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The epidemiology of hepatitis b virus infection in Uganda after two decades of vaccination: a meta-analysis and meta-regression

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Abstract

Introduction Hepatitis B virus (HBV) remains a public health threat in Uganda, despite the introduction of the HBV vaccine and its inclusion in the Expanded Program on Immunization (EPI) more than two decades ago. This study aimed at providing up-to-date information on the epidemiology of HBV in Uganda and inform the way forward when designing the interventions to control and prevent the virus.

Methods A systematic search for records published between 1st January 2002 and 30th June 2024 from PubMed and African Journal Online (AJOL) was done from which data on the overall and subgroup prevalence of HBV was extracted. Both the random and fixed effect models were used to pool data for the overall and sub group meta-analysis. The overall and subgroup trend of HBV prevalence over the last two decades was evaluated by meta-regression modelling. The predictors of HBV infection were analysed by using odds ratio (OR). The I^2 index in the primary records was used to evaluate the heterogeneity. Publication bias in the primary studies was assessed by using Egger's test and funnel plot asymmetry. All analyses were done at 95% confidence interval (CI) and a $p < 0.05$ was considered significant.

Results A total of 34 original studies were included in the data synthesis with a pooled sample size of 81,416 individuals. The pooled prevalence of HBV was 8.3% but varied with region and study group. It was highest in the eastern region ($p < 0.05$) and among the community-based studies ($p < 0.05$). By meta-regression modelling, there has been an overall decrease in the prevalence of HBV since the integration of the vaccine as part of the EPI in 2002 ($p < 0.05$) and in the central, eastern and northern regions. Conversely, there was an increase in the prevalence of HBV in western Uganda with a strong temporal explanatory power ($R^2 = 0.700$). Familial contact with an HBV infected person; odds ratio (OR) = 3.85, $p = 0.006$ was the most significant risk factor for HBV infection. In contrast, age < 20 year; OR = 0.52, $p = 0.016$ was protective against HBV infection.

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Conclusion Despite the significant progress registered in reducing the prevalence of HBV since the integration of HepB vaccine as part of the EPI, there are still regional and cohort specific disparities in the prevalence of HBV in Uganda. Thus, different interventions should be designed in tandem with the differences in the prevalence by specific groups and regions.

Keywords Hepatitis b virus, Prevalence, Vaccination, Meta-regression, Meta-analysis

Introduction

Hepatitis B virus (HBV) is the causal agent for hepatic inflammation and if not diagnosed in a timely manner and then later managed, is likely to advance to fibrosis, cirrhosis, and liver cancer [1]. In Africa, the prevalence of chronic HBV infection stands at 6.1% [2] in the general population but varies with study cohorts [3]. In east Africa, a prevalence of 6.025% has been recently reported by our research team [4]. In Uganda, approximately 1.845 million Ugandans are chronically infected with the virus [5] and liver cancer caused by HBV contributes 5.1% of all cancer death [6].

The world health organisation (WHO) rolled out vaccination programs in the 1980s and a plasma derived vaccine (HepataVax B) vaccine [7] was made accessible for commercial use in 1981 in the USA and 1982 in France [8]. In 1995, the WHO recommended the introduction of the HBV vaccination program in high endemicity countries where chronic infection is $\geq 8\%$ in the general population and in all countries in 1997 [9]. In most African countries, HBV vaccination was rolled out in 1995 for infants [10]. In Uganda, it was introduced in 2002 as part of the expanded program on immunization (EPI) given to all infants at 6, 10 and 14 weeks after birth. For those persons born before 2002, vaccination has been focused on high risk adults such as the health care workers, persons living with HIV, those having house hold contact with an infected person, pregnant women, people with sickle cell disease (SCD), sex workers, people who have multiple sex partners, men who have sex with men (MSM), people who inject drugs, persons with routine blood transfusion, armed forces and prisoners at first contact with vaccination (0 months), after 1 month and after 6 months [11]. In addition, the ministry of health has recently rolled out two vaccination strategies. First, free regional based immunisation programs starting with the highly endemic areas of northern and eastern Uganda but to eventually cover the whole country [12]. Second, a birth dose to protect the baby from mother to child transmissions and horizontal intra familial transmissions from care takers during the first days of life.

Despite vaccination being a cornerstone in the control and prevention of HBV, there has been some drawbacks in the implementation of vaccination programs in Uganda. First, misconceptions about the vaccine and low awareness have been reported to restrain vaccine uptake [13, 14]. Second, given the low completion of full

vaccination schedule among adults, their vaccination may not be a feasible strategy. Therefore, prioritizing a test-and-treat approach for adults and redirecting vaccination efforts toward administering birth doses appears to be a more practical and effective alternative [15]. Third, the vaccine hesitancy among pregnant women attending antenatal care may hinder the uptake of the HBV vaccine, thereby increasing the risk of vertical transmission of HBV during childbirth [16].

Because of the aforementioned challenges, the rapid decrease in the prevalence of HBV in Uganda from 10 to 4.3% in the general population reported by the ministry of health between 2015 and 2018 appears idealistic rather than realistic [5, 17]. In this study, we aimed at synthesising data from a large sample size to establish the epidemiology of HBV in Uganda since the integration of HBV vaccine as part of the expanded program on immunization in 2002. The findings of the study will inform the stakeholders involved in the control and prevention of HBV on the way forward when designing intervention to control the disease.

Methods

Study protocol registration

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO). This study is part of a large study to evaluate the status of HBV in Uganda since the integration of HBV vaccine in 2002 with registration number CRD42024580337. The results have been reported following guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 [18].

Research questions

1. What is the pooled prevalence of HBV in Uganda after two decades of vaccination?
2. What is the epidemiology of HBV in Uganda after two decades of vaccination?
3. What are the risk factors for HBV infection after two decades of vaccination in Uganda?

Search strategy and selection criteria

The studies were searched from African Journal Online (AJOL) and PubMed by four reviewers (HMK, AK, FM and MN) between the period of 1st September 2024 to 30th September 2024. Only articles published in English

language between Jan 1st 2002 to June 30th 2024 and reported the prevalence of HBV in Uganda were selected. Search terms included those related to HBV prevalence by region, study group and risk factors for HBV infection in line with the research questions (Supplementary file S1). The reviewers also performed a snowball search from the references of the articles to identify and screen the studies citing them. Similarly, references of systematic reviews on the prevalence of HBV in Uganda were manually searched for additional records. Finally, grey literature was searched for in Google Scholar to obtain additional records like thesis publications and pre-prints. All the records retrieved from the data bases and from Google scholar were screened for titles, abstracts or full texts by HMK, AW and MN for inclusion or exclusion in the meta-analysis and meta-regression. Only records with extractable data, well stated methodology, those that reported the outcome using a standard diagnostic procedure and published between Jan 1st 2002 to June 30th 2024 were eligible for inclusion in the data synthesis. In contrast, duplicate records, those with unextractable data, conference abstracts, reviews and records published before Jan 1st 2002 or after June 30th 2024 were not included in the study.

A spread sheet was created in Microsoft Excel (version 16) by HMK and checked by AW. The outcomes of interest were the population, exposure, comparison and outcome (PECO). The study population was the Uganda population regardless of the region of study or study cohort. For exposure, we used the seroprevalence of HBsAg as a surrogate marker of HBV infection. The comparison was between the exposed and unexposed by study cohort, diagnostic test, region, year of publication, sampling method or predictor of infection such as gender, marital status, HIV status among others. The outcome measure was the HBV prevalence detected by the standard diagnostic method (ELISA, RDTs, EIA or PCR).

Data analysis

One reviewer (HMK), extracted the data from the primary records eligible for inclusion using Microsoft Excel (Version 2010). These were checked by NM and any inconsistencies in the data were resolved by DN. The following data were extracted from each record: first author and year, region, study group, sampling technique, sample size, hepatitis B surface antigen positivity (HBsAg+) and HBsAg detection methods. In studies that disaggregated data on the predictors of HBV infection, the following data were extracted: - socio-demographic risk factors (marital status, gender, education level), sexual and reproductive risk factors (number of sexual partners, SIT exposure, parity and HIV status), Cultural/Traditional practices (body piercing and cultural scarification)

as well as parenteral and house hold risk factors (familial contact, history of surgery and blood transfusion).

