



Hepatitis-B virus infection in India: Findings from a nationally representative serosurvey, 2017–18



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ABSTRACT

Introduction: India introduced a hepatitis-B (HB) vaccine in the Universal Immunization Program in 2002–2003 on a pilot basis, expanded to ten states in 2007–2008 (phase-1), and the entire country in 2011–2012 (phase-2). We tested sera from a nationally representative serosurvey conducted during 2017, to estimate the seroprevalence of different markers of HB infection among children aged 5–17 years in India and to assess the impact of vaccination.

Methods: We tested sera from 8273 children for different markers of HB infection and estimated weighted age-group specific seroprevalence of children who were chronically infected (HBsAg and anti-HBc positive), and immune due to past infection (anti-HBc positive and HBsAg negative), and having serological evidence of HB vaccination (only anti-HBs positive). We compared the prevalence of

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serological markers among children born before (aged 11–17 years) and after (aged 5–10 years) introduction of HB-vaccine from phase-1 states.

Results: Among children aged 5–8 years, 1.1% were chronic carriers, 5.3% immune due to past infection, and 23.2% vaccinated. The corresponding proportions among children aged 9–17 years were 1.1%, 8.0%, and 12.0%, respectively. In phase-1 states, children aged 5–10 years had a significantly lower prevalence of anti-HBc (4.9% vs. 7.6%, $p < 0.001$) and higher prevalence of anti-HBs (37.7% vs. 14.7%, $p < 0.001$) compared to children aged 11–17 years. HBsAg positivity, however, was not different in the two age groups.

Conclusions: Children born after the introduction of HB vaccination had a lower prevalence of past HBV infection and a higher prevalence of anti-HBs. The findings of our study could be considered as an interim assessment of the impact of the hepatitis B vaccine introduction in India.

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Introduction

Hepatitis-B (HB) virus infection is a major public health problem worldwide, with an estimated 257 million individuals living with chronic HBV infection. In 2015, globally, 887,000 deaths were estimated to be due to complications of chronic HB virus infection (World Health Organization, 2017). A meta-analysis of published data indicate that the prevalence of chronic HB virus infection in India is 1.46% with an estimated 17 million chronic carriers (Schweitzer et al., 2015).

The Global Health Sector Strategy on viral hepatitis (2016–2021) endorsed by the World Health Assembly in 2016, called for the elimination of viral hepatitis as a public health threat by 2030 (WHO, 2016). HB vaccination of infants is one of the key strategies to tackle the burden of hepatitis B. WHO recommends HB vaccination at birth followed by two or three doses (World Health Organization, 2019). Several countries have documented a marked reduction in the prevalence of chronic HB virus infection as well as the rate of occurrence of hepatocellular cancer after the introduction of HB vaccination (Chang et al., 1997; Liang et al., 2009).

India introduced HB vaccine in the Universal Immunization Program (UIP) on a pilot basis in 14 cities and 33 districts in 2002–2003, expanded to ten states in 2007–2008 (Phase-1) and the entire country in 2011–2012 (phase-2) (Lahariya et al., 2013). Initially, a 3-dose schedule of either 6, 10 and 14 weeks or 0, 6 and 14 weeks (if birth dose could be given) was used; this was later changed to 6, 10 and 14 weeks with an additional dose being given within 24 hours of birth. HB vaccine has been available in the private sector for several years before the introduction in the UIP (Govt of India, 2011). Although, the majority of children receive immunization services through the public sector, the private sector has been contributing substantially to the vaccine delivery in high-income states (Sharma et al., 2016).

Serological surveys estimating the prevalence of different markers of HBV infection such as hepatitis B surface antigen (HBsAg), antibodies to core antigen (anti-HBc), and surface antigen (anti-HBs) are recommended to measure the impact of the Hep-B vaccination program (World Health Organization, 2020a). In India, a few studies have reported the impact of HB vaccination in a limited geographical area (Aggarwal et al., 2014; Bhattacharya et al., 2015; Bhattacharya et al., 2015). There are no data regarding the impact of the hepatitis B vaccine introduction at the national level, and hence there is a need for a nationally representative serological survey (Childs et al., 2018). Conducting national-level surveys, however, is resource-intensive. We conducted a nationally representative serosurvey during 2017, among individuals aged 5–45 years to estimate the age-specific seroprevalence of dengue virus infection in India. We tested the sera from children aged 5–17 years to estimate the seroprevalence of different hepatitis B infection markers.

