Hepatitis B Prevalence among Pregnant Women in Central and West Nile regions of Uganda: Is there a Need to prioritize Prevention of Mother to Child hepatitis B transmission?

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Abstract

Introduction Within sub-Saharan Africa (SSA), the burden of chronic hepatitis B (HBV) is unacceptably high in several countries including Uganda. Elimination of HBV in the context of inadequate resources and several competing health issues, faces challenges including limited data on disease burden in important population sub-groups. In order to optimize available resources, reliable data on HBV among pregnant women is useful to guide policies on prevention. This study estimated HBV prevalence and related factors among pregnant women in Central and West Nile regions of Uganda Methods Using a two-stage sampling approach, we selected a random sample of 310 pregnant women, 18 years or older from public health facility antenatal clinics in central and west Nile, North-western Uganda. Consenting women were interviewed to obtain data on HBV vaccination status, HIV status, selected sexual and lifestyle factors and socio-demographic information. In addition, they underwent phlebotomy to obtain blood for testing for hepatitis B surface antigen, (HBsAg) antibodies to the surface antigen (anti-HBs), and antibodies to the core (anti-HBc), as indicators of chronic infection, prior exposure, and susceptibility (anti-HBs <10 mIU /mL), respectively. Results Out of 310 women, prevalence of chronic HBV infection was 6.2%. Prevalence in the West Nile region was notably higher than in the Central region (11.0% vs. 1.3%), p<0.001. In both regions, majority of pregnant women (61% West Nile region, 76% Central region) were still susceptible to HBV. Overall, proportion who had been tested for HBV and those who reported having been vaccinated was only 5.8% and 11.3% respectively. Conclusion Our findings reveal the burden of HBV in Ugandan pregnant women is still high, with marked regional differences in disease prevalence, and poor levels of HBV testing and vaccination. These data suggest that HBV prevention programs and policies in resource-limited settings like Uganda may need to consider the differential HBV prevalence, as optimizing HBV prevention services in higher prevalence regions may provide greater impact and thereby align with the WHO recommendation on HBV elimination strategy in SSA.

Background

The global public health burden of hepatitis B virus (HBV) is currently recognized to be high particularly in Asia and sub-Saharan Africa (SSA)(1, 2). Approximately 257 million individuals are chronically infected with HBV (1) and both HBV and hepatitis C virus are leading causes of liver disease, including liver cancer (3). In high burden regions, perinatal transmission is the largest contributor to chronic HBV infection, especially when it occurs during early neonatal life (4). Because of this burden, the world health assembly responded with a strategy for global elimination of viral hepatitis as a major public health problem, by 2030 (5). Elimination is seen as feasible, given the availability of a vaccine against HBV and increasing accessibility to effective antivirals which can prevent progression from chronic HBV infection to liver cirrhosis and liver cancer(6-8).

The HBV vaccine, which is highly efficacious, as well as viral suppression using effective antiviral drug regimens, provide an unparalleled moment to reduce the burden of HBV-associated liver cancer. Yet vaccine uptake and coverage with antivirals remains much lower than needed in most of sub-Saharan Africa, where fewer than 5% of persons infected are not aware of their infection, and fewer than 1% of

those needing antivirals do not access them (9). Reducing the burden, to achieve HBV elimination goals, will require multiple, well-coordinated and targeted approaches, particularly among important sub-populations.

Pregnant women constitute an important sub-population regarding HBV control and elimination in high burden settings, due to the risk of mother to child HBV transmission (10), that results in early life chronic HBV infections. Moreover, studies in West Africa have linked perinatally-acquired HBV to liver complications, including liver cancer (11, 12). Yet in most of these settings, including Uganda, pregnant populations continue to be excluded from national HBV control strategies. Currently in Uganda, like most of SSA, services including antenatal HBV education, universal screening or vaccination for HBV among pregnant women and the HBV birth dose vaccination are not standard of care (13-16).

