New progress in HBV control and the cascade of health care for people living with HBV in China: evidence from the fourth national serological survey, 2020

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Summary

Background Since 1992, when recombinant hepatitis B vaccine was introduced in China, government health officials have used nationally representative serological surveys to monitor progress in prevention and control of hepatitis B. In 2020, we conducted the fourth seroepidemiological survey, which for the first time included medical evaluation of the clinical status of HBsAg positive subjects over the age of 15 and their medical management. We report survey results in comparison with the three previous surveys.

Methods Consistent with previous national surveys, the 2020 survey used a stratified, three-stage cluster random sampling method to select for evaluation 1-69-year-olds in 120 national disease surveillance points. Blood samples were tested for HBsAg, anti-HBV surface antigen (anti-HBs), and anti-HBV core antigen (anti-HBc) in the National Hepatitis Laboratory of the Institute for Viral Disease Control and Prevention of China CDC. HBsAg positive subjects aged ≥15-year were evaluated for evidence of liver disease, and through face-to-face questionnaire-based survey, we determined the healthcare management cascade of HBV-infected individuals.

Findings HBsAg prevalence in 1–69-year-olds was 5.86%; in children 1–4 years of age, seroprevalence was 0.30%; 75 million people were living with HBV nationwide. Among HBsAg-positive individuals 15 years and older, expert medical examination found that 78.03% were HBsAg carriers with no evidence of liver damage, 19.63% had chronic HBV with liver enzyme abnormalities, 0.84% had evidence of cirrhosis, and 0.15% had evidence of liver cancer. 59.78% of HBsAg + individuals were aware that they were positive before the survey, 30 million were unaware; 38.25% of those who knew they were positive (17 million) had medical indications for antiviral treatment, and 17.33% of these individuals (3 million) were being treated with antivirals.

Interpretation The decline in HBsAg prevalence in the general population, from 9.72% in 1992 to 5.86% in 2020, and in 1–4-year-olds from 9.67% in 1992 to 0.30% in 2020, shows progress that continues on track toward WHO targets for prevention of new infections. Implementation of acceptable strategies to identify infected individuals and offer long-term medical monitoring and management will be important to prevent complications from hepatitis B infection and for meeting WHO cascade-of-care targets.

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Keywords: Hepatitis B; National serological survey; Disease burden

Research in context

Evidence before this study

China has a heavy burden of hepatitis B, with modeled estimates of approximately 86 million people living with chronic HBV infection in China – nearly one-third of the estimated 290 million people living with chronic HBV infection worldwide. To monitor and guide HBV control efforts, China conducted three national HBV seroepidemiological surveys: in 1992 and 2006 among people 1–59 years old, and in 2014 among people 1–29 years old. These serosurveys provided data important for national and global HBV prevention and control effort.

Added value of this study

We analyzed the 2020 nationally representative HBV survey data to estimate HBsAg seroprevalence by age and demographic characteristics. Individuals who were HBsAg-positive and over 15 years of age were evaluated to determine clinical stage of liver disease and status of medical management. HBsAg prevalence was 5.9% in people 1–69 years of age, representing 75 million people living with chronic hepatitis B infection. Seroprevalence in children 1–4 years old was 0.3%. Expert medical examination of seropositive individuals found that 78% were carriers with no evidence of liver damage; 19% had CHB with liver-enzyme abnormalities; 1% had evidence of cirrhosis; and 0.2% had evidence of liver cancer. Sixty percent of seropositive individuals were aware that they were positive before the survey; 38% of those who knew they were positive had clinical indications for antiviral treatment, and 17% of these individuals were being treated with antivirals.

Implications of all the available evidence

This national survey updates China's progress in preventing HBV mother-to-child transmission, showing that China continues to be on track to achieve seroprevalence targets for children under five years set by the World Health Organization. The survey provides the most recent objective real-world estimate for the number of individuals living with chronic HBV infection in China - 75 million, revising modeled estimates of 79–86 million for the international research community. The 2020 serosurvey estimated for the first time the average clinical staging of CHB and the status of the healthcare management cascade in China. The survey provides a basis for optimizing hepatitis B prevention, control, identification, and clinical management strategies in China and yields important reference values for the prevention and control of viral hepatitis globally.

Introduction

The hepatitis B virus (HBV) epidemic is an ongoing threat to global health and is one of the most common causes of liver cirrhosis, liver cancer, and viral hepatitis-related death.[1,2] WHO endorsed the "Global Health Sector Strategy on Viral Hepatitis" in 2016, which set a goal to eliminate viral hepatitis as a public health threat by 2030.[3] In 2022, the 75th World Health Assembly passed the "2022–2030 Global Health Sector Action Plan on HIV, Viral Hepatitis and Sexually Transmitted Infections", which clarified the indicators for achieving this goal.[4] WHO is urging accelerated country-level viral hepatitis prevention and control.

An estimated 296 million people worldwide were living with hepatitis B in 2019,[5] with approximately one-third of these individuals living in China. Although there is a large number of people with chronic HBV (CHB) infection in China, mother-to-child transmission of HBV, which is the historic main driver of new CHB infections, has been greatly reduced in China through active measures of timely, universal vaccination of newborns with hepatitis B vaccine (HepB), comprehensive screening of pregnant women for HBV serological markers of infection, and administration of HBIG with the birth dose of HepB to infants born to hepatitis B surface antigen (HBsAg) positive women. The prevalence of HBsAg positivity in children aged 1–4 years decreased by 97%, from 9.67% in 1992 to 0.32% in 2014,[6] and modeling studies show that China is likely to achieve the WHO goal of eliminating mother-to-child transmission of HBV by 2030.[7] Continued monitoring of HBsAg prevalence in young children is critically important for achieving the elimination goal on time.

