Seroprevalence of hepatitis B virus: Findings from a population-based household survey in KwaZulu-Natal, South Africa

Natasha Samsunder[a], Sinaye Ngcapu[a], Lara Lewis[a], Cheryl Baxter[a], Cherie Cawood[b], David Khanyile[b], Ayesha B.M. Kharsany[a,*]

[a] Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa
[b] Epicentre AIDs Risk Management (Pty) Limited, Cape Town, South Africa

ABSTRACT

Background: Hepatitis B virus (HBV) infection is a major cause of morbidity and mortality; however, little is known about the prevalence and distribution of HBV in some populations and regions.
Methods: A total of 9791 participants, 15–49 years old, were enrolled in a household survey in KwaZulu-Natal, South Africa. Peripheral blood samples were tested for markers of HBV (hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe)) and analysed, accounting for multilevel sampling and weighted to represent the population.
Results: Overall HBsAg prevalence was 4.0% (95% confidence interval (CI) 3.4–4.5%): 4.8% (95% CI 3.8–5.8%) in men and 3.2% (95% CI 2.5–3.9%) in women ($p = 0.01$). Among HBsAg-positive participants, 35.2% (95% CI 29.2–41.2%) were HBeAg-positive and 66.3% (95% CI 60.1–72.4%) were anti-HBe-positive. HBsAg prevalence was 6.4% (95% CI 5.3–7.5%) among HIV-positive participants compared to 2.6% (95% CI 1.9–3.2%) among HIV-negative participants ($p < 0.01$), and was higher among HIV-positive men (8.7%, 95% CI 6.3–11.2%) than among HIV-positive women (5.0%, 95% CI 3.8–6.2%) ($p < 0.01$).
Conclusions: HBV infection among HIV-positive men remains an important public health problem in communities in KwaZulu-Natal, South Africa. The prevalence of HBsAg and HBeAg highlight the importance of surveillance and an important missed opportunity for the scale-up of programmes to achieve the goal of controlling HBV for public health benefit.

Introduction

Hepatitis B virus (HBV) infection is a common cause of viral hepatitis and affects more than 257 million people worldwide. Almost 8% of this global burden is in Sub-Saharan Africa, with over 80 000 new infections occurring each year (World Health Organisation, 2017). In South Africa, HBV infections account for an estimated 3.5 million infected individuals (Schweitzer et al., 2015). HBV remains endemic in the region. Viral hepatitis from HBV infection is a potentially life-threatening liver infection resulting in acute hepatitis and chronic liver disease, leading to complications of cirrhosis and hepatocellular carcinoma, and contributing to high rates of morbidity and mortality (World Health Organisation, 2017).

The transmission of HBV is known to occur through multiple routes. The most common is mother-to-child transmission at birth or through exposure to infected blood (Kiire, 1996). Other routes of transmission include sexual transmission and percutaneous or mucosal exposure to infected blood and various body fluids. Transmission can also occur through saliva, menstrual, vaginal, and seminal fluids, and iatrogenic spread through the re-use of contaminated needles. Equipment in healthcare settings or among persons who inject drugs, and the use of razors or similar objects during ritual scarification may be other routes of transmission (Kew, 1996; Mphahlele et al., 2002; Heiberg et al., 2010).

South Africa has been at the forefront of new vaccine introduction; the country introduced the HBV vaccine as part of the Expanded Programme on Immunization as early as 1995. By 2015, South Africa had become the first African country to phase out the pentavalent vaccine, and this vaccine was replaced with the more baby-friendly

* Corresponding author at: Centre for the AIDS Programme of Research in South Africa (CAPRISA), 2nd Floor, Doris Duke Medical Research Institute, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, 719 Umbilo Road (Private Bag X7), Congella, 4013 Durban, South Africa.
E-mail address: Ayesha.kharsany@caprisa.org (A.B.M. Kharsany).

hexavalent vaccine (Dlamini and Maja, 2016). Despite the introduction of these vaccines, no nationwide surveillance programme has measured and monitored trends in HBV (Mayaphi et al., 2012). Thus, data on the burden of HBV, including the clinical manifestations of advancing disease, are limited and are based on cohort studies undertaken more than a decade ago. Prior to the immunization programme, approximately 6.5 million South Africans were HBV carriers, with prevalence being highest among school-aged children, people residing in rural areas, and among sexually active individuals (Botha et al., 1984; Di Bisceglie et al., 1986; Burnett et al., 2005). The prevalence of HBV infection in rural areas has been estimated to be between 5% and 16% among men and between 4% and 12% among women, while in urban areas, rates of between 8% and 9% among men and between 3% and 4% among women have been estimated (Kew et al., 1976; Vos et al., 1980; Prozesky et al., 1983; Kew et al., 1987; Abdool Karim et al., 1988; Dusheiko et al., 1989). Currently, there are an estimated three to four million HBV carriers in South Africa (Kew, 2008).