Epidemiologic studies on HBV among pregnant populations in Uganda are still too limited to provide an accurate measure of HBV prevalence and transmission risk, for purposes of informing best approach to HBV control in pregnant women and preventing mother to child HBV transmission. Only one study in the past decade, for instance, has estimated prevalence of hepatitis B e antigen (HBeAg) in a Ugandan hospital-based pregnant population, and found 15% of HBV surface antigen positive women, also positive for HBeAg (17). However, the study did not gather information on HBV testing, or vaccination, both useful measures of maternal HBV care practices. Equally important is data on the main drivers of HBV transmission risk, in order to optimize prevention interventions. Studies elsewhere have documented exposure through unprotected sex (18), unscreened blood products and unsterile medical injections (19) as major risk factors as well as on-going horizontal transmission particularly in early childhood (10, 20). The data currently available from SSA is inadequate to provide evidence in support of more rigorous strategies to prevent MTCT of HBV (21). This study therefore aimed to assess prevalence of HBV infection, susceptibility and immunity to infection, prevention and associated factors among pregnant women in two regions with a differing general adult population HBV prevalence (22). The purpose is to better understand HBV prevalence and susceptibility in the antenatal populations of the two regions in order to inform current approaches to HBV control and elimination among pregnant women in Uganda.

Methods

Study setting and design

The survey was conducted in Government-funded public health facilities at the level of Health center III and IV located in central region districts of Kampala and Wakiso, and in Arua Hospital. Arua Hospital is a regional referral hospital, situated in Arua district, approximately 300 miles north-west from Kampala city, in the West Nile region of north-western Uganda. The hospital has a bed capacity of 323 beds and it serves a population of roughly 782,077 covering districts of West Nile and parts of Northern Uganda (23). It receives about 153,451 out-patients and its antenatal client volume is estimated to be 5,149 antenatal per year. Kampala district is mostly urban, Wakiso district is 92% rural, with rapid urbanization. Kiswa health center III and Kasangati health center IV were the recruitment sites for the central region. Both

these primary care health units receive high patient volumes, averaging 850 -1,000 antenatal clients per month (24).

Study sample

The sample size for this study utilized the formula by Kish Leslie (25) for estimating a single population proportion [$n=z^2pq / d^2$] where z, the standard normal deviate at 95% confidence level takes the value of 1.96, p, the prevalence of hepatitis B of 10% (22); d, the desired level of precision. This yielded a sample size of 155, inclusive of an estimated non-response fraction of 10%. Therefore 155 participants were enrolled from the central and the West Nile regions respectively, for a total of 310 participants. Systematic sampling was used to select participants, whereby every 5^{th} eligible participant was approached for consent to be recruited into the study. Recruitment was spread evenly within each antenatal clinic day, until the total number was accrued.

Participant eligibility, procedures and data collection

To be included in the study, participants had to be at least 18 years old, pregnant, and registered for antenatal care in the health facility registry. Women otherwise fulfilling inclusion criteria were excluded from participation if they did not provide consent, were too sick to participate or to complete all required study procedures, including undergoing phlebotomy to provide a blood sample. Those willing to participate were then screened for eligibility and, if eligible, informed consent was sought from them by the study staff. Study staff interviewed participants and documented data on socio-demographic factors (age, region of residence, education, marital status, religion, occupation, history of testing for HBV (Yes/No), prior vaccination against HBV (Yes/No), number of doses of HBV vaccine received, sexual behaviour (number of lifetime sex partners) plus other health and lifestyle factors(smoking (Yes/No), alcohol use(Yes/No), history of jaundice (Yes/No), history of injection drug use(Yes/No), ever having been diagnosed with: liver cirrhosis(Yes/No), Schistosomiasis(Yes/No), chronic kidney disease(Yes/No) or diabetes(Yes/No). Clinical information on HIV status (infected/not infected), parity and history of abortion was abstracted from medical files of participants.

Blood draws and laboratory procedures

Each participant provided a blood sample equivalent to 9 ml for hepatitis B virus assays. Blood was collected in EDTA vacutainer tubes according to written study procedures. The tests were performed in accordance with the manufacturer's protocol. Quantitative serological assays for hepatitis B surface antigen (HBsAg,) anti bodies to the surface antigen (anti-HBs) and antibodies to the core antigen (anti-HBc) were done. WHO guidelines (26) on cut off values were used to determine presence of antibody

levels corresponding to previous immunity (anti-HBs ≥ 10 mIU /mL). Assays were done at MBN Clinical Laboratories, an internationally certified laboratory.

