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Title: The prevalence and influencing factors of hepatitis B among rural resident population in Zhejiang province

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ABSTRACT

Objectives In order to reveal the prevalence among rural resident population and associated influencing factors of hepatitis B, so as to help developing specific control strategies.

Methods We conducted a cross-sectional study among rural resident population in Zhejiang, China. 16601 participants were sampled from five districts. Univariate and multivariate analysis was applied to evaluate the influencing factors. Odds ratios of each related factor were assessed with or without adjustment separately.

Results The age of participants was 40.28±19.47, and there were 7881 males and 8720 females. The positive rate of hepatitis B surface antigen (HBsAg) was 4.04% (95% CI: 3.74%-4.35%) and it was 3.85% by age and gender standardized. Univariate analysis showed that age, education level, occupation, live status, taken examinations, history of blood transfusion, vaccination, family history, hepatitis B surface antibody (HBsAb), being coastal and district were the potential influencing factors. Multivariate logistic model indicated that occupation, living status, history of examination, vaccination, HBsAb and district were the influencing factors. Undertaking a service based tertiary industry job (OR_a=1.33, 95% CI: 1.04-1.69), non-single live (OR_a=2.66, 95% CI: 2.04-3.46) were the risk factors, while having taken examinations (OR_a=0.68, 95% CI: 0.47-0.99), vaccinated (OR_a=0.52, 95% CI: 0.41-0.65) and HBsAb positive (OR_a=0.11, 95% CI: 0.08-0.15) were the protective factors.

Conclusions Hepatitis B is an intermediate epidemic level in rural resident, with a rate of 3.85%. Enlarging the population of screening, raising the coverage of vaccination especially in adults are suitable strategies to prevention and control of hepatitis B among rural resident population.

Keywords: Hepatitis B; Influencing factors; Cross-sectional study

ARTICLE SUMMARY

Strengths and limitations of this study

- This study focused on the prevalence of hepatitis B among rural resident population.
- The study involved large rural resident population and the logistic regression model provided a quantified result of influencing factors of hepatitis B.
- The main limitation of the study was there could be recall bias, for its cross-sectional designed.

INTRODUCTION

Hepatitis B is a potentially life-threatening liver infection caused by hepatitis B virus (HBV), which attacks the liver and could cause both acute and chronic disease. Two billion people have evidence of past or present infection with HBV, and an estimated 240 million people are chronically infected with hepatitis B virus globally[1-2]. More than 686000 people die annually due to complications of hepatitis B, including cirrhosis and hepatocellular carcinoma (HCC)[3]. Previously study revealed that the incidence of HBV-related HCC in adults remains high, and high serum HBV DNA level increases the risks of cirrhosis and HCC[4-5].

Overall, almost half of global population live in areas of high hepatitis B endemicity[6]. Global prevalence of HBV infection is heterogeneous[2], the prevalence of hepatitis B is highest in sub-Saharan Africa and East Asia, where 5%~10% of the adult population is chronically infected[1]. A nearest large nationwide survey in China was conducted in 2006, and which showed that the weighted prevalence of hepatitis B surface antigen (HBsAg) positive was 7.2% among aged 1~59 years and the rate among children aged <5 years was only 1.0%[7]. According to the endemicity maps[2], hepatitis B in China was at a higher intermediate level. From then on, several

studies[8-14] had been conducted to investigate the prevalence of hepatitis B in different areas among general population in mainland China. The reported rate was 3.49% in Beijing (2007)[8], 4.38% in adults in Northeast China (2007)[9], 7.44% in Anhui province (2006)[10], 5.17% in Henan Province (2006~2009)[11], 7.2% in Northwest China (2010)[12] and 3.17% in Sichuan blood donors (2010~2011)[13] and 2.73% in Beijing (2013~2014)[14]. The values of rate were varied in different areas and time periods.

It is important issue to identify the prevalence of hepatitis B, and it is the basic procedure on the way of eradicating HBV infection. This study aimed to investigate the prevalence of hepatitis B and its potential influencing factors among rural resident population in Zhejiang province, China. By indicating the epidemic of hepatitis B and its associated risk factors clearly in rural areas, we could develop specific prevention and control strategies based on the influencing factors of HBV infection and characteristic endemic of hepatitis B.

METHODS

Study design

A stratified multistage cluster sampling survey was conducted in five districts in Zhejiang province, China from January 2014 to December 2015. Three organization levels of stratification sampling were involved: districts, rural town and villages. All participants were rural resident registered and those who had continuously living at local for at least six months were included.

During the two-year planed investigation, a standard questionnaire was designed for the cross-sectional survey and was used to collect basic information of the rural resident participants and the potential factors for HBV infection.

A house-to-house investigation was completed by trained staffs and local doctors at sampled areas. In order to increase the response rate, staffs were recommended to visit target house at appropriate time period like nightfall. One percent questionnaire will be randomly checked after the survey each time. Basic personal information was collected, including age, gender, ethnicity, education, occupation, marital status, medical insurance, history of hepatitis B examination, history of blood transfusion, history of surgery, history for being out 3 months, vaccination history of hepatitis B, family history of hepatitis B and whether living in coastal. And these data were carried out by staffs with face-to-face interviews.

Serum were collected from blood samples (5 ml for individuals aged ⩾6 years old and 2 ml for children aged ⩽5 years old) and stored at -20 °C by laboratory staffs from the local hospitals. Serum were timely shipped to our state key laboratory of the First Affiliated Hospital, College of Medicine, Zhejiang University. Serum samples were tested by chemiluminescence immunoassay (CLIA) with Abbott reagents centralized. We considered the positive rate of HBsAg among population as the level of hepatitis B prevalence.

Statistical analysis

All collected data was entered into an EpiData 3.1 software database twice. Then we checked the accuracy, consistency and logical of the data. SAS 9.4 (SAS Institute Inc., Cary, NC) software was used for data processing and analysis. Social demographic information was performed by descriptive statistics. Univariate logistic analysis was used to identify potential influencing factors associated with hepatitis B infection, we selected the factor with P <0.1 in univariate model and conducted a stepwise multivariate logistic model to seek the independent risk factors for hepatitis B. Odds ratio (OR), 95% confidence interval (95% CI) and adjusted OR for each factor were also

calculated. The statistical hypothesis test level was 0.05. GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA) was used to draw the figures.

RESULTS

Characteristics of participants

A total of 16601 participants were interviewed including 7881 (47.47%) males and 8720 (52.53%) females in five districts. The age of participants was 40.28±19.47 years old. The prevalence of hepatitis B among whole participants was 4.04% (95% CI: 3.74%-4.35%), and it was 3.85% standardized by age and gender with demographic population of Zhejiang province. It showed that Zhejiang was an intermediate epidemic area of hepatitis B.

The distribution of population and prevalence rate between different age groups were showed in Figure 1. We could see that age below 20 years were the groups which had lowest prevalence rate of hepatitis B, while groups aged 41~60 years had highest rate. There was a rapid increase of prevalence rate between aged 21~25 years and 26~30 years.

Among the five districts, Shaoxing had the most participants with a number of 5416 (32.65%), while Yuhuan had the smallest number with 1447 (8.72%) participants. The numbers of participants in rest Putuo, Tonglu and Tongxiang districts were 4370 (26.32%), 3523 (21.22%) and 1845 (11.11%), separately. The prevalence of hepatitis B was highest in Yuhuan (9.81%), and lowest in Tongxiang (2.49%) in our study (Figure 2).

We collected all the concerned data of participants, basic characteristics of the participants were listed in Table 1. Most of the participants' education level was primary school or lower (44.25%), college or higher level was only 1088 (6.55%) and in which group had the lowest prevalence

(2.21%). Only 13.48% of the participants had taken hepatitis B examination before. Few ones had a history of surgery (3.46%) or blood transfusion (0.57%). There were 6358 (38.30%) participants had a vaccination history of hepatitis B, and it was 75.5% in aged <20 years old, while it was only 29.8% in aged >20 years old. Of all participants, 5817 (35.04%) were living in coastal areas. HBsAb positive rate was 30.00%, and among which HBsAg positive rate was only 1.00%, the value was lower than that in HBsAb negative ones (5.34%).

Table 1 The characteristics of participants in the study and results of univariate analysis

Variables/Values	Sample size (n)	Percent (%)	HBsAg positive (n)	Prevalence (%)
Age**	16601	-	670	4.04
Gender				
Male	7881	47.47	324	4.11
Female	8720	52.53	346	3.97
Education level**				
Primary school or lower	7346	44.25	305	4.15
Junior school	5431	32.71	265	4.88
High or polytechnic school	2736	16.48	76	2.78
College or higher	1088	6.55	24	2.21
Occupation**				
Agriculture based primary industry	5862	35.31	256	4.37

Manufacturing based second industry	623	3.75	39	6.26
Service based tertiary industry	2423	14.60	132	5.45
Others (Students or retired)	7693	46.34	243	3.16
Living status**				
Single live	5299	31.92	81	1.53
Non-single live	11302	68.08	589	5.21
Medical insurance				
Self-pay	339	2.04	13	3.83
Have medical insurance	16262	97.96	657	4.04
History of hepatitis B examination*				
Yes	2238	13.48	71	3.17
No	14363	86.52	599	4.17
History of surgery**				
Yes	575	3.46	48	8.35
No	16026	96.54	622	3.88
History of blood transfusion				
Yes	94	0.57	4	4.26
No	16507	99.43	666	4.03
Vaccination history of hepatitis B**				
Yes	6358	38.30	122	1.92
No	10243	61.70	548	5.35
History for being out 3 months				

Yes	843	5.08	39	4.63
No	15758	94.92	631	4.00
Family history of hepatitis B**				
Yes	446	2.69	69	15.47
No	16155	97.31	601	3.72
Living in coastal**				
Yes	5817	35.04	296	5.09
No	10784	64.96	374	3.47
HBsAb**				
Negative	11621	70.00	620	5.34
Positive	4980	30.00	50	1.00
District**				
Putuo	4370	26.32	154	3.52
Shaoxing	5416	32.62	197	3.64
Tonglu	3523	21.22	131	3.72
Tongxiang	1845	11.11	46	2.49
Yuhuan	1447	8.72	142	9.81

*: P <0.05; **: P< 0.0001.