Given that the World Health Organization (WHO) strategy is to eliminate HBV as a public health threat by the year 2030 (World Health Organisation, 2017; Perz et al., 2006; World Health Organisation, 2016), it is important to establish the HBV seroprevalence through surveillance. The purpose of this study was to assess the HBV seroprevalence as part of a household survey in rural and peri-urban areas in KwaZulu-Natal, South Africa.

Materials and methods

Study design, setting, and population

This secondary analysis was based on the testing of samples from participants enrolled in the HIV Incidence Provincial Surveillance System (HIPSS). The HIPSS study design, source population, and recruitment and enrolment procedures have been described previously (Kharsany et al., 2015; Kharsany et al., 2018). Briefly, HIPSS was a population-based household study conducted in the Vulindlela (rural) and the Greater Edendale (peri-urban) areas in the uMgungundlovu District of KwaZulu-Natal, South Africa. The study used a multi-stage cluster sampling method to randomly select enumeration areas, households, and individuals, resulting in a total of 9812 men and women (15–49 years old) enrolled between June 2014 and June 2015. All enrolled participants provided written informed consent and/or parental consent/child assent for those participants below the age of 18 years for study participation and for long-term storage of clinical samples for future testing. All completed interviewer administered questionnaires, had peripheral blood samples collected, and were allocated a unique identification number with a linking number to link the household, participant's questionnaire, and laboratory data.

The Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal reviewed and approved the HBV seroprevalence protocol (BE057/17), the HIPSS study protocol, and informed consent and questionnaire forms (BF269/13). The US Centers for Disease Control and Prevention and the Provincial Department of Health (KwaZulu-Natal; HRKM 08/14) approved the HIPSS study protocol. All participants were referred to their local primary healthcare clinics to access their study-related laboratory test results and for individualized HIV testing services. Prior to any interaction with household members and participants, community engagement processes were established with key community stakeholders including health-service providers and traditional leadership and key members from community structures.

Laboratory tests

Peripheral blood samples were shipped to the laboratory within 6 h of collection. The blood samples of 21 of the 9812 participants

enrolled in HIPSS (0.2%) were insufficient for any HBV testing and were excluded.

Testing for HBV

Testing for the detection of markers of HBV infection was performed using the automated ADVIA Centaur System (Siemens, Tarrytown, NY, USA), which utilizes magnetic particle separation technology with direct chemiluminescence. The HBV assay panel included the qualitative detection of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and antibody to HBeAg (anti-HBe). HBsAg-positive samples were further tested for HBeAg and anti-HBe. All results were reported as positive or negative. The diagnostic specificity is reported to be 99.4% for the HBsAg assay, 99.5% for the HBeAg assay, and 98.2% for the anti-HBe assay (van Helden et al., 2004; van Helden et al., 2008).

Interpretation of HBV test results

In this study HBV status was defined as follows (North Carolina Hepatitis B Public Health Program Manual, 2012): (1) HBsAg-positive: the presence of HBsAg in serum indicates that the individual has a current infection. (2) HBeAg-positive: the presence of HBV nucleocapsid gene (HBeAg) in serum indicates active viral replication in individuals with high levels of viraemia who are more likely to transmit the virus. (3) Anti-HBe-positive: the presence of antibodies to HBV nucleocapsid gene (HBeAb) indicates that the individual is recovering as a result of an immune system response to HBeAg and has a reduced level of infectivity.

HBV and HIV-positive indicated that the individual was co-infected with HBV (HBsAg-positive) and HIV-1.

Testing for HIV

HIV testing was performed using the fourth-generation HIV enzyme bioMérieux Vironostika Uniform 11 Antigen/Antibody Microelisa system (bioMérieux, Marcy l'Etoile, France) and HIV 1/2 Combi Roche Elecsys (Roche Diagnostics, Penzberg, Germany). Samples testing indeterminate for HIV were further tested using the ADVIA Centaur HIV Antigen/Antibody Combo (CHIV) Assay (Siemens, Tarrytown, NY, USA).

Statistical analysis

Each participant's laboratory and questionnaire data were merged using a unique linking number. All analyses were performed using SAS 9.4 survey procedures (SAS Institute Inc., Cary, NC, USA). Sampling weights were calculated taking into account the probabilities of selecting the enumeration area, the household in the enumeration area, and the individual in the household, weighted for sampling, participation bias, and non-response, and rescaled to the size of the population in the survey area with the StatsSA 2011 Census population (Kharsany et al., 2018). Descriptive statistics with counts and population-weighted percentages with 95% confidence intervals (CI) are presented for key demographic, psychosocial, and behavioral factors. The Taylor series linearization method was used to estimate standard errors of estimates, from which Wald confidence limits were derived. The Rao–Scott Chi-square test was used to test for the association between prevalence and socio-demographic, behavioral, and clinical characteristics.

