World Journal of Hepatology

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World J Hepatol 2024 May 27; 16(5): 843-859

DOI: 10.4254/wjh.v16.i5.843

ISSN 1948-5182 (online)

SYSTEMATIC REVIEWS

Genetic diversity and occult hepatitis B infection in Africa: A comprehensive review

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Specialty type: Biology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade D
Novelty: Grade C
Creativity or Innovation: Grade B
Scientific Significance: Grade C

P-Reviewer: Fallatah H, Saudi Arabia

Received: November 14, 2023
Revised: February 6, 2024
Accepted: April 15, 2024
Published online: May 27, 2024

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Abstract

BACKGROUND

Occult hepatitis B infection (OBI) is a globally prevalent infection, with its frequency being influenced by the prevalence of hepatitis B virus (HBV) infection in a particular geographic region, including Africa. OBI can be transmitted through blood transfusions and organ transplants and has been linked to the development of hepatocellular carcinoma (HCC). The associated HBV genotype influences the infection.

AIM

To highlight the genetic diversity and prevalence of OBI in Africa.

METHODS
This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and involved a comprehensive search on PubMed, Google Scholar, Science Direct, and African Journals Online for published studies on the prevalence and genetic diversity of OBI in Africa.

RESULTS
The synthesis included 83 articles, revealing that the prevalence of OBI varied between countries and population groups, with the highest prevalence being 90.9% in patients with hepatitis C virus infection and 38% in blood donors, indicating an increased risk of HBV transmission through blood transfusions. Cases of OBI reactivation have been reported following chemotherapy. Genotype D is the predominant, followed by genotypes A and E.

CONCLUSION
This review highlights the prevalence of OBI in Africa, which varies across countries and population groups. The study also demonstrates that genotype D is the most prevalent.

Key Words: Occult hepatitis B infection; Blood transfusion; Genetic diversity

Core Tip: The objective of this systematic literature review is to highlight the genetic diversity and prevalence of occult hepatitis B infection (OBI) in Africa. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and involved a comprehensive search on PubMed, Google Scholar, Science Direct, and African Journals Online for published studies on the prevalence and genetic diversity of OBI in Africa. This review highlights the prevalence of OBI in Africa, which varies across countries and population groups. The study also demonstrates that genotype D is the most prevalent.

Citation: Bazie MM, Sanou M, Djigma FW, Compaore TR, Obiri-Yeboah D, Kabamba B, Nagalo BM, Simpore J, Ouédraogo R. Genetic diversity and occult hepatitis B infection in Africa: A comprehensive review. *World J Hepatol* 2024; 16(5): 843-859
URL: https://www.wjgnet.com/1948-5182/full/v16/i5/843.htm
DOI: https://dx.doi.org/10.4254/wjh.v16.i5.843

INTRODUCTION

Occult hepatitis B infection (OBI) refers to the presence of replicating hepatitis B virus (HBV) DNA [cDNA (cccDNA)] in the liver or in the blood of individuals who test negative for hepatitis B surface antigen (HBsAg) on available tests[1] and when the viral load is detectable, it is generally lower than 200 (IU)/mL[2]. OBI is present worldwide, but is more frequent in areas where HBV is endemic[3]. According to WHO, 296 million people were living with chronic hepatitis B in 2019, and this led to 820000 deaths, mostly from cirrhosis or hepatocellular carcinoma (HCC)[4]. OBI can be transmitted through blood transfusions and organ transplants[3]. In low- and middle-income countries, where anti-HBc and/or nucleic acid amplification tests are not implemented, OBI transmission from blood donors remains a significant health issue[1,5-8]. OBI has been implicated in HCC development in patients with chronic hepatitis C virus (HCV) infection, those with cryptogenic or known liver disease, and in patients with HBsAg cleared in their serum after chronic HBV infection[9]. The HBV genotype involved greatly influences clinical presentation, long-term prognosis, and seroconversion profile[10,11].

