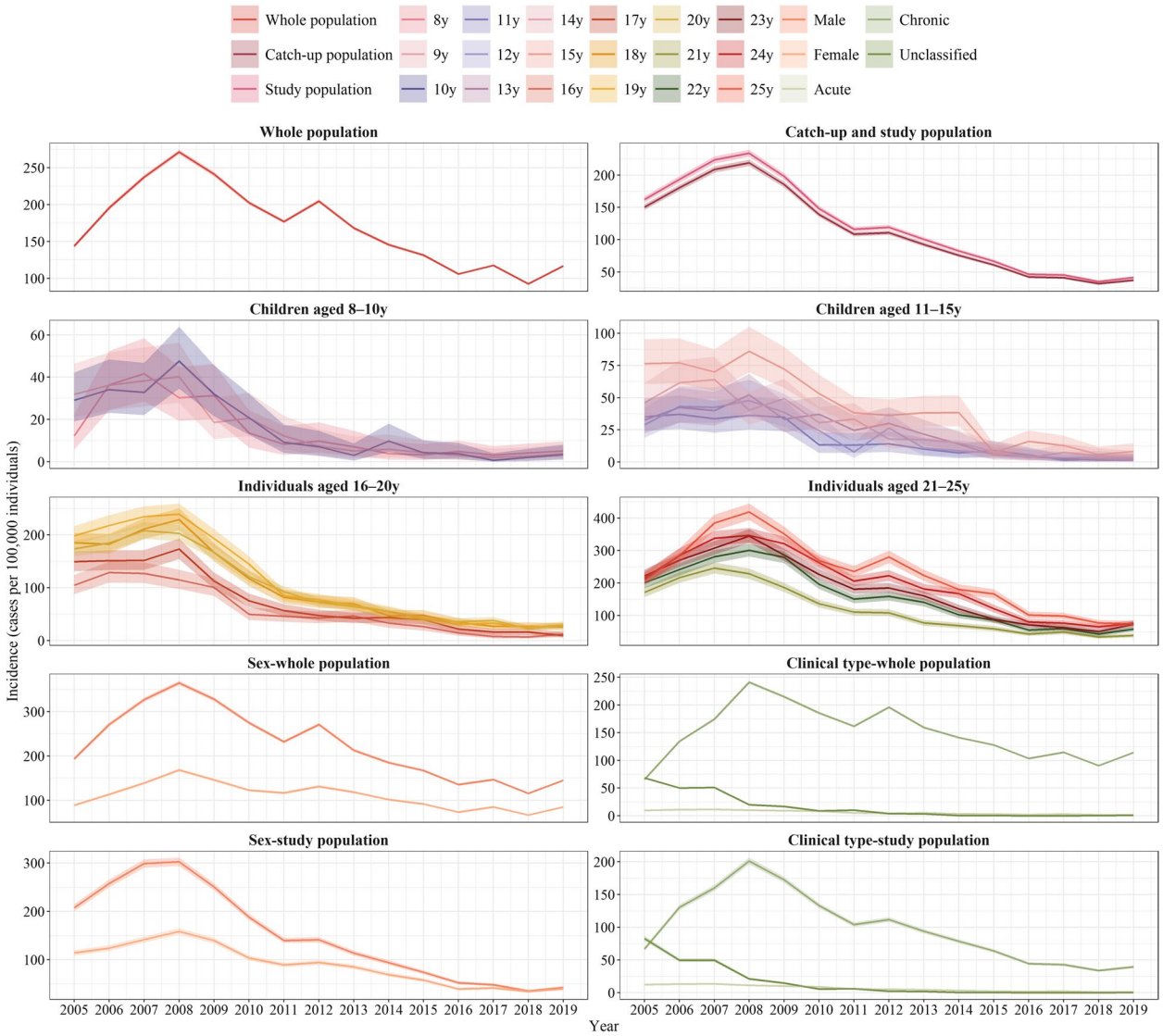

Fig. 1 Yearly crude incidence of hepatitis B and corresponding confidence intervals in Guangzhou from 2005 to 2019

the choice of different time scales on the main results. A two-sided *p*-value less than 0.05 was considered statistically significant. We used the R statistical software (version 4.2.1) to perform all analyses.