Three reviewers (HMK, AW, NM) assessed the risk of bias in each primary record using the Newcastle-Ottawa Scale (NOS) [19] and resolved any discrepancies by consulting HS. The scale is based on exposure, comparison and selection. The exposure status was evaluated by reporting the HBsAg serostatus using standard diagnostic tests. In contrast, comparison was assessed by looking at primary records that reported differences in HBsAg by study groups. Selection was assessed by looking at the vigour of the methodology used to avoid inclusion of studies that would bias our findings. For example, only studies with defined methods of sample size determination, sample selection and HBV detection method were selected for inclusion the data synthesis. Accordingly, scores of 9–8, 7–6 and 5–4 qualified for very good, good and moderate qualities. Conversely, studies with a score ≤ 3 were of poor quality and were not included in the meta-analysis (Supplementary File S2).

The publication bias was assessed using Egger's test [20] and funnel plot asymmetry. A $P > 0.05$ and symmetrical distribution of the standard error against the effect measure in a funnel plot indicated no evidence of publication bias. To provide a summary estimate of the pooled prevalence of HBV in the general population and in the sub-groups, the proportion (%) was used as the effect measure with 95%CI. In addition, the odds ratios (OR) with 95% CI were used as the effect measure to determine the association of the risk factors with HBV infection. The results were presented as forest plots. The estimate of each study has been indicated by the solid blue square in the forest plot. The size of the square represents the weight contributed by each study in the meta-analysis. The pooled effect measure has been shown by the blue diamonds. The $OR > 1$ indicates increased risk to HBV infection whereas the $OR < 1.0$ indicates reduced risk of the infection.

The random effect meta-analysis (REM) or fixed effect meta-analysis (FEM) were used to pool the prevalence and the odds ratios. We evaluated the between study heterogeneity using the I^2 statistics [21]. For studies that demonstrated a high heterogeneity index among the primary records ($I^2 > 50\%$), the REM meta-analysis was used throughout the analysis. In contrast, for studies with low heterogeneity index ($I^2 < 50\%$), the FEM meta-analysis, was used for the analysis [22].

We performed three sensitivity analyses to assess the robustness of the pooled HBV prevalence estimates. First, by excluding the study with the highest sample size to eliminate the single study effect on the prevalence estimate of HBV. Second, by eliminating the single study that used nucleic acid amplification technique (NAAT). Third, by removing the study with the highest sample size from

eastern region during the sub-group analysis of HBV prevalence by region.

To give insights on the trend of the prevalence of HBV over the years since the introduction of the HEP B vaccine as part of the expanded program on immunization from 2002, we performed regression modelling using regression equations with the corresponding p values, slope of the graph and the R² value. All the analyses were performed using the statistical software, MedCalc (version 10.10) available at <http://www.medcalc.org> and GraphPad Prism (version 10.5.0 (774)) at 95% CI and a $p < 0.05$ was taken to be significant.

Results

Study identification

A total of 628, published records were identified (79 from PubMed and 549 from AJOL). In addition, we identified 3 records from Google Scholar as grey literature. From these, 539 records were removed as duplicates leaving 92 records eligible for abstract and title screening. After abstract and title screening, 51 records were excluded leaving 41 records eligible for full text review from which

3 records were excluded. This left 38 records for inclusion for data extraction from which 4 records were excluded with specific reasons. Finally, 34 records were included in the meta-analysis (Fig. 1).

Characteristics of the eligible studies for inclusion in data synthesis

Out of the 34 studies included in the meta-analysis, the largest number were conducted in the central region of Uganda, accounting for 14 out of 34 studies (41%) with a pooled sample size of 12,692. In terms of study populations, most studies focused on pregnant women attending antenatal care, representing 11 out of 34 studies (32%) with a combined sample size of 4,217. With regard to sampling techniques, non-random methods were used in the majority of studies (24 out of 34, 71%), involving a pooled sample size of 68,362. For HBsAg detection, rapid diagnostic tests (RDTs) were the most commonly used method, reported in 18 out of 34 studies (53%) with a pooled sample size of 60,158 (Supplementary file S3). The detailed characteristics of the eligible studies are highlighted in Table 1..

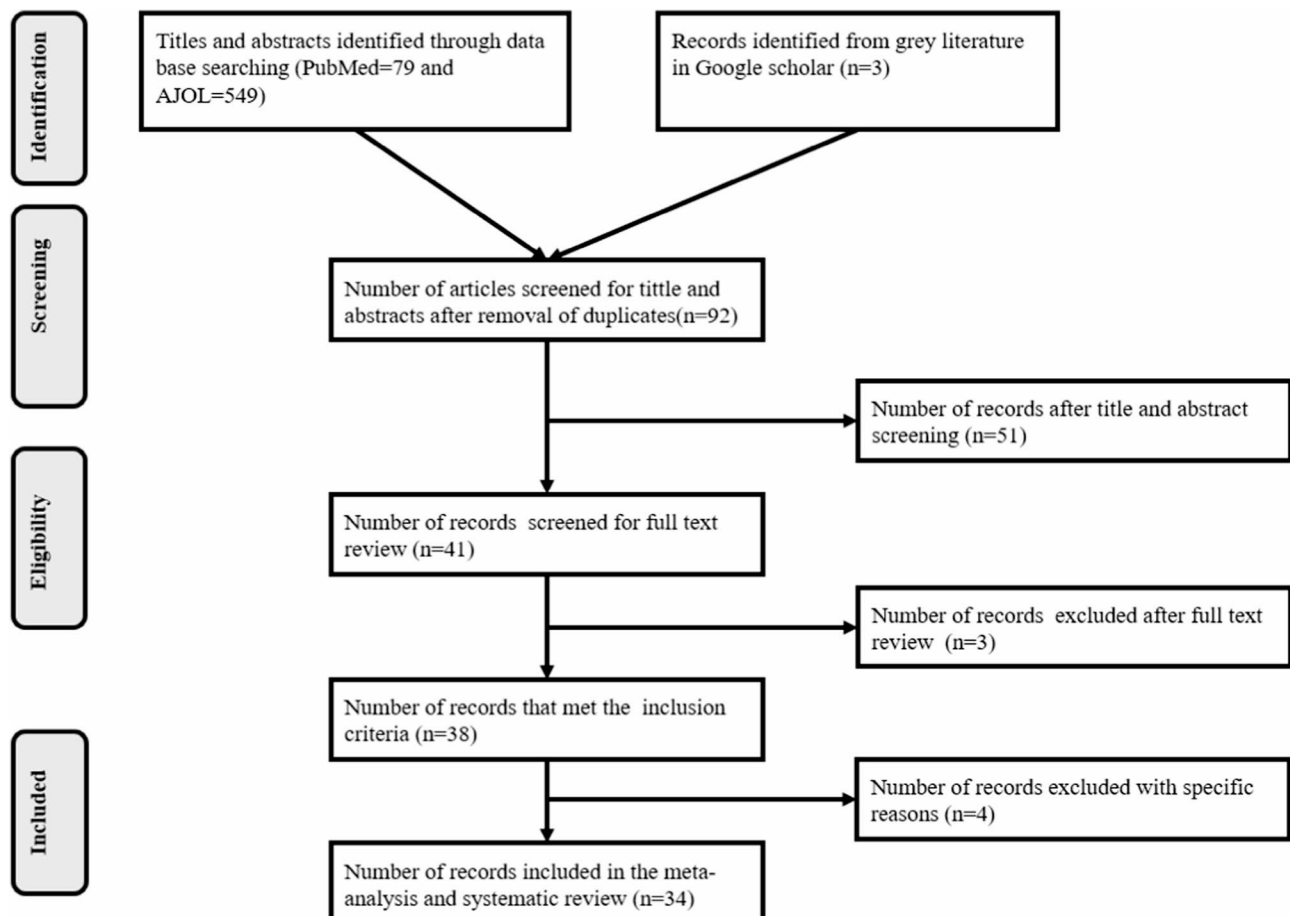


Fig. 1 Flow chart for study eligibility following PRISMA criterion; AJOL: African Journal Online, HBV: Hepatitis B Virus