OBI can be classified based on HBV-specific antibody profiles and HBV DNA levels[12,13]. In seropositive OBI, anti-hepatitis B antibody (anti-HBc) and/or hepatitis B surface antibody (anti-HBs) are positive; in seronegative OBI, both anti-HBc antibody and anti-HBs antibody are negative. There are cases of OBI that have HBV DNA levels similar to those usually detected in the different phases of overt HBV infection[12].

Most cases of OBI are related to a replication-competent virus whose replication and transcription activities are strongly repressed by host defense mechanisms, which may persist at low levels and may be reversible under specific circumstances, leading to viral reactivation and the development of HBsAg typical of positive infection[14].

The prevalence of OBI varies widely and may be attributed to population heterogeneity, viral DNA detection techniques, and the quality of HBsAg screening tests (possibility of false negatives)[15]. However, caution is advised when interpreting these prevalence rates. The prevalence of hepatitis B is highest in sub-Saharan Africa and East Asia, where 5%-10% of the adult population has chronic hepatitis B[16]. As a result, the prevalence of OBI may be higher in areas where chronic hepatitis B is endemic (Africa, Asia) than in areas where it is not (Western Europe and North America). This is seen in blood donor populations, where the prevalence is higher in developing countries and rare in Western countries[17]. The objective of this literature review is to highlight the genetic diversity and prevalence of OBI in Africa.

MATERIALS AND METHODS

This comprehensive review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[18,19]. We searched the literature for scientific articles on OBI. In February 2022, an electronic literature search was conducted and the following databases were used: PubMed, Google Scholar, Science Direct, African Journal Oline. A second update search was conducted in February 2023 to look for additional articles. The investigations were conducted in French and English with the following keywords: "occult hepatitis B infection" or "occult hepatitis B." The filters were "free complete items" on "human" blood samples. The inclusion criterion was open-access articles or worked on the population of an African country. All study groups were included. The study groups concerned were: Blood donors, patients infected with human immunodeficiency virus (HIV), patients infected with HCV, patients with HCC, hemodialyzed and/or kidney transplant patients, thalassemic patients. Studies on the role of hepatitis B vaccine in protecting against o OBI, sickle cell disease patients, and patients with reactivation of OBI after chemotherapy were also taken into account. The data collected included the prevalence of OBI, the type of study, the study population, the country of origin of the patients as well as their age group. Also noted were: The technique used for quantification of viral DNA as well as its limit of detection. When the genotype of the HBV was identified, it was also reported. The articles that do not demonstrate prevalence and those whose study population is not of African origin were excluded. Articles whose detection of OBI was limited only to anti-HBcAb and did not add DNA detection were also excluded from the study. The selection process for articles is outlined in Figure 1.

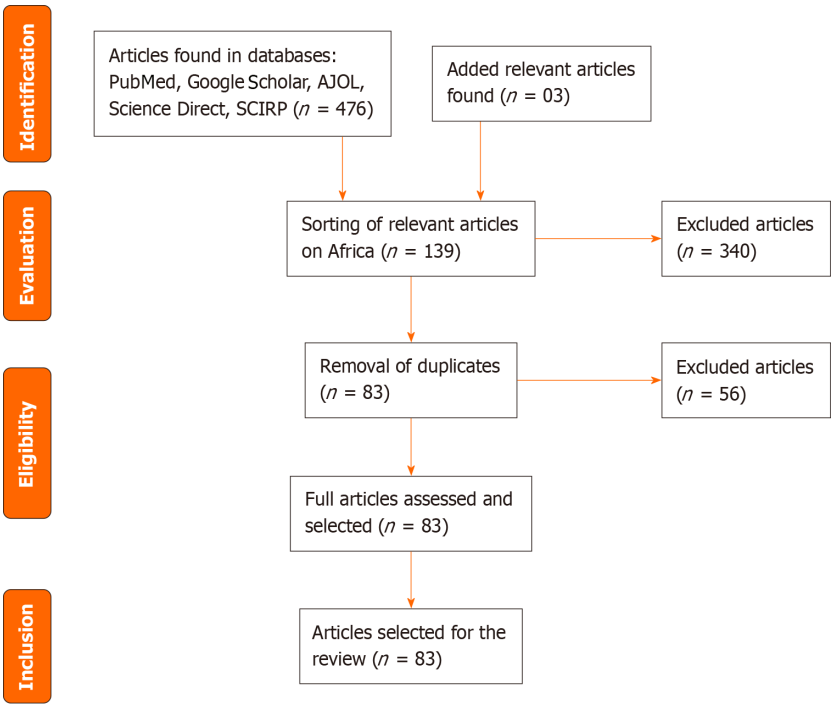

Figure 1 Articles selection procedure.