Results

Epidemiology of hepatitis B in Guangzhou

Figure 1, Tables 1, S3, and S4 present the summary statistics of hepatitis B among the different populations from 2005 to 2019 in Guangzhou. During the study period, there was a total of 322,537 reported hepatitis B cases with an average annual crude incidence of 161.74 cases per 100,000 individuals. 58,833 cases were reported among the catch-up population aged 8–25y (106.09 cases per 100,000 individuals), accounting for about 18.24% of all reported cases. The reported cases amounted to 58,204 among the study population aged 11–25y, corresponding to 114.96 cases per 100,000 individuals. Overall, there was a gradual decline in the annual incidence of hepatitis B among the study population aged 11–25y. The crude incidence of hepatitis B among the study population aged 11–25y swelled from 162.36 cases per 100,000 individuals in 2005 to 233.86 cases per 100,000 individuals in 2008, whereas reported cases pared from 6,445 cases (197.92 cases per 100,000 individuals) in 2009 to 1,605 (41.38 cases per 100,000 individuals) in 2019 (Table S3).

Table 1 Characteristics of hepatitis B cases and incidence in the whole population and different subgroups from 2005 to 2009 in Guangzhou

Category	Cumulative cases (Proportion, %)[b]			Average crude incidence (Age-standardized incidence)[c]		
	Whole population	Catch-up population	Study population	Whole population	Catch-up population	Study population
Overall	322,537	58,833	58,204	161.74 (169.90)	106.09 (108.01)	114.96 (117.30)
Subgroup						
Sex[a]						
Male	222,013 (68.83)	38,095 (64.75)	37,654 (64.69)	212.20 (221.9)	129.61 (131.26)	140.77 (142.87)
Female	100,523 (31.17)	20,737 (35.25)	20,549 (35.31)	106.04 (112.44)	79.57 (81.72)	86.04 (88.58)
Clinical type						
Acute	10,751 (3.33)	3,136 (5.33)	3,102 (5.33)	5.39 (5.38)	5.66 (5.64)	6.13 (6.13)
Chronic	287,423 (89.11)	48,656 (82.70)	48,160 (82.74)	144.13 (152.50)	87.74 (89.79)	95.12 (97.56)
Unclassified	24,363 (7.55)	7,041 (11.97)	6,942 (11.93)	12.22 (12.02)	12.7 (12.58)	13.71 (13.61)

[a] There was one case whose sex was missing

[b] Figures in round brackets denote the percentage of reported cases within each subgroup, relative to the whole population

[c] The unit of incidence is cases per 100,000 persons

The trend of incidence was similar in all age subgroups within the study population aged 11–25y, demonstrating an initial upward trend, followed by a subsequent downward trend (Fig. 1). In the study population aged 11–25y, the burden of hepatitis B incidence was more severe in the older age groups. To be specific, it was observed that the highest number of reported hepatitis B cases occurred in the 25-year-old age group, reaching 9,619 cases, corresponding to an average annual incidence of 207.14 per 100,000 individuals (Table 2). Conversely, among the study population, the lowest incidence (15.45 per 100,000 individuals) was observed in the 11-year-old age group, with a total of 247 cases (Table 2).The incidence in the 25-year-old age group was found to be approximately 13 times higher than that of the 11-year-old age group. There was no periodicity of hepatitis B incidence among the study population aged 11–25y during the entire study period (Fig. S3).

The burden of hepatitis B also varied considerably within each subgroup (Tables 1 and S4). Specifically, the average annual incidence of hepatitis B among males was significantly higher than that among females (140.77 vs. 86.04 cases per 100,000 individuals) among the study population aged 11–25y (Table 1). There were more chronic cases, with about 16 times greater than acute cases on average (95.12 vs. 6.13 cases per 100,000 individuals) among the study population aged 11–25y (Table 1).

Table 2 Characteristics of hepatitis B cases and incidence for individuals aged 8–25y from 2005 to 2019 in Guangzhou

Age group	Cumulative cases (Proportion, %)[a]	Average incidence (per 100,000 cases)
8y	191 (0.06)	11.76
9y	208 (0.06)	13.16
10y	230 (0.07)	14.20
11y	247 (0.08)	15.45
12y	297 (0.09)	18.32
13y	348 (0.11)	21.53
14y	422 (0.13)	25.93
15y	722 (0.22)	40.48
16y	1,187 (0.37)	54.52
17y	1,961 (0.61)	73.63
18y	3,238 (1.00)	101.03
19y	4,298 (1.33)	105.78
20y	5,240 (1.62)	96.42
21y	6,225 (1.93)	114.32
22y	7,423 (2.30)	148.08
23y	8,133 (2.52)	165.05
24y	8,844 (2.74)	183.84
25y	9,619 (2.98)	207.14

[a] Figures in round brackets denote the percentage of reported cases within each specified age group, relative to the whole population

Effect of EPI on hepatitis B incidence

By and large, the catch-up vaccination posed a significant decrease in the incidence of hepatitis B among the study population aged 11–25y (Fig. 2), with an age-standardized ER of −20.02% (95% CI: −23.87%, −15.97%). The catch-up vaccination produced statistically significant effectiveness for individuals in the 17-year age group and above, with the most substantial effectiveness observed in the 18-year age group (ER: −54.95%, 95% CI: −65.26%, −41.59%) (Fig. 2).