Results

Demographic characteristics of the study participants

Among the 9791 participants tested for HBV infection, 3541 (36.2%) were men (median age 27 years, interquartile range (IQR) 21–35 years) and 6250 (63.8%) were women (median age 28 years, IQR 21–37 years). The majority of participants were single (92.1% of men and 85.8% of women), reported having one to five lifetime sexual partners (39.0% men and 51.3% women), and lived in rural areas (57.3% men and 58.7% women). In addition, the prevalence of HIV (28.0% men and 44.0% women) and sexually transmitted infections (STIs) (52.3% men and 78.3% women) was high. Over a third of participants had an incomplete secondary education (38.1% of men and 41.3% of women) and earned a monthly income of between 501 and 2500 South African Rand (ZAR) (44.5% men and 46.3% women). Overall, consistent condom use during sex in the last 12 months was low (Table 1).

Seroprevalence of HBsAg

Among the 9791 participants, 361 were HBsAg-positive, with an overall weighted seroprevalence of 4.0% (95% CI 3.4–4.5%) (Table 2). Seroprevalence in women was 3.2% (95% CI 2.5–3.9%) and was higher in men at 4.8% (95% CI 3.8–5.8%) ($p = 0.01$). Seroprevalence varied with age among men ($p < 0.01$) and women ($p < 0.01$). Seroprevalence was 1.1% (95% CI 0–2.3%) among men in the 15–19 years age group and increased steadily to reach a peak of 9.6% (95% CI 5.0–14.1%) in the 40–44 years age group. In contrast, seroprevalence was consistently lower in each of the age groups among women and was 0.9% (95% CI 0–1.8%) among those 15–19 years old and peaked at 6.0% (95% CI 3.1–9.0%) in the 30–34 years age group. Seroprevalence increased with an increasing number of lifetime sex partners in women ($p < 0.01$), with HIV-positive status among men ($p < 0.01$) and women ($p < 0.01$), and with positive STIs (other than HIV) among men ($p < 0.01$). There was no difference in

Table 1
Socio-demographic, behavioral, and clinical characteristics of participants 15–49 years old, enrolled between June 2014 and June 2015 in rural and peri-urban areas in KwaZulu-Natal, South Africa.

	Men (n = 3541)	Women (n = 6250)
Age, years, median (IQR)	27 (21–35)	28 (21–37)
Age groups in years, number in sample (weighted %)		
15–19	657 (19.6)	956 (18.1)
20–24	813 (20.9)	1262 (19.5)
25–29	602 (18.3)	1085 (17.9)
30–34	459 (13.9)	831 (13.7)
35–39	404 (12.3)	757 (12.2)
40–44	319 (8.6)	660 (9.6)
45–49	287 (6.5)	699 (8.9)
Relationship status, number in samples (weighted %)		
Single (includes divorced, separated, widowed)	3300 (92.1)	5288 (85.8)
Married	180 (5.9)	681 (11.7)
Living with someone	61 (2.0)	175 (2.5)
Education, number in samples (weighted %)[a]		
Incomplete secondary or less	1929 (56.5)	3306 (53.4)
Complete secondary	1403 (38.1)	2597 (41.3)
Tertiary	207 (5.4)	344 (5.3)
Income per household per month, number in samples (weighted %)[b]		
No income	523 (13.2)	764 (10.4)
<ZAR 500	293 (6.2)	610 (7.3)
ZAR 501–2500	1434 (44.5)	2713 (46.3)
ZAR 2501–6000	914 (35.5)	1558 (34.6)
>ZAR 6000	30 (0.9)	70 (1.5)
Geographic location, number in samples (weighted %)		
Peri-urban	2296 (42.8)	4047 (41.3)
Rural	1245 (57.3)	2203 (58.7)
Lifetime number of sexual partners, number in samples (weighted %)[c]		
0 partners	691 (21.2)	816 (15.6)
1 partner	420 (13.8)	1543 (28.9)
1–5 partners	1196 (39.0)	2848 (51.3)
>5 partners	758 (26.1)	280 (4.3)
HIV status, number in samples (weighted %)		
Negative	2531 (72.1)	3305 (56.0)
Positive	1010 (28.0)	2945 (44.0)
Self-reported to be on ART (HIV-positive only), number in samples (weighted %)		
No	669 (63.1)	1695 (54.3)
Yes	341 (36.9)	1250 (45.7)
STI[d] present, number in samples (weighted %)		
No	1689 (47.7)	1354 (21.7)
Yes	1852 (52.3)	4896 (78.3)
Condom use during sex in the last 12 months for those sexually active in the last 12 months, number in samples (weighted %)		
Always	593 (25.2)	992 (22.8)
Sometimes	1290 (54.9)	2317 (53.4)
Never	468 (19.9)	1032 (23.8)

%, population weighted percentage; IQR, interquartile range, ZAR, South African Rand; ART, antiretroviral therapy; STI, sexually transmitted infection.
[a] Two men and three women were missing education data.
[b] Income data were missing for 347 men and 535 women.
[c] A total of 476 men and 763 women refused to provide their number of lifetime sex partners.
[d] Any laboratory diagnosis of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, and/or *Mycoplasma genitalium* DNA from self-collected swabs (women) and first-pass urine (men) samples and antibodies to herpes simplex virus type 2 and *Treponema pallidum* (syphilis).