RESULTS

A total of 476 articles were found in the databases, with an addition of 03 articles from the manual search. After excluding irrelevant articles (340) and removing duplicates (56), 83 articles were examined. Following a thorough evaluation of the full text, all 83 articles were deemed relevant and included in this synthesis.

Geographical distribution of OBI in Africa

Geographical distribution of OBI in Africa has been extensively studied in various population groups across several countries. These studies have reported varying prevalence rates of OBI, ranging from 0 to 90.9%, depending on the country and the population studied[20,21]. The prevalence of OBI is influenced by several factors, including the prevalence of HBV infection, the sensitivity of diagnostic tests, and the population studied. In countries where HBV infection is highly endemic, the prevalence of OBI tends to be higher. This is the case in Burkina Faso where the prevalence of HBV is between 9.1% to 14.4%[22,23] and the prevalence of occult HBV infection is between 4% and 32.8% [24,25] in blood donors, and 7.3% in the general population[26]. In Gambia, the prevalence of occult HBV infection is 18.3% in the general population[27]. A prevalence of 18.7% of OBI was found in a Kenyan population at high risk of HBV infection[28]; Among health care workers, who are a high-risk group for infection, respective OBI prevalences of 5.3% and 6.7% have been demonstrated in Egypt and South Africa[29,30]. However, the presence of OBI has also been reported in countries where HBV infection is less common[3,31]. This is the example of Egypt, where the prevalence of HBV is

around 1.4%[32] while the prevalence of OBI ranges from 0 to 90.7%[20,21]. Research has shown that the prevalence of OBI is not uniform across different regions of Africa. For instance, studies conducted in West Africa have reported relatively higher prevalence rates compared to those in East and Southern Africa. In addition, the prevalence of OBI has been found to vary among different population groups within the same country or region. In febrile patients in Sudan and Tanzania, respective OBI prevalences of 7.7% and 18.2% have been demonstrated[33,34]. Tables 1-5 summarizes the prevalence of OBI in different African countries, highlighting the wide variation in prevalence rates.

OBI genotypes

OBI is known to be caused by HBV, which has ten genotypes (A-J)[35]. However, only five of these genotypes have been identified as causing OBI, namely genotypes A, B, C, D, and E (Table 6). Studies conducted in Africa have highlighted that the three most commonly found genotypes in this region are genotypes A, D, and E[11,35,36].

Genotype D has been identified as the most predominant genotype in Africa, followed by genotypes A and E[37-39]. This information is summarized in Table 6. In contrast, genotypes B and C were initially identified in other regions of the world, such as Asia, Australia, Greenland, and Canada[35]. However, they have been found in Africa as well, specifically in Egypt[40-43] and Ethiopia[44]. The geographic distribution of HBV genotypes is associated with distinct modes of HBV transmission. For instance, genotypes B and C are prevalent in highly endemic areas, where perinatal or mother-to-child transmission plays an important role in the spread of HBV[45].

Methods of HBV DNA detection in included studies

Table 7 summarizes the different methods used and their detection limits. In the majority of studies, real-time PCR was used compared to nested PCR.

OBI in blood donors

The high prevalence of OBI among blood donors in African countries poses a significant risk of HBV transmission during blood transfusions. The prevalence of OBI in blood donors ranges from 0.48% to 38% (Tables 1-5). The prevalence is particularly high in Sudan (38%)[46] and Burkina Faso (32.8%)[24]. In other African countries[37,47-56], the prevalence ranges from 0.48% to 22.7%, with Nigeria having a prevalence of 1% to 17%[6,57-61]. These high prevalences are a cause for concern, as blood transfusion is a major risk factor for HBV transmission, especially in countries that screen potential blood donors using minimal methods[62]. In contrast, the prevalence of OBI among blood donors in China, South Korea, and Japan is relatively low, ranging from 0.016% to 1.01%[63,64]. The prevalence of OBI in blood donors in these countries is significantly lower than that in African countries. The relatively low prevalence of OBI in blood donors in these countries may be due to the use of more sensitive diagnostic tests and the implementation of strict screening measures to detect and exclude donors with OBI.