Ethical Issues:

All study staff received training from the online NIH course on protection of human research subjects and specific training on Uganda National Council for Science and technology (UNCST) national guidelines (27). Potential participants were approached during the general antenatal session and provided with information about the study, and those willing to participate underwent a consenting process. Only those willing and who provided written informed consent were recruited into the study. All participants received pre-testing counseling provided by trained counselors in small groups, prior to blood draws, but post-test counseling was offered individually and privately. This study protocol received review and clearance from Makerere University School of Public Health's higher degrees, Research and Ethics Committee and UNCST.

Data analysis.

Data were double-entered in excel, cleaned and exported into Stata. Analysis was done using Stata, version 14(StataCorp; College station, TX, 77845 USA). Data exploration was done and categories created. Descriptive summary statistics were generated as mean (standard deviation (SD)) for continuous variables, and proportions for categorical variables. The main outcome variable was chronic hepatitis B infection, defined as a single positive hepatitis B surface antigen (HBsAg) test result. Other outcomes of interest were immunity due to prior exposure (HBsAg test negative and positive for antibodies to the surface antigen) and susceptibility to HBV (defined as HBsAg negative and hepatitis B surface antibody negative). Chronic infection, immunity to infection and susceptibility to infection were treated as binary variables. Distribution of HBV infection by age groups, region of residence, religion, education, marital status, occupation, lifetime sexual partners, HIV status and other lifestyle and health factors was performed. Differences in proportions were tested using Pearson's chi-square test *p*-values and Fisher's exact test *p*-values, where appropriate. A two-tailed p-value of ≤0.05 was used for statistical significance.

Results

Participant characteristics

A total of 310 pregnant women participated in the study, aged 18 to 42 years. The mean age was 25.9 (SD±4.9) years. About a half (189/310, 46.9%) had attained at least a secondary education, while slightly more than a half were in employment (165/310, 53.2%) and reported to be in a monogamous marital union (175/310, 56.5%). Of the 310 participants, 27 (8.7%) were infected with HIV, and of these, only 4

(14.8%) were not on anti-retroviral medication. None of the HIV infected participants were co-infected with HBV. The other socio-demographic characteristics are shown in table 1.

Markers of HBV infection, susceptibility and immunity to infection

Overall, out of 310 pregnant women, 19 (6.2%) had chronic HBV infection, marked by HBV surface antigen positive assays. By region, proportion who were HBV surface antigen positive in the Central region were 1.3% (2/155), but 11% (17/155) in the West Nile region (Figure 1). Proportion who had markers of previously acquired immunity to HBV, either via a naturally acquired infection, or through previous vaccination were 22.6% and 27.7% in the central and northern regions, respectively. Majority of pregnant women in both regions showed markers of susceptibility to HBV, 76% in the Central and 61% in the West Nile region.

Participants' hepatitis B testing and vaccination status

Figure 2 shows proportion of pregnant women who reported having been tested and vaccinated against HBV. Only 5.8% (18/310) of pregnant women reported having taken a hepatitis B test, and 11.3% (35/310) reported having been vaccinated against HBV. Of those who reported having been vaccinated, 16 women had received only one vaccine dose, 4 women had received two doses and only 15/35 (43%) had received all three doses of HBV vaccine.

Association of HBV sero-positivity with clinical, socio-demographic and lifestyle factors

Table 2 reports the association of hepatitis B infection positivity with socio-demographic, clinical and behavioral lifestyle factors among pregnant women.

As shown on this table, statistically, there was a significant association between HBV sero-positivity and region of residence (p=0.001), type of marital relationship (p=0.018), level of education (p=0.026) and lifetime sexual partners (p=0.012). Conversely, no statistically significant association was found between HBV sero-positivity and age (p=0.605), parity (p=0.632), religion (p=0.988), type of occupation (p=0.737), previous HBV vaccination status (p=1.00), a family history of jaundice (p=0.722) or HIV infection (p=0.390). We further examined distribution of selected correlates of HBV infection by region, and as

shown in table 3, only proportion of women who self-reported to be in monogamous marriage differed, being higher in the northern region. Distribution of other factors including median age and lifetime sexual partners was similar in both regions.