After effectively controlling perinatal and childhood HBV infection, current and future work is to improve screening, treatment, and clinical management of people infected with HBV to reduce risk of cirrhosis, liver cancer, and HBV-related death. Highly effective HBV antiviral drugs have been developed and are available in China.[8,9] Through centralized procurement, the price of

a month's supply of the tenofovir disoproxil fumarate (TDF) has been reduced by 96% - from 1500 RMB to 18 RMB,[10] facilitating affordable, standardized treatment and clinical management of patients with CHB. Previous estimates were that approximately 86 million people were living with chronic HBV infection in China, but often-invisible progression of disease, low CHB patient visit rates, and unclear clinical and epidemiological characteristics affect evidence-based decision-making for CHB management.

In 2020, we conducted a fourth China national seroepidemiological survey. The primary purpose of this survey was to measure HBsAg seroprevalences using methods consistent with the three previous national surveys. A second purpose was to evaluate the stage of liver disease and explore the cascade of clinical management of HBsAg-positive subjects over the age of 15 years. We report survey results in the context of China's HBV prevention and control measures and in comparison with the 1992, 2006, and 2014 serosurveys.

Methods

Survey conduct

Target populations for all 4 surveys were local residents residing in national disease surveillance points (DSPs) for >6 months. DSPs were selected by the Chinese Academy of Preventive Medicine (now the Chinese Center for Disease Control and Prevention [China CDC]) to be representative of the population of China. The surveys' targeted age ranges were 1–59 years in 1992 and 2006, 1–29 years in 2014, and 1–69 years in 2020. Sampling strategies in 1992, 2006, and 2014 were described previously.[6,11,12] The 2020 survey used a stratified, three-stage cluster random sampling method to select subjects from DSP target populations. In the first stage, 120 counties/districts were selected at random from among 160 disease surveillance points nationwide; in the second stage, probability proportional to size (PPS) sampling was used to randomly select 2–5 villages in each county/district, and the registered resident population of sampled villages/neighborhood committees served as the indexed sampling universe; in the third stage, potential subjects aged 1–4, 5–14, and 15–69 years were enumerated from the village lists and selected by simple random sample stratified by year of age (one-year strata for the 1–4 year group; two-year strata for the 5–14 year group; five-year strata for the 15–29 year group; ten-year strata for the 30–69 year group) to ensure that no sub-age-group would be empty. Recruitment continued until the target population sample size was met in each age group. Potential subjects were contacted by telephone or at their homes; those willing to participate became subjects. If there were unwilling potential subjects, the simple random sample selection was continued until the target population size was reached for each age group.

We conducted a pre-survey in 2019 to test the survey methods and instruments for feasibility. The 31-province field serosurvey was conducted during November and December of 2020. China CDC issued a unified investigation protocol and work manual, and held an on-line training meeting for investigating staff in the 120 DSP counties/districts. Training included sampling methods, questionnaire requirements, specimen collection, specimen storage and transportation, and data reporting requirements. The investigation was conducted in village or district health centers as a centralized procedure. Provincial CDC personnel supervised and provided guidance on the spot when conducting on-site investigations. Data entry was reviewed at the provincial level. Five percent of the questionnaires collected by the provinces to check the core variables. If errors were found in excess of 5%, the questionnaires from the province were re-entered and rechecked. In 2021, a team of experienced clinicians went to the 31 provinces one by one to examine and interview the HBsAg positive subjects to determine their liver disease status and treatment status to assess the cascade of care.

Laboratory testing

Blood sample specimens in this and the other three serosurveys were tested in the National Hepatitis Laboratory of the Institute for Viral Disease Control and Prevention, China CDC. For the 2006, 2014, and 2020 serosurveys, ELISA reagents were used to detect levels of HBsAg, anti-HBV surface antigen (anti-HBs), and anti-HBV core antigen (anti-HBc). ELISA reagents were purchased from Beijing Wantai Production Company (The batch numbers of HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBC reagent purchased in 2020 were B20200928, R20200906B, X29200704B, Z20200710B, K20200909B, respectively). The ELISA instrument is ThermoFisher 1510. Specimens yielding inconsistent or indeterminate results were retested using microparticle enzyme immunoassay (MEIAreagents) (ARCHITECH® i2000SR, Abbott Laboratories, Chicago, IL, USA; The batch number of HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBC were 20306FN01, 13534FN01, 19124BE01, 19143BE01, 20039BE01, respectively). For the 1992 serosurvey, HBsAg, anti-HBs, and anti-HBc were tested by solid-phase radioimmunoassay (SPRIA).