However, even in countries where screening measures are in place, a residual risk of HBV transmission associated with donors with occult B infection and deficient levels of viral DNA that are undetectable or detected intermittently by the most sensitive unitary viral genome tests persists[5]. This residual risk of transmission has been reported in several African countries, including Ghana[7], Burkina Faso[8] and Cameroon[6] with percentages ranging from 0.24% to 11.16%.

OBI in patients with HIV infection

Co-infection with both HBV and HIV is common, as these viruses share common routes of transmission. In HIV-positive patients, the prevalence of OBI ranges from 1.71% to 88.4%, with South Africa having the highest prevalence[65,66]. Among pregnant women living with HIV, prevalences are 1.71% in South Africa[65] and 6.6% in Botswana[67]. Among HIV patients starting antiretroviral therapy (ART), prevalences are 3.7% in South Africa[68], 26.5% in 8.3% in Mozambique[69], and 5.3% in Kenya[70]. A study conducted among HIV-infected African migrants in the United Kingdom found that the overall prevalence of occult HBV co-infection was 4.5%, with 6.5% and 0.8% prevalence among ART-naïve and ART-experienced patients, respectively[71]. Several other studies have highlighted varying prevalences of occult hepatitis B infection in various groups of patients with HIV infection[39,72-84].

OBI in patients with HCV infection

OBI is frequently found in patients with chronic hepatitis C (CHC)[85]. A range of prevalence rates from 3.2% to 90.9% [21,86] and all studies found were conducted in Egypt[87-91] (Table 2). A low prevalence of 3.2% was found in blood donors[86], whereas the highest prevalence of 90.9% was found in patients undergoing antiviral therapy for hepatitis C [21]. Children with cancer had a prevalence rate of 32% for OBI, according to a study by Raouf *et al*[92]. Additionally, a study by Omar *et al*[93] reported a prevalence of 12.8% in OBI/HCV patients with schistosomiasis, compared to 8.5% in those without schistosomiasis. The prevalence of OBI was higher in Egyptian hepatitis C patients with HCC at 17.5% than in those without the condition at 5%[42]. Since HBV and HCV share the same transmission routes and many risk factors, OBI detection in HCV patients is not unexpected[94].

OBI in patients with HCC

HCC is the most common form of liver cancer[95] and HBV infection is the most significant risk factor for its development, accounting for approximately 33% of cases[96]. The prevalence of OBI in HCC patients varies from 17.5% to 24% (Tables 2 and 5). Studies conducted by Hassan *et al*[41] in Egypt, and Gouas *et al*[97] in Gambia, have shown a high prevalence of OBI in HCC patients. In CHC patients with HCC, OBI prevalences are around 17.5% compared to 5% in those who do not have HCC[42]. Studies conducted in Asia and Europe have also reported high prevalences of OBI in chronic HCV patients with HCC compared to those without HCC, ranging from 15% to 49% *vs* 73%, respectively[9,98].

Table 1 Distribution of occult hepatitis B infection prevalence in the southern region of Africa

