Hepatitis B Needs Assessment - Bylakuppe Tibetan Settlement

Central Tibetan Administration's Department of Health

and Johns Hopkins University

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Table of Contents

Executive Summary

Untreated active hepatitis B leads to liver cirrhosis, liver cancer, and liver failure. A hepatitis B prevalence and treatment needs survey was conducted between July and October 2013 among household residents, boarding school pupils, and monastery residents in Bylakuppe Tibetan settlement. Representative sampling of households was conducted using random number generation; students and monks were invited to participate without random sampling. The survey included a brief questionnaire and laboratory testing from blood samples. In addition to the survey, blood was obtained from each participant for testing for evidence of chronic hepatitis B (hepatitis B surface antigen positive). Participants with chronic hepatitis B had further testing for hepatitis B e antigen and ALT and AST. A portion of participants negative for hepatitis B had further testing to assess cleared prior hepatitis B infection (antibodies to hepatitis B core antibody). We enrolled 2,769 participants in total and 945 household participants from 299 households. The prevalence of chronic hepatitis B among household residents was 11.9%. Of those, 60.7% had "active" chronic hepatitis B as defined by a positive hepatitis B e antigen result. Using published treatment criteria from the United States or Asian countries, approximately 25% of household residents with chronic hepatitis B met treatment initiation criteria (3% of the entire population). Based on this representative survey, 3% of the Tibetan population in India may be candidates for initiation of hepatitis B treatment to prevent liver related death or complications. Additional costing estimates considering treatment costs and costs of managing liver complications of untreated hepatitis B may help with guiding plans for hepatitis B care among the Tibetan population.

Background

Hepatitis B Virus (HBV) infection is a serious global public health concern, with an estimated 240 million people chronically infected world-wide leading to 132,000 deaths annually[1]. Chronic HBV infection is a leading cause of liver-related mortality, resulting from liver failure, cirrhosis, and hepatocellular carcinoma [2]. Hepatitis B is uneven distributed globally and within sub-populations. East Asia and areas of Africa have a high endemicity of chronic hepatitis B, defined as a prevalence of 8% or higher. For example the prevalence is between 5-15% in the People's Republic of China, Taiwan, and Mongolia, and within immigrant communities from these regions, including Tibetans [3][4]. Chronic hepatitis B prevalence is lower (<5%) in Nepal, India, and Bangladesh [5]. In high endemicity regions of Asia, transmission is believed to mostly occur perinatally, from mother to child [2]. Transmission via this route can be reduced with infant vaccination and hepatitis B immunoglobulin and birth and maternal treatment with antivirals active against HBV during pregnancy. Transmission can also occur later in life through blood exposure, sexual intercourse, and use of needles for injection drugs or tattoos [6]. Transmission later in life can be effectively prevented by vaccination.

Effective treatment is also available for individuals with chronic hepatitis B. The increasing availability of some medications, such as tenofovir, entecavir, and lamivudine, opens the possibility of providing treatment for CHB affordable to low and middle income countries. With currently available agents, a clearer understanding of treatment needs, diagnostic limitations, and costs would allow for health system planning for a rational approach to chronic hepatitis B diagnosis and management.

The Tibetan diaspora is a population believed to have a high endemicity of chronic hepatitis B. Furthermore, large Tibetan communities exist in India (approximately 94,000 people), as well as smaller communities in Nepal, Australia, North America, and Europe, as a result of refugee flows from Tibet. These refugee flows started in 1959 and continue to the present. To rationally plan resource allocation for the prevention and management of chronic hepatitis B, accurate prevalence estimates overall and by subgroups of Tibetans are needed but currently lacking. A small convenience sample study done in Nepal reported significantly higher prevalence of chronic hepatitis B among Tibetans living in Nepal compared to the ethnic Nepalese, 16% and 0.7%, respectively [3] and another study completed in villages in China reported a 21% prevalence of chronic hepatitis B[4].

