Original Article

Hepatitis B Viral Load Monitoring Insight Across India: Needs Lucidity on Burden of Silent Killer

Chaitali Nikam[1,*], Caesar Sengupta[2], Praveenkumar Ganesan[3]

[1]Applied Biology Manager TB and PCR Laboratories, Thyrocare Technologies Limited, Navi Mumbai, Maharashtra, INDIA.
[2]General Manager, Thyrocare Technologies Limited, Navi Mumbai, Maharashtra, INDIA.
[3]Molecular Biology, Thyrocare Technologies Limited, Navi Mumbai, Maharashtra, INDIA.

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ABSTRACT

Background: Hepatitis B virus (HBV) infection is one of the most serious infectious diseases that needs a critical attention in India. The current study aims to estimate the prevalence of the seropositive patients to assess the burden of the disease. **Methods:** Blood samples were collected from 14,440 individuals for the diagnosis of hepatitis B surface antigen using the real-time PCR quantification between July 2017 to July 2018. **Results:** The mean age of the participants is 36.9 ± 14.4 in years. In total, 9657 (67%) were found to be positive for HBV infection and positivity was higher in males than females (63% vs. 37%) (odds ratio (OR)=1.10;95% CI;1.031-1.189). The highest Hep B prevalence was 50.8% in adult (19-49 years) age group and the lowest were 0.2% in less than 6 year age. **Conclusion:** The adult population is most commonly affected and this raises the alarm to take stringent infection-control measures to prevent the spread of HBV infection in the population.

Key words: Hepatitis, Hepatitis B Virus, HBV viral load, Seropositive, HBV prevalence, India.

Correspondence:
Dr. Chaitali Nikam,
Applied Biology Manager TB and PCR laboratories, Thyrocare Technologies Limited,
Navi Mumbai-400703, INDIA.
Phone no: +91 9967459591

Email: chaitali_nikam@ymail.com

INTRODUCTION

Hepatitis (Hep) refers to an inflammatory condition of the liver and viruses are the most common cause, referred to as types hepatitis A, B, C, D and E. Particularly, types B and C lead to chronic disease condition.[1,2] The execution of effective vaccination programs in many countries has resulted in a substantial decrease in the occurrence of new hepatitis B virus (HBV) cases. However, HBV infection remains an important cause of morbidity and mortality.[2,3] In India, viral hep is recognized as a serious public health problem. In particular, HBV infection is one of the most serious infectious diseases pose a significant social and economic burden on the health system. India is considered as intermediate endemic country with 4% to 7% prevalence of HBV. Over the past three decades, public health activities to control viral hep have increased progressively.[4]

The WHO estimated around 257 million people are living with HBV infection based on hep B surface antigen positive. In 2015, HBV resulted in 8,87,000 deaths, mostly from cirrhosis and hepatocellular carcinoma (HCC).[2] In South-East Asia, 100 million people are currently estimated to be living with HBV, and 30 million with HCV. It has been estimated that India has around 40 million HBV carriers and harbors 10 –15% of the entire pool of HBV carriers of the world.[5] As per latest estimates, 40 million people are chronically infected with HBV.[6] Out of the 26 million infants born every year in India; around 1 million, carries the life time risk of developing chronic HBV infection.[7]

However, health care associated infection remains a significant concern in both resource-poor[8,9] and well-resourced settings.[10] The data from numerous studies show comprehensive terrestrial variations, which may represent differences in socio-economic status or traditional practices in different provinces. There is a dearth

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of large scale population studies of the prevalence of HBV in India. Some of the available data is based on blood bank screening, community based studies, meta-analysis or area based genotyping studies, which can have its integral bias and may not accurately reflect the national prevalence.[10] Most of the data is based on antigen antibody and reflects surface antigen (sAg) reactivity. Some of the studies and meta-analysis is entirely based on the estimate the sero-prevalence of HBs-Ag and antibodies with varied distribution. The epidemiology of hep B can be described in terms of the prevalence of hep B surface antigen (HBsAg) in a population, broadly classified into high (8%), intermediate (2% –7%) and low prevalence (2%) areas.[10,11]

At present, molecular epidemiology in addition to the traditional sero-epidemiological studies have improved understanding of the significance of the problem, particularly in terms of development of disease and formulating management strategies by monitoring treatment of the seropositive patient. In this situation, an effective diagnosis presenting high sensitivity and specificity is crucial. Each detection method presents advantages and limitations. Although several previous studies have shown HBV prevalence, burden studies across India depending on antigen antibody or surface antibody testing studies. But to our knowledge, this is the first report describing HBV seropositive participants, across the country based on molecular testing of 14,440 samples at one setting.

