

Epidemiology of Hepatitis B and Hepatitis C Infections and Benefits of Programs for Hepatitis Prevention in Northeastern China: A Cross-Sectional Study

Qian Zhang,^a Wenqian Qi,^a Xu Wang,^a Yonggui Zhang, Yan Xu, Shaoyou Qin, Ping Zhao, Honghua Guo, Jian Jiao, Changyu Zhou, Shangwei Ji, and Jiangbin Wang

Department of Gastroenterology, China-Japan Union Hospital of Jilin University, Changchun, Jilin Province, China

Background. To investigate the epidemiology of hepatitis B and C infections and the benefits of programs aimed at hepatitis prevention and control in Northeastern China.

Methods. Individuals receiving health examinations were recruited to complete a questionnaire and undergo laboratory tests for hepatitis infection. Data on demographic characteristics, results of hepatitis B virus (HBV) and hepatitis C virus (HCV) serological tests, for HBV and HCV infection were analyzed.

Results. Among 227 808 study participants, the hepatitis B surface antigen (HBsAg) and anti-HCV-positive rates were 6.1% and 3.0%, respectively. Among HBsAg-positive participants, 63.8% tested positive for HBV DNA, 20.2% had an abnormal alanine aminotransferase (ALT) level, and 10.7% had cirrhosis. Among anti-HCV-positive participants, 57.2% tested positive for HCV RNA, 29.6% had an abnormal ALT level, and 8.4% had cirrhosis. Among HBsAg- or anti-HCV-positive participants, 47.1% and 32.0%, respectively, were aware of their infection. Among participants infected with HBV or HCV and suitable for antiviral treatment, 23.5% and 16.1%, respectively, had received antiviral treatment. The HBV plus HCV coinfection rate was 0.08%.

Conclusions. The HBsAg-positive rate decreased significantly after implementation of recently introduced HBV control programs in China. However, the anti-HCV-positive rate showed only a slight decrease, indicating that programs for the prevention and control of hepatitis viruses require continued strengthening.

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Keywords. hepatitis B virus; hepatitis C virus; epidemiology; cross-sectional study.

Viral hepatitis is one of the most serious infectious diseases worldwide. Recent studies have shown that the hepatitis B virus (HBV) and hepatitis C virus (HCV) infection rates have decreased in many countries throughout the world [1–3]. Additionally, the hepatitis infection rate among individuals aged <18 years was found to be significantly lower compared with the rate in adults [4, 5].

In China, the “blood donation law,” which was issued in 1998, introduced a system of voluntary blood donation and strengthened the management of blood products. Furthermore, since 2002, the Chinese government has gradually implemented a nationwide policy of free hepatitis B vaccination for newborns and children. The results of 2 nationwide viral hepatitis serological surveys conducted in 1992 and 2006 showed hepatitis B surface antigen (HBsAg)-positive rates of 9.8% and 7.2%, respectively [6].

The prevalence of chronic HCV infection is currently controversial in China. The survey data from 1992 and 2006 showed that the prevalence rate had decreased from 3.2% in 1992 to 0.4% in 2006 [6–9]. However, recent reports from the Chinese Ministry of Health showed that the incidence of chronic HCV infection had increased from 70 681 cases in 2006 to 201 622 cases in 2012. In addition, it should be emphasized that the HCV infection rate of 0.4% in 2006 was reported based on testing that was conducted in 2011 using frozen serum samples collected in 2006. Furthermore, the 2006 sample included only 80 000 people, and thus, the objectivity of the data needs to be further confirmed. In response to these problems and to further observe the effects of the government’s implementation of nationwide free vaccination for HBV, the voluntary blood donation, and incorporation of antiviral drugs into all levels of health insurance, with the support of the Ministry of Health, we focused on the epidemiologic characteristics of HBV and HCV infections in 50 cities/counties and 4 major ethnic groups in northern China. Jilin, which is located in northeastern China, was one of the first regions to provide free hepatitis B vaccinations and to implement blood management policies. Thus, a large epidemiological sample study of HBV and HCV infections in Jilin should objectively reflect the trends of these

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^aQ. Z., W. Q., and X. W. contributed equally to this work.