Table 2

Seroprevalence of HBsAg and association with socio-demographic, behavioral, and clinical characteristics of 9791 participants (15–49 years of age), enrolled between June 2014 and June 2015 in rural and peri-urban KwaZulu-Natal, South Africa.

Variable	Men			Women		
	n/N	HBsAg seroprevalence Weighted % (95% CI)		*n/N*	HBsAg seroprevalence Weighted % (95% CI)	
Seroprevalence of HBsAg						
Overall	165/3541	4.8	(3.8–5.8)	196/6250	3.2	(2.5–3.9)
By age group in years						
15–19	7/657	1.1	(0–2.3)	8/956	0.9	(0–1.8)
20–24	26/813	3.6	(1.7–5.4)	32/1262	2.7	(1.5–3.8)
25–29	30/602	4.5	(2.4–6.6)	39/1085	3.8	(2.2–5.4)
30–34	40/459	7.8	(4.5–11)	40/831	6.0	(3.1–9)
35–39	23/404	5.6	(3.1–8.1)	27/757	2.9	(1.4–4.5)
40–44	24/319	9.6	(5–14.1)	26/660	4.1	(1.9–6.3)
45–49	15/287	6.6	(2.3–10.8)	24/699	2.5	(1.3–3.8)
		p < 0.01[a]			*p* < 0.01[a]	
Relationship status						
Single (includes divorced, separated, widowed)	150/330	4.7	(3.7–5.7)	173/5394	3.1	(2.4–3.9)
Married	12/180	5.7	(2.3–9.2)	16/681	2.9	(1.1–4.7)
Living with someone	3/61	8.6	(0–20.3)	7/175	4.3	(0.6–8.1)
Other (divorced, separated, widowed)	0/13	0	(0–0)	5/106	5	(0–10.4)
		p = 0.52[a]			*p* = 0.79[a]	
Education[b]						
Incomplete secondary or less	96/1929	5.3	(4–6.7)	116/3306	3.3	(2.6–4.0)
Complete secondary	60/1403	4.1	(2.6–5.6)	75/2597	3.3	(2.1–4.5)
Tertiary	9/207	4.3	(0.4–8.3)	5/344	1	(0–2.1)
		p = 0.49[a]			*p* = 0.16[a]	
Income per household per month[c,d]						
No income	28/523	5.5	(2.9–8.1)	23/764	3	(1.2–4.8)
<ZAR 500	19/293	5.5	(2.6–8.3)	24/610	4.5	(2.2–6.8)
ZAR 501–2500	66/1434	4.9	(3.2–6.5)	96/2713	3.3	(2.5–4.1)
ZAR 2501–6000	37/914	4.2	(2.6–5.9)	39/1558	2.8	(1.3–4.3)
>ZAR 6000	1/30	5.4	(0–15.9)	3/70	7	(0–15.5)
		p = 0.91[a]			*p* = 0.48[a]	
Geographic location						
Peri-urban	104/2296	4.6	(3.5–5.7)	133/4047	3.2	(2.6–3.8)
Rural	61/1245	5.0	(3.4–6.5)	63/2203	3.1	(2–4.2)
		p = 0.69[a]			*p* = 0.92[a]	
Lifetime number of sexual partners[e]						
0 partners	16/691	3.2	(1.1–5.2)	10/816	1.7	(0.3–3.1)
1 partner	18/420	3.4	(1.6–5.2)	30/1543	1.9	(1–2.9)
1–5 partners	64/1196	5.2	(3.4–7.1)	103/2848	3.7	(2.7–4.8)
>5 partners	28/758	4.5	(2.4–6.6)	17/280	6.8	(2.8–10.9)
		p = 0.41[a]			*p* < 0.01[a]	
HIV status						
Negative	74/2531	3.3	(2.3–4.3)	58/3305	1.7	(1.1–2.3)
Positive	91/1010	8.7	(6.3–11.2)	138/2945	5.0	(3.8–6.2)
		p < 0.01[a]			*p* < 0.01[a]	
Self-reported to be on ART (HIV-positive only)						
No	57/669	6.9	(4.5–9.4)	78/1695	4.9	(3.5–6.4)
Yes	34/341	11.9	(6.8–16.9)	60/1250	5.2	(3.6–6.8)
		p = 0.05[a]			*p* = 0.78[a]	
STI[f] present						
No	49/1689	2.8	(1.7–3.8)	20/1354	1.9	(0.7–3.1)
Yes	116/1852	6.7	(5.2–8.3)	176/4896	3.6	(2.8–4.4)
		p < 0.01[a]			*p* = 0.06[a]	
Condom use in the last 12 months (sexually active in last 12 months only)						
Always	24/593	3.6	(1.9–5.4)	34/992	2.9	(1.5–4.3)
Sometimes	66/1290	5.3	(3.5–7.1)	73/2317	3.7	(2.3–5.1)
Never	27/468	6.1	(3.1–9.0)	35/1032	3.5	(2.1–4.9)
		p = 0.33[a]			*p* = 0.72[a]	