Ref.	Year	Countries	Patients	OBI prevalence, *n* (%)	Types of studies	Methods	DNA limit of detection	Effective	HBV genotype
Peliganga *et al* [47]	2021	Angola	Blood donors	2.9	Cross-sectional	Real-time PCR	ND	500	
Mbangiwa *et al* [67]	2018	Botswana	Pregnant women with/without HIV	6.6	Prospective study	COBAS AmpliPrep	ND	622	D3, A1, E
Ryan *et al*[72]	2017	Botswana	HIV patient	26.5	ND	COBAS AmpliPrep	ND	272	
Mabunda *et al* [51]	2020	Mozambique	Blood donors	0.98	Cross-sectional	PCR	20 UI/mL	1435	
Carimo *et al*[69]	2018	Mozambique	ART naïve HIV patient	8.3	Cross-sectional	Real-time PCR	ND	206	
Sondlane *et al* [30]	2016	South Africa	Healthcare workers	6.7	Descriptive study	Real-time PCR	ND	314	
Amponsah-Dacosta *et al* [119]	2015	South Africa	Post-vaccination	66 and 70.4	ND	Real-time PCR	ND	62 and 139	
Powell *et al*[81]	2015	South Africa	HIV patient	13.5	ND	Real-time PCR	250 copies/mL	394	
Hoffmann *et al* [65]	2014	South Africa	Pregnant women with HIV	1.71	Case-control study	Real-time PCR	20 IU/ mL	175	
Ayuk *et al*[82]	2013	South Africa	HIV/HBV Co-infection	33.7	Unmatched study	Nested PCR	ND	181	
Bell *et al*[68]	2012	South Africa	ART naive HIV	3.79	Cohort	Real-time PCR	20 IU/ mL	79	
Mayaphi *et al* [83]	2012	South Africa	HIV/HBV Co-infection HIV patient	3.5 in AIDS 1 in no AIDS	Cross-sectional	Nested PCR	ND	200/200	
Firnhaber *et al* [66]	2009	South Africa	HIV patient	88.4	ND	Real-time PCR	ND	53	

OBI: Occult hepatitis B infection; HBV: Hepatitis B virus; PCR: Polymerase chain reaction; HIV: Human immunodeficiency virus; ND: Not defined; HCV: Hepatitis C virus; ART: Antiretroviral therapy.

The detection of OBI in HCC patients is critical for early diagnosis and treatment of HCC.

A prevalence of 5.56% of OBI was found in patients with chronic liver disease of unidentified cause[99].

OBI in haemodialysis and renal transplant patients

The prevalence of OBI in haemodialysis patients ranges from 0% to 51.4%, as reported in studies conducted in Egypt and Sudan[100,101] (Tables 2 and 4). Renal transplant patients have also shown a high prevalence of OBI, ranging from 18% to 51.4%, according to studies conducted by Ibrahim *et al*[102] and Mustafa *et al*[101] in Sudan. Haemodialysis patients are at a higher risk of HBV transmission due to frequent blood transfusions[103], making the detection of OBI in these patients a critical concern. Non-negligible prevalences of occult hepatitis B infection in hemodialysis patients with or without hepatitis C have been found in certain studies[104-112].

OBI reactivation after chemotherapy and in sickle cell disease

Reactivation of OBI has been demonstrated in Egypt by Elkady *et al*[113] and Elbedewy *et al*[114] in patients following chemotherapy. In Elkady's study, Five HBsAg-negative and Anti-HBC-positive patients demonstrated HBV reactivation criteria, with two patients becoming serologically positive for HBsAg and three becoming detectable for HBV DNA[113]. Elbedewy's study showed that of the 10 OBI patients with diffuse large B-cell lymphoma, five patients demonstrated reactivation with positive HBsAg after 7 to 11 months since the start of chemotherapy (all cycles)[114]. The chemotherapy used in this study was Cyclophosphamide, Hydroxyadriamycine, Oncovin and Prednisone). A case of occult hepatitis B reactivation was reported in a homozygous sickle cell patient in Senegal by Diop *et al*[115].

OBI in thalassemia patients

Thalassemia patients require frequent blood transfusions, which increase their risk of contracting HBV and developing OBI. However, few studies in Africa have assessed the prevalence of OBI in thalassemia patients. In Egypt, a study found

Table 2 Distribution of occult hepatitis B infection prevalence in the northern region of Africa