Correspondence: J. Wang, Department of Gastroenterology, China-Japan Union Hospital of Jilin University, No.126 XianTai Street, Changchun, Jilin Province 130033, China (zrlwangjb@medmail.com.cn).

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diseases after implementation of the control measures. Additionally, it should also provide data indicating the benefits of establishing an HBV vaccination program and the social effects of implementing HBV/HCV infection prevention measures [10].

MATERIALS AND METHODS

Participants

From 2010 to 2013, 227 808 volunteers from 50 cities/counties, representing 4 major ethnic groups, in the Jilin region (population approximately 26.99 million) of China were recruited to participate in this study. The participants included adults receiving health examinations, participants organized as units, and children in kindergarten or undergoing school entrance examinations. Individuals aged <1 year or with incomplete medical examination items, questionnaire information, or a duplicated examination were excluded from the study.

The ethics committee of China-Japan Union Hospital, Jilin University, approved the study protocol. A signed informed consent document was obtained from each participant or their legal guardians prior to enrollment.

Data Collection

All participants received a questionnaire designed to collect information on demographic characteristics and history with the hepatitis B vaccine, blood transfusion, surgery, acupuncture, teeth cleaning, traumatic cosmetic procedures, and HBV and HCV infection among family members. The participants underwent an HBV/HCV serological marker test, a blood biochemistry test, and an abdominal color Doppler ultrasound exam. All participants with an HBsAg- and/or anti-HCV-positive specimen underwent further quantitative testing for levels of HBV DNA and HCV RNA. General characteristics including infection rates, quantitative blood virus levels, alanine aminotransferase (ALT) levels, risk factors for HBV or HCV infection, awareness of infection, and use of antiviral treatment were analyzed for HBV- or HCV-positive participants.

Awareness of HBV or HCV infection was defined as the participant already being aware of their chronic HBV or HCV infection status prior to enrollment in the study. Excessive drinking was assessed according to the 1982 World Health Organization alcohol use disorders identification test and defined by a score of >8 [11].

Indications for antiviral treatment in the study were defined according to the Chinese guidelines [12, 13].

Antiviral treatment for HBV or HCV infection was defined as the receipt of treatment of any type of nucleoside analogues (lamivudine, adefovir, telbivudine, entecavir) or interferon (IFN; ordinary IFN or pegylated IFN) by HBV-infected participants or receipt of treatment with IFN (ordinary IFN or pegylated IFN) together with ribavirin among HCV-infected individuals. Individuals were considered to have received antiviral treatment independent of the indication criteria used for

the treatment, the occurrence of virological response after treatment, achievement of a sustained virological response, discontinuation, or the period of treatment. In this study, cirrhosis was diagnosed based on criteria used by the China Hepatitis Prevention and Control Program [14]. The Infectious and Parasitic Diseases Branch and the Liver Disease Branch of the Chinese Medical Association jointly revised these criteria. The diagnostic criteria included disease signs and symptoms and the results of liver function tests and imaging examinations.

Laboratory Examination

HBV and HCV serological markers were detected by enzyme-linked immunosorbent assays (Abbott microparticle enzyme immunoassay method; Abbott Diagnostics Divisions, Santa Clara, California) [15]. Tests for liver function, kidney function, and blood and urine biochemistry were performed using an automatic biochemical analyzer (Beckman-Coulter Corporation, Brea, California). Based on information provided by the test manufacturer, 40 IU/L was accepted as the upper limit for a normal ALT test result. Quantitative levels of HBV DNA and HCV RNA were obtained using real-time fluorescence quantitative polymerase chain reaction (Roche Ltd., Basel, Switzerland), with the lowest detection limit being 300 copies/mL [16].

Statistical Analyses

The survey data were audited and then entered into a database using logic-control and double-entry methods to ensure the quality of data entry. The data were analyzed using SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, New York). Measurement data are presented as the mean \pm standard error and were compared using the *t* test. The χ^2 test was used for comparisons of qualitative data. *P* values <.05 were considered statistically significant.