The age-standardized ERs of hepatitis B were statistically significant for both males (ER: −23.24%, 95% eCI: −27.71%, −18.50%) and females (ER: −17.55%, 95% eCI: −25.10%, −9.24%) following the systematic vaccination

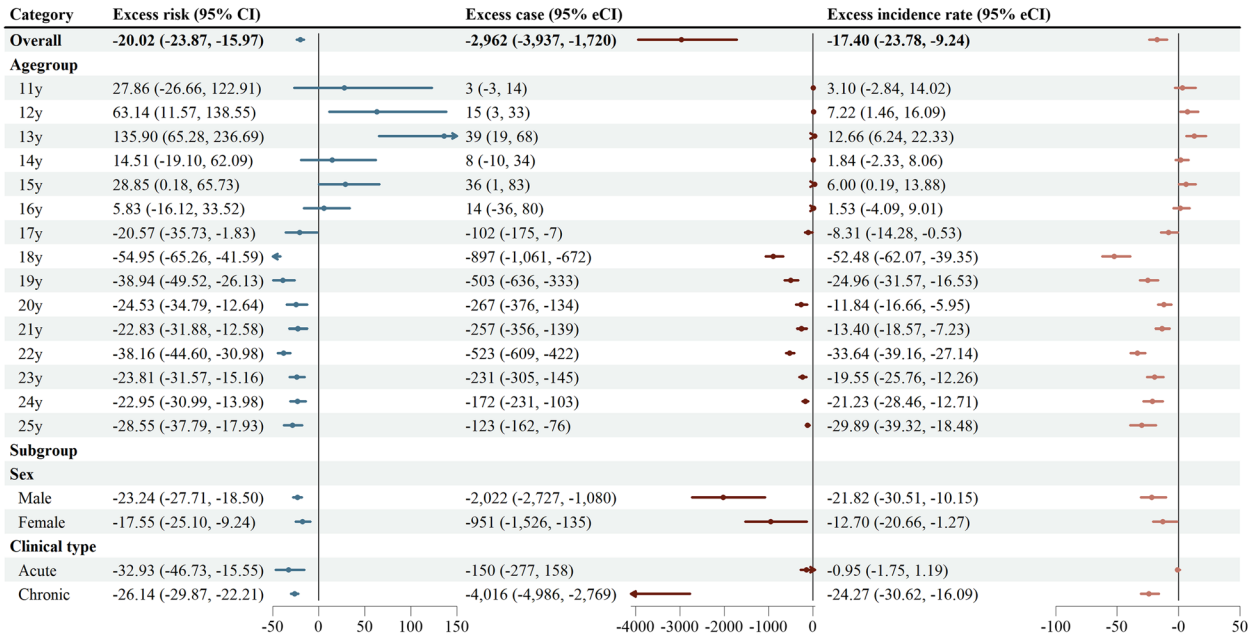

Fig. 2 Excess risks, cases, and incidence rates of hepatitis B attributable to catch-up vaccination. The units of excess risks and excess incidence rates were % and cases per 100,000 individuals, respectively. Abbreviation: CI, confidence interval; eCI, empirical confidence interval

towards the study population aged 11–25y (Fig. 2). The intervention effect among chronic cases was less than that among acute cases, associated with a 26.14% (95% CI: 22.21%, 29.87%) decrease in the risk of hepatitis B incidence (Fig. 2).

There were approximately 2,962 (95% eCI: 1,720, 3,937) cases being prevented among the catch-up population, corresponding to a yearly age-standardized average of 17.40 (95% eCI: 9.24, 23.78) cases per 100,000 individuals (Fig. 2). There was the greatest number of averted people against hepatitis B among individuals aged 18 years (EIR: −52.48, 95% eCI: −62.07, −39.35 cases per 100,000 individuals) (Fig. 2).

The intervention defended people in different subgroups from hepatitis B infection (Fig. 2). Specifically, more people were prevented against hepatitis B following the intervention among males (age-standardized EIR: −21.82, 95% eCI: −30.51, −10.15 cases per 100,000 individuals), and chronic patients (age-standardized EIR: −24.27, 95% eCI: −30.62, −16.09 cases per 100,000 individuals).