We attempted to give insight regarding state wise HBV viral load monitoring, testing, distribution received at Thyrocare laboratory along with state wise percentage (%) positivity, Gender distribution, age wise male - female categorical data in the form of percentage and frequencies. This data is calculated from the hep B seropositive participants from different states across the country. Status of seropositive participants is unknown for Chronic Hep B (CHB), Acute Hep B (AHB), liver diseases (LD), Chronic liver diseases (CLD) and HCC.

MATERIALS AND METHODS

Sample Collection, Transportation and Settings

Total 14,440 Ethylenediaminetetraacetic acid (EDTA) blood Samples were collected through Thyrocare service providers (TSPs) present all over the country. Data generated for one year from July 2017 to July 2018. Samples were transported at desired temperature with mandate work order entries to Central Processing Laboratory (CPL) of Thyrocare. Samples were accepted from all age groups without any defined age criteria. Sample storing, DNA Extraction, PCR set up, data analysis was performed in CPL at Thyrocare Technologies Limited, Navi Mumbai, India.

Ethics and confidentiality

This paper is exempt from ethical committee approval as the samples were transported via unique barcode through TSPs with no traceability to the logistics or transportation team. Reports were released online with unique access to each of TSP with user name and password and the patients' details were thus kept confidential.

HBV DNA extraction

Only non-hemolyzed plasma samples were included in the study. Nucleic acid extraction was performed using QIAamp DSP Virus/Pathogen Mini kit in QIAsymphony SP/AS - an automated extraction system, according to manufacturer's recommendation.

Real Time PCR Assay performance

Purified samples then transferred manually to the QIAgility module (separate operation) for assay setup.[12] The QIAgility sets up the PCR reaction by mixing master mix and DNA template. The master mix contains reagents and enzyme for the direct detection and specific amplification a 134-bp region of the HBV core gene. The real-time PCR was performed on Rotor-Gene Q instruments as per the cycling conditions described by the manufacturer. Data were analyzed with the Rotor-Gene Q software version 2.02 by adjusting thresholds of 0.03 to 0.04 to detect signals from HBV target and the internal control (IC). Quantification of HBV DNA was determined by using 5 external standards. The linear range of quantification is from 40 to 2.0×10^7 IU/mL (1.5-7.3 log10 IU/mL).

Statistical tests

Continuous data was expressed as mean ± standard deviation (SD). The categorical data is summarized as frequencies and percentages. The continuous variables are analyzed using unpaired t test. Odds ratio with 95% confidence intervals was calculated for categorical data and p value <0.05 was considered as statistically significance. Statistical analyses were performed using IBM SPSS Version 21.0 and Microsoft Office Excel 2007.

RESULTS

Characteristics of the Study population

This study includes 14,440 participants between the age of one year to 99 years. Among these, 121 participants (0.8%) were included from Bangladesh and Bahrain. The mean age of the participants is 36.9 ± 14.4. Overall

9657 (67%) samples were HBV positive with inclusive of 68 samples (n=121) from Bangladesh and Bahrain region and 4873 (33%) were HBV negative. The male to female ratio among the study participants is 63% and 37% respectively with indicative odds ratio (OR) of 1.10 (95% CI: 1.031- 1.189).

In India, 67% (9589/14,319) samples were found to be positive for HBV infection with inclusive of 62.9% of males and 37.1% of females with indicative OR of 1.09 (95% CI: 1.022-1.179). The mean age of the HBV positive participants was 36.4 ± 14.2 and the mean age of the HBV negative participants was 38.0 ± 14.9 and statistically significant difference (p<0.0005) was observed between the groups (Table 1).