RESULTS

General Epidemiological Characteristics of HBV and HCV Infections

A total of 236 920 participants were enrolled in the study; 4430 participants with incomplete medical examination items and 4682 participants with incomplete questionnaire information were excluded from the final analysis. The response rate for the questionnaire was 98.13%. Among the 227 808 participants who completed the study, the incidences of HBsAg- and anti-HCV-positive results were 6136 (6.1%) and 2979 (3.0%) per 100 000 persons, respectively. Among HBsAg-positive participants, 61.0% were male, which was significantly higher than the proportion of males (51.6%) among anti-HCV-positive participants (*P* < .001). The HBsAg-positive rate was highest among participants aged 45–55 years, whereas those aged >55 years showed the highest rate of anti-HCV-positive results (Table 1).

The HBsAg- and anti-HCV-positive proportions among participants with a higher educational level were lower than those among participants with a lower educational level (*P* < .001). Additionally, the HBsAg- and anti-HCV-positive proportions among participants living in rural areas were significantly higher

Table 1. General Characteristics of Study Participants

Characteristic	Total Population	HBsAg (+)			Anti-HCV (+)			HBsAg (+) and Anti-HCV (+)		
		n (%)	Prevalence Rate ^a	P Value ^b	n (%)	Prevalence Rate ^a	P Value ^b	n (%)	Prevalence Rate ^a	P Value ^b
Total number	227 808	13 979	6136		6786	2979		184	81	
Gender				<.001			<.001			.017
Male	114 088	8529 (61.0)	7475		3503 (51.6)	3070		111 (60.3)	98	
Female	113 720	5450 (39.1)	4626		3283 (48.4)	2779		72 (39.1)	61	
Ethnic group				<.001			<.001			<.001
Han	222 030	13 618 (97.4)	6134		6579 (97.0)	2963		148 (80.4)	79	
Man	2639	218 (1.6)	7367		77 (1.1)	2933		7 (3.8)	273	
Korean	1670	57 (0.4)	3448		101 (1.5)	6034		29 (15.8)	0	
Mongol	1469	86 (0.6)	5882		29 (0.4)	1961		0 (0.0)	0	
Age (y)				<.001			<.001			<.001
<15	12 348	240 (1.7)	3483		32 (0.5)	710		3 (1.6)	15	
15–25	15 577	731 (5.2)	4691		122 (1.8)	786		7 (3.8)	54	
25–35	24 678	1667 (11.9)	6754		378 (5.6)	1532		16 (8.7)	76	
35–45	43 880	2930 (21.0)	6678		806 (11.9)	1838		25 (13.6)	66	
45–55	52 589	3821 (27.3)	7263		1508 (22.2)	2875		29 (15.8)	60	
55–65	41 609	2941 (21.0)	7069		1739 (25.6)	4179		49 (26.6)	121	
>65	37 127	1649 (11.8)	4441		1933 (28.5)	5207		54 (29.3)	145	
Education level (age >15 y)				<.001			<.001			<.001
College and above	22 896	457 (3.3)	1997		169 (2.5)	739		7 (3.8)	31	
High school	38 419	3542 (25.3)	9220		1462 (21.5)	3804		36 (19.6)	94	
Primary school and middle school	150 275	8871 (63.5)	5903		4129 (60.9)	2748		94 (51.1)	62	
No school education	16 218	1109 (7.9)	6837		1026 (15.1)	6326		47 (25.5)	289	
Region				<.001			<.001			.018
Urban	154 199	5913 (42.3)	3836		2855 (42.1)	1851		69 (37.5)	44	
Suburb	73 609	8064 (57.7)	10 955		24 289 (54.0)	4979		115 (62.5)	157	
Excessive drinking				<.001			<.001			.289
Yes	46 882	3218 (23.0)	6864		1573 (23.2)	3356		47 (25.5)	100	
No	180 926	10 761 (77.0)	5948		5213 (76.8)	2386		137 (74.5)	63	
Smoking				.206			.241			.054
Yes	46 242	2920 (20.9)	6314		1433 (21.1)	3098		70 (21.7)	151	
No	181 566	11 059 (79.1)	6091		5353 (78.9)	2948		144 (78.3)	79	

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

^a Number of positive results per 100 000 persons.^b Compared with total population.

than those among participants living in a city. The positive proportion among participants who reported excessive alcohol consumption was higher than that among those who did not report excessive alcohol consumption ($P < .05$).