Table 1. Characteristics of the included studies in the systematic review and meta-analysis for the prevalence of hepatitis B virus in Uganda

First author, Year	Region	Study group	Sampling technique	Examined samples	HBsAg + Samples	Detection method
Ainebyona et al., 2024[23]	Eastern	ANC Mothers	Non random	70	13	RDT
Baseke et al., 2015[25]	Central	HIV + patients	Non random	89	15	ELISA
Pirillo et al., 2007[26]	Central	ANC Mothers	Non random	164	8	ELISA
Bongomin P et al., 2005[27]	Central	Medical students	Non random	170	19	ELISA
Kabajulizi et al., 2019[28]	Western	ANC Mothers	Non random	254	3	RDT
Kayondo SP et al., 2019[29]	Central	ANC Mothers	Random	340	10	RDT
Atwine et al., 2022[30]	Northern	ANC Mothers	Non random	341	7	RDT
Ziraba et al., 2010[31]	Central	HCWs	Non random	370	30	ELISA
Mugabirwe et al., 2022[32]	Central	ANC Mothers	Non random	384	8	RDT
Madrama et al., 2022[33]	Northern	Community	Non random	384	29	RDT
Aheisibwe H et al., 2019[34]	Western	ANC Mothers	Non random	385	12	EIA
Ndibarema et al., 2022[35]	Western	OPD	Non random	400	22	RDT
Bayo P, et al., 2014[36]	Northern	ANC Mothers	Random	402	47	ELISA
Kafeero et al., 2022[37]	Eastern	OPD	Non random	424	48	RDT
Ssuuna et al., 2022[38]	Central	Community	Non random	460	17	ELISA
Kitandwe et al., 2021[39]	Central	Community	Non random	517	36	EIA
Teshale et al., 2015[40]	Northern	Community	Non random	656	62	RDT
Ochola et al., 2013[41]	Northern	Community	Random	790	139	RDT
Chiesa et al., 2020[42]	Northern	HIV + patients	Random	950	75	RDT
Mayanja et al., 2023[43]	Central	SIVET	Random	998	46	ELISA
Thahir et al., 2023[44]	Western	ANC Mothers	Non random	1065	50	RDT
Malamba et al., 2021[45]	Northern	Community	Random	2421	288	EIA
Bwogi et al., 2009[46]	National survey	Community	Random	5,875	606	EIA
Rachel et al., 2018[47]	Central	HIV + patients	Non random	8042	359	ELISA
Ssegawa et al., 2018[24]	Eastern	Community	Non random	52,603	3939	RDT
Ocama et al., 2008[48]	Central	HIV + Patients	Non random	77	11	PCR
Stabinski et al., 2011[49]	Central	Community	Non random	438	181	EIA
Seremba E et al., 2017[50]	Northern	ANC Mothers	Non random	612	53	RDT
Nakwagala et al., 2002[51]	Central	OPD	Non random	258	49	ELISA
Ocama et al., 2015[52]	Northern	HIV + patients	Non random	300	20	RDT
Kharono et al., 2022[53]	Eastern	ANC Mothers	Non random	200	2	RDT
Masika et al., 2016[54]	Eastern	Community	Random	281	58	RDT
Braka et al., 2006[55]	National survey	HCWs	Non random	311	28	EIA
Muhammad et al., 2023[56]	Central	MSM	Random	385	12	RDT

Abbreviations: EIA Enzyme Immunoassay, ELISA Enzyme Linked Immunosorbent Assay, RDT Rapid Diagnostic Test, HBsAg Hepatitis B Surface Antigen, SIVETs Simulated HIV vaccine efficacy trials

Hepatitis B Virus (HBV) Prevalence in Uganda

The pooled prevalence of HBV was estimated at 8.3% (95% CI: 6.918 to 9.701), based on a total sample size of 81,416 individuals. This estimate was calculated using a random-effects meta-analysis model, which indicated substantial heterogeneity across the included studies ($I^2 = 96.49\%$, $P < 0.001$). Egger's test showed no significant evidence of publication bias ($p = 0.535$) (Supplementary file S4).

However, the prevalence varied notably across subgroups, depending on the study population, geographic region, and sampling technique used (Fig.2). Among community-based studies (10 studies; $n = 64,425$), the pooled prevalence was 12.3% (95%CI=9.33 to 9.70) which

was significantly higher than that of other study groups ($p < 0.05$). For people living with HIV (PLWHIV), the prevalence was 8.7% (95% CI=5.51 to 12.55), based on five studies with a combined sample size of 9,458. Among pregnant women attending antenatal care (11 studies; $n = 4,217$), the pooled prevalence was lower, at 4.6%. (95% CI=2.77 to 6.89). Healthcare workers showed a pooled prevalence of 8.8% (95% CI=6.64 to 10.85), derived from two studies with a total sample size of 6,398. Among the OPD, a pooled prevalence of 11.3% (95% CI=5.17 to 19.63) from 3 studies with a pooled sample size of 1,082. Other groups included in the studies were men who have sex with men (1 study), medical students (1 study), and participants in Simulated HIV Vaccine Efficacy Trials