Sensitivity analyses

We obtained similar results from the sensitivity analyses. First, we found that the effectiveness of the catch-up vaccination on the incidence did not change substantially when applying a natural cubic spline to ambient temperature with 3 *dfs* (age-standardized ER −19.83% [95% CI: −23.69%, −15.77%]), or additionally incorporating the 7-day moving average of relative humidity, wind speed, and total precipitation into the model (age-standardized ER −23.01% [95% CI: −26.96%, −18.84%]). Second, the effectiveness estimate remained robust when using a negative binomial regression model (age-standardized ER −17.68% [95% CI: −21.60%, −13.56%]). Finally, there was little difference between the results of models with monthly data (age-standardized ER −20.53% [95% CI: −26.36%, −14.23%]) and those with daily data.

Discussion

China implemented the catch-up hepatitis B immune program for all children aged 8–15y in 2009. This study provided a comprehensive evaluation of the vaccination effect on hepatitis B infection among the study population from different subgroups from 2005 to 2019 in Guangzhou. The study population accounted for a small part of the whole population. The major results show that with the systematic hepatitis B vaccination to children under the age of 15 came the decrease of hepatitis B incidence in Guangzhou among the study population by 20.02% and nearly 2962 individuals being prevented from hepatitis B after 2009.

In Guangzhou, whole people suffered a heavy burden of hepatitis B, with an annual incidence of 161.74 cases per 100,000 individuals from 2005 to 2019, about twice the average level of the Chinese mainland (about 76.66 cases per 100,000 individuals from 2005 to 2020), of which nearly 90% are chronic cases [33–35]. In addition,

those born before 1994 comprised a large percentage of all reported cases in Guangzhou. Although the progression from chronic hepatitis B to cirrhosis and hepatocellular carcinoma is relatively slow [36], most chronic cases were contracted in the newborn stage or early childhood and the risk of the liver disease progress increases with age. Slowing the progression of hepatitis B is high on the list of priorities to alleviate the burden of chronic patients. In addition, attention should be paid to high-risk occupations, such as healthcare workers [37], workers, farmers, retirees, etc. [38]. It is important for these high-risk occupations to inoculate hepatitis B vaccines, to proactively test for hepatitis B, and to raise prevention awareness [39].

To our best knowledge, this is the first study assessing the effectiveness of the catch-up vaccination project from 2009 to 2011 for all children on the incidence of hepatitis B. Previous literature focused on evaluating the effectiveness of NPI on the incidence of hepatitis B among newborns [19, 20]. Follow-up studies demonstrated that the primary hepatitis B vaccination can provide long-term protection and maintain high antibody levels (anti-HBs < 10 mIU/mL) in vaccinated children and adults [40, 41]. A few modeling studies found the hepatitis B catch-up vaccination for children under the age of 15 was cost-saving [42, 43]. Our study using surveillance data confirmed that the catch-up vaccination gave impetus to a further drop in the incidence of hepatitis B in Guangzhou in the case of low prevalence among children. A prior prevalence study in China found that there was no significant difference between HBsAg (2.02% vs. 1.95%) and HBsAb (59.13% vs. 57.80%) among the sampled catch-up population in 2006 and 2014 [44]. However, the present study found a significant decrease in the incidence of hepatitis B among the catch-up population. The inconsistency of results can be summed up as two reasons. Firstly, serological indices and reported confirmed cases represent different hepatitis B statuses. The former generally indicates the status of individuals' infection, including HBV carriers, asymptomatic infected people, confirmed cases, etc. The latter is a clinical manifestation of liver damage due to the HBV infection. Secondly, two serological surveys with long intervals cannot account for time-varying confounding variables. The present study indicated that the adoption of a free catch-up hepatitis B vaccination program has generated health benefits to the decrease in the incidence of hepatitis B among corresponding age groups in Guangzhou, China.

In this work, we found that among the study population, the burden on the males was still heavier at the end of 2019 and the intervention effect was weaker in females than in males. The possible reason for this sex disparity in the disease burden is the effect of sex hormones on HBV infection. The liver is regarded as a sexually dimorphic organ, thus being responsive to sex hormones [45]. Animal studies indicated that the HBV X protein enhances the activity of the androgen receptor and the liver in males is more able to facilitate HBV gene expression, replication, and transcription [46, 47]. Two studies in Taiwan, China reported that males had a poorer immune response to HBV infection after vaccination in the newborn stage and worse immune tolerance and clearance phases of serum HBsAg than females [47, 48]. However, the findings of the present study demonstrate that the decline in incidence observed in the males exceeded that observed in the females. The underlying reason for the observed discrepancy is likely to be that the study population comprised children aged 10 years and older, rather than newborns. The question of whether age eliminates differences in immune response to hepatitis B vaccines in males and females requires elucidation in future studies. This finding can assist policymakers in determining the impact of sex on the cost-effectiveness of future massive hepatitis B vaccination for adolescents and adults.