Objectives

The objective of this survey was to determine the prevalence of chronic hepatitis B, identify sub-groups with a higher CHB prevalence, and to assess the treatment need among Tibetans living in India. The overall goal is to enable improved planning regarding prevention and treatment of hepatitis B among the Tibetan population in India by the Department of Health, Central Tibetan Administration. A secondary objective was to provide accurate data for use in advocacy work regarding hepatitis B in the Tibetan population to raise awareness and seek additional funding.

Methods

Three cross-sectional surveys were performed among three populations in Bylakuppe Tibetan settlement: (1) households, (2) a boarding school, and (3) a monastery. Prior to participating, all potential participants aged 18 or older were informed of the study and provided written informed consent. Participants younger than 18 were told about the study, provided assent, and a guardian provided consent. Study procedures were similar for each of the three populations.

Study Procedures

A brief questionnaire was completed that included demographics, place of birth, and hepatitis vaccination and symptom history. Following the questionnaire, a single tube of blood was obtained via venapunture using a serum separation vacutainer tube. Rapid hepatitis B surface antigen (HBsAg) lateral flow testing (Alere Determine HBsAg, Alere, Waltham, Massachusetts, USA or SPAN Crystal HBsAg Device, SPAN Diagnostics, Surat, India) was performed within 5 hours of blood collection at the site of collection or at the local hospital laboratory on serum sample prepared by centrifugation at 1000xg for 10 minutes in the Vacutainer Serum Separation tubes. Serum-separated samples were then transported to a research laboratory for testing as follows: Participants with a positive rapid HBsAg test result had further testing for alanine transaminase (ALT), aspartate transaminase (AST), and hepatitis B 'e' antigen (HBeAg). Participants with a negative HBsAg test had testing for hepatitis B core antibody (anti-HBc). Anti-HBc testing was completed for all community participants with a negative HBsAg test and a randomly selected (by random number generation) subset of monks and students with a negative HBsAg test. In addition, a subset of lateral flow HBsAg positive tests and 300 randomly selected HBsAg negative tests were confirmed by laboratory-based HBsAg ELISA to assess the accuracy of the rapid tests.

Participant sampling

Community mobilization

Prior to the initiation of survey recruitment the survey team from Tso Jhe Hospital, the Department of Health, and Johns Hopkins University sensitized the community to the study. This was achieved through (1) community meetings with presentations and question and answer sessions in each of the 22 residential camps, (2) meetings with the administrative leaders in Dickey Larsoe and Lugsum Samdupling Settlements of Bylakuppe, (3) presentations were made at local schools, including the Tibetan SOS TCV school at Bylakuppe, and (4) a presentation to monks was made at Sera Mey monastery and monastery health and administrative officials were informed regarding the study.

The community engagement and mobilization was critical for smooth recruitment activities. In addition, community leaders provided valuable suggestions and guidance regarding optimizing our recruitment approaches. In addition, community leaders demonstrated a clear understanding of issues around hepatitis B and the hepatitis B survey.

Household

Random household sampling was performed within the residential community using satellite images from Google Earth that were imported into ArcGIS with polygons drawn around each of the 22 residential 'camps' forming the settlement. Random GPS coordinates were produced in each of the 22 polygons within ArcGIS using python code (ESRI, Redlands, California, USA). We selected the three houses closest to the coordinates for sampling. All individuals residing in the house (defined as spending the prior night sleeping in the house) were invited to participate (Figure 1). Through this method we obtained a representative population sample best able to reflect the true population prevalence of chronic hepatitis B infection.

Figure 1: Household survey

Boarding School (Bylakuppe SOS TCV)

All students at the school were invited to participate in the study during recruitment periods. We sought high uptake to reduce bias in sampling. Bias could occur if students more or less likely to have chronic hepatitis B differentially choose to come to participate.

Monastery (Bylakuppe Sera Mey)

All monks at the monastery were invited to participate in the study during recruitment periods (Figure 2).

Figure 2: Community mobilization at the monastery

Definitions

Because most individuals in this population are believed to have been exposed early in life, we used a single HBsAg positive test as a surrogate for chronic hepatitis B. We acknowledge that the clinical definition of chronic hepatitis B is two positive HBsAg tests at least 6 months apart but selected a single test because most individuals are expected to have been infected early in life and it is unlikely that many or any of the positive HBsAg tests will reflect acute hepatitis B infection. Prior exposure was defined as HBsAg negative and anti-HBc positive. Individuals were classified as never infected if they were HBsAg negative and anti-HBc negative. Prior HBV vaccination was based on self-report (confirmed with a vaccination card when available).