The anti-HCV–positive rate in the Korean population (6.0%) was significantly higher than that in the other ethnic groups (Han, 3.0%; Manchu, 2.9%; Mongolian, 2.0%; $P < .001$); however, there was no significant difference between the HBsAg–positive rate in the Korean population and the HBsAg–positive rates in other ethnic groups ($P > .05$; Table 1).

The incidence of being both HBsAg–positive and anti-HCV–positive was 81 per 100 000 persons (0.1%), representing 2.6% and 1.3% of HBsAg–positive and anti-HCV–positive participants, respectively.

Prevalence of HBV and HCV Infections Among Different Age Groups

Among children born after the implementation of planned immunizations and strengthening of the blood management system by the Chinese government, those aged 1–5 years had the lowest HBsAg–positive rate (0.6%) among all age groups ($P < .001$). Furthermore, children aged 5–10 years also had a significantly lower HBsAg–positive rate (1.3%) compared with that of adults. The HBsAg–positive rate among participants aged 20–55 years was similar (nearly 7.4%; 7387 per 100 000 persons). However, children aged 1–5 years showed the highest hepatitis B surface antibody (anti-HBs)–positive rate (79.2%; 79 231 per 100 000 persons; $P < .001$), and participants aged >60 years showed the lowest anti-HBs–positive rate (39.0%; 38 973 per 100 000 persons). The vaccine coverage rate in

children aged 1–5 years was 78 395 per 100 000 individuals (78.4%). Participants aged >60 years had the lowest anti-HBs-positive rate (2650 per 100 000 individuals, 2.7%; Figure 1).

Children aged <5 years were least likely to be anti-HCV positive (197 per 100 000 persons, 0.2%; $P < .05$), whereas participants aged >60 years were mostly likely to be anti-HCV positive (5207 per 100 000 persons, 5.2%; $P < .05$; Figure 2).

Serum HBV DNA- and HCV RNA-Positive Proportions Among HBV/HCV-Positive Participants

Among the 13 979 HBsAg-positive participants, 63.8% tested positive for HBV DNA, and the mean HBV DNA level was 6.9 ± 1.3 log₁₀ copies/mL. Furthermore, among the 6786 anti-HCV-positive participants, 57.2% tested positive for HCV RNA, and the mean HCV RNA level was 5.2 ± 1.0 log₁₀ copies/mL.

Prevalence of Abnormal ALT Levels Among HBV- or HCV-Positive Participants and Relationship With Gender and Age

The percentage of participants with an abnormal ALT level among HBsAg-positive participants was significantly lower than that among anti-HCV-positive participants (20.1% vs 29.6%, $P < .05$). After excluding the participants who were

receiving antiretroviral treatment, the proportions of patients with an abnormal ALT among HBsAg- or anti-HCV-positive participants were 20.5% and 29.6%, respectively. The proportions of patients with an abnormal ALT among HBV DNA- or HCV RNA-positive participants were 30.2% and 50.1%, respectively. The peak ages of abnormal ALT levels among HBsAg-positive participants were 35–55 years for males and approximately 55 years for females. The peak ages for abnormal ALT levels among anti-HCV-positive participants were 35–45 years for males and approximately 45 years for females (Supplementary Figure 1).