Hep B seropositivity based on age group of the participants inclusive of Bangladesh and Bahrain

The study participants with inclusive of Bangladesh and Bahrain is broadly classified into pediatric (0-6 years (yrs.)), children (7-18 yrs.), adults (19-49 yrs.), mid ld group (50-65 yrs.) and old group (66 yrs. and above). We also carried out gender wise systematic analysis for HBV positive and negative results of study participants for better lucidity on age groups and gender bias if any; along with percentages.

In total 75% (10787/14400) of the seropositive participants were from adult group (19 to 49 yrs.) coalescing from all states inclusive of Bangladesh and Bahrain of which, 68% (7340/10787) were tested positive and 32% (3447/10787) were tested negative. Total 17% (2445/14440) were from mid old group (50 to 65 yrs.); of which 63.1% (1544/2445) were tested positive and 36.9% (901/2445) were tested negative. These two yrs. groups were major age groups contributing 92% of total data (Table 2).

Hep B seropositivity based on age group of the participants (India)

We further calculated the age-wise distribution of study samples based on hep B seropositivity. As the result shows, majority of the study participants were from adult group (19 to 49 yrs.) as 74% (10692/14410) coalescing from all states. Of which, 50.8% (7280/14319) were tested positive and 23.8% (3412/14319) were tested negative followed by old age (10.7%; 1538/14319) group. The age-wise distribution of hep B seropositivity is summarized in Table 2. The adult and old-age groups were the major constitutions of hep B seropositivity contributing 61.5% of total positive cases (Supplementary Table 1) and statistically significant difference was observed between the groups (p<0.0005).

Systematic analysis of gender wise bifurcation of data along with age groups providing significant lucidity on age-wise percent positivity and ratio of male and female. In 0-5 yrs. of age group; sample count is relatively low as compared with 5-10 yrs. Also positivity rate is much lesser as 63.3% over 75.5% respectively. Also sample count ratio of male over female was 1:2 and 1:3.5 in 0-5 yrs. and 5-10 yrs. of age groups respectively. As compared to any other age group the highest positivity in male and female participants was observed in 5-10 yrs. followed by 20-30 yrs. and 40-50 yrs. respectively. Apart from these major observations, rest of the ratios and percentages are in accordance with different age groups (Supplementary Table 1).

Table 1: Hep B seropositivity based on Gender of the participants in India.

Gender	Positive n (%)	Negative n (%)	Total	Odds ratio (95% CI)
Female	3559 (24.9)	1860 (13)	5419 (37.9)	
Male	6030 (42.1)	2870 (20)	8900 (62.1)	1.098 (1.022 – 1.179)
Total	9589 (67)	4730 (33)	14319 (100)	

n=number of samples; %, Percentage; CI, Confidence Interval

Table 2: Hep B seropositivity based on age group of the participants across India.

Age Groups (yrs.)	Test (n=14319)		Total (%)
	Positive (%)	Negative (%)	
< 6	31 (0.2)	18 (0.1)	49 (0.3)
6 – 18	292 (2)	132 (0.9)	424 (3)
19 – 49	7280 (50.8)	3412 (23.8)	10692 (74.6)
50 – 65	1538 (10.8)	890 (6.2)	2428 (17)
> 65	448 (3.2)	278 (1.9)	726 (5)
Total	9589 (67)	4730 (33)	14319 (100)

Yrs, Years; n=number of samples; yrs, years; %, Percentage

Hep B seropositivity mapping for the study participants from India

We further mapped the distribution of Hep B seropositivity at nationwide. We removed few states which having less than 2 samples from the analysis such as Himachal Pradesh, Manipur and Tripura. Figure 1 represents the distribution of state-wise Hep B seropositivity. Remaining states were categorized based on the positive rates as more than 70% positive includes Delhi (74.3%), Uttarakhand (72.2%), Haryana (71.4%), Karnataka (70.6%), Telangana (70.6%), and Punjab (70.4%); positivity rate more than 60% but less than

Supplementary Table 1: Hep B seropositivity based on age and gender of the participants across India [n (%)].