Univariate and multivariate analysis

Univariate analysis showed that age, educational level, occupation, living status, history of hepatitis B examination, vaccination history of hepatitis B, history of surgery, history for

being out 3 months, family history of hepatitis B, living in coastal, HBsAb and district could be the potential influencing factors associated with hepatitis B among general population (Table 1).

A stepwise multivariate analysis showed that occupation, living status, history of hepatitis B examination, vaccination history of hepatitis B, HBsAb and district were the independent influencing factors of hepatitis B among rural resident population in Zhejiang. An age and gender adjusted model revealed that undertaking a service based tertiary industry job (OR_a=1.33, 95% CI: 1.04-1.69), non-single live (OR_a= 2.66, 95% CI: 2.04-3.46) were the risk factors for hepatitis B prevalence, while taken an examination of hepatitis B (OR_a= 0.68, 95% CI: 0.47-0.99), hepatitis B vaccinated (OR_a= 0.52, 95% CI: 0.41-0.65) and HBsAb positive (OR_a= 0.11, 95% CI: 0.08-0.15) were the protective factors for hepatitis B (Table 2). Figure 3 illustrated the values of OR and OR_a in the two logistic models.

Table 2 Results of multivariate analysis for hepatitis B

Variables/Values	OR (95% CI)	*P* value	OR_a (95% CI)	*P* value
Occupation				
Agriculture based primary industry	ref.		ref.	
Manufacturing based second industry	1.17(0.80-1.71)	0.4259	1.14(0.78-1.68)	0.5034
Service based tertiary industry	1.35(1.07-1.71)	0.0124	1.33(1.04-1.69)	0.0236

Others	0.73(0.60-0.90)	0.0029	0.73(0.59-0.89)	0.0026
Living status				
Single live	ref.		ref.	
Non-single live	2.59(2.02-3.33)	<0.0001	2.66(2.04-3.46)	<0.0001
History of hepatitis B examination				
Yes	0.68(0.47-0.99)	0.0459	0.68(0.47-0.99)	0.0456
No	ref.		ref.	
Vaccination history of hepatitis B				
Yes	0.52(0.42-0.66)	<0.0001	0.52(0.41-0.65)	<0.0001
No	ref.		ref.	
HBsAb				
Positive	0.11(0.08-0.15)	<0.0001	0.11(0.08-0.15)	<0.0001
Negative	ref.		ref.	
District				
Putuo	ref.		ref.	
Shaoxing	0.81(0.65-1.02)	0.0714	0.81(0.65-1.02)	0.0690
Tonglu	0.67(0.51-0.88)	0.0045	0.67(0.51-0.88)	0.0047
Tongxiang	0.28(0.19-0.39)	<0.0001	0.28(0.20-0.40)	<0.0001
Yuhuan	4.15(3.19-5.39)	<0.0001	4.15 (3.19-5.40)	<0.0001

OR: odds ratio; OR_a: odds ratio adjusted by age and gender; ref.: reference.

DISCUSSION

Viral hepatitis is a leading cause of death and disability worldwide, deaths from acute infection, cirrhosis and liver cancer were the tenth leading cause worldwide in 1990, while it ranked seventh in 2013. And the number of deaths worldwide attributable to viral hepatitis increased by 63% from 1990 to 2013[15]. World Health Organization (WHO) adopted the first-ever global hepatitis strategy with a goal to eliminate viral hepatitis B and C as a public health threat by 2030, defined as a reduction in incidence by 90% in new chronic infections and mortality by 65% of viral hepatitis B and C[16]. Hepatitis B is a major health problem and a significant socio-economic impact all over the world currently[17].

China has the world's largest rural population and labor[18], rural population flow is a main component of China's population flow and has an important impact on the spatial pattern of population on regional economic and social development[19]. A hepatitis B prevalence of 3.7% (642) of a large sample was reported previously[20], while it was 6% (124274) tested positive for HBsAg among males in rural areas by another study[21]. Rural economy lags behind the city in China, along with the resource and level of health or education. Vaccination coverage related to the economy status, former study suggested that higher HBV vaccination coverage rates among adults are obtainable and user fees, time needed of vaccination and travel costs had acted as economic barriers to vaccination[22]. The vaccination of hepatitis B was reported as low as 13.89% in rural China[23].

The prevalence of hepatitis B among whole rural resident participants was 4.04% in Zhejiang (It was 3.85% standardized by age and gender). Which indicated that Zhejiang rural resident population would be categorized as an intermediate group, and the prevalence rate of hepatitis B

was significantly lower than reported 9.8% in 1992 and 7.2% in 2006 across inland China[7]. Following a series of interventions by the Chinese government, there was a significantly decline of the hepatitis B epidemic. A larger nation-wide survey would be needed to assess the epidemic of hepatitis B in China in order to provide the epidemiological features and update the controlling or preventing strategies, especially in rural population.

There was no significantly association between hepatitis B prevalence and age in our study. Although previous studies referred age as a factor[24-27], and showed that an older age caused a higher prevalence in population. Our univariate analysis also indicated this phenomena. We thought it was a result of confounding by hepatitis B vaccination or other factors. A former study reported a reverse result too[28]. For the factor of gender, the results were varied. Studies[11, 25, 28-30] showed that the prevalence rate was higher in male than in female ones, while there was no association founded between gender and hepatitis B by a study[24] just like ours did.

Our study showed that education was not an independent influencing factor on hepatitis B, while other studies pointed this out[31-32]. But there could be a possible trend that hepatitis B prevalence decreasing with increasing of education level from univariate analysis and Table 1, higher education level in our study had a lower rate of hepatitis B prevalence. Potential reasonable explanations for this phenomena were: Well prevention or protection awareness of infectious diseases like hepatitis B in higher educated population; A higher acceptance of vaccination, having at least a college education (OR= 2.55, 95% CI: 1.28-5.07) was an important predictor of vaccine completion[33].

We found that only 13.48% in whole had taken hepatitis B examinations before and among those participants had a lower prevalence of hepatitis B, while those who had not been examined existed

a higher prevalence rate. We could infer that those infected by hepatitis B virus who had not been diagnosed by the examinations could be the potential sources of hepatitis B. By encouraging people to take part in hepatitis B examination along with routine physical examination, we could benefit: First, we could find out those infected one; Second, we could treat them immediately; Third, it could be the right opportunity to raise awareness of hepatitis B among population especial in rural areas.

Service based tertiary industry of occupation seemed to be a risk factor compared to other ones, non-single live (OR_a= 2.66, 95% CI: 2.04-3.46) were the risk factors for hepatitis B prevalence. Above factors had the same feature: it likely to result in more communications between people. We should take consideration of these since hepatitis B is an infectious disease and has a sign of clustering among population.

Epidemics of hepatitis B were scattered in different areas globally[2, 27], prevalence rates of hepatitis B among districts were also varied in our study. This circumstance would be caused by geographic, economic level, density of the population, living habits or other factors. Regardless of all these, we should take district as a non-negligible factor especially district with a high prevalence like Yuhuan (9.81%) when develop and implement strategies fighting for hepatitis B.

Chinese government had made great progresses with vaccination for hepatitis B[34], the national hepatitis B immunization plan was established in 1992. In 2002, the Global Alliance on Vaccine and Immunization (GAVI) partnered with the government of China to provide hepatitis B vaccine for free[35]. And fully integrated into the routine immunization program and provided completely free among infants nationally in 2005[36]. The carrier rate in Chinese children aged <5 years fell to less than 1% in 2006, and 0.32% in 2014, which was 10% in the 1990s[37]. Recently data from

WHO estimated of newborns in China receive a timely birth dose (TBD) and third dose of hepatitis B vaccine (HepB3) were 96% and 99% respectively[38]. Our study shows that Hepatitis B vaccinated (OR_a= 0.52, 95% CI: 0.41-0.65) and HBsAb positive (OR_a= 0.11, 95% CI: 0.08-0.15) were the protective factors for hepatitis B, same results had been observed[12-13, 31].

Our sampled survey showed the vaccination rate was 75.5% in aged <20 years old, while it was only 29.8% in aged >20 years old. There was a trend that rate of hepatitis B vaccination was increased when the vaccination program conducted and expanded since 1992, along with the decreasing of hepatitis B prevalence nationwide. Preventing hepatitis B through vaccine is currently the most efficient way to decrease HBV-related cirrhosis and liver cancer incidence, as well as to suppress the HBV reservoir[17]. The role of the vaccination program for effective control of hepatitis B should be emphasized[39]. In the near future, we should focus on adults about hepatitis B vaccination under the consideration of policies for universal vaccination delayed, especially in countries with high endemicity.

CONCLUSIONS

In conclusion, though our study showed Zhejiang rural area is categorized as an intermediate epidemic level in China, it is still an important issue and big challenge to deal with the problem of hepatitis B in rural areas among resident population. Specific methods like enlarging the population of hepatitis B examination, raising the coverage of vaccination particularly in adults are considered as suitable and effective strategies to prevention and control of hepatitis B in Zhejiang rural areas.

LIMITATION

This study was cross-sectional designed, there was a certain of recall bias. We excepted to control it at a low level during design and conduct periods. Sample sizes seemed not so balanced between districts in our study. We considered taking a vaccination history of hepatitis B as vaccine success, for the effectiveness of vaccination[17]. In order to interpreter the results, we simply divided variables into few groups like occupation. A more precise classification of factors could be involved in later studies, along with much more potential factors associated with hepatitis B.

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Footnotes

SY and CD contributed equally.

Contributors

LL, JR, BR, JY and SY conceived and designed the study. CD, YC, JW, CY, CP, KX, MD, YL, JL, PY. WR, YQ, QC and YZ collected data, cleaned, analyzed the data and revised the paper. CD and SY wrote the first draft of the paper, contributed to figures and paper preparation and all authors critically revised the paper and gave final approval for publication.

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Competing interests

None declared.

Ethics approval

This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University and consent was obtained from all participants.

Data sharing statement

No additional data are available.