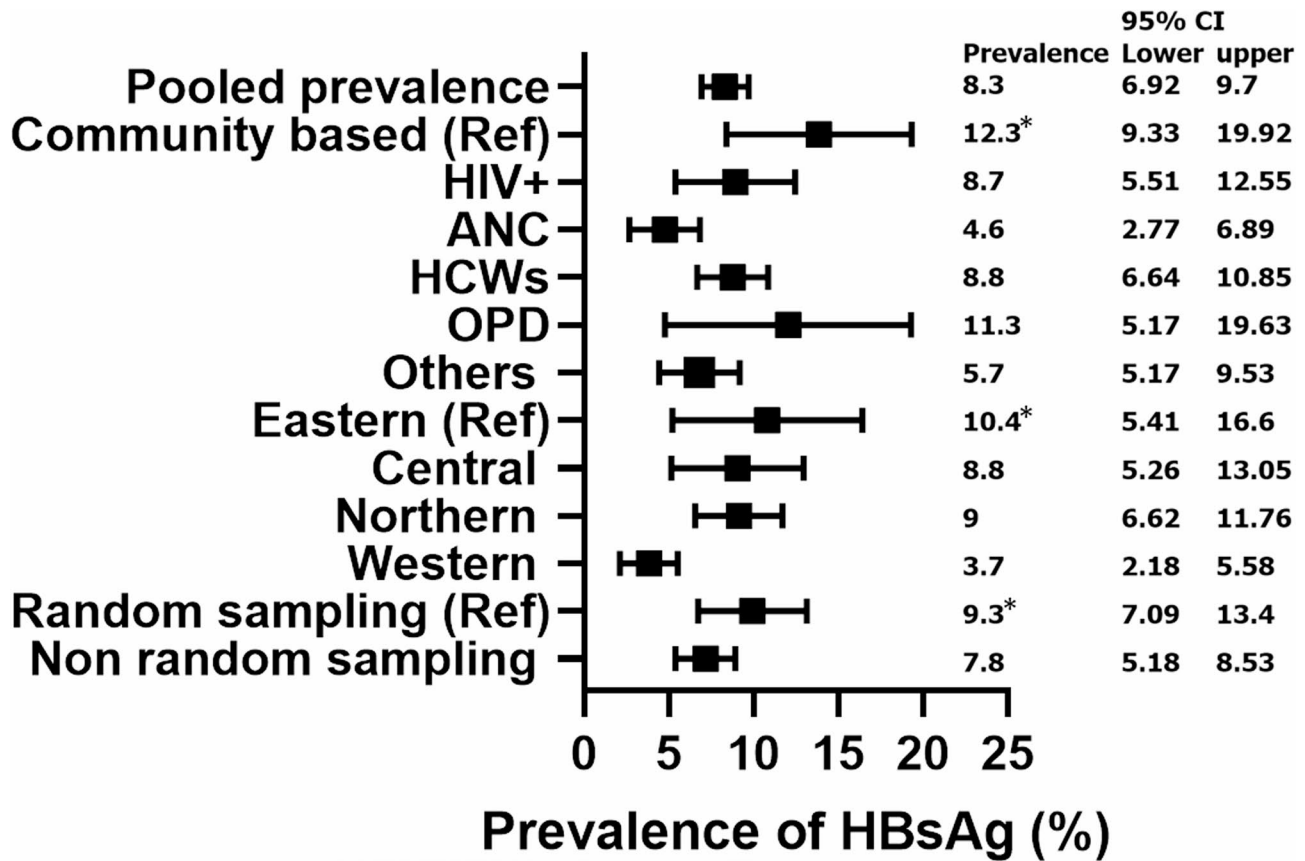


Fig. 2 Forest plot showing the overall and sub-group prevalence of HBV: Abbreviations; HIV: Human immunodeficiency virus, ANC: antenatal care, HCWs: Health care workers, OPD: outpatient department, ELISA: Enzyme linked immunosorbent assay, EIA: Enzyme immune assay, RDT: Rapid diagnostic test; *prevalence significantly higher in the reference category

(SiVETs) (1 study), with a combined sample size of 1,553 and an overall prevalence of 5.7% (95% CI=5.17 to 9.53). Marked regional differences in HBV prevalence were also observed. The eastern region reported the highest prevalence at 10.4% (95% CI=5.41 to 16.60) from five studies with a pooled sample size of 53,578 which was significantly greater than that of other regions ($p < 0.05$). This was followed by the northern region at 9.0% (95% CI=6.62 to 11.76) from nine studies with a pooled sample of 6,856 and the central region at 8.8% (95%CI=5.26 to 13.05) from 14 studies ($n = 12,692$). In contrast, the western region recorded the lowest prevalence at 3.7% (95%CI=2.18 to 5.58) based on four studies with a sample size of 2,104. Additionally, the prevalence was influenced by the sampling method. Studies employing random sampling reported a significantly higher prevalence of 9.3% (95% CI=7.09 to 13.4) from 10 studies with a sample size of 13,052 ($p < 0.05$) compared to those using non-random sampling, which yielded a pooled prevalence of 7.8% (95% CI=5.18 to 8.53) pooled from 24 studies with a sample size of 68,362. High heterogeneity was observed across all subgroup analyses ($I^2 > 73%$, $p < 0.05$), necessitating the use of a random-effects model. An exception

was observed for studies involving healthcare workers, where heterogeneity was negligible, and a fixed-effects model was applied. Publication bias was not evident for most subgroups (Egger’s test $p > 0.05$), except for studies involving HIV-HBV co-infection and healthcare workers, where Egger’s test indicated potential bias ($p < 0.05$), possibly due to selective reporting or publication of statistically significant results (Supplementary File S5).

Meta-regression analysis

We conducted a linear regression analysis to assess temporal trends in HBV prevalence following the introduction of the HBV vaccine into the Expanded Programme on Immunization (EPI) (Supplementary File S6). Overall, there has been a general decline in HBV prevalence since the vaccine's integration into the EPI in 2002. Regarding study groups and geographical regions, notable reductions were observed in central, eastern, and northern Uganda, and among community-based studies, individuals living with HIV, and among pregnant women attending antenatal clinics. Conversely, an increase in HBV prevalence was observed in western Uganda. Although the decline was only statistically significant for

the overall prevalence of HBsAg ($p < 0.05$), the temporal decline showed moderate explanatory power in community-based studies ($R^2 = 0.376$) and in northern Uganda ($R^2 = 0.361$). In contrast, the rise in HBV prevalence in western Uganda demonstrated strong explanatory power ($R^2 = 0.700$) (Figure 3).

Sensitivity analysis

The single study effect was evaluated by carrying out three sensitivity tests. First, by removing the study with the largest sample size [24]. Second by removing the only study that detected the prevalence of HBV by using NAATs [48]. Third by removing the study with the largest sample size from eastern region [24] during the subgroup analysis of HBV prevalence by region. The pooled prevalence before removal of the study with the largest sample size and the study that used PCR was 8.3%, 95% CI= 6.918 to 9.701 with the heterogeneity score (I^2) of 96.49%. After removal of the study with the largest sample size, and the study that used PCR the pooled prevalence remained almost unaltered at 8.3% (95% CI= 6.561 to 10.312) and 8.1% (95% CI=6.796 to 9.589%) respectively. In addition, after removal of the study from eastern region with the highest sample size, the prevalence by region remained highest in eastern region at 11.3% (95% CI=3.505 to 22.815). For all the analyses, heterogeneity (I^2) between studies remained high ($I^2 > 95\%$) and the REM meta-analysis was used. Moreover, there was no evidence of publication bias as assessed by Egger's test ($p > 0.05$) (Supplementary file S7).

Meta-analysis of the Predictors of HBV infection in Uganda

From the records, we obtained 13 studies with data on marital status (Married or unmarried), 10 on gender (male or female), 10 on blood transfusion (transfusion naïve or not), 4 on scarification (yes or no), 7 on HIV serostatus (positive or negative), 5 on parity (one or none versus two or more), 4, on age (< 20 or ≥ 20 years); 11 on level of education (Primary or less versus secondary and above), 8 on number of sex partners (one or none versus two or more), 7 on history of infection with STIs (yes or no), 5 on HBV familial HBV contact (yes or no), 5 on history of surgery (yes or no), and 4 on body piercing (yes or no) (Supplementary file S8). The predictors of HBV infection were categorised into socio-demographic factors, sexual and reproductive risk factors, cultural/traditional risk factors as well as parenteral and house hold exposure risk factors. The results for the association between these factors and the risk of HBV infection have been indicated as OR with corresponding 95% confidence interval (Table 2). Similarly, forest plots showing the OR estimate of each study and the pooled prevalence have been plotted (Figs. 4, 5, 6, 7).

Regarding the socio-demographic factors and their association with prevalence of HBV, our results have shown that the married persons (OR=0.81; 95%CI= 0.562 to 1.161; $p=0.249$), the females (OR=1.10; 95% CI=0.725 to 1.657; $p=0.667$) and those who either attended primary or had no formal education (OR=0.99; 95% CI=0.809 to 1.212; $p=0.924$) were not significantly associated with HBV infection. In contrast, the age < 20 years (OR=0.52; 95%CI= 0.303 to 0.885; $p=0.016$) was significantly associated with HBV infection (Table 2, Figure 4). Therefore, persons under the age of 20 years were associated with