HBsAg, hepatitis B surface antigen; CI, confidence interval; %, population weighted percentages; ZAR, South African Rand; ART, antiretroviral therapy; STI, sexually transmitted infection.

[a] *p*-Value for the association of the variable with HBsAg status.

[b] Data on education missing for two men and three women.

[c] ZAR 20 approximately equal to GBP 1.

[d] Income data were missing for 347 men and 535 women.

[e] A total of 476 men and 763 women refused to provide their number of lifetime sex partners.

[f] Any laboratory diagnosis of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis* and/or *Mycoplasma genitalium* DNA from self-collected swabs (women) and first-pass urine (men) samples and antibodies to herpes simplex virus type 2 and *Treponema pallidum* (syphilis).

seroprevalence among rural and peri-urban men (*p* = 0.69) or between rural and peri-urban women (*p* = 0.92).

Seroprevalence of HBeAg

Of the 361 participants with HBsAg-positive samples, 357 had sufficient sample remaining for HBeAg testing. Of these, 133 were

Table 3
Seroprevalence of hepatitis B virus markers (HBsAg, HBeAg, and anti-HBe) among 9791 participants (15–49 years of age), enrolled between June 2014 and June 2015, in rural and peri-urban areas in KwaZulu-Natal, South Africa.

Variable	Men		Women		p-Value[a]
	n/N	Weighted % (95% CI)	n/N	Weighted % (95% CI)	
Seroprevalence of HBsAg					
Overall	165/3541	4.8 (3.8–5.8)	196/6250	3.2 (2.5–3.9)	0.01
By age group in years					
15–19	7/657	1.1 (0–2.3)	8/956	0.9 (0–1.8)	0.66
20–24	26/813	3.6 (1.7–5.4)	32/1262	2.7 (1.5–3.8)	0.40
25–29	30/602	4.5 (2.4–6.6)	39/1085	3.8 (2.2–5.4)	0.59
30–34	40/459	7.8 (4.5–11)	40/831	6.0 (3.1–9.0)	0.47
35–39	23/404	5.6 (3.1–8.1)	27/757	2.9 (1.4–4.5)	0.08
40–44	24/319	9.6 (5–14.1)	26/660	4.1 (1.9–6.3)	<0.01
45–49	15/287	6.6 (2.3–10.8)	24/699	2.5 (1.3–3.8)	0.02
		$p < 0.01$[b]		$p < 0.01$[b]	
Seroprevalence of HBeAg[c,d]					
Overall	65/164	36.9 (27.5–46.2)	68/193	32.8 (23.7–41.9)	0.58
By age group in years					
15–19	6/7	92.2 (75.8–100)	1/8	4.4 (0–13.7)	<0.01
20–24	10/26	43.3 (18.3–68.4)	17/32	56.7 (32.6–80.8)	0.45
25–29	11/30	29.8 (11.1–48.5)	12/39	30.2 (9.6–50.7)	0.98
30–34	15/39	24.8 (9.4–40.1)	14/39	31.0 (11.5–50.5)	0.62
35–39	7/23	24.7 (6.2–43.1)	8/27	24.6 (7.0–42.3)	1.00
40–44	11/24	55.5 (30.6–80.4)	9/25	27.7 (10.4–45.0)	0.05
45–49	5/15	23.3 (0.7–45.9)	7/23	34.0 (12.4–55.5)	0.51
		$p = 0.09$[b]		$p = 0.18$[b]	
Seroprevalence of anti-HBe[c,e]					
Overall	104/163	64.5 (54.7–74.3)	133/193	68.8 (59.3–78.3)	0.51
By age group in years					
15–19	1/7	7.8 (0–24.2)	7/8	81.0 (45.5–100)	<0.01
20–24	17/26	64.7 (40.3–89.2)	20/32	65.9 (44.1–87.8)	0.94
25–29	20/30	69.7 (50.5–88.8)	27/39	62.9 (42.9–82.9)	0.63
30–34	23/39	70.0 (52–87.9)	25/39	65.4 (40.2–90.6)	0.77
35–39	18/22	83.0 (66.4–99.5)	20/27	78.5 (60.0–97.1)	0.72
40–44	15/24	47.1 (21.6–72.6)	17/25	76.8 (60.9–92.7)	0.03
45–49	10/15	75.2 (51.5–98.8)	17/23	68.3 (46.7–90.0)	0.68
		$p = 0.11$[b]		$p = 0.91$[b]	