Prevalence of Cirrhosis Among HBV- or HCV-Positive Participants and Relationship With Gender and Age

The prevalence of cirrhosis in HBV- and HCV-positive participants was 10.7% and 8.4%, respectively, and the difference was not statistically significant ($P > .05$). The peak age for cirrhosis among both male and female HBsAg-positive participants was approximately 55 years, and the proportion of patients with cirrhosis showed an obvious decline after 65 years of age. Among anti-HCV-positive participants, the peak age group for cirrhosis was >55 years, and among those aged 15–55 years, males had

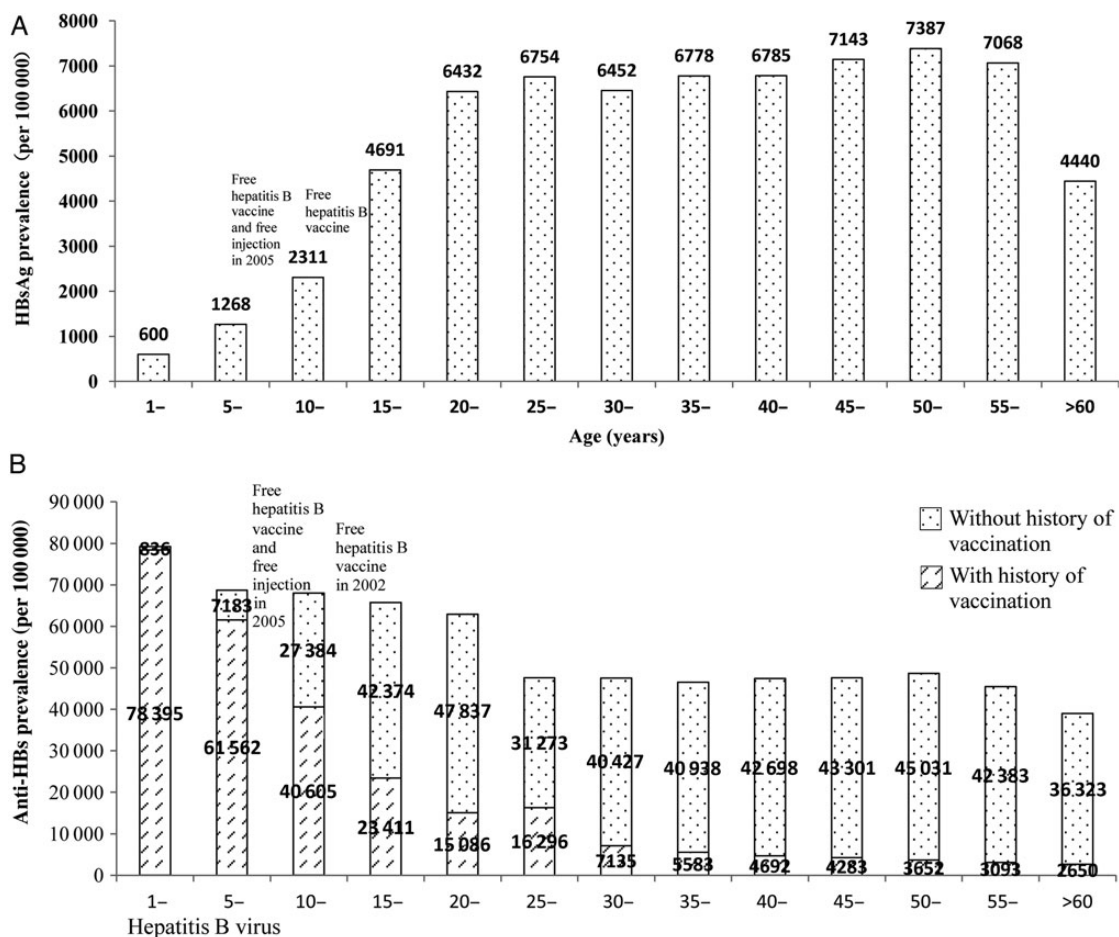


Figure 1. Age distribution of (A) hepatitis B surface antigen (HBsAg)-positive and (B) anti-HBs-positive participants.