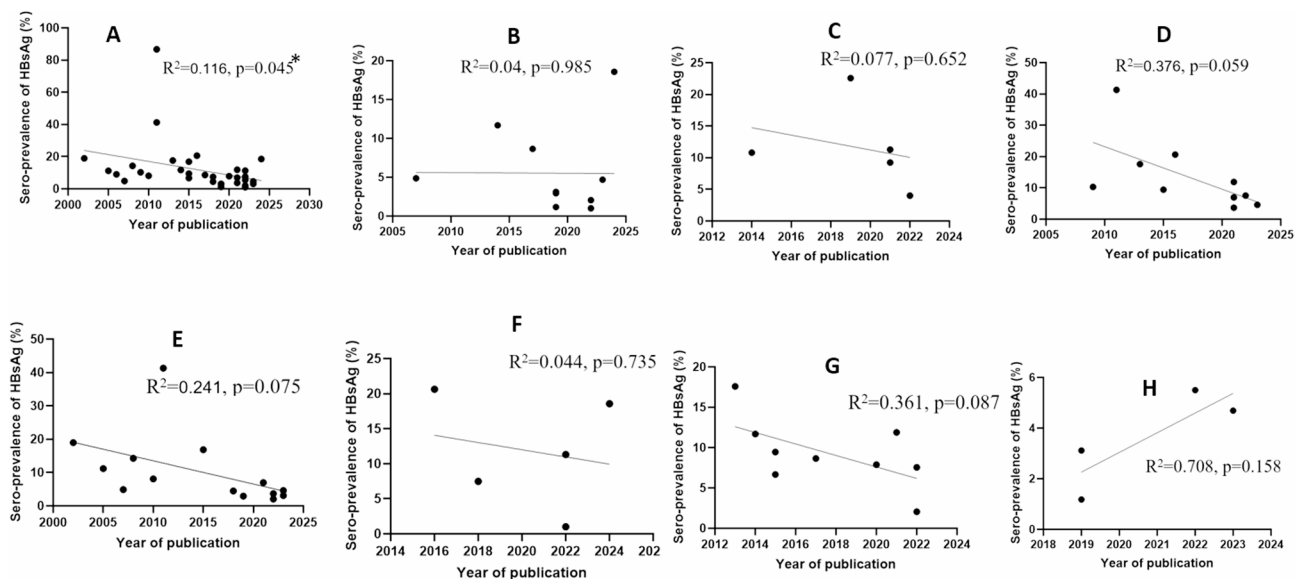


Fig. 3 Meta-regression analysis showing the HBsAg seropositivity over the years in different study groups: - **A**: Overall, **B**: ANC, **C**: HIV+, **D**: Community based studies, **E**: Central region, **F**: Eastern region, **G**: Northern region, **H**: Western region. * p -value is significant

Table 2 Analysis of the risk factors associated with HBV infection in Uganda from 2002 to 2024

Risk factor	No	Odds Ratio	p-value	Analysis of heterogeneity and Publication Bias			
				I ² index	p-value	Model	Egger's p value
Socio-demographic factors							
Married	13	0.81(0.562 to 1.161)	0.249	61.08(28.73 to 78.75)	<0.001	Random	0.7537
Female	10	1.10(0.725 to 1.657)	0.667	74.04(51.33 to 86.16)	<0.001	Random	0.3412
Age < 20 years	4	0.52(0.303 to 0.885)	0.016*	22.7(0.0 to 90.02)	0.275	Fixed	0.2425
Primary or less Educ level	11	0.99(0.809 to 1.212)	0.924	25.14(0.0 to 62.8)	0.204	Fixed	0.1522
Sexual and reproductive risk factors							
One or no sex partner	8	0.89(0.433 to 1.851)	0.765	78.01(56.66 to 88.85)	<0.001	Random	0.645
STI Naïve	7	0.76(0.306 to 1.891)	0.557	84.7(70.2 to 92.1)	<0.001	Random	0.9987
Uni-parity or none	5	0.85(0.624 to 1.155)	0.297	16.6(0.0 to 83.68)	0.309	Fixed	0.751
HIV positive	7	1.81 (0.93 to 3.473)	0.077	77.2(52.4 to 89.0)	0.002	Random	0.2371
Cultural/Traditional practices							
Body piercing	4	1.21(0.463 to 3.149)	0.700	54.98(0.0 to 83.4)	0.064	Random	0.8708
History of body scarification	4	1.16 (0.78 to 1.725)	0.461	5.90 (0.0 to 87.85)	0.3635	Fixed	0.8357
Parenteral and house hold exposure risk factors							
HBV familial contact	5	3.85(1.47 to 10.092)	0.006*	68.2(18.1 to 87.7)	0.013	Random	0.1783
History of surgery	5	1.01(0.545 to 1.862)	0.980	0.00(0.0 to 49.94)	0.815	Fixed	0.9446
History of Blood transfusion	10	1.18(0.789 to 1.771)	0.416	7.44(0.0 to 65.35)	0.373	Fixed	0.7125

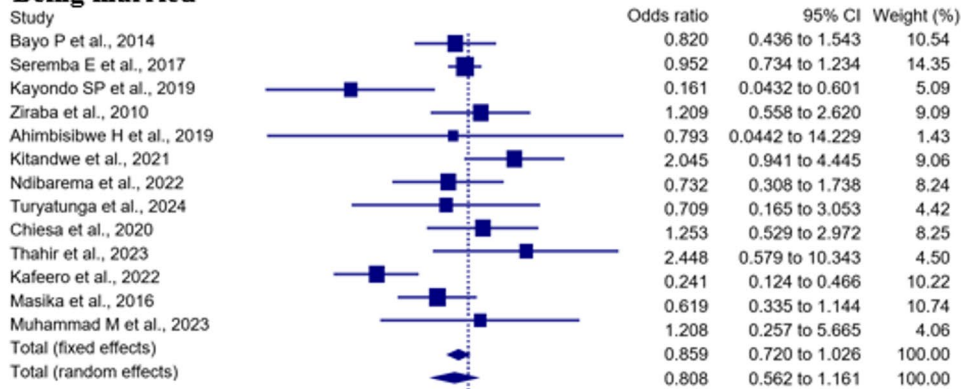
Abbreviations: *STI* sexually transmitted infection, *HIV* Human immunodeficiency virus

48% reduced odds of HBV infection compared to the persons aged ≥ 20 years. For both marital status and gender, the heterogeneity (I^2) between studies was high (61.08% and 74.04% respectively) and the REM was used to pool the ORs. However, it was reduced for age and level of education (22.7% and 25.14% respectively) and the FEM was used to pool the ORs.

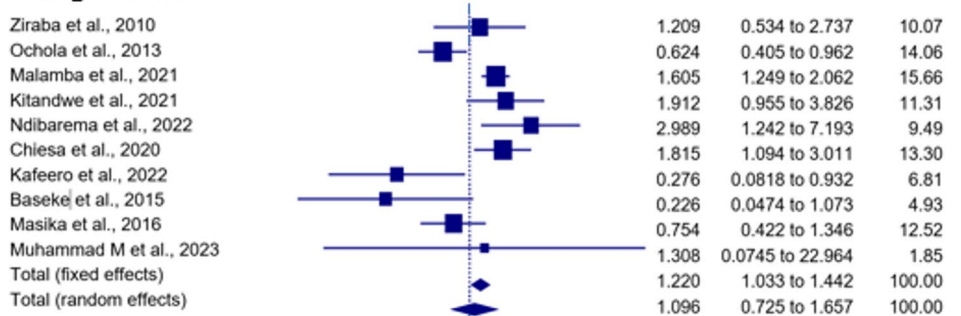
Pertaining the sexual and reproductive risk factors and their association with the prevalence of HBV, the results of our meta-analysis have shown that having one or no sexual partner (OR=0.89; 95%CI=0.433 to 1.851, $p=0.765$), being STI naïve (OR=0.76; 95%CI= 0.306 to 1.891, $p=0.557$) and parity of one or none (OR=0.85; 95%CI=0.624 to 1.155; $p=0.297$) were protective against HBV infection. In contrast, HIV seropositivity (OR=1.81; 95% CI= 0.93 to 3.473, $p=0.077$) was associated with increased odds of HBV infection. Thus, the chances of HBV infection are 81% higher among the HIV positive patients compared to HBV naïve persons (Table2, Figure5). For all the analyses, the heterogeneity (I^2) between the included studies remained high ($I^2 > 50\%$) and the REM was used for the analysis. However, it was reduced between studies for the parity ($I^2=16.6\%$) and the FEM was used to pool the OR. Concerning the cultural/traditional practices and their association with the prevalence of HBV, body piercing (OR=1.21; 95%CI=0.463 to 3.149; $p=0.7$) and body scarification (OR=1.16; 95%CI=0.78 to 1.725; $p=0.461$) were not significantly associated with HBV infection. However, the odds of association with HBV infection were 21% and 16% higher among those with the history of body piercing and scarification respectively (Table2, Figure6). The between study