In terms of different clinical types of hepatitis B among the catch-up population, even though the diminution in the incidence was greater in chronic patients than in acute patients, there was the higher incidence of hepatitis B among chronic patients. This phenomenon can be boiled down to three reasons. Firstly, some chronic patients progress from acute infection. Others are caused by mother-to-child transmission. Acute HBV infection usually occurs in the wake of exposure and contact with infected blood and semen in childhood and adulthood [1]. Acute HBV infection lasting for more than six months could progress to chronic infection. Asymptomatic chronic infection occurs in over 90% of mother-to-child transmitted neonates and infants [49]. Maternal antigen levels may affect the efficacy of hepatitis B vaccination. Secondly, there were more children with chronic HBV infection during the study period. Hence, in addition to prophylactic vaccines, healthcare providers can boost the use of antiviral drugs or consider other blocking forms to avoid mother-to-child transmission and the progression of HBV-associated liver diseases [1].

This study has two implications for future vaccination. First and foremost, the beneficial effect of hepatitis B catch-up vaccination in 2009 can provide the basis for whether to expand the population of further catch-up vaccination in the future. In addition to directly reducing the incidence of hepatitis B, hepatitis B vaccines also help vaccinated individuals emerge from a series of liver diseases associated with HBV. A systematic review showed that the protective efficacy of hepatitis B vaccination could persist for 14–30 years [50]. Hepatitis B vaccines could reduce the risk of HBV

infection and even prevent the progression of hepatitis B (e.g. hepatocellular carcinoma and deaths associated with fulminant hepatitis in children) [51–54]. Previous modeling studies indicated that massive vaccination for people over 14 years old and universal screening among adults aged 18–70 years with various willingness-to-pay thresholds may be cost-saving and beneficial to alleviating the current burden of hepatitis B among those who have not been systematically vaccinated in China [42, 55, 56]. Therefore, health authorities need to consider whether to implement expanded catch-up vaccination and other universal strategies among adult people based on the local burden of hepatitis B. Additionally, the findings would serve as a paradigm of hepatitis B catch-up vaccination for other countries and regions bearing the burden of hepatitis B (e.g., southeast Asia, most of Africa, etc.) [1, 57], which could contribute to controlling the incidence of hepatitis B worldwide.

Several limitations should be acknowledged in this study. First, there was an inevitable under-reporting of hepatitis B cases. Particularly, chronic infections can have a long asymptomatic phase and are more likely to be under-reported among the younger population [22]. However, the probability of under-reporting and misdiagnosis is likely to diminish over time, as a result of the introduction of new diagnostic criteria for hepatitis B in 2008, the advancement of medical technology, and the refinement of the reporting process. In conclusion, such differential under-reporting may result in an underestimation of the effectiveness. Second, due to the lack of data on asymptomatic infections and the low proportion of diagnosed cases (0.16%, equivalent to 161.74 per 100,000 persons) in the general population, the population offset in the model was based on the total resident population of the specific group under study, including previously diagnosed individuals. This approach may underestimate the incidence rate, especially post-intervention, potentially leading to an overestimation of the intervention's effectiveness. Third, prior research found an association between an individual's economic status and their inclination to receive the hepatitis B vaccine [58]. The lack of individual information on lifestyle and socioeconomic status thwarts a further exploration of the effectiveness of the intervention in subgroups. Fourth, previous studies found that human mobility has an impact on infectious diseases, such as COVID-19 [59], hepatitis A [60], HIV [61], etc. Should the human mobility data at the inter-city and intra-city level become available, understanding the association between the mobility patterns and the incidence of hepatitis B during the study period would provide more insights into the impact of human behaviors on hepatitis B transmission. Finally, our study did not take hepatitis B cases after 2020 into consideration. Further studies are required to focus on whether the effectiveness of hepatitis B vaccination changes significantly in the pandemic and post-pandemic era of COVID-19 and to re-examine the feasibility of meeting the WHO's targets.

Conclusions

The massive catch-up hepatitis B vaccination on children is associated with the decrease in the incidence of hepatitis B in Guangzhou. The findings could be considered to support policy updates that extend the vaccination age to all children under the age of 15 in other regions or countries with high- and middle-endemic of hepatitis B.

Abbreviations

HBV	Hepatitis B virus
WHO	World Health Organization
HBsAg	Hepatitis B surface antigen
NIP	National Immunization Program
CDC	Center for Disease Control and Prevention
IRR	Incidence rate ratio
ER	Excess risk
95% CI	95% Confidence interval
EIR	Excess incidence rate
EC	Excess cases
95% eCI	95% Empirical confidence interval
dfs	Degrees of freedom

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22437-5.