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; anti-HBe, antibody to hepatitis B e antigen; %, population weighted percentages; CI, confidence interval.
[a] p-Value for the association of HBsAg/HBeAg/anti-HBe status and sex by age category.
[b] p-Value for the association of age with HBsAg/HBeAg/anti-HBe status by sex.
[c] Based on HBsAg-positive samples.
[d] Four samples insufficient for HBeAg testing.
[e] Five samples insufficient for anti-HBe testing.

HBeAg-positive, with an overall weighted seroprevalence of 35.2% (95% CI 29.2–41.2%) (Table 3). HBeAg seroprevalence in men was 36.9% (95% CI 27.5–46.2%) and in women was 32.8% (95% CI 32.3–41.9%) ($p = 0.58$). Among men 15–19 years old, HBeAg seroprevalence was 92.2% (95% CI 75.8–100%) compared to 4.4% (95% CI 0–13.7%) in women in the same age group ($p < 0.01$). Similarly, HBeAg seroprevalence was higher among men aged 40–44 years (55.5%, 95% CI 30.6–80.4%) than among women in the same group (27.7%, 95% CI 10.4–45.0% $p = 0.05$). However, seroprevalence of HBeAg among men and women across the other age groups was similar. There was no difference in seroprevalence of HBeAg among men in rural (34.0%, 95% CI 24.0–44.0%) and peri-urban areas (38.9%, 95% CI 24.6–53.2%) ($p = 0.58$), or between women in rural (36.7%, 95% CI 26.9–45.9%) and peri-urban areas (30.0%, 95% CI 16.1–43.9%) ($p = 0.43$).
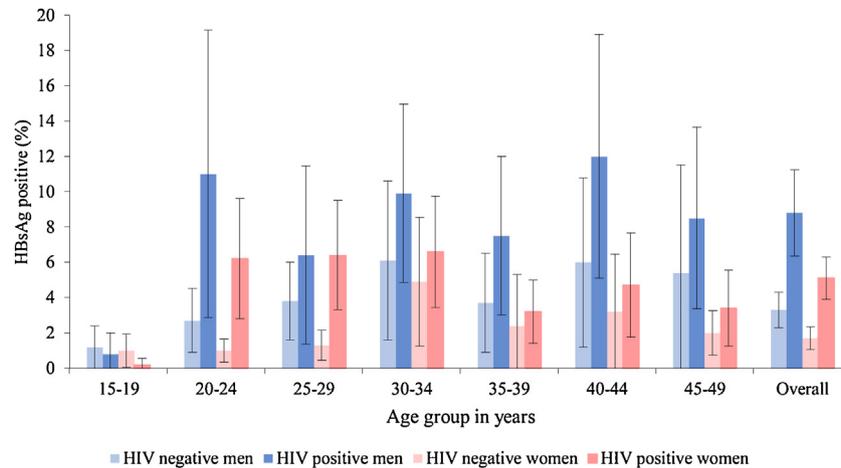
Seroprevalence of anti-HBe

Of the 361 participants with HBsAg-positive samples, 356 had sufficient remaining sample for anti-HBe testing. Of these, 237 samples were positive for anti-HBe, with an overall weighted seroprevalence of 66.3% (95% CI 60.1–72.4%) (Table 3). Seroprevalence in men was 64.5% (95% CI 54.7–74.3%) and was similar in women at 68.8% (95% CI 59.3–78.3%) ($p = 0.51$). Anti-HBe seroprevalence was high among men and women across most age

groups. More women than men in the age group 15–19 years were anti-HBe-positive (81.0%, 95% CI 45.5–100% vs. 7.8%, 95% CI 0–24.2%) ($p < 0.01$). Similarly, among women in the age group 40–44 years, seroprevalence was 76.8% (95% CI 60.9–92.7%) compared to 47.1% (95% CI 21.6–72.6%) in men in the same age group ($p = 0.03$). There was no difference in seroprevalence of anti-HBe between men in rural areas (61.4%, 95% CI 46.7–76.1%) and peri-urban areas (68.9%, 95% CI 57.4–80.3%) ($p = 0.43$) or between women in rural areas (69.3%, 95% CI 54.4–84.2%) and peri-urban areas (68.1%, 95% CI 58.6–77.6%) ($p = 0.89$).