Investigation of HBV infected person in 2020 survey

After the National Hepatitis Laboratory completed HBV sero-marker testing of all blood samples, the test results were provided to the appropriate DSPs' corresponding county-level CDCs. The county-level CDCs contacted the HBsAg positive individuals aged ≥15 years one by one to make an appointment at a designated hospital to conduct clinical testing and administer a questionnaire. HBsAg positive subjects aged ≥15 years were evaluated for evidence of liver disease with alanine amino transferase

(ALT), aspartate amino transferase (AST), albumin, globulin, and total bilirubin (TBiL) blood tests; with liver B-ultrasound; and with transient liver elasticity testing by FibroScan. Through face-to-face questionnaire-based survey, we recorded HBsAg + subjects' histories of HBV testing or screening, healthcare seeking behavior, and antiviral treatment. Based on the results of the medical examinations, a clinical expert group determined the liver disease status of each HBsAg positive patient using the following criteria from the *Chinese Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019)*[13]:

(1) HBsAg carriers: including chronic HBV carrier state (immune tolerance phase) and inactive HBsAg carrier state (immune control phase). Chronic HBV carrier state refers to HBsAg and HBeAg positive, ALT normal, and HBV DNA >2×10^7 IU/mL. Inactive HBsAg carrier state refers to HBsAg and anti-HBe positive, HBeAg negative, ALT normal, and HBV DNA <2000 IU/mL.
(2) Chronic hepatitis B: includes HBeAg positive CHB (immune clearance phase) and HBeAg negative CHB (re-activation phase). HBeAg positive CHB refers to those with HBsAg and HBeAg positive, ALT abnormal (above upper limit of normal), and HBV DNA >20,000 IU/mL. HBeAg negative CHB refers to those HBsAg positive but HBeAg negative, ALT abnormal, and HBV DNA ≥2000 IU/mL.
(3) Hepatitis B cirrhosis: HBsAg positive patients who met at least two of the following criteria: 1) liver ultrasound imaging suggestive of cirrhosis and/or portal hypertension (splenomegaly, ascites); 2) liver stiffness measurement indicating cirrhosis; and 3) ALB level <35 g/l.
(4) Suspected hepatocellular carcinoma (HCC): HBsAg positive patients who have imaging findings of focal lesions suspected to be HCC by liver ultrasound test.

Indications for antiviral therapy

According to the Chinese Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019),[13] meeting any of the following criteria is an indication for antiviral therapy: (1) HBV DNA positive, ALT abnormal; (2) HBV DNA positive with hepatitis B cirrhosis; (3) HBV DNA positive, ALT normal, meeting one of the following criteria: ①a family history of HBV cirrhosis or hepatocellular carcinoma and age >30 years, or ② age >30 years, liver transient elastography indicating liver fibrosis.

Quality control

China CDC convened expert groups to guide the study design, field work, laboratory testing, and analyses for the 4 surveys. For the 2020 survey, a clinical team from Beijing Friendship Hospital conducted investigations and clinical testing of HBV-infected subjects in all 31 provinces, which ensured consistency of testing instruments, operation, and diagnostic standards.

Statistical analysis

We used SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) for statistical analyses. The statistical methods for the 2020 serosurvey were identical to those of the 2006 and 2014 serosurvey.[6,11,14] To ensure representativeness of post-stratification adjustments, sample weighting components were the village-selection probability and age-specific and person-selection probabilities within the village. Demographic weights of age and sex were adjusted to match 2020 census data. As the investigation of HBV infected persons in 2020 survey was based on completion of the serosurvey, we added demographic weights of age and sex for the followed-up HBsAg positive patients to match all the HBsAg positive patients found in serosurvey. We calculated point estimates and 95% confidence interval (CIs) of HBsAg prevalence, with Taylor series linearization being used for variance estimations. The 1992 survey was not weighted, so we estimated unweighted point prevalences and 95% CIs for that survey. Prevalences reported in this paper are therefore weighted prevalences, with the exception of the 1992 survey. We considered 95% confidence intervals that did not overlap as statistically significant.

Ethical review

The 1992 survey was approved by Chinese Academy of Preventive Medicine's Ethical Review Committee; the 2006, 2014 and 2020 surveys were approved by China CDC's Ethical Review Committee. In each survey, participants were informed of the study purpose and their right to keep information confidential. Consent was obtained from legal guardians/caretakers of children and from all adult participants before interview and blood drawing.

Role of the funding source

The funder had no role in the design, data collection, or data analysis of the study, nor in the interpretation of the result, writing of the report and the decision to submit the paper for publication.

Results

Response rate

The required sample size for the 2020 survey was 90,200 people, and the target sample size was expanded to 128,240 people to account for attrition from each age group. A total of 91,971 people was surveyed on site; 44 people were excluded due to incomplete survey questionnaires and 31 people were excluded due to missing blood samples, resulting in an effective sample of 91,896 subjects (Table 1 and Fig. 1).

Item	1992	2006	2014	2020
Population (million)	1143.33[a]	1267.43[a]	1340.91[a]	1412.12
Age (Years)	1–59	1–59	1–29	1–69
Sample size (N)	61,702	81,775	31,713	91,896
Sex [n (%)]				
Male	29,693 (48.12)	38,895 (47.56)	15,814 (49.86)	39,627 (43.12)
Nationality [n (%)]				
Han	55,484 (89.92)	70,815 (86.60)	26,781 (84.45)	75,170 (81.80)
Region [n (%)]				
Eastern	18,463 (29.92)	27,457 (33.58)	10,424 (32.87)	31,381 (34.15)
Middle	27,587 (44.71)	27,218 (33.28)	10,362 (32.67)	27,564 (29.99)
Western	15,652 (25.37)	27,100 (33.14)	10,927 (34.56)	32,951 (35.86)
Urban/Rural, [n (%)]				
Urban	19,676 (31.89)	40,840 (49.94)	15,739 (50.73)	45,259 (49.25)
Rural	42,026 (68.11)	40,935 (50.06)	15,974 (51.49)	46,637 (50.75)

[a]The populations in 1992, 2006, and 2014 were based on the 1990, 2000, and 2010 national censuses data, respectively.