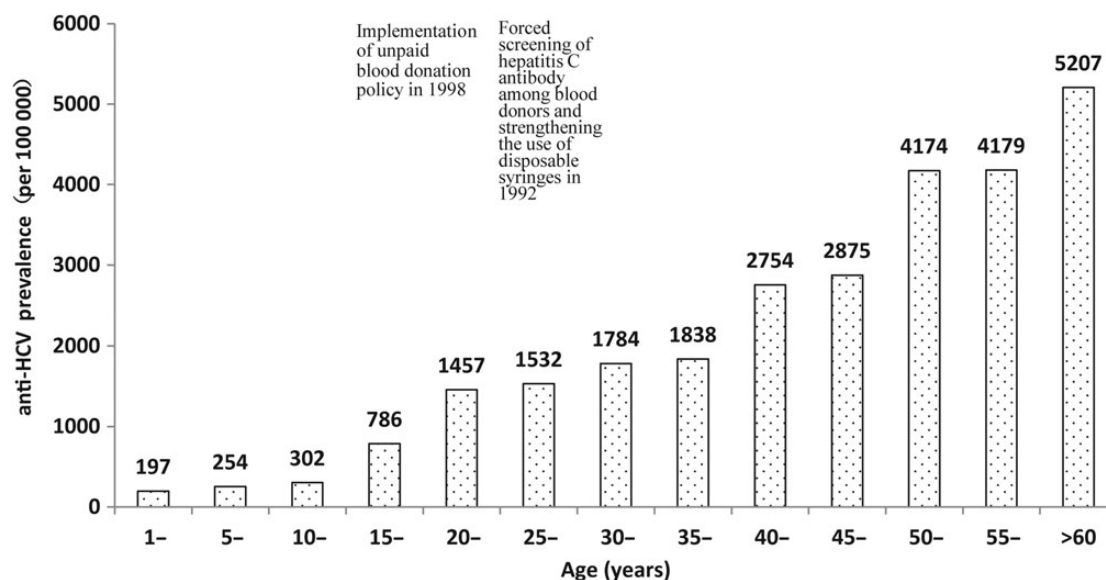


Figure 2. Age distribution of anti-hepatitis C virus (HCV)-positive participants.

a higher incidence of cirrhosis than females. There was no obvious decrease in the proportion of patients with cirrhosis among participants aged >65 years (Supplementary Figure 2).

Self-Awareness of Chronic HBV and HCV Infection and Proportion of Individuals Receiving Antiretroviral Treatment

Among all HBsAg-positive or anti-HCV-positive participants, 47.1% and 32.0%, respectively, reported being aware of their infection, and newly diagnosed HBV or HCV infections accounted for 52.9% and 68.0% of the respective cases. Among participants with either a chronic HBV or HCV infection or who were eligible for treatment with an antiretroviral therapy (3654 and 2354 participants, respectively), the proportions of patients who received antiviral treatment were 23.4% and 16.1%, respectively.

Overlapping HBV and HCV Infections

The rate of overlapping HBsAg- and anti-HCV-positive results was 0.1% (81 per 100 000 persons), and these individuals accounted for 1.3% and 2.7% of participants who were HBsAg-positive alone and anti-HCV-positive alone, respectively. The participants with both HBsAg- and anti-HCV-positive results not only had a significantly lower serum HBV DNA level compared with participants who were only HBsAg positive but also had a significantly lower HCV RNA level compared with participants who were only anti-HCV positive. However, the HBV DNA- or HCV RNA-positive rates were similar to those among participants who were only HBsAg positive or anti-HCV positive (Supplementary Figure 3). Among participants with overlapping HBsAg- and anti-HCV-positive results, the proportion with abnormal ALT levels was significantly higher than that among participants who were only HBsAg positive

or anti-HCV positive (46.2% vs 20.1%, or 29.6%; all P values <.05; Figure 3A). Furthermore, the incidence rate with cirrhosis was significantly higher among participants with overlapping HBsAg- and anti-HCV-positive results than that among participants who were either HBsAg positive or anti-HCV positive (18.5% vs 10.7%, or 8.4%; all P values <.05; Figure 3B).