Gender		Male		Female		Total	
Test result		+	-	+	-	+	-
Age-group (yrs.)	0 - 5	23 (69.7)	10 (30.3)	8 (50)	8 (50)	31 (63.3)	18 (36.7)
	6 - 10	60 (78.9)	16 (21.1)	14 (66.7)	7 (33.3)	74 (76.3)	23 (23.7)
	11 - 20	424 (68.9)	191 (31.1)	280 (66.2)	143 (33.8)	704 (67.8)	334 (32.2)
	21 - 30	1796 (71.2)	727 (28.8)	1535 (66.5)	773 (33.5)	3331 (69)	1500 (31)
	31 - 40	1501 (68.8)	680 (31.2)	757 (65.9)	392 (34.1)	2258 (67.8)	1072 (32.2)
	41 - 50	1063 (65.3)	565 (34.7)	481 (69.4)	212 (30.6)	1544 (66.5)	777 (33.5)
	51 - 60	701 (64.5)	385 (35.5)	313 (61.7)	194 (38.3)	1014 (63.7)	579 (36.3)
	61 - 70	365 (61.9)	225 (38.1)	133 (55.9)	105 (44.1)	498 (60.1)	330 (39.9)
	71 - 80	84 (57.1)	63 (42.9)	34 (59.6)	23 (40.4)	118 (57.8)	86 (42.2)
	81 - 90	10 (55.6)	8 (44.4)	4 (57.1)	3 (42.9)	14 (56)	11 (44)
	91 -99	3 (100)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)
Total		**6030**	**2870**	3559	1860	9589	4730

n=number of samples; %, Percentage; yrs, years; +, Positive; -, Negative.

70% includes, Madhya Pradesh (69.6%), Jammu and Kashmir (69.5%), Odisha (69.2%), Gujarat (68.6%), Bihar (68.5%), Chhattisgarh (68.1%), Uttar Pradesh (67.9%), Jharkhand (67.5%), Andhra Pradesh (66.6%), Tamil Nadu (66.6%), west Bengal (66.1%), Kerala (64.5%), Chandigarh (64%) and Maharashtra (60%); positivity rate more than 50% but less than 60% includes, Rajasthan (57.6%) and Assam (54.5%) and Goa has shown lowest positivity rate; 34%.

Proportion contribution of Hep B seropositive participants by the States of India

As shown in Supplementary Figure 1, states were divided based on the distribution and contribution of total Hep B seropositive cases collected. The states contributing for more than 8% of total sample size are placed discretely which include Bihar (*n*=2066, 22%), Maharashtra (*n*=1292, 13%), Karnataka (*n*=925, 10%), Andhra Pradesh (*n*=745, 8%). The states contributed the total samples between 300-600 include, Uttar Pradesh, Madhya Pradesh, West Bengal, Tamil Nadu, Telangana, Odisha and Delhi; collectively contributing 33% (*n*=3182). The states contributed the total samples between 50-300 include Punjab, Jharkhand, Haryana, Jammu and Kashmir, Kerala and Chhattisgarh contributing 12% (*n*=1161) of total sample size. The states contributed the total samples less than 50 include, Manipur, Gujarat, Himachal Pradesh, Assam, Uttarakhand, Rajasthan, Goa, Tripura and Chandigarh contributing 2% (*n*=217) of total sample size (Supplementary Figure 1).