Supplementary Material 1

Acknowledgements

Not applicable.

Authors' contributions

CQO and ZBZ conceptualized the study. WHL and ZBZ collected data. BWM, WHL, ZJL, JL, JJM and HNH analyzed data. BWM and LL wrote the first draft. CQO reviewed and edited the writing. All authors contributed to the interpretation of the results and edited the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (81973140, 82473727) and the Guangdong Basic and Applied Basic Research Foundation (2024A1515011957).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Southern Medical University (NFYKDX-ER2022012). The need for the informed consent was waived by the Research Ethics Committee, since the de-identified summarized data were derived from Guangzhou Center for Disease Control and Prevention for analyses in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]State Key Laboratory of Multi-organ Injury Prevention and Treatment, Department of Biostatistics, Guangdong Provincial Key Laboratory of Tropical Disease Research, School of Public Health, Southern Medical University, Guangzhou, Guangdong 510515, China. [2]Guangzhou Center for Disease Control and Prevention, Guangzhou, Guangdong, China.

Received: 14 December 2023 Accepted: 21 March 2025
Published online: 25 April 2025

References

1. Trépo C, Chan HLY, Lok A. Hepatitis B virus infection. Lancet. 2014;384:2053–63.
2. Hepatitis B virus infection. Nat Rev Dis Primers. 2018;4:18036.
3. Wang M, Yan L, Wang J, Jin Y, Zheng Z. Global burden of hepatitis B attributable to modifiable risk factors from 1990 to 2019: a growing contribution and its association with socioeconomic status. Global Health. 2023;19:23.
4. Seto W, Lo Y, Pawlotsky J, Yuen M. Chronic hepatitis B virus infection. Lancet. 2018;392:2313–24.
5. Hsu Y, Huang DQ, Nguyen MH. Global burden of hepatitis B virus: current status, missed opportunities and a call for action. Nat Rev Gastroenterol Hepatol. 2023;20:524–37.
6. Broderick AL, Jonas MM. Hepatitis B in children. Semin Liver Dis. 2003;23:59–68.
7. Cao G, Jing W, Liu J, Liu M. Countdown on hepatitis B elimination by 2030: the global burden of liver disease related to hepatitis B and association with socioeconomic status. Hepatol Int. 2022;16:1282–96.
8. Hepatitis B. https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b. Accessed 23 Nov 2023.
9. Global health sector strategy on viral hepatitis 2016-2021. https://www.who.int/publications/i/item/WHO-HIV-2016.06. Accessed 04 Apr 2023.
10. Kang G, Ma F, Chen H, Yang Y, Guo S, Wang Z, et al. Efficacy of antigen dosage on the hepatitis B vaccine response in infants born to hepatitis B-uninfected and hepatitis B-infected mothers. Vaccine. 2015;33:4093–9.
11. Qiu J, Zhang S, Feng Y, Su X, Cai J, Chen S, et al. Efficacy and safety of hepatitis B vaccine: an umbrella review of meta-analyses. Expert Rev Vaccines. 2024;23:69–81.
12. Liao S, Li R, Li H, Yang J, Zeng X, Gong J, et al. Long-term efficacy of plasma-derived hepatitis B vaccine: a 15-year follow-up study among Chinese children. Vaccine. 1999;17:2661–6.
13. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Evaluation of the impact of hepatitis B vaccination among children born during 1992–2005 in China. J Infect Dis. 2009;200:39–47.
14. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Reprint of: epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. Vaccine. 2013;31:J21–8.
15. Cui F, Shen L, Li L, Wang H, Wang F, Bi S, et al. Prevention of chronic hepatitis B after 3 decades of escalating vaccination policy. China Emerg Infect Dis. 2017;23:765–72.
16. Ni Y, Chang M, Jan C, Hsu H, Chen H, Wu J, et al. Continuing decrease in hepatitis B virus infection 30 years after initiation of infant vaccination program in Taiwan. Clin Gastroenterol Hepatol. 2016;14:1324–30.
17. Xiao J, Zhang J, Wu C, Shao X, Peng G, Peng Z, et al. Impact of hepatitis B vaccination among children in Guangdong Province, China. Int J Infect Dis. 2012;16:e692–6.
18. Whitford K, Liu B, Micallef J, Yin JK, Macartney K, Van Damme P, et al. Long-term impact of infant immunization on hepatitis B prevalence: a systematic review and meta-analysis. Bull World Health Organ. 2018;96:484–97.
19. Liu Z, Li M, Hutton DW, Wagner AL, Yao Y, Zhu W, et al. Impact of the national hepatitis B immunization program in China: a modeling study. Infect Dis Poverty. 2022;11:1–106.