Table 1: **Demographic characteristics of subjects in four hepatitis B serosurveys, China, 1992–2020.**

HBsAg prevalence changes

Data from four national sero-epidemiological surveys showed that the prevalence of HBsAg in the general Chinese population decreased from 9.72% in 1992 to 7.18% in 2006, and further decreased to 5.86% in 2020. The prevalence of HBsAg in children also decreased significantly. In 1992, the HBsAg prevalence in children aged 1–4 years (9.67%) was not statistically different from that in adults aged ≥30 years (9.24%). In 2006, 2014, and 2020, the prevalence of HBsAg in children aged 1–4 years was 0.96%, 0.32%, and 0.30%, respectively, representing decreases of 90.07%, 96.69%, and 96.89% compared with 1992. HBsAg prevalence in people over 35 years old in 2020 was similar to same-age prevalences in the previous surveys (Table 2, Fig. 2 and Supplement material).

The HBsAg prevalence among women in the reproductive age range of 15–49 years in China decreased significantly, from 8.18% in 1992 to 6.61% in 2006, and to 5.87% in 2020. Age-specific analysis showed that the prevalences of HBsAg among women in the peak fertility ages of 20–29 years and 30–39 years were 8.09% and 8.17% in 1992, decreasing to 7.24% and 6.76% in 2006. In 2020, the HBsAg prevalences in women aged 20–29 and 30–39 years were 2.83% and 5.89%, representing decreases of 65.02% and 27.91% compared with 1992, and representing decreases of 60.91% and 12.87% compared with 2006 (Table 3).

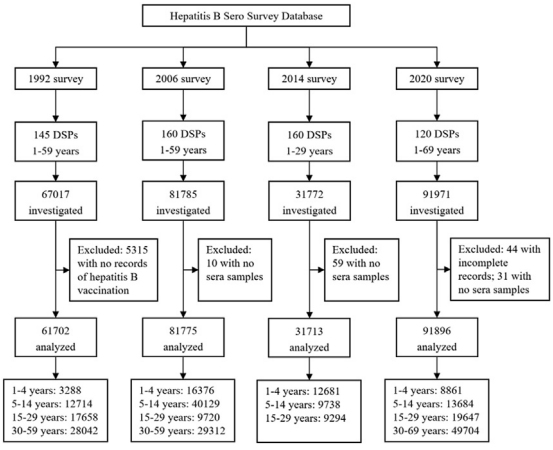

Fig. 1: Study eligibility and select characteristics of persons participating in the national serosurveys for hepatitis B virus, China. China, 1992–2020.

HBV disease burden and HBV infected persons' disease status

In the 2020 survey, we attempted follow-up evaluation of 4236 HBsAg-positive individuals aged 15 years old and above to conduct medical examination and diagnostic staging; 1259 (29.72%) were lost to follow-up (LTFU). Among the 2977 (70.28%) individuals able to be evaluated, 1332 (44.74%) were male; the average age was 47 ± 13 years; eastern, central, and western regions accounted for 40.01%, 26.13%, and 33.86%; and urban and rural areas accounted for 39.54% and 60.46%. There were statistically significant differences in age, gender, region, and urban-rural areas between the followed-up group and the LTFU group; there were no differences in ethnicity (Table 4).

Among the 2977 HBsAg positive subjects who underwent medical testing, 2311 (77.63%) were determined to be HBsAg carriers (including chronic HBV carrier status and inactive HBsAg carrier status); 573 (19.25%) were determined to have CHB (including HBeAg-positive CHB and HBeAg-negative CHB); 30

Survey Year	Age (year)	Samples (N)	HBsAg positive number (n)	Positive proportion (%)	Prevalence (%, 95% CI)
1992[a]					
	1-	3288	318	9.67	9.67 (8.93–10.83)
	5-	12,714	1366	10.74	10.74 (10.11–11.19)
	15-	17,658	1724	9.76	9.76 (9.41–10.28)
	≥30	28,042	2590	9.24	9.24 (8.85–9.54)
	Subtotal	61,702	5998	9.72	9.72 (9.48–9.95)
2006					
	1-	16,376	177	1.08	0.96 (0.75–1.17)
	5-	40,129	590	1.91	2.08 (1.78–2.38)
	15-	9720	769	7.91	8.29 (6.82–10.04)
	≥30	29,312	2614	8.92	8.39 (7.58–9.27)
	Subtotal	81,775	4150	5.07	7.18 (6.67–7.68)
2014					
	1-	12,681	48	0.38	0.32 (0.22–0.46)
	5-	9738	94	0.97	0.94 (0.66–1.34)
	15-	9294	375	4.03	4.38 (2.95–5.42)
	≥30	–	–	–	–
	Subtotal	31,713	517	1.63	2.64 (2.28–3.06)
2020					
	1-	8861	28	0.32	0.30 (0.14–0.64)
	5-	13,684	62	0.45	0.38 (0.25–0.60)
	15-	19,647	546	2.78	2.62 (2.13–3.21)
	≥30	49,704	3690	7.42	7.54 (6.80–8.36)
	Subtotal	91,896	4326	4.71	5.86 (5.24–6.53)

[a]Prevalence in 1992 was unweighted; all other surveys were weighted to be nationally representative.