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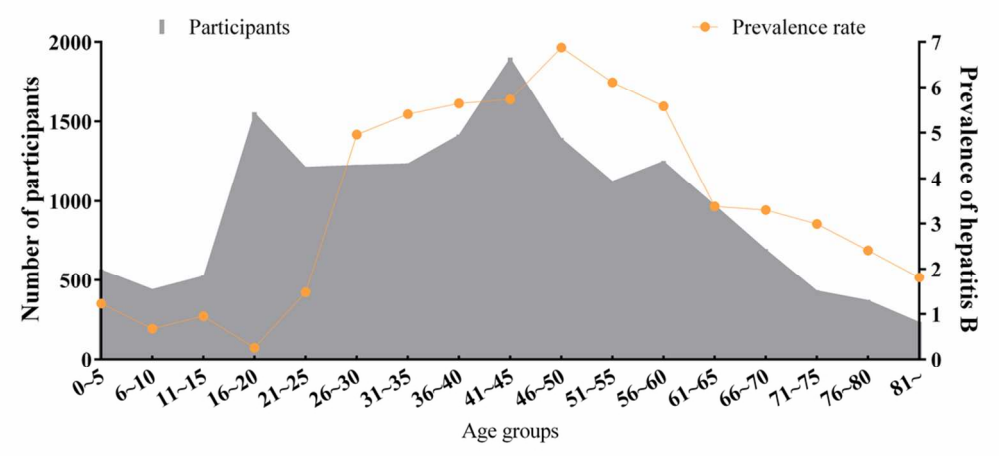
Figure 1 The prevalence of hepatitis B among different age groups

Figure 2 The distribution of participants and prevalence of hepatitis B in different districts

Figure 3 The values of OR and OR_a in the logistic models.



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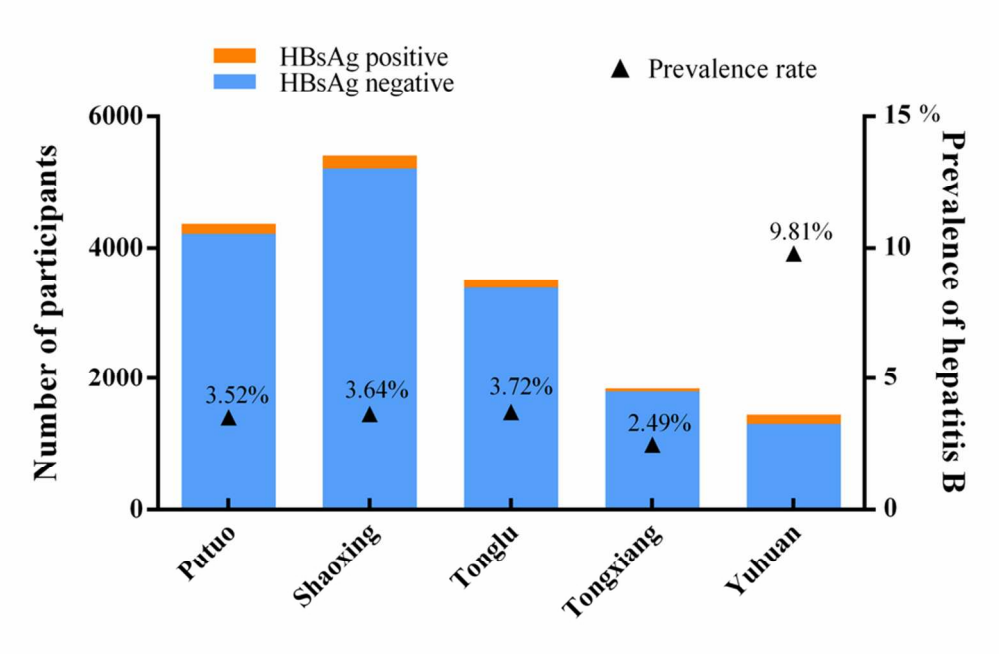

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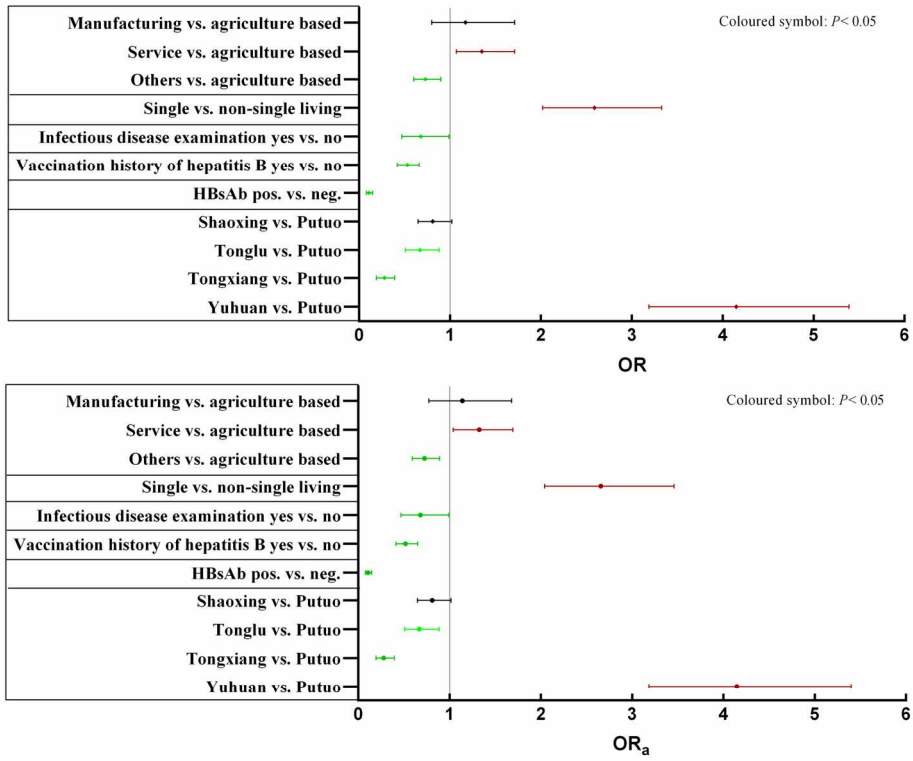

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	*18*
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8,9
		(b) Indicate number of participants with missing data for each variable of interest	7
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The prevalence and influencing factors of hepatitis B among a rural residential population in Zhejiang Province, China: a cross-sectional study

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Health policy, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, Infection control < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

Title: The prevalence and influencing factors of hepatitis B among a rural residential population in Zhejiang Province, China: a cross-sectional study

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ABSTRACT

Objectives To reveal the prevalence and associated influencing factors of hepatitis B among a rural residential population in Zhejiang, China to help developing specific control strategies.

Methods We conducted a cross-sectional study among a rural residential population in Zhejiang, China. Stratified multistage cluster sampling was utilized in five districts, questionnaires were completed by trained local staffs and all data were collected. Then univariate and multivariate analyses were applied to evaluate the influencing factors. The odds ratios of each related factor were assessed with or without adjustment separately.

Results The mean age of the 16601 participants who completed the survey was 40.28±19.47 years, and there were 7881 males and 8720 females. The positive rate of hepatitis B surface antigen (HBsAg) was 4.04% (95% CI: 3.74%-4.35%), it was 3.85% standardized by age and gender. Univariate analysis showed that age, educational level, occupation, living status, examinations taken, history of blood transfusion, vaccination, family history, being coastal, and district were the potential influencing factors. Multivariate logistic regression indicated that occupation, living status, history of examination, vaccination and district were the influencing factors. Undertaking a service-based tertiary industry job (OR_a=1.19, 95% CI: 0.94-1.51) and non-single living (OR_a=2.84, 95% CI: 2.17-3.70) might be risk factors, while vaccinated (OR_a=0.43, 95% CI: 0.34-0.53) and having taken examinations (OR_a=0.71, 95% CI: 0.48-1.03) were potential protective factors.

Conclusions Hepatitis B is at an intermediate epidemic level in a rural residential population in Zhejiang, China, with a prevalence rate of 3.85%. Raising vaccination coverage, especially in adults, is a suitable strategy for the prevention and control of hepatitis B in a rural residential

population in Zhejiang, China.

Keywords: Hepatitis B; Influencing factors; Cross-sectional study

ARTICLE SUMMARY

Strengths and limitations of this study

This study focused on the prevalence of hepatitis B in a rural residential population.

The study involved a large rural residential population and the logistic regression model provided a quantified result of the influencing factors of hepatitis B.

The main limitation of the study was that there could be recall bias due to its cross-sectional design.

INTRODUCTION

Hepatitis B is a potentially life-threatening liver infection caused by hepatitis B virus (HBV), which attacks the liver and could cause both acute and chronic disease. Two billion people have evidence of past or present HBV infection, and, globally, an estimated 240 million people are chronically infected with hepatitis B virus [1 2]. More than 686000 people die annually due to complications of hepatitis B, including cirrhosis and hepatocellular carcinoma (HCC)[3]. Previously, studies revealed that the incidence of HBV-related HCC in adults remains high, and a high serum HBV DNA level increases the risks of cirrhosis and HCC[4 5].

Overall, nearly half of the global population lives in areas of high hepatitis B endemicity[6]. The global prevalence of HBV infection is heterogeneous[2], and the prevalence of hepatitis B is the highest in sub-Saharan Africa and East Asia, where 5%~10% of the adult population is chronically infected[1]. The most recent large, nationwide survey in China was conducted in 2006, which

showed that the weighted prevalence of hepatitis B surface antigen (HBsAg) positive was 7.2% among those aged 1 to 59 years, and the rate among children aged <5 years was only 1.0%[7]. According to the endemicity maps[2], hepatitis B in China was at a higher intermediate level. Since that time, several studies[8-14] have been conducted to investigate the prevalence of hepatitis B in different areas among the general population in mainland China. The reported prevalence rate was 3.49% in Beijing (2007)[8], 4.38% in adults in Northeast China (2007)[9], 7.44% in Anhui Province (2006)[10], 5.17% in Henan Province (2006-2009)[11], 7.2% in Northwest China (2010)[12], 3.17% in Sichuan blood donors (2010-2011)[13] and 2.73% in Beijing (2013-2014)[14]. The values of rate were varied in different areas and time periods.

China has the world's largest rural population and labor resources[15], and the rural population flow is a main component of China's population flow and has an important impact on the spatial pattern of the population in terms of regional economic and social development[16]. A hepatitis B prevalence of 3.7% (642) in a large sample was previously reported[17]; while this figure was 6% (124274) among males in rural areas who tested positive for HBsAg by another study[18]. The rural economy lags behind the urban economy in China, along with the resources, health and education levels.