Discussion

This study aimed to investigate HBV infection, testing and vaccination among pregnant women attending routine antenatal care in two of four of Uganda's geographic regions, with varying adult HBV population prevalence. Of the two regions analysed, the West Nile region in North-Western Uganda had a much higher HBV infection prevalence of 11%. This prevalence from the West Nile region is not very different that previously reported by Bayo *et al* (17), 12% chronic HBV prevalence among pregnant women in two private, not-for-profit hospitals located in the Northern Uganda. Our findings, the first within the past decade to come from obstetric populations of North-Western and Central regions, continue to reflect a pattern of regional disparity in Uganda's HBV burden that was much earlier reported in a national survey (22) conducted more than a decade ago, with the Northern corridor having a much higher prevalence than elsewhere, even within the pregnant population. A plausible factor for a high HBV burden in Northern Uganda seems to stem from a steadily growing refugee population mainly from neighboring South Sudan and the Democratic Republic of Congo. In these countries, large populations of adults and children live in conflict situations and are often unimmunized. South Sudan is a high burden HBV country, which, until very recently, has been without a structured national HBV control program. It is estimated that 1 in every 10 persons in South Sudan is infected with either HBV or hepatitis C virus (28). Our findings also support recent observations in SSA, where the burden of HBV in pregnant sub-populations remains proportionately high in localities with a high HBV population-level endemicity (29-33).

Like studies elsewhere in SSA (29, 34), majority of our participants were unaware of their HBV status. Very few pregnant women reported ever having tested for HBV, or having received HBV vaccination. And of those that sought vaccination services, fewer than half completed the required three dose vaccination schedule. Moreover, the women who reported having been tested or vaccinated for HBV received these services from private clinics, and paid privately. This finding may be an indicator of a general lack of awareness about HBV and its prevention. We have previously reported poor HBV knowledge and awareness in this region (35). This may be partially due to sub-optimal, even absent, hepatitis B services for pregnant women in most of SSA (13, 36). Without testing pregnant women for HBV, it becomes a challenge, not only to identify infected women who require further follow-up testing to ascertain those eligible for anti-viral treatment, but also to plan for timely birth dose vaccination of newborns of these women. Absence of routine HBV testing for pregnant women in Uganda continues to be a significant barrier to HBV status awareness among pregnant women, which further disables the chain of HBV care.

It is also noteworthy, that none of the HBV infected pregnant women in our study sample had HIV co-infection. Unlike our finding, other studies within the region have reported HIV among HBV infected pregnant women (37, 38). Our result might be explained by the fact that all our HIV infected women were already taking ART. Several ART regimens have been shown to be anti-HBV active (39-42), and a recent

longitudinal analysis in rural Rakai, Uganda, showed that HIV infected adults who were taking ART were less likely to acquire HBV (43). We report an unexpected negative correlation between HBV infection and risky sexual behavior, a finding that we believe to be due to participant under-reporting and social desirability bias, as data on type of marital relationship and lifetime sexual partners were self-reported.

The WHO elimination strategy for HBV in high burden settings (5) prescribes an approach involving understanding the local HBV epidemic, in order to adapt the response to local disease epidemiology. Our descriptive findings lend support to this narrative, by reporting locally-derived data that not only highlights intra-country differences in disease prevalence, but also is suggestive of flexible modalities of maternal and new born HBV prevention, guided by existing disease patterns. The findings suggest a need to intensify HBV prevention efforts among pregnant women in Uganda, particularly antenatal HBV testing in the most-affected regions, plus effective follow-up and appropriate management of infected women to prevent mother to child HBV transmission. The available resources could be optimally used, to afford at-risk pregnant women an opportunity to know their HBV status, and their newborns to receive a birth dose of HBV vaccine.

Note is taken, regarding limitations of this study. The cross-sectional and descriptive nature of the study limits strong inference regarding the observed associations. Also, much of the data on socio-demographic and behavioral variables were self-reported, and as such, liable to subjectivity, and the bias thereof. In addition, the few numbers of HBV infected cases meant that we were unable to adequately assess factors associated with HBV infection. Studies with larger sample sizes, and designed to evaluate HBV incidence and risk factors may increase our understanding of HBV risk factors in both regions, thereby, enabling implementation of the appropriate interventions in affected regions. Nonetheless, this work contains useful information on current HBV prevalence in two regions, and can ably contribute to local evidence to support policy options.

Strategies to control and eventually eliminate the health threat of HBV, will need to include prevention of mother to child transmission. This may entail introduction of testing and vaccination for pregnant women. Our findings reveal very low levels of HBV testing and vaccination among pregnant women even in high-endemic regions of Uganda, implying a missed opportunity to offer HBV prevention services to women who interface with the health system.