DISCUSSION

Chronic HBV and HCV infections are a major health problem throughout the world [17–20], and China has a high incidence of both HBV and HCV infections. In recent years, the Chinese government increased investment in the prevention and control of viral hepatitis. However, studies with large sample sizes are needed to further demonstrate whether the current situation regarding epidemic chronic HBV and HCV infections has been improved by the government's efforts. In this study, 6.1% of tested individuals were HBsAg positive, which was less than the 7.2% positive rate reported from an epidemiological survey conducted in 2006. In addition, the anti-HCV-positive rate of 3.0% was higher than the 0.4% rate reported in the 2006 survey.

Among children aged <15 years, the large decrease in the HBsAg-positive rate, in conjunction with the increase in the anti-HBs-positive rate, suggests that the HBV vaccination policy implemented in China has played an important role in preventing and controlling HBV infections in children. However, the anti-HBs-positive rate among children aged 1–5 years was only 79%, whereas a US study showed rates as high as 87% [21]. A wide range of factors could cause this discrepancy. First, in some remote areas, the vaccine coverage for children has not yet reached 100%, and people need to gain a greater awareness

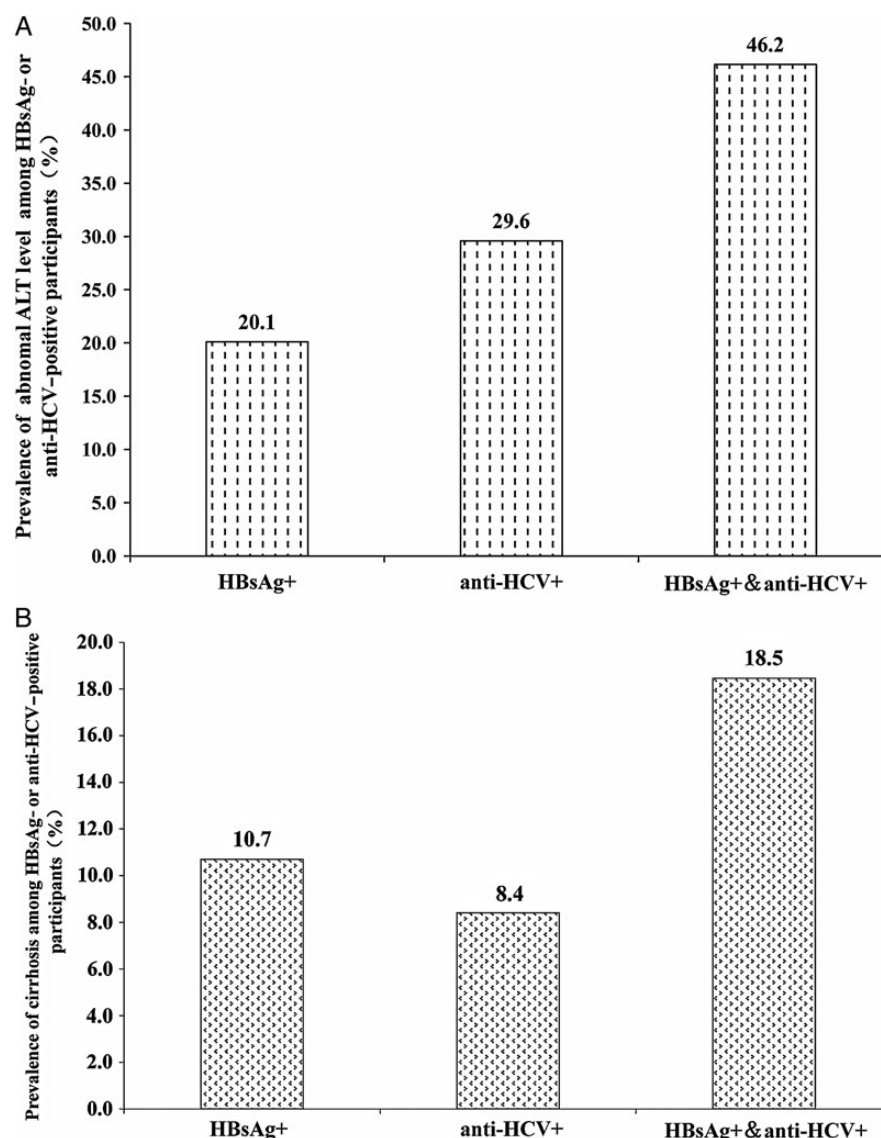


Figure 3. Incidence of (A) abnormal alanine aminotransferase levels and (B) cirrhosis among participants with hepatitis B virus and hepatitis C virus (HCV) coinfection. Abbreviations: ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen.