It is important issue to identify the prevalence of hepatitis B and the basic procedure for eradicating HBV infection. This study aimed to investigate the prevalence of hepatitis B and its potential influencing factors in a rural residential population in Zhejiang Province, China. By clearly indicating the epidemic of hepatitis B and its associated risk factors in rural areas, we could develop specific prevention and control strategies based on the influencing factors of HBV infection and the characteristics of hepatitis B endemic.

METHODS

Study design

A survey with stratified multi-stage cluster sampling survey was conducted in five districts in Zhejiang Province, China from January 2014 to December 2015. We took geographic characteristics and economic levels into consideration when choosing the five districts in our study, coastal areas such as Putuo and Yuhuan, inland areas such as Shaoxing, Tonglu, and Tongxiang, higher economic level areas such as Shaoxing and Tongxiang, and lower economic level areas such as Putuo, Yuhuan and Tonglu. Further stratified sampling was based on the population in rural town and villages. All participants, who were registered rural residents and had been continuously living at the local for at least six months were included.

During the two-year planned investigation, a standard questionnaire was designed for the cross-sectional survey and was used to collect basic information about the rural residential participants and the potential factors for HBV infection.

A house-to-house investigation was completed by trained staffs and local doctors in the sampled areas. To increase the response rate, staffs were recommended to visit target houses at an appropriate time period, such as nightfall. One percent of the questionnaires were randomly checked, each time, after conducting the survey. Basic personal information was collected, including age, gender, ethnicity, education, occupation, living status, medical insurance, history of hepatitis B examination, history of blood transfusion, history of surgery, history of being away 3 months, vaccination history of hepatitis B, family history of hepatitis B, and whether living in a coastal area. These data were collected by staffs in face-to-face interviews.

Sera were collected from blood samples (5 ml for individuals aged ⩾6 years and 2 ml for children aged ⩽5 years) and stored at -20 °C by laboratory staffs from the local hospitals. Sera were timely shipped in a timely manner to our state key laboratory of the First Affiliated Hospital, College of Medicine, Zhejiang University. Serum samples were tested by chemiluminescence immunoassay (CLIA) with Abbott reagents (Abbott Laboratories, Abbott Park, IL, USA). We considered the positivity rate of HBsAg in the population as the prevalence level of hepatitis B.

Statistical analysis

All collected data were entered into an EpiData 3.1 software database twice. Then, we checked the accuracy, consistency and logistics of the data. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) software was used for data processing and analysis. Social demographic information was analysed by descriptive statistics. Univariate logistic analysis was used to identify potential influencing factors associated with hepatitis B infection; we selected the factors with P <0.1 in the univariate model and conducted a stepwise multivariate logistic model to seek the independent risk factors for hepatitis B. Odds ratio (OR), 95% confidence interval (95% CI) and adjusted OR for each factor were also calculated. The statistical hypothesis test level was 0.05. GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used to draw the figures.

RESULTS

Characteristics of participants

Of the 22000 eligible participants, 16601 completed the survey with a response rate of 75.5%, including 7881 (47.47%) males and 8720 (52.53%) females in five districts. The mean age of the participants was 40.28±19.47 years. The prevalence of hepatitis B in all participants was 4.04%

(95% CI: 3.74%-4.35%), and it was 3.85% when standardized by age and gender, using the demographic population of Zhejiang Province as the standard population. The results showed that Zhejiang was an intermediate epidemic area of hepatitis B.

The distribution of the population and the prevalence rate between the different age groups are shown in Figure 1. We can observe that an age below 20 years is the group that had the lowest prevalence rate of hepatitis B, while groups aged 41-60 years had the highest rates. There was a rapid increase in the prevalence rate between those aged 21-25 years and 26-30 years.

Among the five districts, Shaoxing had the most participants with a number of 5416 (32.65%), while Yuhuan had the smallest number with 1447 (8.72%) participants. The numbers of participants in the rest of the areas, Putuo, Tonglu and Tongxiang districts, were 4370 (26.32%), 3523 (21.22%) and 1845 (11.11%), respectively. In our study, the prevalence of hepatitis B was highest in Yuhuan (9.81%), and lowest in Tongxiang (2.49%) in our study (Figure 2).

We collected all the relevant data of the participants; participant's basic characteristics are listed in Table 1. Most of the participants' educational level was primary school or lower (44.25%), college level or higher was only 1088 (6.55%), and the group, which had the lowest prevalence (2.21%). Only 13.48% of the participants had undergone hepatitis B examination before, and few had a history of surgery (3.46%) or blood transfusion (0.57%). There were 6358 (38.30%) participants, who had a vaccination history of hepatitis B, and this figure was 75.5% for aged <20 years, and only 29.8% in aged >20 years. Of all participants, 5817 (35.04%) were living in coastal areas and the HBsAb positive rate was 30.00%, and among which the HBsAg

positive rate was only 1.00%, a value that was lower than that in HBsAb negative participants (5.34%).

Table 1 Characteristics of participants in the study and univariate analysis results

Variables/Values	Sample size (n)	Percent (%)	HBsAg positive (n)	Prevalence (%)
Age**	16601	-	670	4.04
Gender				
Male	7881	47.47	324	4.11
Female	8720	52.53	346	3.97
Educational level**				
Primary school or lower	7346	44.25	305	4.15
Junior school	5431	32.71	265	4.88
High or polytechnic school	2736	16.48	76	2.78
College or higher	1088	6.55	24	2.21
Occupation**				
Agriculture-based primary industry	5862	35.31	256	4.37
Manufacturing-based secondary industry	623	3.75	39	6.26
Service-based tertiary industry	2423	14.60	132	5.45
Other (Students or retired)	7693	46.34	243	3.16

Living status**				
Single living	5299	31.92	81	1.53
Non-single living	11302	68.08	589	5.21
Medical insurance				
Out-of-pocket	339	2.04	13	3.83
Has medical insurance	16262	97.96	657	4.04
History of hepatitis B examination*				
Yes	2238	13.48	71	3.17
No	14363	86.52	599	4.17
History of surgery**				
Yes	575	3.46	48	8.35
No	16026	96.54	622	3.88
History of blood transfusion				
Yes	94	0.57	4	4.26
No	16507	99.43	666	4.03
Vaccination history of hepatitis B**				
Yes	6358	38.30	122	1.92
No	10243	61.70	548	5.35
History for being away 3 months				
Yes	843	5.08	39	4.63
No	15758	94.92	631	4.00
Family history of hepatitis B**				

Yes	446	2.69	69	15.47
No	16155	97.31	601	3.72
Living in coastal area**				
Yes	5817	35.04	296	5.09
No	10784	64.96	374	3.47
HBsAb				
Negative	11621	70.00	620	5.34
Positive	4980	30.00	50	1.00
District**				
Putuo	4370	26.32	154	3.52
Shaoxing	5416	32.62	197	3.64
Tonglu	3523	21.22	131	3.72
Tongxiang	1845	11.11	46	2.49
Yuhuan	1447	8.72	142	9.81

*: P <0.05; **: P< 0.0001.

Univariate and multivariate analysis

Univariate analysis showed that age, educational level, occupation, living status, history of hepatitis B examination, vaccination history of hepatitis B, history of surgery, history for being away 3 months, family history of hepatitis B, and living in a coastal area and district could be the potential influencing factors associated with hepatitis B among the population (Table 1).

A stepwise multivariate analysis showed that occupation, living status, history of hepatitis B examination, vaccination history of hepatitis B and district were the independent influencing factors of hepatitis B in a rural residential population in Zhejiang. An age and gender adjusted model revealed that undertaking a service-based tertiary industry job (OR_a=1.19, 95% CI: 0.94-1.51), non-single living (OR_a=2.84, 95% CI: 2.17-3.70) were the risk factors for hepatitis B prevalence; while having taken an examination of hepatitis B (OR_a=0.71, 95% CI: 0.48-1.03) and hepatitis B vaccinated (OR_a=0.43, 95% CI: 0.34-0.53) might be the protective factors for hepatitis B (Table 2). Figure 3 illustrates the values of OR and OR_a in the two logistic models.

Table 2 Results of multivariate analysis for hepatitis B

Variables/Values	OR (95% CI)	*P value*	OR_a (95% CI)	*P value*
Occupation				
Agriculture-based primary industry	ref.		ref.	
Manufacturing-based secondary industry	1.26(0.87-1.82)	0.2155	1.18(0.82-1.72)	0.3857
Service-based tertiary industry	1.25(1.00-1.58)	0.0548	1.19(0.94-1.51)	0.1586
Other	0.79 (0.65-0.97)	0.0237	0.77(0.63-0.94)	0.0113
Living status				
Single living	ref.		ref.	

Non-single living	2.63(2.05-3.37)	<0.0001	2.84(2.17-3.70)	<0.0001
History of hepatitis B examination				
Yes	0.72(0.49-1.04)	0.0787	0.71(0.48-1.03)	0.0705
No	ref.		ref.	
Vaccination history of hepatitis B				
Yes	0.45(0.36-0.56)	<0.0001	0.43(0.34-0.53)	<0.0001
No	ref.		ref.	
District				
Putuo	ref.		ref.	
Shaoxing	0.77(0.62-0.97)	0.0236	0.77(0.62-0.96)	0.0208
Tonglu	0.79(0.60-1.05)	0.1031	0.79(0.60-1.05)	0.1025
Tongxiang	0.38(0.27-0.53)	<0.0001	0.38(0.27-0.54)	<0.0001
Yuhuan	2.09(1.63-2.67)	<0.0001	2.09(1.63-2.67)	<0.0001

OR: odds ratio; OR_a: odds ratio adjusted by age and gender; ref.: reference.

DISCUSSION

Prevalence of hepatitis B

Viral hepatitis is a leading cause of death and disability worldwide, deaths from acute infection, cirrhosis and liver cancer were the tenth leading cause of death worldwide in 1990, while it ranked seventh in 2013. The number of deaths worldwide attributable to viral hepatitis increased by 63% from 1990 to 2013[19].