Table 2: **Age-specific HBsAg prevalence in China, 1992, 2006, 2014, and 2020.**

(1.01%) had evidence of hepatitis B cirrhosis, and 5 (0.17%) had evidence of HCC. Among HBsAg positive subjects over 15 years of age, the weighted proportions of HBsAg carrier, CHB, cirrhosis, and suspected HCC diagnoses were 78.03%, 19.63%, 0.84%, and 0.15%, respectively. Fifty-eight cases could not be diagnosed due to missing test results, with a weighted proportion of 1.34% (Table 5).

The health care cascade of HBV infected person in 2020

Among the 2977 HBsAg-positive subjects, 1801 were previously aware that they were HBsAg-positive by screening or testing, a weighted proportion of screening or testing of 59.78%. Among those previously tested cases, 681 had indications for antiviral treatment, with a weighted proportion of 38.25%, and 106 had started antiviral therapy, with a weighted proportion of 17.33% (Fig. 3).

Discussion

HBsAg prevalence is the most important indicator for assessing a country's burden of HBV infection. Case classification and status of the CHB health care cascade are instrumental for developing strategies for reducing the burden of medical consequences of CHB, especially cirrhosis and hepatocellular cancer. The 2020 mainland China sero-epidemiological survey found that the HBsAg prevalence in people 1–69 years of age was 5.86%, representing approximately 75 million people living with chronic hepatitis B infection. Expert medical examination of HBsAg-positive individuals 15 years and older found that 78.03% were HBsAg carriers with no evidence of liver damage, 19.63% had CHB with liver enzyme abnormalities, 0.84% had cirrhosis, and 0.15%

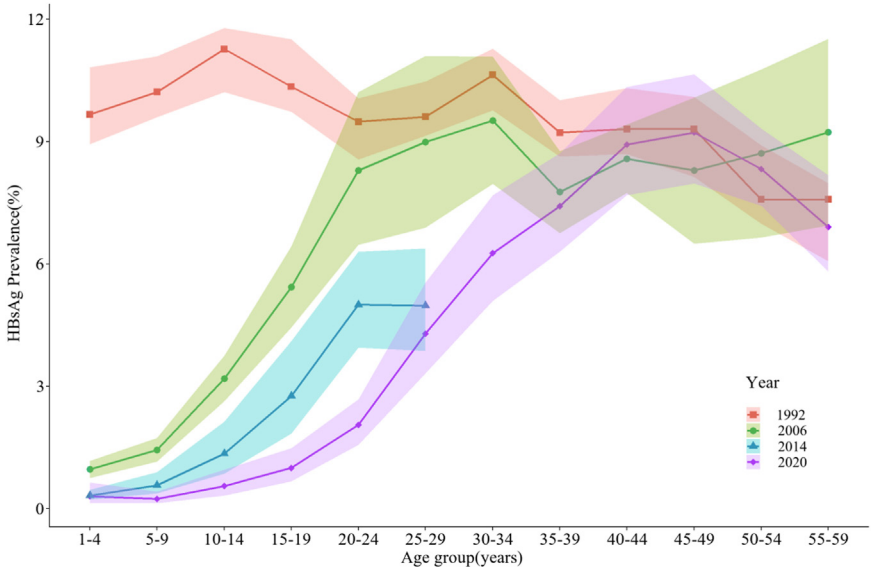

Fig. 2: Age specific HBsAg prevalence in China with confidence intervals, China, 1992–2020. Note: Prevalence in 1992 was un-weighted; prevalences in 2006, 2014, and 2020 were weighted to be nationally representative.

Year	Age	HBsAg			HBeAg and anti-HBe				
		Sample Size (N)	Positive Number [n, (%)]	Prevalence (%, 95% CI)	HBsAg Positive cases (N)	HBeAg		anti-Hbe	
						Positive Number [n, (%)]	Weighted proportion (%, 95% CI)	Positive Number [n, (%)]	Weighted proportion (%, 95% CI)
1992[a]					–	–	–	–	–
	15-	2464	221 (8.97)	8.97 (7.90–10.16)	–	–	–	–	–
	20-	7866	636 (8.09)	8.09 (7.50–8.71)	–	–	–	–	–
	30-	7394	604 (8.17)	8.17 (7.57–8.82)	–	–	–	–	–
	40–49	4530	359 (7.92)	7.92 (7.17–8.75)	–	–	–	–	–
	Sub-total	22,254	1820 (8.18)	8.18 (7.83–8.55)	–	–	–	–	–
2006					–	–	–	–	–
	15-	1398	81 (5.79)	4.75 (3.54–6.36)	81	46 (56.79)	55.97 (42.83–69.11)	33 (40.74)	42.8 (29.71–55.89)
	20-	4096	288 (7.03)	7.24 (3.96–12.87)	288	119 (41.32)	38.67 (32.96–44.37)	167 (57.99)	61.06 (55.27–66.84)
	30-	7661	505 (6.59)	6.76 (5.48–8.30)	505	102 (20.2)	14.98 (10.57–20.80)	394 (78.02)	84.1 (78.26–88.60)
	40–49	5963	408 (6.84)	6.44 (5.82–7.13)	408	72 (17.65)	17.12 (13.33–21.71)	331 (81.13)	81.41 (75.31–86.29)
	Sub-total	19,118	1282 (6.71)	6.61 (5.40–8.08)	1282	339 (26.44)	23.50 (20.65–26.61)	925 (72.15)	75.55 (72.07–78.72)
2014									
	15-	1337	23 (1.72)	2.70 (1.19–5.97)	23	11 (47.83)	47.83 (27.23–68.42)	11 (47.83)	47.83 (27.23–68.42)
	20-	3904	175 (4.48)	4.44 (3.47–5.65)	175	50 (28.57)	28.57 (21.82–35.32)	117 (66.86)	67.24 (60.21–74.28)
	30-	–	–	–	–	–	–	–	–
	40–49	–	–	–	–	–	–	–	–
	Sub-total	5241	198 (3.78)	3.78 (3.29–4.33)	198	61 (30.81)	30.81 (24.32–37.30)	128 (64.65)	64.97 (29.78–55.36)
2020									
	15-	3633	51 (1.4)	0.82 (0.46–1.45)	51	25 (49.02)	42.57 (29.78–55.36)	21 (41.18)	40.33 (15.88–64.77)
	20-	7497	231 (3.08)	2.83 (2.04–3.92)	231	70 (30.3)	33.43 (18.94–47.92)	153 (66.23)	59.52 (44.24–74.89)
	30-	7074	409 (5.78)	5.89 (4.75–7.30)	409	67 (16.38)	13.1 (9.79–17.31)	328 (80.2)	82.97 (78.19–86.88)
	40–49	7597	566 (7.45)	8.19 (7.05–9.48)	566	52 (9.19)	8.50 (5.82–12.26)	493 (87.1)	85.73 (80.49–89.74)
	Sub-total	25,801	1257 (4.87)	5.87 (5.13–6.70)	1257	214 (17.02)	12.73 (10.17–15.82)	995 (79.16)	81.99 (78.95–84.68)