Methods

Survey procedure

The details of the study design, survey procedures, and participants' profiles are described elsewhere (Murhekar et al., 2019). Briefly, the national-level survey to estimate the age-specific seroprevalence of dengue virus infection was conducted in five geographic regions (north, east, west, south, and northeast) of India. Three states were selected randomly from each geographic region, and four districts were selected by a probability proportional to population size from each state. Within each district, four clusters (two in urban and two in rural) were selected randomly. One Census Enumeration Block (CEB) was randomly selected from each cluster; all households in the CEB were enumerated, and basic demographic details of the household members were collected. From this sample frame, 25 individuals were selected randomly from the age groups 5–8, 9–17, and 18–45 years. Sera were collected from 12,300 individuals from three age groups, covering 240 clusters (118 rural, 122 urban) from 60 selected districts of 15 Indian states spread across all five geographic regions.

Laboratory investigations

All sera from children aged 5–8 and 9–17 years were tested for the presence of HBsAg (a marker of chronic infection), total anti-HBc (a marker of HBV infection, either cleared or persistent), and anti-HBs (a marker of protective antibodies) using commercial enzyme-linked immunosorbent assays (HBsAg: Monolisa HBsAg Ultra, Biorad, France; Anti-HBc: Anticorase B-96 (TMB), General Biologicals Corporation, Taiwan; Anti-HBs: Antisurase B-96 (TMB-II), General Biologicals Corporation, Taiwan). The sensitivity and specificity of Monolisa HBsAg ultra (BIO-RAD, 2020) is 100% and 99.94%, respectively. The corresponding values for Anticorase B-96 (TMB) (anti-HBc total) (General Biologicals Corporation, Taiwan, 2020) were 100% and 99.8% and for Antisurase B-96 (TMB-II) (anti-HBs) (General Biologicals Corporation, Taiwan, 2020) were 100% and 99.52%, respectively. Sera with equivocal results were retested using the same assay. Specimens that were equivocal on repeat testing were considered as negative. Samples with an anti-HBs titer of 1:10 or more were considered seroprotected. Patients whose sera were positive for HBsAg and anti-HBc were considered as chronically infected; positive for anti-HBc and negative for HBsAg were considered as immune due to past infection, and positive for anti-HBs but negative for anti-HBc and HBsAg were considered as having serological evidence of HB vaccination, and negative for all markers were considered as susceptible for HBV infection (Centres for Disease Control, 2020).

Statistical analysis

Prevalence of HBV infection

Using the survey data analysis module in STATA SE version 13.0, we estimated weighted age-group specific prevalence along with a 95% confidence interval (CI) of individuals who were (a) showing serological evidence of HB vaccination, (b) chronically infected, and (c) immune due to past infection for each geographical region, using design weight and adjusting for non-response.

Impact of Hep-B vaccination

Of the 15 states where serosurvey was conducted, the Hep-B vaccine was introduced during 2002–2003 in the National Capital

Territory of Delhi, during 2007–2008 in seven states (Punjab, West Bengal, Madhya Pradesh, Maharashtra, Tamil Nadu, Andhra Pradesh, and Karnataka) (phase-1) and during 2011–2012 in the remaining seven states (Uttar Pradesh, Assam, Meghalaya, Tripura, Odisha, Bihar, Rajasthan) (phase-2). We compared the unweighted proportion of children residing in phase-1 states who were showing serological evidence of HB vaccination, chronically infected due to HBV, and who were immune due to past infection among those aged 11–17 years (children born during 2000–2006, before the introduction of hepatitis B vaccine) with children aged 5–10 years (children born during 2007–2012, after the introduction of vaccine) using the χ^2 test. We also compared the age-group specific prevalence of HBV markers in phase-1 and phase-2 states. A p-value of <0.05 was considered significant.