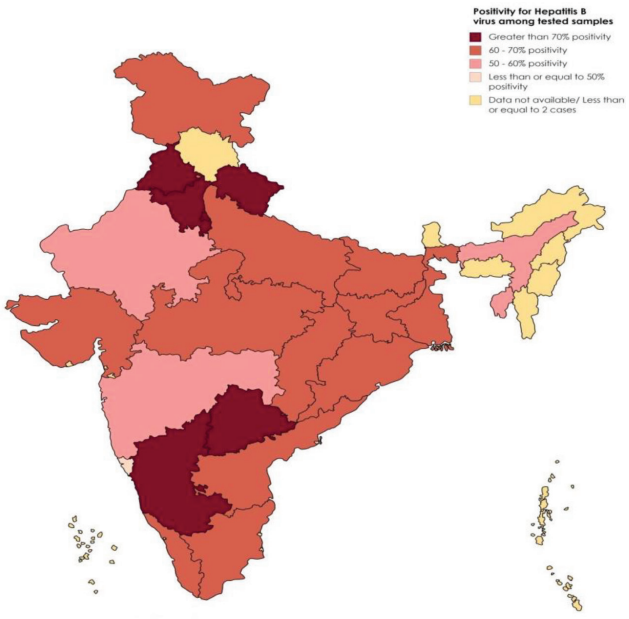
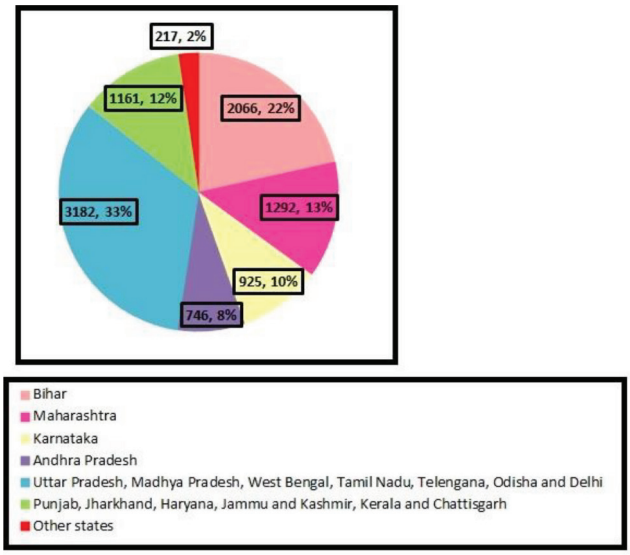


Figure 1: Hep B Seropositivity mapping of states in India.

State wise proportion of Male and Female hep B seropositive participants

Unable to witness a particular trend over gender preference; as in general hep B seropositivity rate was higher in males than females (63% vs. 37%). But in some states the hep B seropositivity rate was observed higher in females and vice-versa. Such as Chandigarh showed 68.8% positivity rate in females over 61.1% in males; Goa showed 47.2% positivity rate in females over 34% in males, J&K showed highest percent positivity in females (74.4%) over males (66.4%), Jharkhand showed 69.2% positivity in female over males (66.4 %),



Supplementary Figure 1: Contribution of Hep B seropositive.

Karnataka has 71.9% and 70% positivity in female and in males respectively. Kerala possesses minor as 0.2% of difference in females (64.6%) and males (64.4%), Odisha, Telangana, and West Bengal has showed 70.2% and 68. and %, 70.9% and 70.5, 66.9 and 65.7% positivity in females and males respectively. In rest of the states it is dominated by males (Supplementary Table 2).

DISCUSSION

Geographical position of India is between West and Central Asian countries and East Asian countries, having different HBV genotype distributions. Gene flow from these neighboring countries due to, anthropological immigration in the past years has contributed to noteworthy genetic, geographic and socio-cultural diversity of the Indian population.[13,14] Among the South-East Asian countries, India is in intermediate zone of prevalence (2-5%).[15] India reported a 3.7% point prevalence which is equal to 40 million HBV carriers in India.[16]

India is a vast country, comprised of multi-ethnic communities with wide variations in culture, ethnicity, food habits, and lifestyle of different communities and thus infectious and with chronic disease patterns.[17,18] Apart from exposure from peripheral sources, interfamilial accumulation of HBV infected persons in a family has been well documented in India. Contamination of surfaces is widespread in homes of chronically infected persons. This may explain the non-sexual interpersonal spread of HBV. Household contacts of subjects with chronic HBV infection are known to be at high risk of acquiring infection through multiple modes.[19-21] High rates of these infections in many South Asian countries are attributable to poverty, unhygienic living conditions, illiteracy, unsafe blood supply, poor medical facilities, and reuse of contaminated syringes, unsafe sexual practice, and frequent use of intravenous drugs.