HBV–HIV co-infection

Of the 3955 HIV-positive participants, 229 were also infected with HBV, of whom 91 were men and 138 were women. HBV seroprevalence was 6.4% (95% CI 5.3–7.5%) among HIV-positive participants compared to 2.6% (95% CI 1.9–3.2%) among HIV-negative participants ($n = 5836$) ($p < 0.01$). Among HIV-positive men, seroprevalence of HBsAg was 8.8% (95% CI 6.3–11.2%) compared to 3.3% (95% CI 2.3–4.3%) among HIV-negative men ($p < 0.01$). Among HIV-positive women, seroprevalence of HBsAg was 5.1% (95% CI 3.8–6.3%) compared to 1.7% (95% CI 1–2.3%) among HIV-negative women ($p < 0.01$). The difference in HBsAg prevalence among HIV-positive and negative individuals was greatest in age groups 20–24 years and 25–29 years. Overall, seroprevalence of HBsAg was higher among HIV-positive

Figure 1. Seroprevalence of HBV (HBsAg)-HIV co-infection by sex and age group.

participants in the 20–24 years and 25–29 years age groups ($p < 0.01$) (Figure 1). Among HIV-positive men in the age group 20–24 years, HBsAg seroprevalence was 11% (95% CI 2.8–19.2%) compared to 2.7% (95% CI 1.0–4.5%) among HIV-negative men in the same age group ($p < 0.01$). Among HIV-positive women in the age group 20–24 years, HBsAg seroprevalence was 6.2% (95% CI 2.8–9.7%) compared to 1.0% (95% CI 0.3–1.6%) among HIV-negative women in the same age group ($p < 0.01$). Similarly, among HIV-positive women in the 25–29 years age group, HBsAg seroprevalence was 6.4% (95% CI 3.3–9.5%) compared to 1.3% (95% CI 0.4–2.1%) among HIV-negative women in the same age group ($p < 0.01$).

Discussion

In this population-based survey in rural and peri-urban areas of KwaZulu-Natal, South Africa, the overall HBsAg seroprevalence among men and women in the age group 15–49 years was 4.0%, with a seroprevalence of 4.8% in men and 3.2% in women. While lower than the HBsAg seroprevalence of 6.1% reported for Sub-Saharan Africa (Spearman et al., 2017), and between 5.3% and 9.7% in recent cohort studies among pregnant women (Thumbiran et al., 2014; Matthews et al., 2015), this still represents a substantial HBV burden. In fact, worldwide, despite the availability of hepatitis B vaccine, the overall prevalence of HBV infection has declined little in recent years (Ocama et al., 2005; O'Hara et al., 2017). South Africa has been reported to be at the forefront of the implementation of the Expanded Programme on Immunization, which includes HBV immunization (Dlamini and Maja, 2016); however, the prevalence of HBV infection remains moderate to high, especially in the age group 15–19 years, as this age group should have benefitted from the immunization programme. In the absence of an active HBV surveillance programme, it is unlikely that HBV immunization and treatment programmes are easily accessible and reach individuals where the need is the greatest. These findings emphasize that HBV remains an important public health problem and all efforts to achieve the WHO targets for the elimination of viral hepatitis are urgently needed (World Health Organisation, 2016). In 2016, the WHO set ambitious targets of a 90% reduction in new cases of HBV infection and an associated 65% decline in HBV-related mortality to be achieved by the year 2030. These measures rely on 80% of treatment-eligible individuals with chronic HBV infection to be on treatment (World Health Organisation, 2016).

Whilst vertical transmission of HBV is the most common route of transmission, the age-specific HBV data highlight several important findings. Firstly, men had higher seroprevalence compared to women in every age group. Secondly, the data showed a bimodal distribution of seroprevalence of HBsAg among men in the 30–34 years and 40–44 years age groups, whilst in women, peak seroprevalence occurred in the 30–34 years age group. These findings show that the peak prevalence occurred among men and women in the age groups that are likely to sustain the transmission of HBV. Thirdly, overall estimates are useful to understand the burden of HBV infection in the general population; however, disaggregation by sex and age provides a more precise understanding of the age group that might be affected and allows for prioritization and targeted interventions to further reduce this burden. Several studies have shown urban–rural differences, with the highest prevalence of HBsAg found in men residing in rural areas, placing a greater burden on rural healthcare services (Vos et al., 1980; Abdool Karim et al., 1988; Abdool Karim et al., 1991; Lodenyo et al., 2000; Hoffmann et al., 2008; Firnhaber et al., 2008; Di Bisceglie et al., 2010). However, this study found no difference in the seroprevalence of HBsAg among men and women, irrespective of their area of residence being rural or peri-urban. It is possible that extensive in- and out-migration in the study community and cultural practices of scarification (Abdool Karim et al., 1988) may not clearly delineate urban–rural differences.