heterogeneity (I^2) was moderate for studies that investigated body piercing ($I^2=54.98\%$) and the REM meta-analysis was used. However, it reduced for studies that assessed the risk of body scarification with HBV infection ($I^2=5.9\%$) and the FEM meta-analysis was used. Finally, relating to the parenteral and house hold exposure risk factors and their association with the prevalence of HBV, the HBV familial contact (OR=3.85; 95%CI=1.47 to 10.092; $p=0.006$) was significantly associated with increased odds of HBV infection. Thus, participants with a chronically HBV infected member in the family were 4 times more likely to get the infection. In contrast, history of blood transfusion was not significantly associated with HBV infection (OR=1.18; 95%CI=0.789 to 1.771; $p=0.416$). However, the odds of association of HBV with blood transfusion was 18% higher among those with history of blood transfusion compared to their transfusion naïve counterparts. Interestingly, there was no association between the exposure to surgery and HBV risk of infection (OR=1.00; 95% CI=0.545 to 1.862; $p=0.98$) (Table2, Figure7). When we compared the between study heterogeneity (I^2) for the three variables, it was high for primary studies that investigated the effect of HBV familial contact and risk of transmission ($I^2=68.2\%$) and the REM meta-analysis was used to pool the OR. However, it was reduced for history of blood transfusion ($I^2=7.44\%$) and vanished for history of surgery ($I^2=0.00\%$) and the FEM meta-analysis was used to pool the odds ratio. For all the analyses, there was no evidence of publication bias when assessed by both Egger's test ($p>0.05$) (Table 2) and funnel plot inspection for asymmetry (Supplementary file S9).

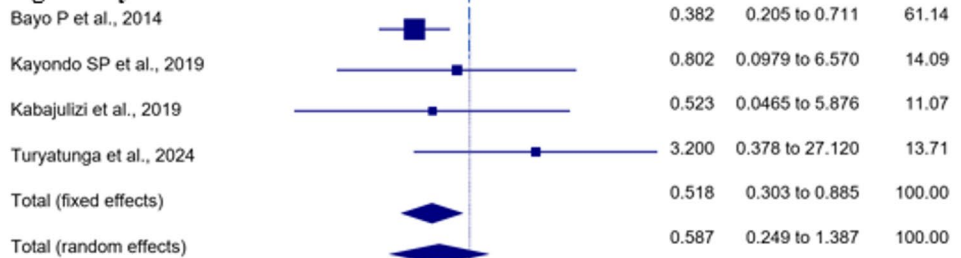
Being married



Being a female



Age < 20 years



Primary or no formal education

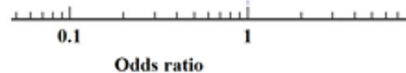
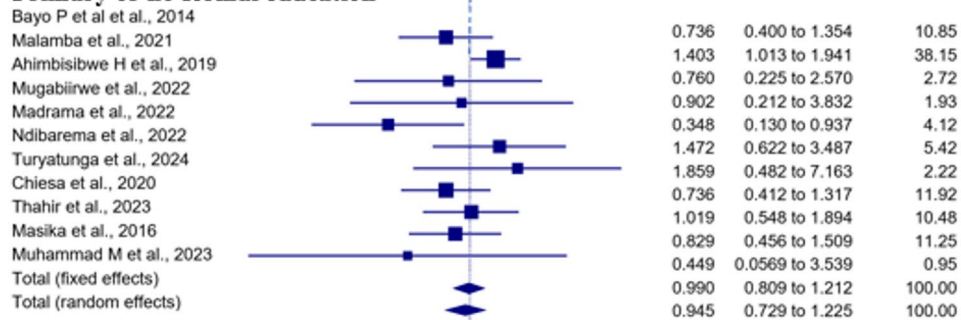


Fig. 4 Socio-demographic factors associated with prevalence of HBV. OR>1 indicates increased risk of HBV infection

Discussion

The pooled prevalence of 8.3% reported in this meta-analysis is slightly higher than the WHO 8.0% threshold for the high transmission areas[57]. This prevalence is comparable to the prevalence estimate of 8.4% reported

in our previous work [4]. With the current population of 45.9 million Ugandans[58], a pooled estimate of 8.3% presupposes that 3.8 million Ugandans are grappling with chronic HBV infection. Thus, HBV is still a significant public health threat straining the national health systems

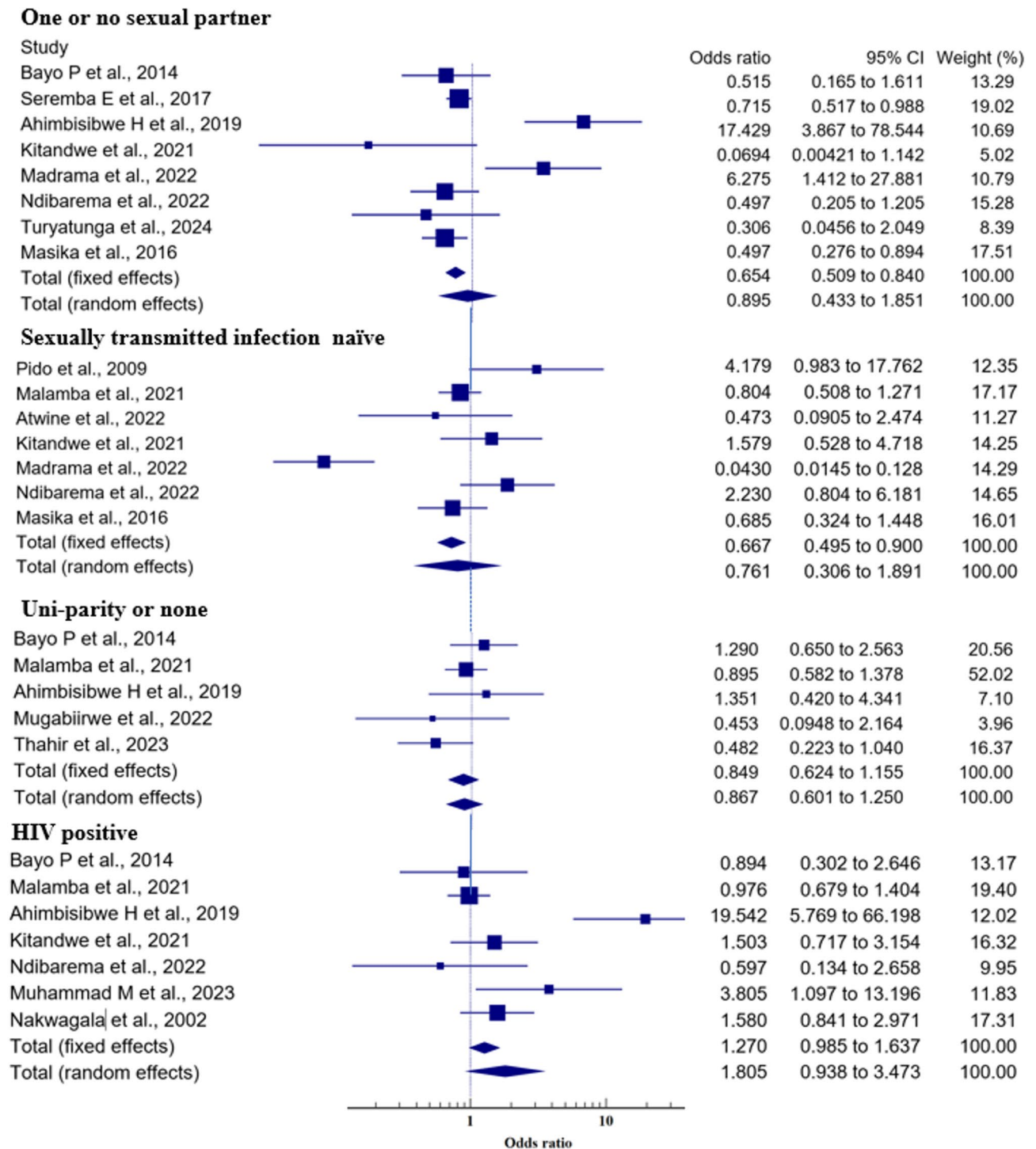


Fig. 5 Sexual and reproductive risk factors associated with the prevalence of HBV. OR>1 indicates increased risk of HBV infection

that are not only weak but still battling with other infectious diseases such as HIV, tuberculosis, malaria and recently Corona Virus Disease (COVID)-19. This suggests an unmet need in the fight against HBV in Uganda. Therefore, scaling up interventions to control the disease is paramount if the UN target of eliminating the virus by