In conclusion, we have identified high HBV prevalence among pregnant women, with significant regional differences in prevalence, differences that highlight the need for flexible policy options in order to strengthen and speed-up HBV elimination actions. These findings underscore a need to intensify and optimize HBV prevention efforts among antenatal populations, testing pregnant women and implementing interventions to prevent mother to child HBV transmission, within the context of less than sufficient resources.

Declarations

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Availability of data and materials

Datasets used for analysis and writing of this manuscript are available from the corresponding author, on reasonable request.

Author's contributions

JNM conceptualized the study, participated in collecting data, analysis and writing the first draft. PO, FM, LA & GDK supported conceptualization of the study. PO JA FM & GDK contributed to analysis and writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study received approval from Makerere University School of Public Health Higher Degrees, Research and Ethics Committee (IRB Number 00005876; FWA Number 00011353). All eligible study participants went through a consenting process and provided written informed consent in English or one of the local languages (Luganda in central region, and Lugbara in northern region) to participate in the study.

Competing interests

The authors declare that they have no competing interests

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Tables

Table 1. Participant socio-demographic and clinical characteristics

Characteristic	Frequency (N=310)	Percent (%)
Age group (years)		
≤19	30	9.7
20-24	102	32.9
25-29	96	31.0
30-34	47	15.2
≥35	35	11.2
Age (years): Mean (SD)	25.8 (4.94)	
Education Level		
Primary or lower	175	43.42
Secondary	189	46.90
Post-secondary	39	9.68
Tribe		
Lugbara	115	37.1
Ganda	74	23.9
Others	121	39.0
Region of residence		
West-Nile	155	50.0
Central	155	50.0
Employment status		
Employed	165	53.2
Not employed	145	46.8
Marital status		
Single	24	7.7
Co-habiting	91	29.3
Married monogamous	175	56.5
Married Polygamous	20	6.5
Religion		
Roman Catholic	109	35.2
Protestant	99	31.9
Muslim	65	21.0
Others*	37	11.9
Parity		
0	95	30.7
1-3	176	56.8
4+	39	12.6
HIV Status		
positive	27	8.7
negative	283	91.3

Table 2. Association of hepatitis B infection with clinical, socio-demographic, behavioral lifestyle factors among pregnant women in Northern and Central Uganda

	HBV status			
	Yes	No	X^2	p-value*
Socio-demographic factors				
Age (Years)				
≤19	1 (5.26)	29 (9.97)	3.3939	0.605
20-24	6 (31.58)	106 (36.43)		
25-29	7 (36.84)	92 (31.62)		
30-34	5 (26.32)	46 (15.81)		
≥35	0 (0.00)	18 (6.19)		
Region of residence				
West Nile	17 (89.47)	138 (47.42)	12.6153	0.001
Central	2 (10.53)	153 (52.58)		
Education				
≤Primary	5 (26.32)	122 (41.92)	7.3066	0.026
Secondary	9 (47.37)	145 (49.83)		
Post-secondary	5 (26.32)	24 (8.25)		
Religion				
Catholic	7 (36.84)	102 (35.05)	0.0251	0.988
Protestant	8 (42.11)	126 (43.30)		
Muslim	4 (21.05)	63 (21.65)		
Marital status				
Not currently married	0 (0.00)	24 (8.25)		0.018
Married-monogamous	16 (84.21)	159 (54.64)		
Married-polygamous	2 (10.53)	18 (6.19)		
Co-habiting	1 (5.26)	90 (30.93)		
Occupation				
Farmer	8 (42.11)	86 (29.55)		0.737
Restaurant & bar worker	7 (36.84)	140 (48.11)		
Housewife	0 (0.00)	10 (3.44)		
Teacher or civil servant	2 (10.53)	25 (8.59)		
Hairdresser	2 (10.53)	30 (10.31)		
Clinical and behavioral factors				
HIV status				
Infected	0 (0.00)	27 (9.28)		0.390
Not infected	19 (100.00)	264 (90.72)		
parity				
0	4 (21.05)	91 (31.27)	0.9187	0.632
1-3	12 (63.16)	164 (56.36)		
4+	3 (15.79)	36 (12.37)		
Previously vaccinated for HBV				
Yes	1 (5.26)	17 (5.84)	0.0109	1.00
No	18 (94.74)	274 (94.16)		
Family h/o jaundice				
Yes	3 (15.79)	37 (12.71)	0.1500	0.722
No	16 (84.21)	254(87.29)		
Lifetime sexual partners				
One	12 (63.16)	97 (33.33)		
More than one	7 (36.84)	194 (66.67)	6.9588	0.012

P-value is for Fisher's exact test.