Results

Demographic details

Of the 8324 sera specimens collected from children aged 5–17 years, 51 sera were insufficient and excluded from analysis; thus, 8273 sera were tested for three HBV markers. This included 4034 (48.8%) sera from children aged 5–9 years and 4239 (51.2%) from children aged 10–17 years. About half of the sera tested were from boys (n = 4,255, 51.4%), residing in rural areas (n = 4226, 51.1%) (Table 1).

Overall prevalence of HBV markers

Of the 8273 sera tested, 94 (1.1%), 554 (6.7%), and 2135 (25.8%) were positive for HBsAg, anti-HBc, and anti-HBs, respectively. The weighted prevalence of children who were chronic carriers, immune due to past infection, and having serological evidence of HB vaccination was 1.1% (0.7–1.7), 7.1% (5.7–8.7), and 15.8% (13.6–18.3), respectively (Table 2). Of the 906 children aged 5 years, eleven (1.2%) were positive for HBsAg.

Table 1
Demographic characteristics of the children surveyed (n = 8273).

Characteristics	Number (%)
Age group (years)	
5–8	4,034 (48.8)
9–17	4,239 (51.2)
Sex	
Male	4,255 (51.4)
Female	4,018 (48.6)
Area of residence	
Urban	4,047 (48.9)
Rural	4,226 (51.1)
Region	
North	1620 (19.6)
North-east	1492 (18.0)
East	1689 (20.4)
West	1577 (19.1)
South	1895 (22.9)

Table 2
Prevalence of Hepatitis B virus infection (%) in different geographic regions of India by selected sociodemographic characteristics.

Characteristics	5–8 years				9–17 years				5–17 years			
	No. tested	Chronic infection (95% CI)	Immune due to past infection (95% CI)	Vaccinated (95% CI)	No. tested	Chronic infection (95% CI)	Immune due to past infection (95% CI)	Vaccinated (95% CI)	No. tested	Chronic infection (95% CI)	Immune due to past infection (95% CI)	Vaccinated (95% CI)
Region												
North	794	1.5 (0.5–4.3)	5.8 (3.7–9.2)	17.7 (11.4–26.5)	826	1.5 (0.5–4.4)	8.8 (4.8–15.5)	9.6 (6.2–14.5)	1620	1.5 (0.7–3.3)	7.9 (4.9–12.5)	12.1 (8.8–16.4)
Northeast	707	3.3 (1.3–8.0)	3.0 (0.8–9.8)	21.2 (11.6–35.6)	785	0.6 (0.2–2.1)	3.3 (1.1–9.7)	18.6 (9.3–33.7)	1492	1.5 (0.6–4.0)	3.2 (1.4–7.2)	19.5 (12.1–29.8)
East	815	0.6 (0.2–2.3)	5.1 (2.6–9.9)	26.1 (22.2–30.3)	874	0.5 (0.1–1.8)	9.2 (7.3–11.5)	10.1 (6.3–15.9)	1689	0.6 (0.2–1.4)	7.8 (6.0–10.0)	15.7 (12.0–20.2)
West	759	0.5 (0.1–2.0)	6.3 (4.1–9.6)	15.5 (9.4–24.3)	818	1.7 (0.7–3.8)	7.5 (4.8–11.4)	10.1 (5.1–18.9)	1577	1.3 (0.6–2.7)	7.0 (5.1–9.6)	12.1 (8.0–17.9)
South	959	0.9 (0.3–2.4)	3.1 (1.7–5.7)	47.8 (41.3–54.4)	936	0.3 (0.1–1.3)	6.5 (4.3–9.7)	22.9 (18.9–27.5)	1895	0.5 (0.2–1.2)	5.4 (3.8–7.5)	31.2 (27.2–35.5)
Area of Residence												
Urban	1971	1.3 (0.4–4.0)	4.5 (2.9–7.2)	30.6 (25.1–36.6)	2076	0.3 (0.1–0.7)	6.7 (4.9–9.2)	15.9 (10.5–23.3)	4047	0.6 (0.2–1.6)	6.0 (4.6–7.8)	20.6 (15.8–26.3)
Rural	2063	1.0 (0.5–2.0)	5.5 (4.0–7.4)	21.6 (17.4–26.4)	2163	1.3 (0.7–2.5)	8.3 (6.1–11.3)	11.1 (8.5–14.4)	4226	1.2 (0.7–2.0)	7.3 (5.7–9.4)	14.7 (12.3–17.5)
Gender												
Male	2155	0.7 (0.3–1.4)	3.3 (2.2–4.9)	21.7 (17.4–26.8)	2100	1.5 (0.7–3.1)	8.0 (6.0–10.5)	12.9 (10.0–16.5)	4255	1.2 (0.6–2.2)	6.4 (4.9–8.2)	16.0 (13.5–18.9)
Female	1879	1.5 (0.7–3.4)	7.5 (5.3–10.4)	24.9 (20.8–29.6)	2139	0.7 (0.2–2.8)	8.0 (5.7–11.1)	11.1 (8.2–14.9)	4018	1.0 (0.5–2.2)	7.8 (6.1–10.1)	15.6 (13.0–18.7)
Overall	4034	1.1 (0.6–1.9)	5.3 (4.0–6.9)	23.2 (19.6–27.4)	4239	1.1 (0.6–2.0)	8.0 (6.1–10.4)	12.0 (9.6–14.9)	8273	1.1 (0.7–1.7)	7.1 (5.7–8.7)	15.8 (13.6–18.3)