[a]HBsAg prevalence in 1992 was unweighted.

Table 3: **HBsAg prevalences and proportions of HBeAg and anti-HBe among women of childbearing age in China, 2006–2020.**

Item	Followed-up (N = 2977)	Lost to follow-up (N = 1259)	P-Value
Age (mean ± *SD*)	47 ± 13	45 ± 13	<0.001
Sex, [n, (%)]			0.003
Male	1332 (44.74)	625 (49.64)	
Female	1645 (55.26)	634 (50.36)	
Region, [n, (%)]			<0.001
Eastern	1191 (40.01)	495 (39.32)	
Middle	778 (26.13)	267 (21.21)	
Western	1008 (33.86)	497 (39.48)	
Urban/Rual, [n, (%)]			0.009
Urban	1177 (39.54)	552 (43.84)	
Rural	1800 (60.46)	707 (56.16)	
Nationality, [n, (%)]			0.442
Han	2392 (80.35)	998 (79.27)	
Others	585 (19.65)	261 (20.73)	

Table 4: **Demographic characteristics of HBsAg + individuals over 15 years of age who were followed up or were lost to follow-up in the disease status investigation, China, 2020.**

Age (Year)	Sex	Number of observers (N)	Chronic HBsAg carrier		CHB		Cirrhosis		HCC		Unknown	
			Cases (n)	Weighted proportion (%, 95% CI)	Cases (n)	Weighted proportion (%, 95% CI)	Cases (n)	Weighted proportion (%, 95% CI)	Cases (n)	Weighted proportion (%, 95% CI)	Cases (n)	Weighted proportion (%, 95% CI)
15-												
	Male	151	106	76.44 (66.61–84.06)	42	22.67 (15.17–32.47)	1	0.62 (0.10–3.58)	0	/	2	0.27 (0.02–2.99)
	Female	179	153	76.71 (61.32–87.26)	24	22.93 (12.41–38.46)	0	/	0	/	2	0.35 (0.04–2.75)
	Subtotal	330	259	76.56 (69.67–82.27)	66	22.79 (17.07–29.72)	1	0.35 (0.06–1.98)	0	/	4	0.31 (0.05–1.70)
30-												
	Male	565	364	70.25 (64.18–76.32)	184	27.13 (21.70–32.56)	6	1.09 (0.38–3.07)	1	0.34 (0.06–1.94)	10	1.18 (0.32–4.35)
	Female	708	594	83.75 (78.59–87.86)	98	15.14 (11.07–20.35)	4	0.25 (0.06–1.07)	1	0.002 (0.00–0.54)	11	0.87 (0.40–1.86)
	Subtotal	1273	958	77.18 (72.95–80.91)	282	20.98 (17.41–25.05)	10	0.66 (0.27–1.62)	2	0.16 (0.03–0.94)	21	1.02 (0.36–2.86)
50–69												
	Male	616	463	76.23 (71.29–80.56)	123	19.90 (15.82–24.72)	14	1.97 (1.04–3.69)	2	0.13 (0.02–0.86)	14	1.77 (0.59–5.17)
	Female	758	631	82.17 (76.89–86.45)	102	15.44 (11.68–20.14)	5	0.28 (0.08–0.99)	1	0.18 (0.03–1.01)	19	1.92 (0.66–5.43)
	Subtotal	1374	1094	79.22 (75.05–83.85)	225	17.66 (14.46–21.39)	13	1.12 (0.63–1.99)	3	0.15 (0.04–0.57)	33	1.85 (0.65–5.20)
Total												
	Male	1332	933	73.30 (68.95–77.65)	349	23.65 (19.90–27.86)	21	1.44 (0.85–2.45)	3	0.22 (0.05–0.93)	26	1.38 (0.43–4.35)
	Female	1645	1378	82.70 (79.51–85.48)	224	15.67 (13.11–18.62)	9	0.25 (0.10–0.65)	2	0.08 (0.01–0.45)	32	1.30 (0.53–3.19)
	Subtotal	2977	2311	78.03 (74.90–810.88)	573	19.63 (17.10–22.42)	30	0.84 (0.51–1.38)	5	0.15 (0.05–0.43)	58	1.34 (0.48–3.70)

Table 5: Age-specific clinical status of people living with chronic HBV infection, China, 2020.

were suspected to have liver cancer. Of these HBsAg-positive individuals, 59.78% were aware that they were positive before the survey; 38.25% of those who knew they were positive had indications for antiviral treatment, and 17.33% of these individuals were being treated with antivirals.