Ref.	Year	Countries	Patients	OBI prevalence, *n* (%)	Types of studies	Methods	DNA limit of detection	Effective	HBV genotype
Amer *et al* [106]	2020	Egypt	Haemodialysis patients with HCV	33.8	ND	Real-time PCR	ND	325	
Abdel-Maksoud *et al* [104]	2019	Egypt	Haemodialysis	7.3	Cohort	Nested PCR	30 copies/mL	150	
Elmaghloub *et al*[29]	2017	Egypt	Healthcare workers	5.3	Cross-sectional	Nested PCR	ND	132	
Omar *et al*[93]	2017	Egypt	HCV patients with/without schistoso-miasis	With schistosomias 12.8% without schistosomias 8.5%	ND	Real-time PCR	ND	200	
Esmail *et al* [40]	2016	Egypt	Haemodialysis without HCV	8.3	ND	Real-time PCR	ND	144	B, C, D
Mahmoud *et al*[87]	2016	Egypt	HCV patients	18	Cross-sectional	Real-time PCR	ND	100	
Elbedewy *et al* [114]	2015	Egypt	Patient with malignant tumors of the lymphatic system	13.89	Cross-sectional	Real-time PCR	12 IU/mL	72	
Elsawaf *et al* [21]	2015	Egypt	ART in chronic hepatitis C patients	90.9	ND	Nested PCR	ND	11	
Helaly *et al* [108]	2015	Egypt	Haemodialysis	32	Cross-sectional	Real-time PCR	ND	100	
Kishk *et al*[58]	2015	Egypt	Blood donors	22.7	ND	Real-time PCR	100 copies/mL	343	D
Mandour *et al* [109]	2015	Egypt	HCV and Haemodialysis	8.5% in CHC and 1.8% in HD	ND	Nested PCR	ND	210 et 165	
Raouf *et al*[92]	2015	Egypt	HCV positive cancer children	32	case–control study	Nested PCR	ND	50	
Elrashidy *et al* [20]	2014	Egypt	Diabetic children and adolescents following hepatitis B vaccination	0	ND	Nested PCR	100 copies/mL	170	
Kishk *et al*[88]	2014	Egypt	CHC patient	7.5	ND	Real-time PCR	ND	162	D
El-Ghitany *et al*[86]	2013	Egypt	Blood donors with hepatitis C	4.16 (3.2 HVC+ et 5.1 HCV-)	case–control study	Real Time PCR	45 copies/mL	504	
Elkady *et al* [113]	2013	Egypt	Hematological malignant patients	5.66	ND	Real-time PCR	20 IU/mL	18	D1
Said *et al*[48]	2013	Egypt	Blood donors	1.64	Cross-sectional	Real-time PCR	3.8 IU/mL	3167	
Taha *et al*[42]	2013	Egypt	HCV patients with/without hepato-cellular carcinoma	22.5 (17.5 with CHC 5 without CHC)	Cross-sectional	Nested PCR	ND	40	D, B, C, A
Youssef *et al* [36]	2013	Egypt	Children with acute HBV	29.16	ND	Real-time PCR	ND	24	D (D1, D2)
Abu El Makarem *et al* [105]	2012	Egypt	Haemodialysis with/without HCV	4.1	ND	Real-time PCR	6 IU/mL	145	
Elgohry *et al* [107]	2012	Egypt	Haemodialysis	26.8	ND	PCR	ND	93	
Shaker *et al* [116]	2012	Egypt	Thalassemic children	32.5	Prospective study	Real Time PCR	ND	80	
Hassan *et al* [41]	2011	Egypt	Hepatocellular carcinoma patient	22.5	ND	Nested PCR	ND	40	D, B, A, C
Selim *et al*[89]	2011	Egypt	HCV patients	38.3	ND	Real-time PCR	45 copies/mL	60	

Antar *et al*[59]	2010	Egypt	Blood donors	0.48	ND	Real-time PCR	ND	1021	
Emara *et al*[90]	2010	Egypt	HCV patients	3.9	Cross-sectional	Real-Time PCR	12 IU/mL	155	
El-Sherif *et al* [91]	2009	Egypt	HCV patients	16	ND	Real-Time PCR	30 copies/mL	100	
Said *et al* [118]	2009	Egypt	Children with malignant hematological disorders	21	case–control study	Nested PCR	ND	100	
Youssef *et al* [43]	2009	Egypt	Patient with elevated transaminases	64.8	ND	Nested PCR	ND	119	C (C2), D (D1)
El-Zayadi *et al* [49]	2008	Egypt	Blood donors	1.26	ND	PCR	ND	712	
El-Sherif *et al* [50]	2007	Egypt	Blood donors	1.3	ND	PCR	ND	150	

OBI: Occult hepatitis B infection; HBV: Hepatitis B virus; PCR: Polymerase chain reaction; ND: Not defined; HCV: Hepatitis C virus; ART: Antiretroviral therapy; CHC: Chronic hepatitis C; HD: Haemodialysis.