Prevalence of HBV markers by age group and gender

Among children aged 5–8 years, 1.1% (0.6–1.9) were chronically infected, 5.3% (4.0–6.9) were immune due to past infection, while 23.2% (19.6–27.4) were showing serological evidence of HB vaccination. The corresponding proportions among children aged 9–17 years were 1.1% (0.6–2.0), 8.0% (6.1–10.4), and 12.0% (9.6–14.9), respectively. The proportion of children who were chronically infected and were immune due to past infection was not different in the two age groups, whereas the prevalence of children with serological evidence of HB vaccination was significantly higher among those aged 5–8 years compared to older children (Table 2). The proportion of children with evidence of HB vaccination also did not differ by gender.

Prevalence of HBV markers by geographic region

The overall prevalence of chronic carriers among children aged 5–17 years in the north, northeast, and west regions ranged between 1.3% and 1.5%, whereas the prevalence was 0.6 and 0.5% in the eastern and southern regions. The proportion of children with evidence of HB vaccination was highest in the south region (31.2%, 95% CI: 27.2–35.5) and lowest in the northern (12.1%, 95% CI: 8.8–16.4) and western (12.1%, 95% CI: 8.0–17.9) regions (Table 2). Overall, children residing in urban areas (20.6%, 95% CI: 15.8, 26.3) had a higher prevalence of anti-HBs on account of HB vaccination than those residing in rural areas (14.7%, 95% CI: 12.3–17.5).

Prevalence of HBV markers in phase-1 states before and after the introduction of hepatitis B vaccination

In the seven phase-1 states, the proportion of children chronically infected was not different among children aged 11–17 years (born before the introduction of the HB vaccine) and children aged 5–10 years (born after the introduction of the hepatitis B vaccine) ($\chi^2 = 0.255$, $p = 0.614$). On the other hand, the proportion of children immune due to past infection was lower among children born after the introduction of vaccine (4.9%) as compared to those born before the introduction of vaccine (7.6%; $\chi^2 = 12.56$, $p < 0.001$). A higher proportion of children born after the introduction of the HB vaccine had evidence of vaccination (37.7% vs. 14.7%; $\chi^2 = 249.0$, $p < 0.001$) (Table 3).