20. Pan J, Wang Y, Cao L, Wang Y, Zhao Q, Tang S, et al. Impact of immunization programs on 11 childhood vaccine-preventable diseases in China: 1950–2018. Innovation (N Y). 2021;2:100113.
21. Liu J, Liang W, Jing W, Liu M. Countdown to 2030: eliminating hepatitis B disease. China Bull World Health Organ. 2019;97:230–8.
22. Cooke GS, Andrieux-Meyer I, Applegate TL, Atun R, Burry JR, Cheinquer H, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2019;4:135–84.
23. Liu J. Liu M [Progress and challenges in achieving the WHO goal on "Elimination of Hepatitis B by 2030" in China]. Zhonghua Liu Xing Bing Xue Za Zhi. 2019;40:605–9.
24. Yu R, Fan R, Hou J. Chronic hepatitis B virus infection: epidemiology, prevention, and treatment in China. Front Med. 2014;8:135–44.
25. Guangzhou Statistics Bureau. http://tjj.gz.gov.cn/. Accessed 8 Aug 2023.
26. Liu J, Cai Y, Chen J, Li Z, Xu J, Wang M. Analysis of the prevalence of viral hepatitis B for general population in Guangzhou Municipal. Chin J Vacc Immun. 2010;16:438–42.
27. Diagnostic criteria for viral hepatitis B. https://www.whcdc.org/view/12097.html. Accessed 10 Oct 2023.
28. Li Z, Wang M, Cai Y, Xu J, Chen J. Evaluation on supplementary immunization activities strategy of hepatitis B vaccine among children under 15 years old in Guangzhou. Progress Microbiol Immunol. 2012;40:38–44.
29. Kojima N, Roshani A, Brobeck M, Baca A, Klausner JD. Incidence of SARS-CoV-2 infection among previously infected or vaccinated employees. Int J Infect Dis. 2022;118:21–3.
30. Greenland S. Interval estimation by simulation as an alternative to and extension of confidence intervals. Int J Epidemiol. 2004;33:1389–97.
31. Gasparrini A, Leone M. Attributable risk from distributed lag models. BMC Med Res Methodol. 2014;14:55.
32. Ming B, Li L, Huang H, Ma J, Shi C, Xu X, et al. The effectiveness of national expanded program on immunization with hepatitis A vaccines in the Chinese Mainland: interrupted time-series analysis. JMIR Public Health Surveill. 2024;10:e53982.
33. Zheng J, Zhang N, Shen G, Liang F, Zhao Y, He X, et al. Spatiotemporal and seasonal trends of class A and B notifiable infectious diseases in China: retrospective analysis. JMIR Public Health Surveill. 2023;9:e42820.
34. Zeng F, Guo P, Huang Y, Xin W, Du Z, Zhu S, et al. Epidemiology of hepatitis B virus infection: results from a community-based study of 0.15 million residents in South China. Sci Rep. 2016;6:6.
35. Zhu Q, Shao X, Chen S, Li D, Chen X, Liu W, et al. Epidemiological serosurvey of hepatitis B virus among children aged 1–14 years in Guangdong Province, China. Int J Infect Dis. 2018;71:25–9.
36. Locarnini S, Hatzakis A, Chen D, Lok A. Strategies to control hepatitis B: Public policy, epidemiology, vaccine and drugs. J Hepatol. 2015;62:S76–86.
37. Liu Y, Ma C, Jia H, Xu E, Zhou Y, Zhang Z, et al. Knowledge, attitudes, and practices regarding hepatitis B vaccination among hospital-based doctors and nurses in China: results of a multi-site survey. Vaccine. 2018;36:2307–13.
38. Du J, Xu Y, Wang J, Liu S, Liu Y, Zhang X, et al. 24 year outcomes of hepatitis B vaccination in Hangzhou, China. Hum Vaccin Immunother. 2015;11:2051–60.
39. Aspinall EJ, Hawkins G, Fraser A, Hutchinson SJ, Goldberg D. Hepatitis B prevention, diagnosis, treatment and care: a review. Occup Med. 2011;61:531–40.
40. Bruce MG, Bruden D, Hurlburt D, Zanis C, Thompson G, Rea L, et al. Antibody levels and protection after hepatitis B vaccine: results of a 30-year follow-up study and response to a booster dose. J Infect Dis. 2016;214:16–22.
41. Bruce MG, Bruden D, Hurlburt D, Morris J, Bressler S, Thompson G, et al. Protection and antibody levels 35 years after primary series with hepatitis B vaccine and response to a booster dose. Hepatology. 2022;76:1180–9.
42. Hutton DW, So SK, Brandeau ML. Cost-effectiveness of nationwide hepatitis B catch-up vaccination among children and adolescents in China. Hepatology. 2010;51:405–14.
43. Jia Y, Li L, Cui F, Zhang D, Zhang G, Wang F, et al. Cost-effectiveness analysis of a hepatitis B vaccination catch-up program among children in Shandong Province. China Hum Vaccin Immunother. 2014;10:2983–91.
44. Wang FZ, Zheng H, Miao N, Sun XJ, Zhang GM, Liang XF, et al. Analysis on sero-epidemiological characteristics of hepatitis B virus among people