Mother-to-child transmission (MTCT) during childbirth is the main source of chronic HBV infection in China.[14] WHO assesses status of HBV MTCT prevention by monitoring HBsAg seroprevalence among children under 5 years of age. The 2020 survey was the fourth national HBsAg serological survey conducted in mainland China in the hepatitis B vaccination era, allowing assessment of progress in prevention of MTCT - in 1992, 2006, 2014, and 2020. HBsAg prevalence among 1–4-year-olds declined 90% during 1992–2006 (from 9.67% to 0.96%), a further 67% during 2006–2014 (from 0.96% to 0.32%), and a further 6% during 2014–2020 (from 0.32% to 0.30%). The 0.30% HBsAg seroprevalence in 2020 demonstrates progress toward the WHO health sector strategy goal of 0.1% seroprevalence among children under 5 years of age.

The Global Burden of Disease (GBD) study estimated that in 2019, the year prior to our survey, HBsAg seroprevalence in China's population was 7.8%, with 86 million people living with chronic hepatitis B infection.[15] Our nationally representative survey estimated 11 million fewer chronic infections and two percentage points lower seroprevalence.

We found that HBsAg seroprevalence was 5.87% among reproductive-age women in China in 2020. China has universal HBsAg screening during pregnancy as a component of the program for prevention of mother-to-child transmission of HBV, HIV, and syphilis. Between 2015 and 2020, 91 million pregnant women were screened, and 5.4% were HBsAg positive, which is highly consistent with the results of our serological survey.[16] HBsAg seroprevalence among Chinese women 20–29 years of age, who have the highest fertility rate, has decreased to 2.83%, which is 36.3%, 60.9% and 65.0% lower than same-aged seroprevalence in 2014, 2006 and 1992. Women 15–19 years old will enter the highest fertility ages in the next five years, and their HBsAg prevalence had been reduced to less than 1%. This low seroprevalence will accelerate the decline in the prevalence of HBsAg in children under 5 years of age in China. That the decline in seroprevalence among children under 5 years was disproportionate to the decline among women of childbearing age is likely due to the challenge of measuring such a low seroprevalence. Larger sample sizes or other designs may be needed to accurately document very low seroprevalence. Our survey data support previous modeling findings that at current HepB coverage levels, China will achieve the WHO 2030 target of less than 0.1% HBsAg prevalence in children under five years by 2029.[7]

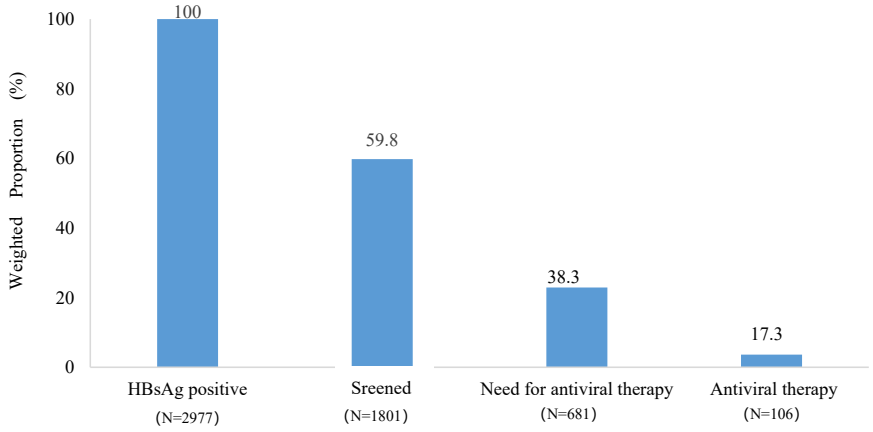

Fig. 3: The health care cascade among HBsAg positive subjects, China, 2020. Note: Survey-weighted results are further weighted by sex and age. The denominators for the percentages are the Ns of the immediately leftward bar.

HBsAg positive pregnant women who are positive for HBeAg usually have higher HBV DNA loads and significantly higher mother-to-child-transmission rates than e antigen-negative mothers, making them an important population for prevention of HBV transmission from mother to child. There is scientific consensus that antivirals administered to pregnant women with high viral loads of HBV DNA in the late pregnancy can further reduce MTCT.[9,17,18] The 2020 survey showed that 12.73% of HBsAg-positive women of reproductive age were co-positive for e-antigen, which was lower than the proportion (23.50%) in 2006. In addition, with recent-year birth rates declining[19] to around 10 million annual live births, we estimate there will be 600,000 HBsAg positive mothers giving birth each year - nearly 430,000 fewer than in 2015 (1.04 million).[20] The decrease in the number of HBsAg and HBeAg double positive pregnant women will improve the feasibility of antiviral treatment strategy for pregnant women with high HBV DNA viral load in China.