The prevalence of hepatitis B in all rural residential participants was 4.04% in Zhejiang (It was 3.85% standardized by age and gender). Our results indicated that the Zhejiang rural residential population would be categorized as an intermediate group and that the hepatitis B prevalence rate was significantly lower than reported in 1992 of 9.8% and in 2006 of 7.2% across inland China[7]. Following a series of interventions by the Chinese government, there was a significantly decline of the hepatitis B epidemic. A larger nation-wide survey would be needed to assess the current epidemic of hepatitis B in China to provide the epidemiological features and update the controlling or prevention strategies, especially in the rural population.

Influencing factors of hepatitis B

There was no significantly association between hepatitis B prevalence and age in our study. Although, previous studies referred to age as a factor[20-22], and showed that an older age group had a higher prevalence in the population. Our univariate analysis also indicated this phenomenon. We thought this outcome was a result of confounding, by hepatitis B vaccination or other factors. A former study also reported an inverse result[23]. For the factor of gender, the results were varied. Previous studies[11 21 23-25] showed that the prevalence rate was higher in males than in females; while there was no association founded between gender and hepatitis B in one study[20] similar to our own.

Our study showed that education was not an independent influencing factor on hepatitis B; while other studies also notes this[26 27]. However, there could be a possible trend of decreasing hepatitis B prevalence with increasing educational level from our univariate analysis in Table 1; it can be observed in our study that higher educational level had a lower rate of hepatitis B prevalence rate. Potential reasonable explanations for these phenomena are better prevention or

protection awareness of infectious diseases, such as hepatitis B, in the higher-educated population and a higher acceptance of vaccination; furthermore, having at least a college education (OR=2.55, 95% CI: 1.28-5.07) was an important predictor of vaccine completion[28].

We found that only 13.48% of all participants had taken a hepatitis B examinations before, and among those participants, there was a lower prevalence of hepatitis B; while in those participants who had not been previously examined, there was a higher prevalence rate. We could infer that those infected by hepatitis B virus, who had not been diagnosed by the examinations, could be the potential sources of hepatitis B. By encouraging people to take part in hepatitis B examination, along with routine physical examination, we could benefit: First, we could find out those who are infected; Second, we could immediately treat them; Third, the right opportunity could exist to raise awareness of hepatitis B among the population, especially in rural areas.

Compared to other occupation types, service-based tertiary industry of occupation seemed to be a risk factor, along with non-single living (OR_a=2.84, 95% CI: 2.17-3.70), which were the risk factors for hepatitis B prevalence. The factors above had the same feature: likely to result in more communications between people. We should take consideration of these factors, since hepatitis B is an infectious disease, which has a sign of clustering among the population.

Hepatitis B epidemics are scattered in different areas globally[2 22], and hepatitis B prevalence rates also varied among the districts in our study. These circumstances would be caused by geography, economic level, population density, living habits or other factors. Economic level seems to be a potential factor, since lower economic level areas such as Yuhuan had a higher prevalence rate and higher areas such as Shaoxing and Tongxiang had prevalence lower rates. Regardless of all features, we should consider district as a non-negligible factor, especially a

district with a high prevalence, when developing and implementing strategies for fighting hepatitis B.

Control strategies for hepatitis B

World Health Organization (WHO) adopted the first-ever global hepatitis strategy with a goal to eliminate viral hepatitis B and C as public health threats by 2030, which was defined as a reduction in incidence by 90% in new chronic infections and mortality by 65% for viral hepatitis B and C[29]. Currently, hepatitis B is a major health problem and has a significant socio-economic impact all over the world currently[30]. HBV vaccination is the mainstay of HBV prevention and it is the most effective prevention strategy[31 32].

The Chinese government has made great progresses with hepatitis B vaccination[33]: the national hepatitis B immunization plan was established in 1992. In 2002, the Global Alliance on Vaccine and Immunization (GAVI) partnered with the government of China to provide free hepatitis B vaccine[34] and fully integration into the routine immunization program, and the vaccine was provided completely free to infants, nationally in 2005[35]. The carrier rate in Chinese children aged <5 years fell to less than 1% in 2006, and 0.32% in 2014, which previously was 10% in the 1990s[36]. Recently, WHO estimated that new-borns in China, who received a timely birth dose (TBD) and third dose of hepatitis B vaccine (HepB3), was 96% and 99% respectively[37]. Our study shows that Hepatitis B vaccination (OR_a=0.43, 95% CI: 0.34-0.53) was the protective factors for hepatitis B, and the same results have previously been observed[12 13 26].

Regarding vaccination coverage related to the economy status, a former study suggested that higher HBV vaccination coverage rates among adults are obtainable and that user fees, time needed for vaccination and travel costs acted as economic barriers to vaccination[38]. Hepatitis B

vaccination has been reported as low as 13.89% in rural China[39]. We call for strengthening HBV vaccination in rural areas, and raising the vaccine coverage rate.

Our survey also showed that the vaccination rate was 75.5% in aged <20 years, and was only 29.8% in aged >20 years. There was a trend that the rate of hepatitis B vaccination was increased when the vaccination programme conducted and expanded since 1992, along with decreasing nationwide hepatitis B prevalence. Preventing hepatitis B through vaccination is currently the most efficient way to decrease HBV-related cirrhosis and liver cancer incidence and reduce the HBV reservoir[30]. The role of the vaccination programme for the effective control of hepatitis B should be emphasised[40]. In the near future, we should focus hepatitis B vaccination efforts on adults, under the consideration of policies for delayed universal vaccination, especially in countries with high endemicity.

CONCLUSIONS

In conclusion, though our study showed that the Zhejiang rural area is categorized as an intermediate epidemic level for hepatitis B in China, there remains the important issue and formidable challenge of dealing with the problem of hepatitis B in rural areas among the resident population. Specific methods such as raising the coverage of vaccination particularly in adults, are suitable and effective strategies to prevent and control hepatitis B in Zhejiang rural areas. Furthermore, increasing the percentage of the population that has had hepatitis B examination may also be considered as a potential strategy.

LIMITATION

This study was cross-sectionally designed, and we could not exclude the acute infection case; thus the hepatitis B prevalence rate may be overestimated in the population when using the HBsAg positive rate as the level of chronic HBV infection, and there was also a certainty of recall bias in this study design. Additionally, the sample sizes were not balanced between districts in our study. We considered taking a vaccination history of hepatitis B as an indicator of vaccine success due to the effectiveness of vaccination[30]. To interpreter the results, we simply divided the variables into few groups, such as occupation. A more precise classification of factors could be assessed in later studies, along with other more potential factors, such as family income.

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The funders had no role in study design, data collection, data analysis or writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Footnotes

SY and CD contributed equally.

Contributors

LL, JR, BR, JY and SY conceived and designed the study. CD, YC, JW, CY, CP, KX, MD, YL, JL, PY. WR, YQ, QC and YZ collected data, cleaned, and analysed the data and revised the paper. CD and SY wrote the first draft of the paper, contributed to figures and paper preparation and all authors critically revised the paper and gave final approval for publication.

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Competing interests

None declared.

Ethics approval

This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University and consent was obtained from all participants.

Data sharing statement

No additional data are available.

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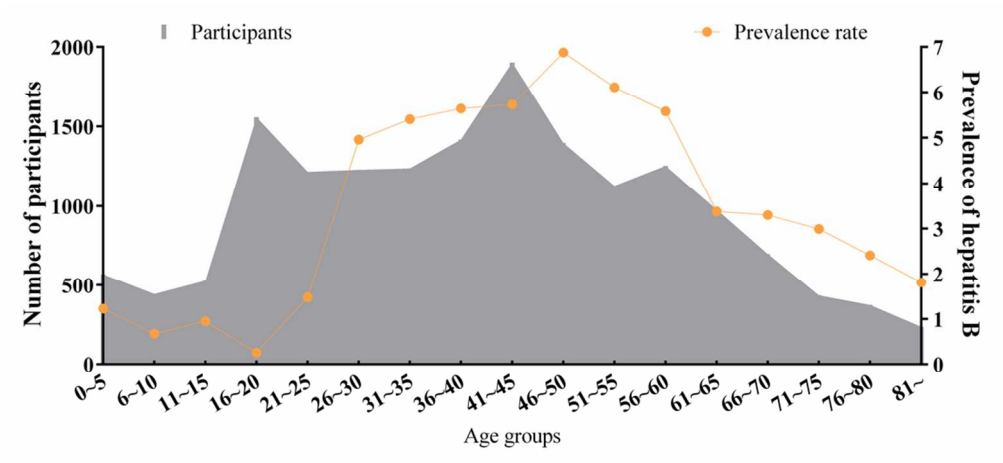
Figure 1 The prevalence of hepatitis B among different age groups

Figure 2 The distribution of participants and prevalence of hepatitis B in different districts

Figure 3 The values of OR and OR_a in the logistic models.