This study found that at least a third of men (36.9%) and women (32.6%) were HBeAg-positive and therefore more likely to be infectious. These prevalence values are higher than the 16.7–30.0% observed in cohorts of pregnant women in South Africa (Thumbiran et al., 2014). Whilst men in the 15–19 years age group and women in the 20–24 years age group had low seroprevalence of HBsAg, more than 90% of these men and about 60% of these women were positive for HBeAg, suggesting that these individuals are likely to have a high viral load (Spearman et al., 2017) and are therefore highly infectious. The high prevalence of HBeAg among both men and women highlights the sustained transmission in this community. Reaching out to men and women at high risk of transmitting HBV with messaging on immunization and treatment options, could further guide and scale-up targeted programming and strategies to further reduce the spread of HBV and the opportunity for a catch-up immunization programme targeting young boys (Stabinski et al., 2011).

An overall seroprevalence of HBsAg of 6.4% among HIV-positive individuals was observed, with a higher seroprevalence amongst HIV-positive men (8.8%) compared to HIV-positive women (5.1%). Since, HBV and HIV share similar routes of transmission, co-infections are likely to be common and are reported to range from 5% to 30% (Abdool Karim et al., 1991). Although co-infections were

low at 0.8% in the 15–19 years age group, co-infections were high in all other age groups, ranging from 6.4% to 11.9%. Identifying co-infections is important, as HBV infections are associated with an increased risk of liver disease. Antiretroviral therapy (ART) use in HIV-positive individuals may be compromised by drug-associated hepatotoxicity, leading to the use of complex regimens (Di Bisceglie et al., 2010). In addition, this study showed that among women, HBV–HIV co-infections were above 6% in the age groups belonging to the reproductive years and those already disproportionately burdened with HIV (Kharsany et al., 2018). This could potentially increase the risk of HBV and HIV transmission. Expanding treatment for HBV and HIV-positive individuals could limit onward transmission of both infections and reduce the risk of mother-to-child transmission of HBV (Di Bisceglie et al., 2010; Seremba et al., 2017). Even initiating ART in the absence of HBV reduces the risk of new HBV cases. Therefore, public sector ART and antenatal care programmes are missed opportunities to screen for HBV at the time of testing for HIV and when initiating ART. These individuals would benefit from immunization if HBV-negative or from treatment to prevent the onward and mother-to-child transmission of HBV if positive (Cui et al., 2018).

This study has several strengths and limitations. A key strength is the measurement of HBV seroprevalence in a large randomly selected study sample from a population-based household survey. Furthermore, the sex and age disaggregated data provide a nuanced understanding of the segments of the population that might be affected, although the sample was not representative of all age groups. The results are from cross-sectional data and are limited to the Greater Edendale and Vulindlela areas of KwaZulu-Natal, South Africa and are not necessarily generalizable to other settings. It is important to note that this study was not able to fully assess the impact of the HBV immunization programme on the seroprevalence of HBV markers, as the benefit would be in the <15 years age groups rather than those included in the sample (Tsebe et al., 2001). The testing strategy did not include the full HBV testing panel to comprehensively classify individuals; for example, no testing was performed for occult HBV infection, HBV viral load, or for hepatitis B core antibody (anti-HBc) or hepatitis B surface antibody (anti-HBs) to determine recovery and/or immunity from HBV infection. Lastly, the prevalence of HBeAg may be unreliable due to the small sample sizes in the age-specific strata. Nevertheless, the HBeAg data provide a reasonable signal of the sustained HBV transmission in this community.

In conclusion, the study findings show that HBV infection is an important public health problem. Men across all age groups and women in the age groups 20–24 years and 25–29 years had the highest seroprevalence of HBsAg. Furthermore, more than a third of these men and women were HBeAg-positive, underscoring the risk of sustained onward HBV transmission in this community. Ensuring that HIV-positive individuals with HBV infection are initiated on treatment to reduce viral loads of both HIV and HBV is essential. These findings highlight the importance of surveillance and an important missed opportunity for the scale-up of programmes to achieve the overall goal of controlling HBV for public health benefit.

Disclaimer

The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the funding agencies.

Role of the funding source

The funders of the survey contributed to the primary survey design and study monitoring, and reviewed the manuscript. ABMK, NS, SN, and LL had full access to all data. ABMK, NS, SN, and CC had final responsibility for the decision to submit for publication.

Conflict of interest

All authors declare no conflict of interest.

Author contributions

ABMK is the principal investigator of the HIPSS study; ABMK, NS, and SN designed the study; NS and ABMK were responsible for writing the manuscript; LL was responsible for the statistical analysis; NS, ABMK, SN, LL, and CB contributed to the analysis and interpretation of the data; NS and SN were responsible for the laboratory measurements and quality assurance; ABMK, CC, and DK were responsible for the field work, quality assurance, and for community and stakeholder engagement activities. All authors critically reviewed and approved the final version of the manuscript.

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