of the need to be vaccinated against hepatitis B. Second, the cold chain transport and storage conditions used for vaccines need to be enhanced, and the quality of the vaccination needs to be further improved. Finally, different individuals can show different degrees of immune response to a vaccination. Furthermore, greater supervision of the program and the availability of supplementary vaccinations sponsored by the Chinese government are required to increase its effectiveness.

In 1998, the blood donation law was issued in China, and a volunteer blood donation system was completely implemented, which further improved the quality of donated blood. However, the report on HCV infection issued by the Ministry of Health showed that in the years from 2006 to 2012, the numbers of new cases of HCV infection were 70 681, 92 378, 108 446, 131 849,

153 039, 173 872, and 201 622, respectively, which showed an obvious increase in prevalence. The results of our study show that the anti-HCV-positive rate was 3.0%, which was higher than that in 2006 by 0.4%. However, it should be stressed that the data for the HCV infection rate reported in 2011 were based on testing of cryopreserved serum samples from the national HBV hepatitis epidemiological survey conducted in 2006, and the objectivity of testing specimens after 5 years remains to be confirmed. Our study showed the HCV infection rate among children aged <15 years was significantly lower than that among adults, which coincides with the implementation time of the Chinese blood source management policy.

In our study, the HBV DNA-positive rate among HBsAg-positive participants was 63.8%, and the HCV RNA-positive

rate among anti-HCV-positive participants was 57.2%. These rates were slightly lower than the corresponding rates of 53%–78% [22–24] and 51%–93% [25] reported in previous studies. In our study, only 63% of HBsAg-positive patients had detectable HBV DNA, and this might be due to the following reasons. First, due to the limited availability of certain assay reagents, the HBV DNA detection limit in our study was 300 copies/mL, which is less sensitive than the detection limit currently used in China following the development of new reagents. If some patients in our study had low levels of replication and HBV DNA levels lower than 300 copies/mL, they would have tested negative for HBV DNA. Second, our study included some patients who were receiving antiretroviral therapy and had achieved a HBV DNA response. Third, our study also included patients who demonstrated natural clearance of HBV DNA but no natural clearance of HBsAg. Our results showed that 47.1% and 32.0% of HBsAg- and anti-HCV-positive participants, respectively, were aware of their infection. Furthermore, only 23.4% of HBsAg-positive and 16.1% of anti-HCV-positive participants had received appropriate antiviral therapy. These findings demonstrate that measures need to be taken in China to increase the awareness of chronic HBV and HCV infections. Furthermore, a government program should be implemented to enable the timely screening of individuals for HBV and HCV infections.

Our study also had some limitations. Due to the limited availability of certain assay reagents at the initial phase of the study, the detection limits for HBV DNA and HCV RNA were 300 copies/mL, which could mean that patients with a low viral replication level went undetected. In addition, further studies are needed to investigate the long-term condition of patients with chronic HBV and/or HCV infection and the relationship with antiviral treatment.

In conclusion, our study included a sample size of 227 808 individuals from 50 cities/counties in the Jilin Province of northeastern China and likely reflects the true status of HBV and HCV infections among the 26.99 million people in China. When compared with data from a national survey conducted in 2006, our results showed that the HBV infection rate had obviously declined (most noticeably among children) as a result of a strengthened hepatitis B vaccination program and blood management policies implemented by the Chinese government. However, there was no obvious decline in HCV infections. Increased awareness of HBV and HCV infections and better knowledge of available antiviral treatments are needed to further reduce hepatitis infection rates in China.

Supplementary Data

Supplementary materials are available at <http://cid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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