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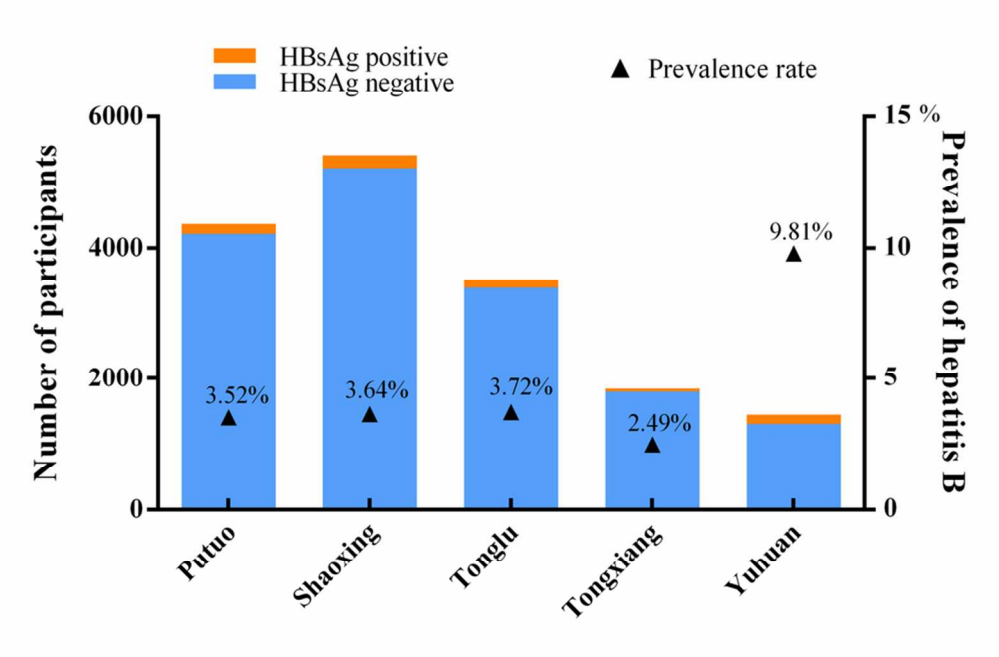

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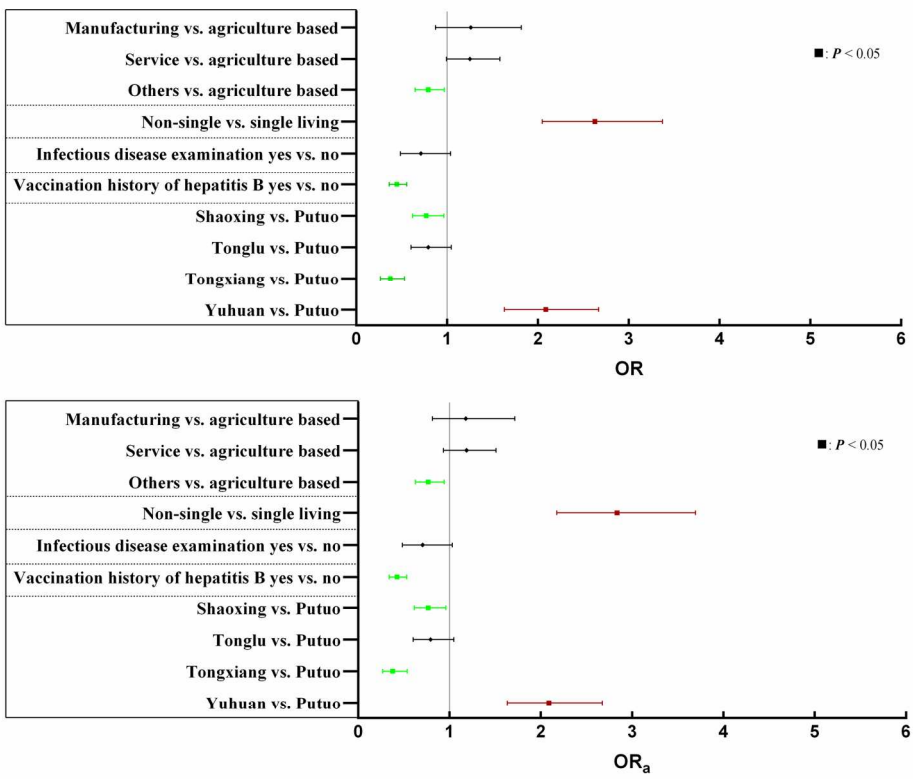

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	*18*
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8,9
		(b) Indicate number of participants with missing data for each variable of interest	7
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The prevalence and influencing factors of hepatitis B among a rural residential population in Zhejiang Province, China: a cross-sectional study

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Health policy, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, Infection control < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

Title: The prevalence and influencing factors of hepatitis B among a rural residential population in Zhejiang Province, China: a cross-sectional study

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Word count (2964 excluding tables)

ABSTRACT

Objectives To reveal the prevalence and associated influencing factors of hepatitis B among a rural residential population in Zhejiang, China, so as to help develop specific control strategies.

Methods We conducted a cross-sectional study among a rural residential population in Zhejiang, China. Stratified multistage cluster sampling was utilized in five districts, a structured questionnaire was used to collect the information such as age, gender, education, occupation, living status, and other health related information of the participants by the trained local staff, participants' HBV infection status were determined by chemiluminescence immunoassay test. Univariate and multivariate analyses were applied to evaluate the influencing factors of HBV infection. The odds ratio of each related factor was assessed with or without adjustment separately.

Results The mean age of the 16601 participants, including 7881 males and 8720 females, who completed the survey was 40.28±19.47 years. The positive rate of hepatitis B surface antigen (HBsAg) was 4.04% (95% CI: 3.74%-4.35%), and 3.85% after standardized by age and gender. Univariate analysis showed that age, educational level, occupation, living status, history of taking hepatitis B examinations, history of blood transfusion, vaccination, family history, coastal living, and district were the potential influencing factors. Multivariate logistic regression indicated that occupation, living status, history of taking hepatitis B examinations, vaccination and district were the influencing factors. Undertaking a service-based tertiary industry job (OR_a=1.19, 95% CI: 0.94-1.51) and non-single living (OR_a=2.84, 95% CI: 2.17-3.70) might be risk factors, while vaccination (OR_a=0.43, 95% CI: 0.34-0.53) and history of takeing hepatitis B examinations (OR_a=0.71, 95% CI: 0.48-1.03) were potential protective factors.

Conclusions The prevalence of hepatitis B is at an intermediate epidemic level in a rural

residential population in Zhejiang, China. Raising vaccination coverage, especially in adults, is a suitable strategy for the prevention and control of hepatitis B.

Keywords: Hepatitis B; Influencing factors; Cross-sectional study

ARTICLE SUMMARY

Strengths and limitations of this study

- This study focused on the prevalence of hepatitis B in a rural residential population.
- The study involved a large rural residential population and the logistic regression model provided a quantified result of the influencing factors of hepatitis B.
- The main limitation of the study was that there could exist recall bias due to its cross-sectional design.

INTRODUCTION

Hepatitis B is a potentially life-threatening infection caused by hepatitis B virus (HBV), which attacks the liver and could cause both acute and chronic disease. Two billion people have evidence of past or present HBV infection, and, globally, an estimated 240 million people are chronically infected with hepatitis B virus [1 2]. More than 686000 people die annually due to complications of hepatitis B, including cirrhosis and hepatocellular carcinoma (HCC)[3]. Previously, studies revealed that the incidence of HBV-related HCC in adults remains high, and a high serum HBV DNA level increases the risks of cirrhosis and HCC[4 5].

Overall, nearly half of the global population lives in areas of high hepatitis B endemicity[6]. The global prevalence of HBV infection is heterogeneous[2], and the prevalence of hepatitis B is highest in sub-Saharan Africa and East Asia, where 5%~10% of the adult population is chronically infected[1]. The most recent large, nationwide survey in China was conducted in 2006, which showed that the weighted positive rate of hepatitis B surface antigen (HBsAg) was 7.2% among those aged 1 to 59 years, and the rate among children aged <5 years was only 1.0%[7]. According to the disease distribution maps[2], hepatitis B in China was at a higher intermediate level. Since that time, several studies[8-14] have been conducted to investigate the prevalence of hepatitis B in different areas among the general population in mainland China. The reported prevalence was 3.49% in Beijing (2007)[8], 4.38% in adults in Northeast China (2007)[9], 7.44% in Anhui Province (2006)[10], 5.17% in Henan Province (2006-2009)[11], 7.2% in Northwest China (2010)[12], 3.17% in Sichuan blood donors (2010-2011)[13] and 2.73% in Beijing (2013-2014)[14]. The rates were varied in different areas and at different time periods.

China has the largest rural population and labor resources around the world[15], and the rural

population flow is the main component of China's population flow and has an important impact on the spatial pattern of the population in terms of regional economic and social development[16]. A hepatitis B prevalence of 3.7% (642) in a large sample was previously reported[17]; while another study[18] reported a 6% (124274) HBsAg positive rate among males in rural areas. The rural economy lags behind the urban economy in China, along with the resources of health and education.

It is important to identify the prevalence of hepatitis B and the basic procedure for eradicating HBV infection. This study aimed to investigate the prevalence of hepatitis B and its potential influencing factors in a rural residential population in Zhejiang Province, China. By clearly indicating the characteristics of hepatitis B and its associated risk factors, we intend to develop specific prevention and control strategies.

METHODS

Study design

A stratified multi-stage cluster sampling survey was conducted in five districts in Zhejiang Province, China from January 2014 to December 2015. We took geographic characteristics and economic levels into consideration when choosing the five districts in our study, coastal areas such as Putuo and Yuhuan, inland areas such as Shaoxing, Tonglu, and Tongxiang, higher economic level areas such as Shaoxing and Tongxiang, and lower economic level areas such as Putuo, Yuhuan and Tonglu. Further stratified sampling was based on the population in rural town and villages. All participants were registered as rural residents, who continuously resided in local for at least six months. A total of 22000 people were recruited, and after 5539 people excluded with

missing information, 16601 eligible participants were ultimately received completed survey. The research Ethics Committee at the First Affiliated Hospital, School of Medicine, Zhejiang University approved the study, and all participants gave the written informed consent.

During the two-year of investigation, a structured questionnaire was designed to collect basic information such as age, gender, ethnicity, education, occupation, living status, medical insurance etc., and the potential factors related to HBV infection such as history of blood transfusion, surgery, vaccination of hepatitis B, family history of hepatitis B, and whether moving away from resident location more than three months etc.

The investigation was completed by trained staff and local doctors. To increase the response rate, investigators were recommended to visit target houses at an appropriate time, such as nightfall. One percent questionnaires were randomly selected to be checked for the completeness and accuracy. During the investigation, blood samples (5 ml for individuals aged ⩾6 years and 2 ml for children aged ⩽5 years) were collected from the participants. Sera was separated and stored at -20 °C by laboratory staff from the local hospitals. After timely transported to our state key laboratory of the First Affiliated Hospital, College of Medicine, Zhejiang University, the serum samples were tested by chemiluminescence immunoassay (CLIA) with Abbott reagents (Abbott Laboratories, Abbott Park, IL, USA). The positive rate of HBsAg in the population was considered as the prevalence level of hepatitis B.

Statistical analysis

All collected data were doubly entered into an EpiData 3.1 software database by two staff, independently. Then, we checked the accuracy, consistency and logicality of the data. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) software was used for data processing and analysis. Social

demographic information was analysed by descriptive statistics. Univariate logistic analysis was used to identify potential influencing factors associated with hepatitis B infection; we selected the factors with P <0.1 in the univariate model and conducted a stepwise multivariate logistic model to seek the independent risk factors for hepatitis B. Odds ratio (OR), 95% confidence interval (95% CI) and adjusted OR for each factor were also calculated. The statistical hypothesis test level was 0.05. GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used to draw the figures.