Success preventing perinatal HBV infection by universal screening, vaccination, and HBIG administration for babies born to HBsAG-positive women prevents the vast majority of new chronic infections. However, the disease burden caused by previous HBV infections remains high in the general population, with our survey-estimated 75 million chronic HBV infections in 2020. Most CHB infections are among people over 35 years of age, who were born before availability of hepatitis B vaccine. The four national surveys consistently show that prevalence of HBsAg in people over 50 years old has declined, reflecting excess or premature deaths due to HBV cirrhosis and HCC, consistent with aging of the HBsAg-positive population and the natural history of HBV infection.

Timely diagnosis and treatment of HBV are key measures to reduce HBV-related death. WHO recommends that country HBV diagnosis rate and antiviral treatment rate should reach 90% and 80% by 2030. Our 2020 survey data showed that about 60% of HBV infected people ≥15 years old were aware of their HBV infection status. Based on criteria in China's Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019 edition), among HBsAG-positive individuals who were aware of their HBV infection status, 38% needed antiviral treatment, but only 17% received antivirals. We estimate that among the 75 million people living with chronic HBV infection, approximately 30 million were unaware of their infection status and therefore could not carry out standardized diagnosis and treatment. Of those aware of their HBV infection, 17 million need antiviral treatment but only 3 million were receiving antivirals.

Our estimate of the HBV testing rate was higher than previous studies have estimated (20%–36%).[21] Routine HBV testing is conducted for three groups of people in China: pregnant women, blood donors, and surgery in-patients. Free HBV screening for pregnant women and blood donors and the increase in the number of surgeries conducted in hospitals have greatly improved rates of HBV detection and diagnosis.[22] A caveat to the higher rate of screening that we found is that the four national hepatitis B serosurveys were conducted in the same counties, and repetitive surveys may have increased local residents' attention to hepatitis B and encouraged self-screening. In 2022, China issued new guidelines for the diagnosis and treatment of chronic hepatitis B, recommending expansion of HBV antiviral treatment. Therefore, the number of HBV infected people with indications for antiviral treatment in China will be higher than our estimate. China requires further efforts to meet the rate of HBV diagnosis and treatment set by WHO health sector targets for 2030.

Our research has several strengths. First, all four surveys, including the 2020 survey, were nationally representative of China's mainland. The 2006 and 2020 surveys were similar in survey sites, target populations, laboratory testing, sampling methods, and statistical analysis methods. Second, the 2020 survey was the first to investigate the clinical status and health-care cascade of HBsAg positive patients in a community sampling in China. Community sampling is more representative than the earlier studies that sampled from hospitals. Third, professional doctors of Beijing Friendship Hospital, which is a class A tertiary comprehensive hospital, went to 31 provinces to conduct on-site clinical examinations and diagnoses of HBsAg-positive subjects in the 2020 survey, ensuring consistency and accuracy of B-ultrasound testing, FibroScan testing, and use of standardized diagnostic practices for HBV infected individuals.

Our study has several limitations. First, from 1992 to 2020, due to the long time interval, the four national hepatitis B sero-surveys may have had some differences in testing, with changes in methods and increasing sensitivity of reagents, which may affect the comparability of results. However, except for the 1992 survey, laboratory testing for each survey was conducted by the same national laboratory using the same methods for specimen detection, which ensures consistency and comparability of laboratory test results. Second, due to the COVID-19 epidemic, the 2020 survey required more than one year to complete, which could cause a difference between the sampled age group and the actual surveyed age group. This difference may affect the estimate of HBsAg prevalence in children aged 1–4 years. Third, in the 2020 survey, 29.7% of subjects that were HBsAg-positive and eligible for liver staging were unable to be followed up, potentially biasing our results. Fourth, our survey was conducted during 2020–2021, and we used treatment guidelines in effect during the survey because clinicians interpreted antiviral medications and their indications for HBsAg-positive subjects. Subsequently, the *Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2022 version)* lowered the ALT threshold indication for antiviral therapy. Lowering the threshold will make our result that 38% (17 million) of HBV-infected individuals have an indication for antiviral therapy an underestimation.

In conclusion, our nationally representative sero-epidemiological surveys confirmed that China continues on-target achievement in the control of new HBV infections, with the HBsAg prevalence in the general population declining to 5.86%, and 1-4-years children declining to 0.30% in 2020. There were approximately 75 million people infected with HBV in China in 2020; 30 million were unaware of their HBV infection status and therefore not able to be clinically diagnosed and started on treatment if indicated. Among individuals known to have HBV infection, 17 million needed antiviral treatment, but only 3 million were receiving antivirals.

Contributors

ZH, WFZ, YZD and WY had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. ZH, WY, WFZ, SLP, ZGM, LJH, WF, MN, WHQ, LZF, YWZ, AZJ, LQ, FZJ, YZD and WY were involved in the design of the survey. ZH, WY, WFZ, SLP, ZGM, LJH, WF, MN, LJ, DGW, MTT,TL, ZS, LY, SQD, WM, LL, HQ, LY, YSD, JJD were involved in the implementation of the survey procedures. ZH,WFZ, LJH,TL, LMS, WXQ, LQQ, ZQ, WD, YTT and LYX did the data cleaning and statistical analysis. ZH,WFZ, TL, LER, YZD and WY wrote the first draft of the manuscript. All authors had final responsibility for the decision to submit for publication.

Data sharing statement

The data will be available following publication with a clear data sharing agreement. For data access, please contact the corresponding author.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101193.

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