Data generated from this single site study showed, 76.4% of the seropositive participants were from adults (19-49 yrs.) and showed 50.8% of positivity rate. This peaking rate in adulthood in Indian population has been observed in earlier studies as well.[22] Previous study from cases of eastern India revealed that interfamilial horizontal transmission is more significant mode of transmission than sexual mode of transmission in later life for maintaining HBV carrier pool in community.[22] Also as compared to any other age group, the highest positivity in male participants was observed in 5-10 yrs which is 78.9%. It has been projected that Hep B infection is largely acquired by horizontal transmission in childhood and perinatal transmission plays a less important role. However the knowledge of dynamics of HBV transmission is imprecise and the role of perinatal transmission and horizontal transmission of this disease among children is based on inadequate evidence. The contribution by vertical transmission may be underestimated if we look at the high prevalence of replicative markers in HBsAg-positive pregnant women as reported earlier.[20]

In this study, while mapping percentage of positivity across states we didn't consider population weights. We have given positivity rate for seropositive participants which are aiming for active hep B infection than carriers. There was lack of data to compare essentially percentage burden of HBV. Here some of the northern states like Delhi, Punjab, Haryana showed >70% of positivity rate. Hep B virus prevalence at community level in Tripura is 3.6 %, West Bengal 2.97%,[23] Tamil Nadu 5.7%[24] and North India 2.1%.[25]

Increase in occupation, trafficking and use of banned drugs and frequent visits to and from different countries have also considerably influenced the epidemiology of HBV and other parenteral infections in India and specially in the eastern and north eastern parts of India. HBV positivity rate were reported earlier as 2.7-10.8% among drug users.[26] As documented before, few states are having high HBSAg positivity rate as compare to others states. Some studies it was reported as 7 % in Chennai,[27] 9.7% in Delhi[28] and 5.1% in Punjab.[29]

Also there was lack or fewer data from Northeast states like Manipur, Tripura, Assam and also from other states like Gujarat and Himachal Pradesh nevertheless

Supplementary Table 2: State-wise Hep B seropositivity based on gender of the participants [n (%)].

State	Test result	Male	Female	Total
Andhra Pradesh	+	509 (68.3)	237 (63.2)	746
	-	236 (31.7)	138 (36.8)	374
Assam	+	14 (60.9)	4 (40)	18
	-	9 (39.1)	6 (60)	15
Bihar	+	1138 (68.6)	928 (68.5)	2066
	-	522 (31.4)	426 (31.5)	948
Chandigarh	+	33 (61.1)	22 (68.8)	55
	-	21 (38.9)	10 (31.3)	31
Chhattisgarh	+	80 (69.6)	46 (65.7)	126
	-	35 (30.4)	24 (34.3)	59
Delhi	+	235 (75.3)	109 (72.2)	344
	-	77 (24.7)	42 (27.8)	119
Goa	+	36 (34)	25 (47.2)	61
	-	70 (66)	28 (52.8)	98
Gujarat	+	20 (76.9)	4 (44.4)	24
	-	6 (23.1)	5 (55.6)	11
Haryana	+	138 (71.5)	62 (71.3)	200
	-	55 (28.5)	25 (28.7)	80
Himachal Pradesh	+	0 (0)	1 (100)	1
	-	1 (100)	0 (0)	1
Jammu and Kashmir	+	97 (66.4)	67 (74.4)	164
	-	49 (33.6)	23 (25.6)	72
Jharkhand	+	144 (66.4)	101 (69.2)	245
	-	73 (33.6)	45 (30.8)	118
Karnataka	+	638 (70)	287 (71.9)	925
	-	273 (30)	112 (28.1)	385
Kerala	+	85 (64.4)	51 (64.6)	136
	-	47 (35.6)	28 (35.4)	75
Madhya Pradesh	+	312 (70)	191 (69)	503
	-	134 (30)	86 (31)	220
Maharashtra	+	832 (63.5)	460 (54.6)	1292
	-	479 (36.5)	382 (45.4)	861
Manipur	+	0 (0)	1 (100)	1
	-	0(0)	1(100)	1
Odisha	+	241 (68.7)	132 (70.2)	373
	-	110 (31.3)	56 (29.8)	166
Punjab	+	190 (72)	100 (67.6)	290
	-	74 (28)	48 (32.4)	122
Rajasthan	+	22 (62.9)	12 (50)	34
	-	13 (37.1)	12 (50)	25
Tamil Nadu	+	332 (68)	154 (63.6)	486
	-	156 (32)	88 (36.4)	244
Telangana	+	277 (70.5)	156 (70.9)	433
	-	116 (29.5)	64 (29.1)	180
Tripura	+	6 (54.5)	4 (57.1)	10
	-	5 (45.5)	3 (42.9)	8
Uttar Pradesh	+	333 (69.8)	210 (65)	543
	-	144 (30.2)	113 (35)	257
Uttarakhand	+	8 (72.7)	5 (71.4)	13
	-	3 (27.3)	2 (28.6)	5
West Bengal	+	310 (65.7)	190 (66.9)	500
	-	162 (34.3)	94 (33.1)	256