2030 is to be realised[59] targeting the following interventions. First, Rolling out the catch-up vaccination programs for the adults & adolescents in high endemic areas and where hepatitis delta virus co-infection (HDV) is high[15]. This has been adopted in other settings[60] and appears to be cost effective and efficient when combined

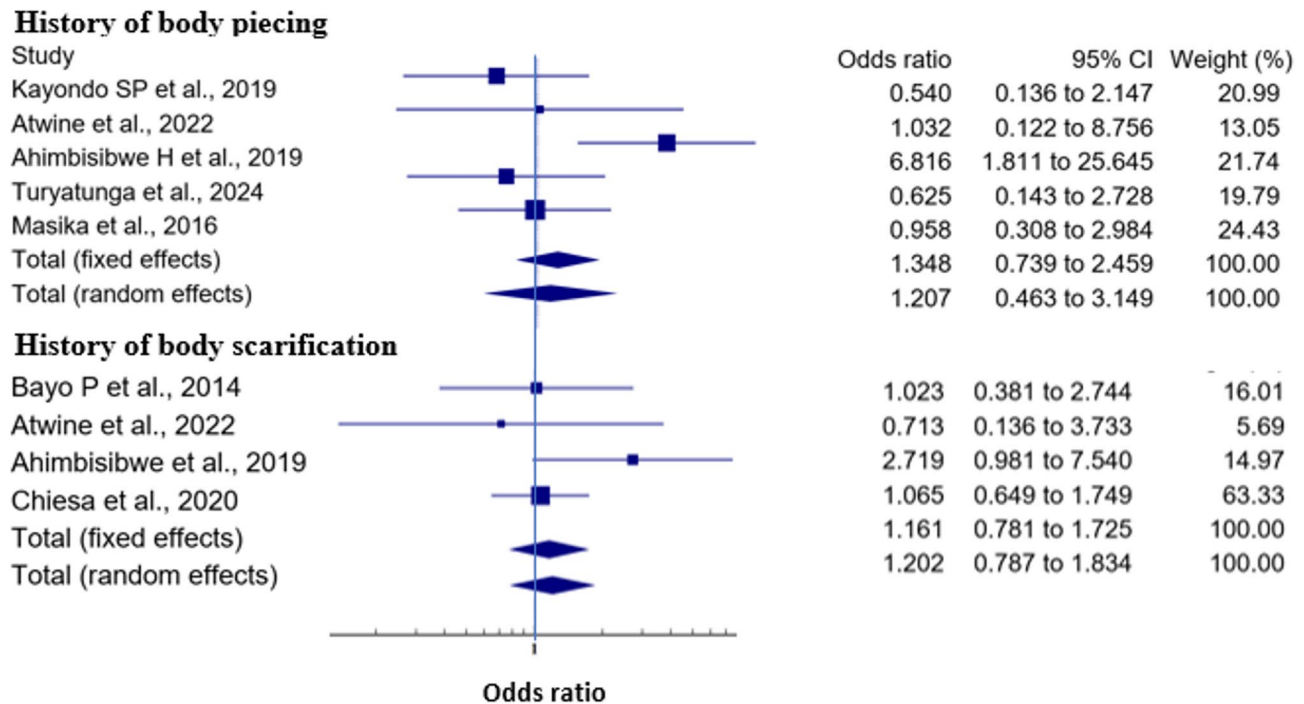


Fig. 6 Cultural/Traditional practices associated with the prevalence of HBV. OR>1 indicates increased risk of HBV infection

with screening[61]. Second, scaling up infant vaccination including the birth dose as well as vaccinating the high risk groups [15]. For instance, the WHO is targeting $\leq 0.1\%$ prevalence of HBsAg under 5 years with timely hepatitis B birth dose (HepB BD) followed by the three doses (HepB3)[62]. Moreover, the birth dose has received substantial acceptance by the mothers[63]. Third, introducing Test & Treat (T & T) programs among the older children and adults leveraging on the experience acquired from HIV's T & T strategy[64]. This will reduce community transmissions of HBV[65]. Finally, scaling up screening pregnant mothers on ANC and treatment of those that are eligible. For example, the WHO has recommended screening of $\geq 90\%$ of the pregnant women on ANC and treating $\geq 90\%$ of those found eligible for treatment[62]. Compared to studies conducted elsewhere, the prevalence reported in this meta-analysis is higher than the prevalence estimate reported in Ethiopia of 6.0% [66], Tanzania of 6.91%[67], Democratic Republic of Congo of 4.9% [68] and the WHO African region of 6.1%[57]. In contrast, the HBV pooled prevalence rate observed in this study is lower than the prevalence reported by related studies in other African countries including Ghana 12.3% [69], Nigeria 13.6% [70], Sudan 12.07% [71] and Somalia, 19.0% [72]. The differences in the HBV endemicity observed in Uganda compared to other African countries can be accounted for by several factors including, though not limited to differences in; regional specific exposure, transmission rates, the infecting genotypes, the extent of implementation of control strategies,

traditional cultural practices which increase the risk of infection, co-infection with HIV and host-genetic differences[73], [74] [75][76][77].

Using regression modelling, our results have shown that the prevalence of HBV has significantly decreased since the integration of the HBV vaccine in the expanded program on immunization (EPI) in Uganda. The related decrease has been reported in studies elsewhere in the world after introduction of HBV vaccine. [78] [79]. Therefore, it is plausible that the implementation of the control and prevention strategies such as better vaccination coverage recently[80][81] have contributed to the decrease in HBV since the integration of the vaccine as part of the EPI in Uganda as reported elsewhere. Moreover, recently the ministry of health has set up regional based free vaccination centres for adults starting with the high endemic regions [12]. Disaggregating the prevalence data on HBV by study groups, the analysis reported striking differences suggesting a targeted HBV preventive intervention. For example, whereas health promotion messages to improve HBV awareness may be ideal for community-based interventions, these may not be plausible for HCWs. Similarly, while screening and vaccinating pregnant mothers may be ideal to prevent MTCT, this intervention has not been promising when it comes to healthy adults in communities [13] and has sparked off discussion that have seen the initiation of the HepB-birth dose vaccine [15]. The significantly high prevalence of HBV in the community compared to the apparently riskier groups like the HIV+ groups and health care workers can be accounted for by