ALT and AST ranges were based on the laboratory test reference range which went to 40 IU/mL. We classified participants with CHB into management categories based on recommendations from the American Association for the Study of Liver Diseases [7]. In the absence of HBV DNA data we followed the 'HBeAg positivepathway' classifying into the same three categories based on ALT as with the HBeAg positive patients.

Table 1: Chronic hepatitis B treatment recommendations (summarized from the American Association for the Study of Liver Disease)[7]

HBeAg status	ALT	Additional testing	Treatment recommendations
HBeAg (+)	ALT >2x ULN	Repeat ALT in 1-3 months	Treat if ALT remains elevated or evidence of liver disease
HBeAg (+)	ALT 1-2x ULN	Repeat ALT testing in 3 months; if >40 yrs old & ALT remains 1-2x ULN, consider invasive or non-invasive testing for liver fibrosis	Depends on repeated ALT results
HBeAg (+)	ALT in normal range	Repeat ALT in 3-6 months, repeat HBeAg in 6-12 months	Depends on repeated ALT results
HBeAg (-)		Obtain HBV DNA level	Depends on HBV DNA level

Laboratory testing

Rapid HBsAg kits were used (Determine) on serum. Whole blood samples were collected in serum separation tubes and centrifuges to obtain serum. Tubes were then packed in cooler boxes and shipped each week to YRG Care Laboratory in Chennai for laboratory testing for ALT and hepatitis B e antigen or for hepatitis B core antibody.

Analysis methods

Chi-square tests were employed to assess univariable analysis of HBV status and participant characteristics. Stepwise multiple logistic regression was performed to determine the odds ratio for infection given participant demographics and survey responses. We performed separate logistic regression analysis for the community and the school and monastery because we used random sampling with the community; whereas, we invited all monastery and school residents to participate. All analysis were two-sided, with alpha=0.05. Models were assessed for goodness of fit using the Hosmer-Lemeshow test. Statistical analysis was performed using STATA 13 (StataCorp. College Station, TX: StataCorp LP).

Results

Demographics

We recruited 2769 participants, 945 (34.1%) were from 299 randomly selected households (size ranged from 1 to 11 family members), 1153 (41.3%) were from the boarding school, and 671 (24.6%) were from the monastery. Three households declined participation. Monks and students were passively recruited and thus non-participation was not determined for these groups. Overall, the median age was 18 years with a range of 3 months to 94 years; 61% were men (due to recruitment in the monastery; Table 2). The majority of participants were either born in India (1466, 52.9%) or Tibet (1122, 40.5%).

Table 2: Participant Demographics by Sampling Location

	Household	boarding school	monastery	total
	n (%) Median (IQR)	n (%) Median (IQR)	n (%) Median (IQR)	n (%) Median (IQR)
number	945	1,153	671	2769
Sex, Male	455 (48%)	561 (49)	671 (100)	1680 (61%)
Age (years)	42 (23, 61)	16 (12-18)	22 (15, 33)	18 (14, 36)
<15	162 (17)	464(40)	165 (25)	791 (29)
15-29	139 (15)	689 (60)	280 (42)	1108 (40)
30-59	395 (42)	0 (0.0%)	214 (32)	609 (22)
≥60	249 (26)	0 (0.0%)	12 (1.8)	261 (9.4)
Birth Location				
India	581 (62)	641 (55)	244 (37)	1466 (53)
Tibet	331 (35)	471 (41)	320 (48)	1122 (40)
Nepal	2 (0.2)	24 (2.1)	97 (15)	123 (4.4)
Unknown	31 (3.2)	17 (1.5)	10 (1.5)	65 (2.3)

Chronic Hepatitis B

A total of 247 participants (8.9%; 95% CI: 7.9, 9.9) were positive for HBsAg. Focusing just on the household sampling, 11.9% (95% CI: 9.9, 14.1) were positive for HBsAg (Figure 3). Hepatitis B e-antigen testing and ALT and AST were performed on 244 of 247 HBsAg positive individuals. Three participants were excluded from testing due to insufficient sample volume. One-hundred and forty eight (60.7%) HBsAg positive participants were found to be HBeAg positive. Among HBeAg positive participants, 26% (43/146) had an ALT above the upper limit of normal compared to 19% (18/97) of HBeAg negative participants (chi-square p=0.06). Only 7% (17/244) participants had an ALT >2 times the upper limit of normal.