born during 1994–2001 before and after hepatitis B vaccine catch-up vaccination, China. Zhonghua Yu Fang Yi Xue Za Zhi. 2017;51:469–74.
45. Wang AC, Geng J, Wang C, Wu D, Chen S. Sex difference in the associations among risk factors with hepatitis B and C infections in a large Taiwanese population study. Front Public Health. 2022;10:1068078.
46. Yang W, Chang C, Yeh S, Lin W, Wang S, Tsai T, et al. Hepatitis B virus X protein enhances the transcriptional activity of the androgen receptor through c-Src and glycogen synthase kinase-3β kinase pathways. Hepatology. 2009;49:1515–24.
47. Wang SH, Chen PJ, Yeh SH. Gender disparity in chronic hepatitisB: mechanisms of sex hormones. J Gastroenterol Hepatol. 2015;30:1237–45.
48. Su FH, Chen JD, Cheng SH, Lin CH, Liu YH, Chu FY. Seroprevalence of hepatitis-B infection amongst Taiwanese university students 18 years following the commencement of a national Hepatitis-B vaccination program. J Med Virol. 2007;79:138–43.
49. Indolfi G, Easterbrook P, Dusheiko G, Siberry G, Chang MH, Thorne C, et al. Hepatitis B virus infection in children and adolescents. Lancet Gastroenterol Hepatol. 2019;4:466–76.
50. Pattyn J, Hendrickx G, Vorsters A, Van Damme P. Hepatitis B Vaccines. J Infect Dis. 2021;224:S343–51.
51. Mcmahon BJ, Bulkow LR, Singleton RJ, Williams J, Snowball M, Homan C, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. Hepatology. 2011;54:801–7.
52. Kao J, Hsu H, Shau W, Chang M, Chen D. Universal hepatitis B vaccination and the decreased mortality from fulminant hepatitis in infants in Taiwan. J Pediatr. 2001;139:349–52.
53. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med. 1997;336:1855–9.
54. Zhao H, Zhou X, Zhou YH. Hepatitis B vaccine development and implementation. Hum Vaccin Immunother. 2020;16:1533–44.
55. Su S, Wong WC, Zou Z, Cheng DD, Ong JJ, Chan P, et al. Cost-effectiveness of universal screening for chronic hepatitis B virus infection in China: an economic evaluation. Lancet Glob Health. 2022;10:e278–87.
56. Wang X, Du Z, Wang Y, Wang J, Huang S, Wang Y, et al. Impact and cost-effectiveness of biomedical interventions on adult hepatitis B elimination in China: a mathematical modelling study. J Epidemiol Glob Health. 2023;13:517–27.
57. Razavi-Shearer D, Gamkrelidze I, Nguyen MH, Chen D, Van Damme P, Abbas Z, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018;3:383–403.
58. Liu X, Yang C, Zhong Q, Song Q, Huang X, Yang Y, et al. Improved timely birth dose coverage of hepatitis B vaccine narrows the socio-economic inequality in western China in 2011–2016. Vaccine. 2018;36:3901–7.
59. Zhang J, Tan S, Peng C, Xu X, Wang M, Lu W, et al. Heterogeneous changes in mobility in response to the SARS-CoV-2 Omicron BA.2 outbreak in Shanghai. Proc Natl Acad Sci. 2023;120:e2306710120.
60. Xia C, Wang J, Wang Z, Shen J. Correlation between notifiable infectious diseases and transportation passenger traffic from 2013 to 2019 in mainland China. BMC Public Health. 2024;24:3023.
61. Okano JT, Busang L, Seipone K, Valdano E, Blower S. The potential impact of country-level migration networks on HIV epidemics in sub-Saharan Africa: the case of Botswana. The Lancet HIV. 2021;8:e787–92.

Publisher's Note