Table 3. Regional distribution of selected correlates of HBV infection

	Central	North
Correlate		
HBsAg positivity (%)	1	11
Median Age	25	25
>primary education (%)	60	58
Self-reported monogamous marriage (%)	29	84
Median lifetime sexual partners	3	2
>3 pregnancies (%)	19	20

Figures

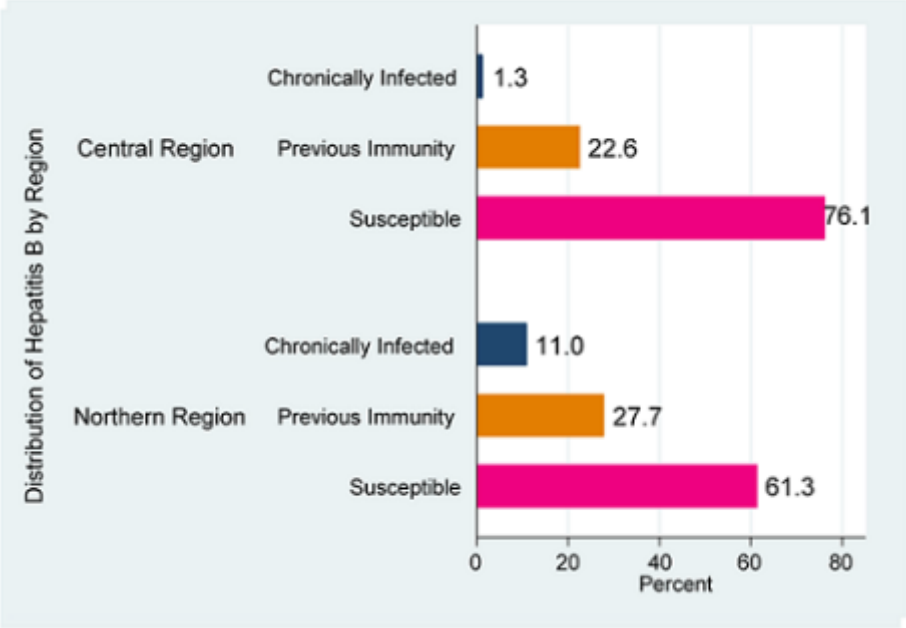
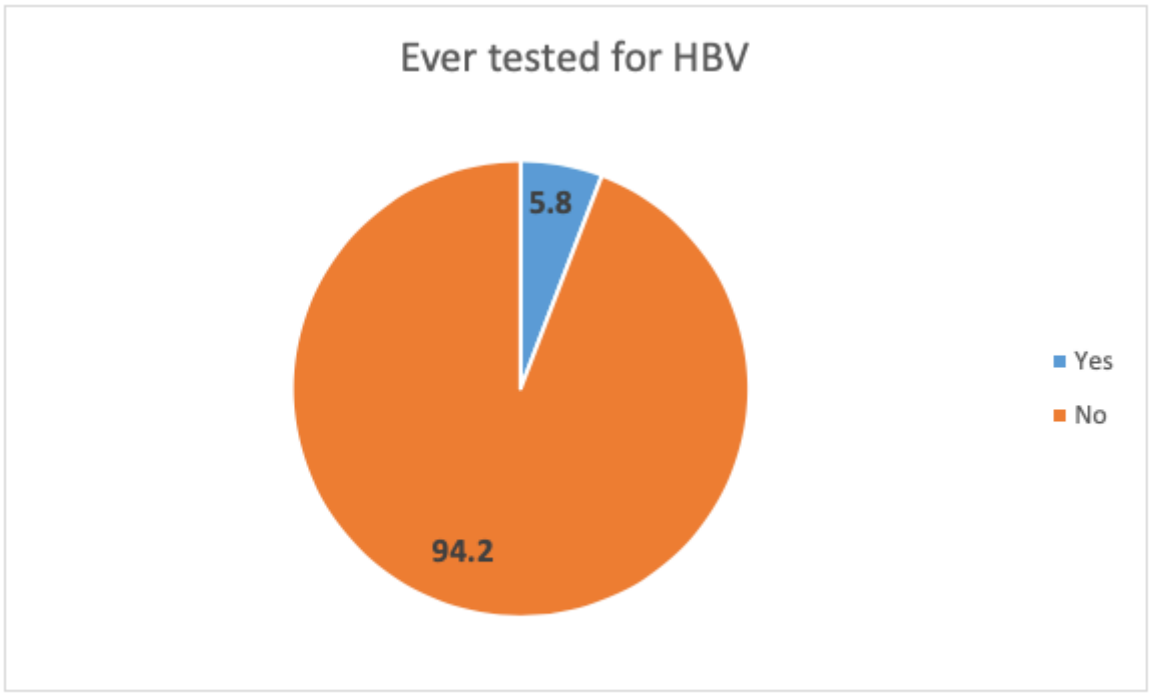