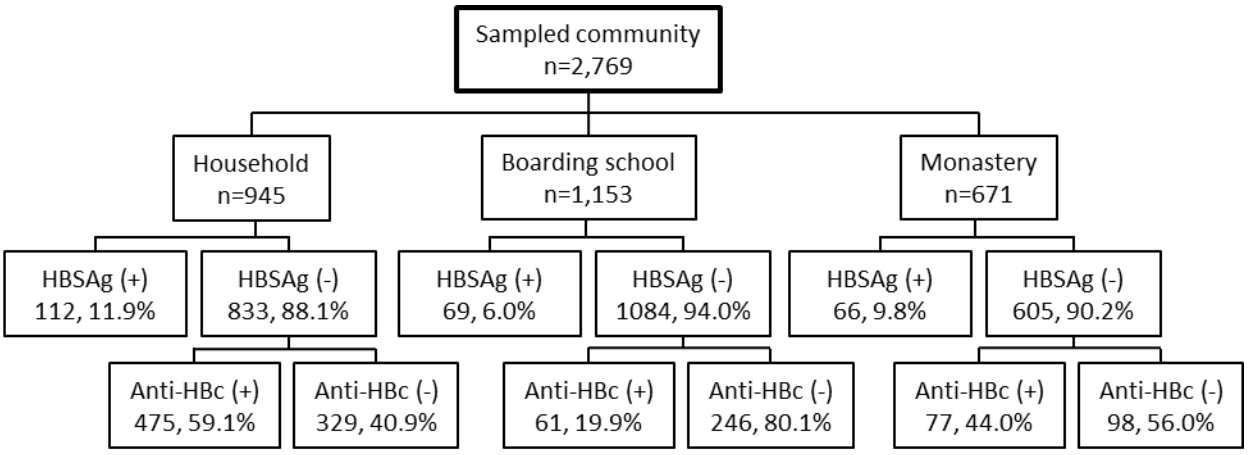

Figure 3: Hepatitis B serology by population surveyed

The median age of HBsAg positive participants was 30 years (IQR: 18-44), compared to 18 years for uninfected individuals (IQR: 13-34). Infection rates were slightly, but non-significantly higher in males than females, and greatest in individuals between the ages of 30-59 (Table 3). HBsAg positivity was higher in those born in Tibet than those born in either India or Nepal (12.4% vs 6.8% vs. 2.4%, p< 0.001).

From the household sampling, individuals with other family members testing positive for either HBsAg or anti-HB core were 3.4 times (95% CI: 2.0-5.6) more likely to have chronic hepatitis B, after adjusting for age. There was also clustering of laboratory-based chronic hepatitis B within households; a participant in a household with another participant with chronic hepatitis B was more likely to have chronic hepatitis B compared to those without a family member tested positive for HBsAg during this study (19.3% vs. 9.4% prevalence, p< 0.001).