RESULTS

Characteristics of participants

Of the 22000 eligible participants, 16601 completed the survey with a response rate of 75.5%, including 7881 (47.47%) males and 8720 (52.53%) females in five districts. The mean age of the participants was 40.28±19.47 years. The prevalence of hepatitis B in all participants was 4.04% (95% CI: 3.74%-4.35%), and it was 3.85% standardized by age and gender when using the population of Zhejiang Province as the standard population. The results showed that Zhejiang was an intermediate epidemic area of hepatitis B.

The distribution of the population and the prevalence between the different age groups are shown in Figure 1. We observed that the age below 20 years was the group that had the lowest prevalence of hepatitis B, while groups aged 41-60 years had the highest rates. There was a rapid increase in the prevalence between those aged 21-25 years and 26-30 years.

Among the five districts, Shaoxing had the most participants with a number of 5416 (32.65%), while Yuhuan had the smallest number with 1447 (8.72%) participants. The number of

participants was 4370 (26.32%), 3523 (21.22%) and 1845 (11.11%) in the rest Putuo, Tonglu and Tongxiang areas, respectively. In our study, the prevalence of hepatitis B was highest in Yuhuan (9.81%), and lowest in Tongxiang (2.49%) (Figure 2).

We collected all the relevant data of the participants; participants' basic characteristics are listed in Table 1. Most of the participants' educational level was primary school or lower (44.25%), college level or higher was only 6.55%, and the group, which had the lowest prevalence (2.21%). Only 13.48% of the participants had undergone hepatitis B examinations before, and few had a history of surgery (3.46%) or blood transfusion (0.57%). There were 6358 (38.30%) participants, who had a vaccination history of hepatitis B, and this figure was 75.5% in aged <20 years, and only 29.8% in aged >20 years. Of all participants, 5817 (35.04%) were living in coastal areas.

Table 1 Characteristics of participants in the study and univariate analysis results

Variables/Values	Sample size (n)	Percent (%)	HBsAg positive (n)	Prevalence (%)
Age**	16601	-	670	4.04
Gender				
Male	7881	47.47	324	4.11
Female	8720	52.53	346	3.97
Educational level**				
Primary school or lower	7346	44.25	305	4.15

Junior school	5431	32.71	265	4.88
High or polytechnic school	2736	16.48	76	2.78
College or higher	1088	6.55	24	2.21
Occupation**				
Agriculture-based primary industry	5862	35.31	256	4.37
Manufacturing-based secondary industry	623	3.75	39	6.26
Service-based tertiary industry	2423	14.60	132	5.45
Other (Students or retired)	7693	46.34	243	3.16
Living status**				
Single living	5299	31.92	81	1.53
Non-single living	11302	68.08	589	5.21
Medical insurance				
Out-of-pocket	339	2.04	13	3.83
Has medical insurance	16262	97.96	657	4.04
History of taking hepatitis B examinations*				
Yes	2238	13.48	71	3.17
No	14363	86.52	599	4.17
History of surgery**				
Yes	575	3.46	48	8.35
No	16026	96.54	622	3.88
History of blood transfusion				

Yes	94	0.57	4	4.26
No	16507	99.43	666	4.03
Vaccination history of hepatitis B**				
Yes	6358	38.30	122	1.92
No	10243	61.70	548	5.35
History for being away 3 months				
Yes	843	5.08	39	4.63
No	15758	94.92	631	4.00
Family history of hepatitis B**				
Yes	446	2.69	69	15.47
No	16155	97.31	601	3.72
Living in coastal area**				
Yes	5817	35.04	296	5.09
No	10784	64.96	374	3.47
District**				
Putuo	4370	26.32	154	3.52
Shaoxing	5416	32.62	197	3.64
Tonglu	3523	21.22	131	3.72
Tongxiang	1845	11.11	46	2.49
Yuhuan	1447	8.72	142	9.81

*: P <0.05; **: P< 0.0001.

Univariate and multivariate analysis

Univariate analysis showed that age, educational level, occupation, living status, history of taking hepatitis B examinations, vaccination history of hepatitis B, history of surgery, history for being away 3 months, family history of hepatitis B, and living in a coastal area and district could be the potential influencing factors associated with hepatitis B among the population (Table 1).

The stepwise multivariate analysis showed that occupation, living status, history of taking hepatitis B examinations, vaccination history of hepatitis B and district were the independent influencing factors of hepatitis B in a rural residential population in Zhejiang. The age and gender adjusted model revealed that undertaking a service-based tertiary industry job (OR_a=1.19, 95% CI: 0.94-1.51), non-single living (OR_a=2.84, 95% CI: 2.17-3.70) were the risk factors for hepatitis B prevalence; while having taken an examination of hepatitis B (OR_a=0.71, 95% CI: 0.48-1.03) and hepatitis B vaccinated (OR_a=0.43, 95% CI: 0.34-0.53) might be the protective factors for hepatitis B (Table 2). Figure 3 illustrates the values of OR and OR_a in the two logistic models.

Table 2 Results of multivariate analysis for hepatitis B

Variables/Values	OR (95% CI)	*P value*	OR_a (95% CI)	*P value*
Occupation				
Agriculture-based primary industry	ref.		ref.	
Manufacturing-based	1.26(0.87-1.82)	0.2155	1.18(0.82-1.72)	0.3857

secondary industry				
Service-based tertiary industry	1.25(1.00-1.58)	0.0548	1.19(0.94-1.51)	0.1586
Other	0.79 (0.65-0.97)	0.0237	0.77(0.63-0.94)	0.0113
Living status				
Single living	ref.		ref.	
Non-single living	2.63(2.05-3.37)	<0.0001	2.84(2.17-3.70)	<0.0001
History of taking hepatitis B examinations				
Yes	0.72(0.49-1.04)	0.0787	0.71(0.48-1.03)	0.0705
No	ref.		ref.	
Vaccination history of hepatitis B				
Yes	0.45(0.36-0.56)	<0.0001	0.43(0.34-0.53)	<0.0001
No	ref.		ref.	
District				
Putuo	ref.		ref.	
Shaoxing	0.77(0.62-0.97)	0.0236	0.77(0.62-0.96)	0.0208
Tonglu	0.79(0.60-1.05)	0.1031	0.79(0.60-1.05)	0.1025
Tongxiang	0.38(0.27-0.53)	<0.0001	0.38(0.27-0.54)	<0.0001
Yuhuan	2.09(1.63-2.67)	<0.0001	2.09(1.63-2.67)	<0.0001

OR: odds ratio; OR_a: odds ratio adjusted by age and gender; ref.: reference.

DISCUSSION

Prevalence of hepatitis B

Viral hepatitis is a leading cause of death and disability worldwide, deaths from acute infection, cirrhosis and liver cancer were the tenth leading cause of death worldwide in 1990, while it ranked seventh in 2013. The number of deaths worldwide attributable to viral hepatitis increased by 63% from 1990 to 2013[19].

The prevalence of hepatitis B in all rural residential participants was 4.04% in Zhejiang (It was 3.85% standardized by age and gender). Our results indicated that the Zhejiang rural residential population would be categorized as an intermediate group and that the hepatitis B prevalence was significantly lower than reported 9.8% in 1992 and 7.2% in 2006 across China[7]. Following a series of interventions conducted by the Chinese government, there was a significantly decline of the hepatitis B epidemic. A larger nation-wide survey would be needed to assess the current epidemic of hepatitis B in China to provide the epidemiological features and update the controlling or prevention strategies, especially in the rural population.

Influencing factors of hepatitis B

There was no significant association between hepatitis B prevalence and age in our study. Although, previous studies referred to age as a factor[20-22], and showed that an older age group had a higher prevalence in the population. Our univariate analysis also indicated this phenomenon. We thought this outcome was a result of confounding, by hepatitis B vaccination or other factors. A former study also reported an inverse result[23]. For the factor of gender, the results were varied. Previous studies[11 21 23-25] showed that the prevalence was higher in males than in females; while there was no association found between gender and hepatitis B by one study[20], which was similar to ours.

Our study showed that education was not an independent influencing factor on hepatitis B, which was also noted in other studies[26 27]. However, there could be a possible trend of decreasing hepatitis B prevalence with increasing educational level from our univariate analysis in Table 1; it can be observed that the population with higher educational level had a lower hepatitis B prevalence. Potential reasonable explanations for these phenomena: among those higher-educated population, there are better prevention awareness of infectious diseases and a higher acceptance of vaccination; furthermore, having at least a college education (OR=2.55, 95% CI: 1.28-5.07) was an important predictor of vaccine completion[28].

We found that only 13.48% of all participants had taken a hepatitis B examinations before, and there was a lower prevalence of hepatitis B among those participants; while in those participants who had not been previously examined, there was a higher prevalence. We could infer that those infected by hepatitis B virus, who had not been diagnosed by the examinations, could be the potential sources of hepatitis B. By encouraging people to take part in hepatitis B examinations, along with routine physical examinations, we could benefit: First, find out those who are infected; Second, treat those infected ones immediately; Third, take the right opportunity to raise the awareness of hepatitis B among the population, especially in rural areas.

Compared to other occupation types, service-based tertiary industry of occupation seemed to be a risk factor, along with non-single living (OR_a=2.84, 95% CI: 2.17-3.70). The factors mentioned above had the same feature: likely to result in more communications between people. We should take these into consideration, since hepatitis B is an infectious disease and has a sign of clustering among the population.

Hepatitis B epidemics are scattered in different areas globally[2 22], and hepatitis B prevalences

also varied among different districts in our study. These circumstances would be caused by geography, economic level, population density, living habits or other factors. Economic level seems to be a potential factor, since lower economic level areas such as Yuhuan had a higher prevalence and higher economic level areas such as Shaoxing and Tongxiang had a lower prevalence. Regardless of all features, we should consider district as a non-negligible factor, especially the district with a high prevalence, when developing and implementing strategies for fighting hepatitis B.