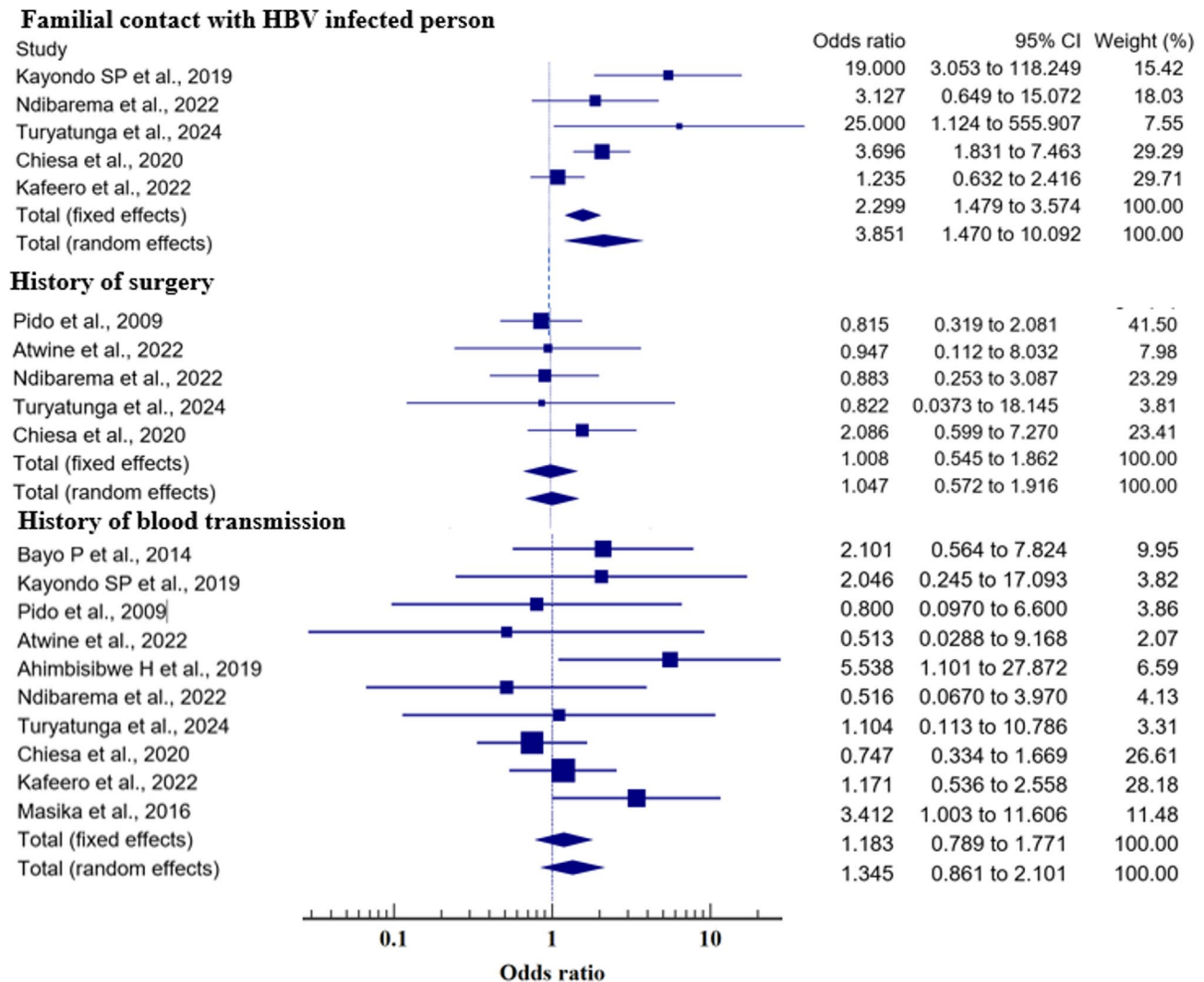


Fig. 7 Parenteral and house hold exposure risk factors associated with the prevalence of HBV. OR>1 indicates increased risk of HBV infection

the improved delivery of prevention and control services to the risky groups compared to the general population [13] [82] [83] [84][85] [86]. The difference in prevalence of HBV by region reported in this study is consistent with findings reported in related studies [67] [66] [68] [87] [69]. The factors responsible for the differences in HBV endemicity by region are multi-faceted and correlate with those responsible for differences in HBV endemicity by country, sub-region or continent[15][77]. These range from the differences in the implementation of the public health interventions to control and prevent the transmission of the virus [82] through differences in molecular epidemiology of the HBV [77] to the differences in host genetic factors which pause different selection pressures to infection risk and differential disease prognosis[88].

In addition, regression analysis revealed a regional variation in HBV prevalence trends across Uganda. An overall increase was observed in western Uganda, while

northern, eastern, and central regions exhibited decreasing trends. These regional disparities may be attributed to differences in the implementation and effectiveness of public health interventions, including HBV awareness campaigns, expanded vaccination coverage, and efforts to mitigate high-risk behaviors such as tattooing and traditional scarification[13] [81] [89][44][4][3]. Interestingly, body piercing appears to predominate in western Uganda [34] and could explain the increased prevalence of HBV in this region Uganda. Therefore, programs to control HBV should design regional specific interventions depending on the specific gap to be addressed. For example, whereas T & T may be ideal in the high endemic regions, awareness campaign aimed at behavioural change may be more plausible in the low endemic regions. We found strong evidence that familial contact with and HBV infected person increases the chances of infection by 4 times. This is in conformity with reports

by Ragheb et al., [90] in Egypt, Lobato et al., [91] in Brazil and Sofian et al., [92] who have shown that presence of an HBV carrier member increases the risk of the family members contracting HBV by 11-57%. This has been attributed to the extremely infectious behavior of the virus. It is 100 times more infectious than HIV and is highly resilient with the potential to stay on the surfaces for a week when it is still potent [93]. Furthermore, household transmission may have a higher likelihood of resulting in chronic infection, particularly due to the increased involvement of children, who are more susceptible to long-term infection. Hence, the village health teams (VHT) should remain abreast with the information about homes with an HBV carrier member. This will provide a cornerstone in designing interventions by the family members and community health providers to reduce intra-familial transmission.

There was also evidence that age < 20 years reduces the odds of HBV infection by 48.2% attributable to the vaccination of this cohort. However, there is still an unmet need since the protection is only about 50%. It is plausible that mothers are still delivering from traditional birth attendants (TBA) [94]. This could be attributable to the failure in health system that have led some mothers to continue delivering with traditional birth attendants rather than skilled professionals. However, improved education and better availability of delivery services could reduce this vice. Besides, the absence of the birth dose could have caused horizontal intra-familial since the first dose was formerly given 1 ½ months after birth[62]. Moreover, all the participants in the studies from which the data were extracted are within this category. Furthermore, our recent work has shown that the protective antibodies wane over time[95].

Finally, our results have shown sufficient evidence implicating HIV as a risk factor of HBV infection consistent with findings reported in other African countries and elsewhere in the world. [96][97][98][99][100]. The increased risk of HBV-HIV co-infection has been associated with first, the shared route of transmission for the two viruses [75] and second, the compromised immunity among PLWHIV increasing the risk of contracting HBV which progresses to chronic infection [101]. Therefore, screening for HBV among the HIV infected persons in all health centers in the country is a cornerstone in the control of HBV.

Conclusion

There has been an overall decrease in the prevalence of HBV in Uganda since the integration of the HepB vaccine as part of the extended program on immunization. Nevertheless, a prevalence rate of 8.3% remains substantially high and represents a significant challenge to achieving the WHO/UN target of eliminating hepatitis B virus

(HBV) as a public health threat by 2030. To achieve this ambitious target, health systems strengthening is critical. For example, HBV screening and scaling up vaccination programs including the catch-up vaccination strategy among the adolescents and young adults is highly recommended. In addition, novel control strategies such as T & T which have received tremendous success in management of HIV can be integrated into HBV care with the aim of reducing transmission of the virus. Furthermore, public health interventions targeting specific regions and riskier groups particularly those with familial contact with an HBV infected person should be implemented with the aim of reducing the transmission cycle.

Limitation of the study

The regression analysis and odds ratios were calculated based on the year of publication. However, there is often a considerable delay between data collection and publication, which may result in prevalence estimates that do not accurately reflect the true incidence at the time of study. Despite this, the overall trends appear consistent regardless of the time gap between data collection and publication. Therefore, the findings of this study should be interpreted with this potential limitation in mind.

Abbreviations

AJOL	African Journal Online
EIA	Enzyme Immuno Assay
ELISA	Enzyme Linked Immunosorbent Assay
FEM	fixed effect model
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B Virus
HIV	Human Immune Deficiency Virus
NOS	Newcastle-Ottawa Scale
QS	Quality Score
RDT	Rapid Diagnostic Tests
REM	random effect model
STIs	Sexually Transmitted Infections
WHO	World health organization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Authors' contributions

"H.M.K. conceived the idea. H.M.K., A.W. and A.K. participated in the search for the articles from the data bases. H.M.K. and A.W. presented, analyzed and discussed the results. H.M.K. wrote the final manuscript draft. P.O., N.D., F.M., N.M. and H.K. reviewed the manuscript draft. All the authors read and approved the publication of the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article and as supplementary materials.

Declarations**Ethics approval and consent to participate**

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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