Age group-specific prevalence of HBV markers in phase-1 and phase-2 states

In the seven phase-1 states where the Hep-B vaccine was introduced during 2007–2008, 0.8% children aged 5–8 years and 0.5% children aged 9–17 years were chronic carriers ($\chi^2 = 1.466$, $p = 0.226$), whereas the proportion of children with serological evidence of HB vaccination in the two age groups was 39.4% and 18.0% respectively ($\chi^2 = 224.7$, $p < 0.001$). In the seven phase-2 states where HB vaccine was introduced during 2011–2012, the proportion of children who were chronic carriers was not different in the two age groups (5–8 years: 1.6%, 9–17 years: 1.9%; $\chi^2 = 0.728$, $p = 0.394$), whereas a higher proportion of children aged 5–8 years (20.8%) had serological evidence of HB vaccination as compared to 9–17 years (13.6%, $\chi^2 = 33.28$, $p < 0.001$) (Table 4).

Discussion

In this nationally representative serosurvey conducted in 15 Indian states, about 1% of children aged 5–17 years were chronic carriers of HBV, whereas less than 20% had antibodies against hepatitis B surface antigen on account of vaccination. In the seven phase-1 states, a higher proportion of children born after the introduction of HB vaccine had serological evidence of HB vaccination compared to those born before vaccine introduction.

The prevalence of HBsAg is used to classify the endemicity of HBV infection as well as to quantify the burden of disease attributable to HBV infection using mathematical models. The prevalence estimated in our serosurvey was lower than the prevalence of 1.46% estimated in a systematic review (Schweitzer et al., 2015). The prevalence, however, varied with geographic regions with the highest prevalence in northeastern and northern states.

The presence of anti-HBs, which protects against HBV infection, in the absence of the anti-HBc, can be attributed to HB-vaccination. In India, the estimated coverage of the third dose of hepatitis-B vaccine has increased from 6% during 2004–2007, to 29% in 2008 and 44% in 2011 (World Health Organization, 2020b). In our study, we found that 37.7% children aged 5–10 years residing in phase-1 states had antibodies to HBsAg on account of vaccination. These children were born during 2007–2012 and thus were eligible to receive the hepatitis B vaccine.

Table 3

Status of hepatitis B virus infection among children from phase-1 states before and after the introduction of hepatitis B vaccination.

Hepatitis B status	Age group		P
	5-10 years (n = 2448)	11-17 years (n = 1594)	
No. Chronically infected (%) (95% CI)	17 (0.7%) (0.4-1.1)	9 (0.6%) (0.3-1.1)	0.614
No. Immune due to past infection (%) (95% CI)	121 (4.9%) (4.1-5.9)	122 (7.6%) (6.4-9.1)	<0.001
No. Vaccinated (%) (95% CI)	923 (37.7%) (35.8-39.6)	235 (14.7%) (13.1-16.6)	<0.001

Table 4

Status of hepatitis B virus infection among children in phase-1 and phase-2 states by age group.

Age	No. of Chronic infection (%) (95% CI)	No. immune due to past infection (%) (95% CI)	No. vaccinated (%) (95% CI)
Phase 1 states			
5-8 years (n = 2009)	16 (0.8%) (0.5-1.3)	97 (4.8%) (4.0-5.8)	791 (39.4%) (37.3-41.5)
9-17 years (n = 2033)	10 (0.5%) (0.3-0.9)	146 (7.2%) (6.1-8.4)	367 (18.0%) (16.4-19.8)
5-17 years (4042)	26 (0.6%) (0.4-0.9)	243 (6.0%) (5.3-6.8)	1158 (28.6%) (27.3-30.1)
Phase 2 states			
5-8 years (n = 1772)	28 (1.6%) (1.1-2.3)	92 (5.2%) (4.2-6.3)	368 (20.8%) (18.9-22.7)
9-17 years (n = 1949)	38 (1.9%) (1.4-2.7)	143 (7.3%) (6.3-8.6)	266 (13.6%) (12.2-15.2)
5-17 years (n = 3721)	66 (1.8%) (1.4-2.2)	235 (6.3%) (5.6-7.1)	634 (17.0%) (15.9-18.3)