Figure 1

Regional distribution of markers of hepatitis B infection, immunity and susceptibility to infection among pregnant women in Northern and Central Uganda. Chronically infected=proportion of pregnant women who tested positive for HBsAg. Previous Immunity= Proportion of pregnant women who tested negative for HBsAg and had anti-HBS antibody titres greater than 10 IU/ml. Susceptible = proportion of pregnant women who tested negative for HBsAg, and had anti-HBS antibody titres less than 10 IU/ml.



Showing the proportion of pregnant women who reported ever having tested for HBV.

Figure 2

Proportion of pregnant women who reported ever having had a hepatitis B test. Yes=proportion of women who reported having tested for HBV; No=proportion of women who reported never having tested for HBV

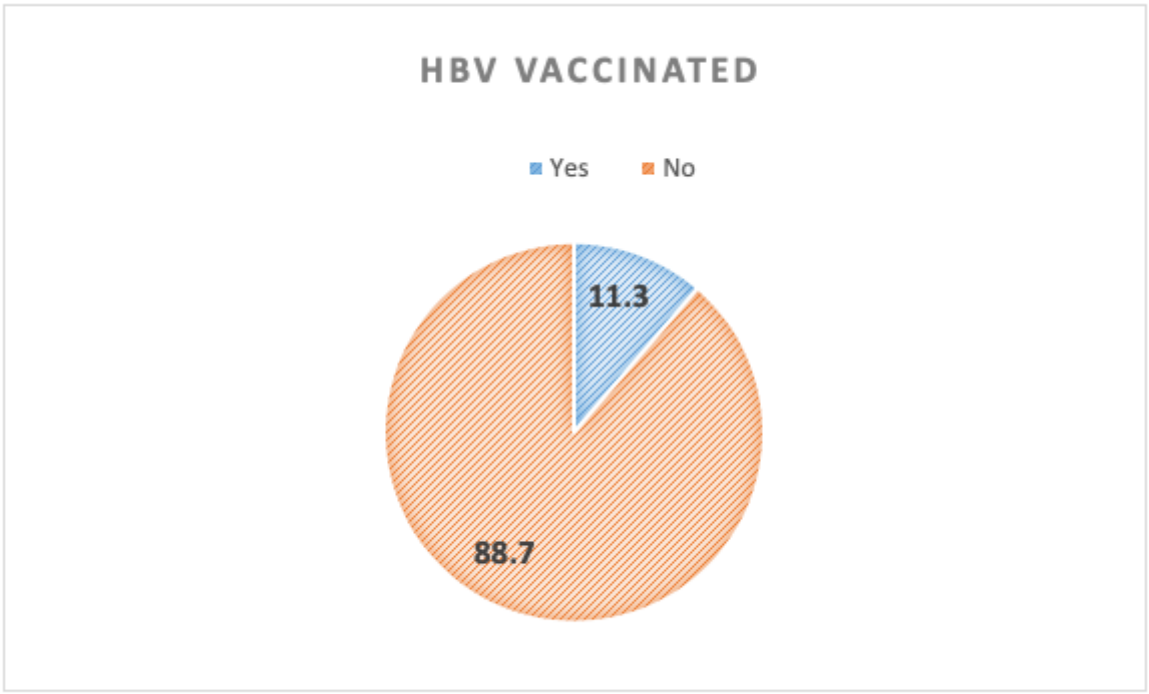


Figure 3

Proportion of pregnant women who reported having been vaccinated against hepatitis B. Yes=proportion of women who reported having been vaccinated for HBV; No=proportion of women who reported never having been vaccinated for HBV