n=number of samples; %, Percentage; +, Positive; -, Negative.

we have calculated positivity rate depending upon number of participants. Essentially detection of the true national positivity needs an epidemiologically representative sample survey from all the different cross sections of society and from all regions of the country. In the absence of such studies, this insight provides the retrospective analysis which is available.

While population weights can correct for falsifications due to some forms of publication bias, which may leads to introduce errors of another type. For example a study of a small sample size like in this study participants from Tripura, Himachal Pradesh and Manipur which is not representative of the population of a state, may get undeserved weightage from the large population of the State and this may lead to partial data. In the present study, the aggregate positive and negative data base from each state was sufficient, as indicated by the small confidence intervals seen in the OR (1.022 – 1.179).

Still, HBV infection remains the most common aetiology of HCC all over India. A recent nationwide survey discovered that 43% of HCC cases are HBV associated.[30-33] Prevalence among HCC cases was 42% in the south,[34] 39–69% in the north[35] and 82% in the west.[36] Which is comparatively nearby to the percentages calculated for seropositive participated in this study. There is also is a need to map out areas of high endemicity levels within each state in superior details. These areas should be the focus of intensive screening and protective measures. Also higher prevalence of HBV among tribal population is of paramount importance. Pockets of higher endemicity are found in tribal areas where the high burden is maintained through intra-caste marriages, tribal customs, illiteracy and poor exposure to health care resources.[37]

CONCLUSION

In conclusion, the results of this study shed light on many important aspects of Hep B prevalence in seropositive participants such as age, gender, state wise and positivity rate across the states in India. This information is important for determining the risk factors associated with HBV infections, to formulate necessary preventive measures to reduce the burden of new infections and spread of newly introduced genotype to other parts. Emergence of new genotypes/sub-genotypes, clinically relevant mutations have immense importance in determining the clinical outcome, efficacy of vaccination and therefore strict surveillance of these variants are extremely important and need of the hour in India. Finally, with contributing unique data on molecular epidemiology of HBV in India, this insight open new avenues for further studying the molecular virology of HBV.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Contributions

CN: Planning and written the manuscript, **CS:** Review the manuscript, **PG:** Helped in manuscript preparation. All authors have read and approved the final manuscript.

ABBREVIATIONS

HBV: Hepatitis B virus; **Hep:** Hepatitis; **HCC:** Hepatocellular carcinoma; **SAg:** Surface antigen; **HBsAg:** Hepatitis B surface antigen; **CHB:** Chronic Hepatitis B; **AHB:** Acute Hepatitis B; **LD:** Liver diseases; **CLD:** Chronic liver diseases; **EDTA:** Ethylenediaminetetraacetic acid; **TSPs:** Thyrocare service providers; **CPL:** Central Processing Laboratory; **IC:** Internal control; **SD:** Standard deviation; **PCR:** Polymerase chain reaction; **DNA:** Deoxyribonucleic acid.

SUMMARY

This study provides information on important risk factors associated with HBV Infection with the unique data on molecular epidemiology of HBV in India and can help to for formulate necessary preventive measures to reduce the HBV Burden.

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