Table 3: Characteristics by Hepatitis B surface antigen status

	HBsAg Negative(n=2522)	**HBsAg Positive(n=247)**	**P**
	n (%) Median (IQR)	n (%) Median (IQR)	
Age (years)	18 (13-34)	30 (18-34)	0.224
Age Category			**<0.001**
<15	770 (97)	21 (2.6)	
15-29	1010 (91)	98 (8.8)	
30-59	512 (82)	109 (18)	
≥60	230 (92)	19 (7.6)	
Gender			0.1
Male	1518 (90)	162 (9.6)	
Female	987 (92)	84 (7.8)	
Sampling Location			**<0.001**
Household	833 (88)	112 (12)	
School	1084 (94)	69 (6.0)	
Monastery	605 (90)	66 (9.8)	
Birth Location			**<0.001**
India	1366 (93)	100 (6.8)	
Tibet	983 (88)	139 (12)	
Nepal	120 (98)	3 (2.4)	
Unknown	53 (91)	5 (8.8)	
HBV Vaccine			**<0.001**
Yes	1533 (96)	56 (3.5)	
No	605 (78)	169 (22)	
Unknown	384 (95)	22 (5.4)	
Family History of HBV (household only)			**<0.001**
Yes	188 (81)	45 (19)	
No	645 (91)	67 (9.4)	

HBsAg: hepatitis B surface antigen

Prior HBV exposure

Prior HBV exposure with subsequent control (anti-HBc positive and HBsAg negative) was identified among 613 (35%; 95% CI: 33-37) of all participants. Among the household population the prevalence of

prior HBV exposure was 50%. Among the household sample, when combining participants positive for either HBsAg+ or anti-HBc antibody, 62% (95% CI 59, 65) either have current CHB or controlled infection (Figure 1).

Hepatitis B treatment needs

Of the participants we identified with chronic hepatitis B and an age greater than 15 years, 16 (7%) had an ALT greater than two-times the reference range, suggesting an indication for treatment (if the elevation is persistent). Another 37 (17%) had an ALT elevation between one and two time the reference range, placing them in the category of re-test ALT in 3 months and assess for liver fibrosis to guide treatment. The majority, 163 (76%), of participants had normal range ALT placing them in the category of monitoring again in 6 months and only evaluating further and considering treatment if the ALT were to rise above the reference range.

Limitations

This survey provides a cross-sectional 'snap-shot' of hepatitis B prevalence and treatment needs. Because of the cross-sectional nature of the survey, we are unable to determine timing of most hepatitis B transmission. We believe some transmission continues to occur at birth, based on an infant born to a mother with chronic hepatitis B who also was HBsAg positive at 3 months of age. It is possible that adult transmission is occurring also – mostly sexually – but this survey does not provide any specific findings regarding adult transmission.

An additional limitation is the possibility of an underestimate of participant ALT levels. ALT degrades over time and it is possible that our approach to batched shipping of samples to Chennai for testing led to an under estimate of ALT levels.

Key points

- Prevalence of chronic hepatitis B (community survey): 11.9%
- Prevalence of 'active' chronic hepatitis B (e antigen positive) in the community survey: 41%
- Groups with higher prevalence of chronic hepatitis B:
    - Living in a household with someone else with hepatitis B
    - Birth in Tibet (compared to India or Nepal)
    - Aged 18 to 44 years old
    - Not having been vaccinated against hepatitis B
- Prevalence of current chronic hepatitis B or cleared hepatitis B infection in household sample: 62%
- Hepatitis B treatment needs based on the results from the household sampling: 1-3% of the population are probable treatment candidates, 9% need routine monitoring to assess liver inflammation and determine treatment needs

Conclusions

This survey confirms the high prevalence of chronic hepatitis B in the Tibetan population in India. Furthermore, through the use of representative sampling this survey provides an accurate population-level estimate of chronic hepatitis B prevalence in Bylakuppe and, we expect, throughout Tibetan settlements in India. These data are very valuable for estimating the likely burden of future liver disease in this population in the absence of providing treatment and an estimate of current treatment needs.

We identified important associations of a higher prevalence of HBV exposure and CHB with birth in Tibet. The potential for a higher CHB prevalence among people living in Tibet was suggested by a convenience sample study from Tibet in which the 26% of participants were HBsAg positive [9].

We believe that our findings reinforce the importance of infant HBV vaccination. Increasing HBV prevalence in the age group between 15 and 59 may be an indication of ongoing HBV transmission among the population born before the start of infant HBV vaccination. If so, adolescent and young adult catch-up vaccination may be prudent. However, in a cross-sectional study such as ours, we are unable to distinguish between ongoing exposure risks versus a cohort effect to explain the increasing HBV prevalence with age.