The coverage of hepatitis B vaccine in India has increased from 28.9% (urban: 43.7%, rural: 23.2%) (International Institute for Population Sciences (IIPS), 2010) in 2007–2008 to 62.8% (urban: 63.3%, rural: 62.5%) in 2015–2016 (Government of India - Ministry of Health and Family Welfare, 2020). The lower proportion of children with anti-HBs in our survey could be due to lower coverage of hepatitis B vaccine. It is also likely that we might have under-estimated the actual prevalence of children who were vaccinated, as anti-HBs titers are known to decline over time after vaccination. Follow-up studies from several countries have shown that only 60% to 85% of vaccinated individuals had anti-HBs titer above the commonly-used cut-off of 10 mIU/mL, 5–7 years after the completion of a 3-dose immunization schedule (Liang et al., 2009; Aggarwal et al., 2014; Bhattacharya et al., 2015). In our survey, we also found that about 14% of children from phase-2 states born before introducing the hepatitis B vaccine in the national program had anti-HBs. This probably suggests that there was vaccination of children from the private sector.

The seroprevalence of different markers of HBV infection among children born before and after the introduction of HB vaccination in phase-1 states provided an opportunity to document the impact of hepatitis B vaccination (World Health Organization, 2020a). Although HBsAg positivity was not different among children born before and after the introduction of the hepatitis B vaccine, children born after the introduction of the vaccine had a significantly lower proportion of past infection. A higher proportion of such children also had antibodies against HB virus and hence were vaccinated. HBsAg positivity was also lower among children from states where the vaccine was introduced in the first phase.

Our study has certain limitations. First, the sample size sample for serosurvey was calculated assuming dengue seroprevalence of 60% in various geographic regions and age groups (Murhekar et al., 2019). This sample size was adequate to capture anti-HBs seroprevalence of 23% with an absolute precision of 5%, design effect of 2, and for a confidence level of 95%. With a low prevalence of HBsAg, a larger sample size would be required to have precise estimates. Second, in the main survey, we did not include children younger than five years of age for logistical reasons. Third, we did not collect information about hepatitis B vaccination from the participants, considering issues about parental recall and low retention of vaccination cards. In the absence of such information, it was not possible to compare the immunity levels according to vaccination status. Fourth, since the anti-HBs titers wane with age, we might have underestimated the proportion of children with serological evidence of HB vaccination. However, such an individual can mount a robust immune response if exposed to the infection (Van Damme, 2016). Lastly, in the absence of individual-level information about vaccination status, we analyzed the data to assess the impact of vaccination based on the period of introduction of the vaccine.

In conclusion, the findings of our study indicate a low prevalence of chronic hepatitis B virus infection among children in India. However, the prevalence was higher in the northeast and northern states. The fact that less than 40% of children born after the introduction of HB- vaccine have anti-HBs due to vaccination, indicates the need to improve the coverage of three doses of HB-vaccine in India. The findings of our study could be considered an interim assessment of the impact of the hepatitis B vaccine introduction, which indicates that India is on track for achieving the South East Asia Regional goal of 1% HBsAg prevalence among 5-year-old children (WHO, 2016).

Contributions

MVM was the principal investigator of the survey. MVM, PK, MSK, NG, and SMM conceived and designed the study. MVM, PK, MSK, SAK, RRA, PVB, BD, SK, UM, SSM, SR, VS, DS, BVT, RKT, SB, GSG,

PVML, CMM, PS, PKS, SKS, CPY, RK, SD, GST, CG, TDR, AJ, AS, DA, and PAK coordinated the field operations. CPGK oversaw all laboratory procedures with the support of TK, AJ, RS, JWBJ. PK, RS, MSK, and MVM managed and analyzed data. MVM drafted the first version of the manuscript, and all authors contributed, reviewed, and approved this article.

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Ethical Approval

Informed consent was obtained from all participants for future testing of residual sera at the time of this survey. The Institutional Ethics Committees of ICMR-National Institute of Epidemiology approved the study protocol for testing Hepatitis B infection markers using serum samples from national serosurvey.

Conflict of Interest

The authors declare no conflict of interest.

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