Control strategies for hepatitis B

World Health Organization (WHO) adopted the first-ever global hepatitis strategy with a goal to eliminate viral hepatitis B and C as public health threats by 2030, which was defined as a reduction in incidence by 90% in new chronic infections and mortality by 65% for viral hepatitis B and C[29]. Currently, hepatitis B is a major health problem and has a significant socio-economic impact all over the world[30]. HBV vaccination is the mainstay of HBV prevention and is the most effective prevention strategy[31 32].

The Chinese government has made great progresses with hepatitis B vaccination[33]: the national hepatitis B immunization plan was established in 1992. In 2002, the Global Alliance on Vaccine and Immunization (GAVI) partnered with the government of China to provide free hepatitis B vaccine[34] and fully integration into the routine immunization program, and the vaccine was provided completely free to infants, nationally in 2005[35]. The carrier rate in Chinese children aged <5 years fell to less than 1% in 2006, and to 0.32% in 2014, which was 10% in the 1990s[36]. Recently, WHO estimated that new-borns in China, who received a timely birth dose (TBD) and third dose of hepatitis B vaccine (HepB3), was 96% and 99% respectively[37]. Our study showed

that Hepatitis B vaccination (OR_a=0.43, 95% CI: 0.34-0.53) was the protective factors for hepatitis B, and the same results have been observed[12 13 26].

Regarding vaccination coverage related to the economy status, a former study suggested that higher HBV vaccination coverage rates among adults were obtainable. The user fees, time needed for vaccination and travel costs acted as economic barriers to vaccination[38]. Hepatitis B vaccination has been reported as low as 13.89% in rural China[39]. We call for strengthening HBV vaccination in rural areas, and raising the vaccine coverage rate.

Our survey also showed that the vaccination rate was 75.5% in aged <20 years, while it was only 29.8% in aged >20 years. There was a trend that the rate of hepatitis B vaccination was increased when the vaccination programme conducted and expanded since 1992, along with decreasing of the nationwide hepatitis B prevalence. Preventing hepatitis B through vaccination is currently the most efficient way to decrease HBV-related cirrhosis and liver cancer incidence, and reduce the HBV reservoir[30]. The role of the vaccination programme for the effective control of hepatitis B should be emphasized[40]. In the near future, we should focus hepatitis B vaccination efforts on adults, under the consideration of policies for universal vaccination, especially in those areas with high hepatitis B endemicity.

LIMITATION

This study was cross-sectionally designed, and we could not exclude the acute infection case; thus the hepatitis B prevalence may be overestimated in the population when using the HBsAg positive rate as the level of chronic HBV infection, and there was also a certainty of recall bias in this study design. Additionally, the sample sizes were not balanced between districts in our study. We

considered taking a vaccination history of hepatitis B as an indicator of vaccine success due to the effectiveness of vaccination[30]. To interpret the results, we simply divided the variables into a few groups, such as occupation. A more precise classification of factors could be assessed in later studies, along with more potential factors, such as family income.

CONCLUSIONS

In conclusion, though our study showed that the Zhejiang rural area is categorized as an intermediate epidemic level for hepatitis B in China, there remains the important issue and formidable challenge of dealing with the problem of hepatitis B in rural areas among the resident population. Specific methods such as raising the coverage of vaccination particularly in adults, are suitable and effective strategies to prevent and control hepatitis B in Zhejiang rural areas. Furthermore, increasing the percentage of the hepatitis B examinations may also be considered as a potential strategy. The significant findings in this study, with potential implications for public health, would be helpful to China and other countries for the fight against hepatitis B.

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Footnotes

SY and CD contributed equally.

Contributors

LL, JR, BR, JY and SY conceived and designed the study. CD, YC, JW, CY, CP, KX, MD, YL, JL, PY. WR, YQ, QC and YZ collected data, cleaned, and analysed the data and revised the paper. CD and SY wrote the first draft of the paper, contributed to figures and paper preparation and all authors critically revised the paper and gave final approval for publication.

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Competing interests

None declared.

Data sharing statement

No additional data are available.

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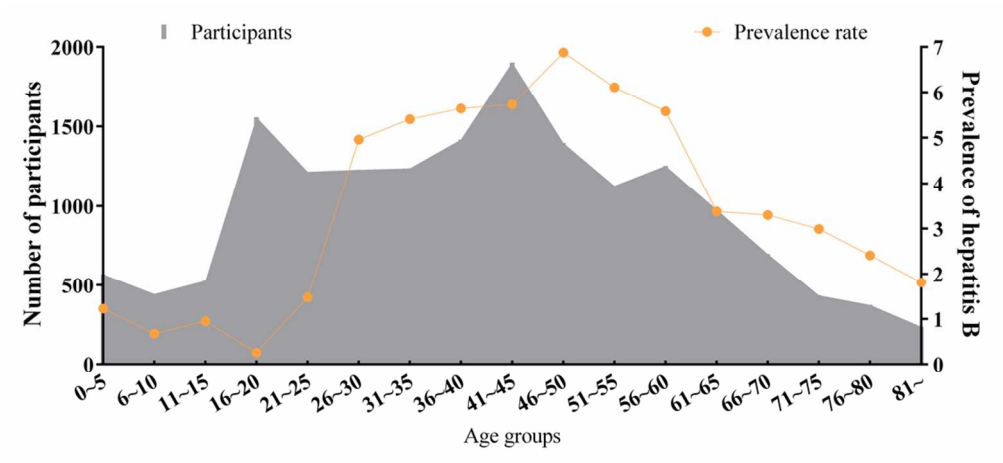
Figure Legends:

Figure 1 The prevalence of hepatitis B among different age groups

Figure 2 The distribution of participants and prevalence of hepatitis B in different districts

Figure 3 The values of OR and OR_a in the logistic models.



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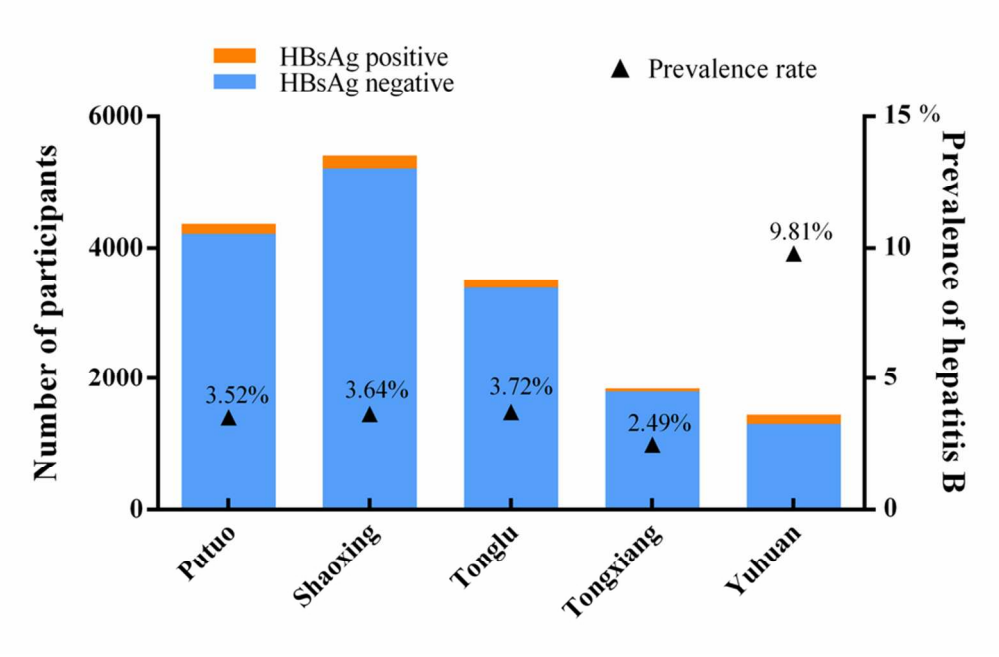

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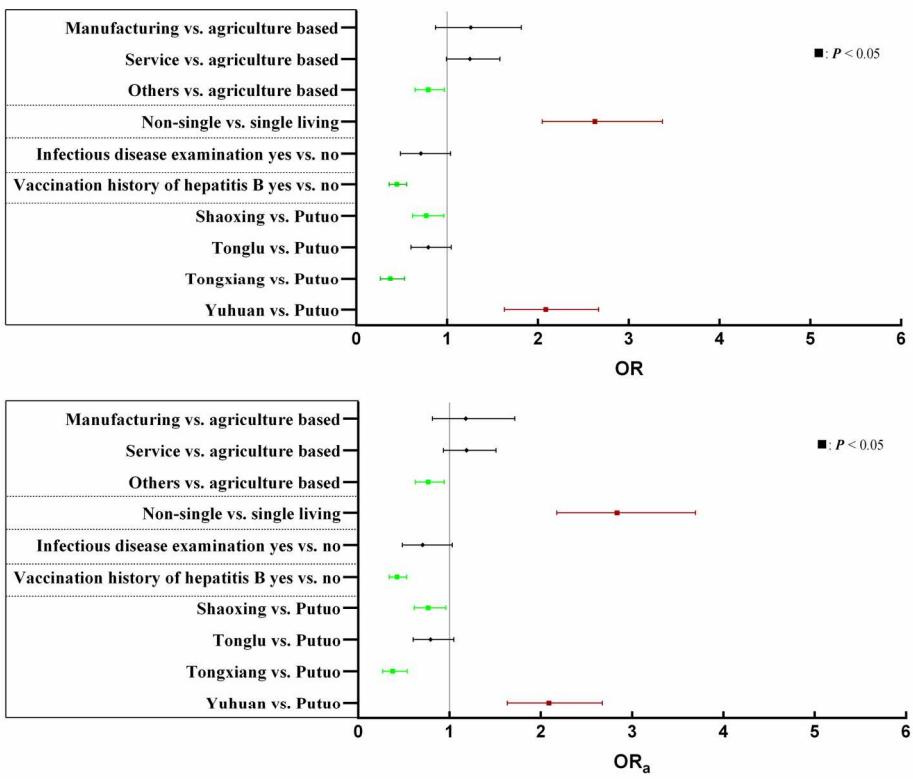

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4, 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	6,7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6,7
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, 8
		(b) Indicate number of participants with missing data for each variable of interest	7
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.