Tibetans in this population generally give birth in hospitals where vaccination and hepatitis B immune globulin are available. However, transmission is not always prevented – as observed in our study with at least one of the mother to child transmission cases. Consideration for maternal treatment with antiviral medication may be reasonable to prevent these infections. Previous studies have found that 8 weeks of lamivudine treatment in late pregnancy significantly lowers maternal HBV viral load and reduces the risk of HBV transmission, with limited health consequences[10].

Using the AASLD recommendations 1% of the adult population in our survey fits into the category of needing treatment for CHB (after confirming sustained ALT elevation). For another 2% of the adult population follow-up ALT and liver histology testing is indicated to determine treatment need. Finally, to adhere to guidelines, 8.8% of the adult population should have routine six-monthly follow-up to monitor for inflammation, fibrosis, and hepatocellular carcinoma. These findings highlight the range of management needs of individuals diagnosed with CHB, the complexity of applying current management guidelines (guidelines available from the Asian Pacific consensus on CHB treatment, European Association for the Study of Liver Disease, and others have similar algorithms and complexity [7, 11, 12]), and the large proportion of the population who need long-term medical follow-up based on CHB management guidelines. Delivering the recommended level of laboratory testing and antiviral treatment to 10% of the population of Tibetans in India (and likely elsewhere in the diaspora) will require considerable health care resources. If we extend these percentages to the approximately 94,000 Tibetans living in exile in India (Based on Tibetan Demographic Survey, 2009) with an estimated one-half over the age of 15, approximately 8000 would need repeated testing, 360 adults are likely to meet recommendations for CBH treatment after confirming an elevated ALT.

Recommendations

Vaccination

Vaccination remains the cornerstone of hepatitis B prevention. Vaccination should start at birth followed by 2 additional vaccinations (three shot series) with consideration for a forth vaccination as a booster. In addition, catch-up vaccination for recent immigrants from Tibet should be considered.

Prevention of mother to child transmission

In addition to vaccination, the use of hepatitis B immune globulin shortly after birth for babies born to mothers with chronic hepatitis B reduces the chance of chronic hepatitis B in the baby. This practice should be continued and strengthened in the Tibetan Health system and Indian hospitals at which Tibetan women give birth. Free screening tests for babies born to mothers with chronic hepatitis B can also be considered. These should ideally be performed at 6 or 12 months (and should not in any way affect the routine hepatitis B vaccination schedule).

The use of specific antivirals during pregnancy can further reduce the risk of transmission. The costs and benefits of this approach should be considered further before instituting such as policy.

Hepatitis B treatment

At present, 12% of the population has chronic hepatitis B. For them, vaccination is too late. The optimal care for this segment of the population is to provide laboratory diagnosis and assessment in the form of hepatitis B surface antigen screening with the use of rapid point-of-care tests followed by testing for hepatitis B 'e' antigen, ALT level, and, possibly, HBV DNA. Ultrasound to assess for liver cancer is appropriate for those at increased liver cancer risk based on age, sex, and comorbidities.

Notably, laboratory assessment alone will not prevent a single death from liver disease. Treatment of hepatitis B is essential to reduce liver-related deaths from hepatitis B. A guideline for basic assessment and treatment for use in the Tibetan community would assist clinicians, policy makers, and potential funders to rationally and consistently provide hepatitis B care. Having a rational guideline is especially important for cost effective and appropriate use of public health resources to provide care for hepatitis B patients. At present, "needy cases" receive support from the Central Tibetan Administration's Department of Health. Guideline-based decisions could lead to better resource allocation to provide for more Tibetans. Specifically seeing how funds will be spent may also encourage added generosity of outside funders.

Cost assessment

Because this survey was cross-sectional, we are unable to directly calculate or estimate the morbidity benefit of hepatitis B treatment. Modeling of potential reduced morbidity and reduced cost could be a next step. This could be completed using data from this survey combined with studies from elsewhere in Asia on the natural history of untreated hepatitis B. We suggest that an important next step will be generating a simple model or adapting available models to predict future costs of either hepatitis B treatment or cost to the individual or health system for management of complications of untreated hepatitis B.

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