Table 3 Distribution of occult hepatitis B infection prevalence in the central region of Africa

Ref.	Year	Countries	Patients	OBI prevalence, *n* (%)	Types of studies	Methods	DNA limit of detection	Effective	HBV genotype
Kengne *et al*[6]	2021	Cameroun	Blood donors	9.83	Cross-sectional et prospective	PCR	ND	193	
Fopa *et al*[57]	2019	Cameroun	Blood donors	2.3	ND	Nested PCR	ND	1162	
Gachara *et al*[73]	2017	Cameroun	HIV patient	5.9	Cross-sectional	Nested PCR	ND	337	
Bivigou-Mboumba *et al* [75]	2018	Gabon	HIV patient	17.5	Cross-sectional	Real-time PCR	50 IU/mL	137	
Bivigou-Mboumba *et al* [76]	2016	Gabon	HIV patient	8	Cross-sectional	Real-time PCR	100 IU/mL	762	A E

OBI: Occult hepatitis B infection; HBV: Hepatitis B virus; PCR: Polymerase chain reaction; HIV: Human immunodeficiency virus; ND: Not defined.

a prevalence of 32.5% of OBI in thalassemia children, highlighting the importance of screening for OBI in this population [116]. These high prevalences may be attributed to residual risks of HBV transmission through blood transfusions, which, although infrequent, are not negligible according to several authors[8,62,117].

An OBI prevalence of 21% was found in Egyptian children and adolescents with hematological disorders and malignancies[118].

Role of hepatitis B vaccine in protecting against OBI

The hepatitis B vaccine has been demonstrated to be highly effective in preventing HBV infection and reducing the prevalence of OBI. A study conducted in Egypt on diabetic children and adolescents followed after vaccination found no cases of OBI[20]. Similarly, in South Africa, the introduction of vaccination led to a decrease in the prevalence of OBI. OBI prevalence's were 70.4% in the study population before vaccine introduction and 66.0% in the study population after vaccine introduction, indicating that the vaccine may play a role in reducing the prevalence of OBI in high-risk populations[119]. It is important to note that the hepatitis B vaccine does not protect against OBI in individuals who have already been exposed to the virus. Therefore, screening for OBI and early detection of infection are crucial in preventing the development of liver disease in high-risk populations.

DISCUSSION

This comprehensive review provides valuable insights into the prevalence of OBI in high-risk populations, including patients with CHC, haemodialysis patients, patients with HCC, and thalassemia patients.

Table 4 Distribution of occult hepatitis B infection prevalence in the eastern region of Africa

Ref.	Year	Countries	Patients	OBI prevalence, *n* (%)	Types of studies	Methods	DNA limit of detection	Effective	HBV genotype
Gissa *et al*[99]	2022	Ethiopia	Patients with chronic liver disease of unidentified cause	5.56	Prospective	Real-Time PCR	15 IU/mL	36	
Ayana *et al*[74]	2020	Ethiopia	HIV negative/positive isolated antiHBc	5.6	ND	Real-Time PCR	ND	306	
Meier-Stephenson *et al*[38]	2020	Ethiopia	Pregnant women	20.3	Prospective	Nested PCR	ND	182	D, C
Patel *et al*[44]	2020	Ethiopia	HIV patient	19.1	Cross-sectional	Nested PCR	ND	291	D, E, A, C
Salyani *et al*[70]	2021	Kenya	HIV patient ART naïve	5.3	Cross-sectional	COBAS AmpliPrep	20 UI/mL	208	
Aluora *et al*[37]	2020	Kenya	Blood donors	2.3	Cross-sectional	Nested PCR	ND	300	A
Jepkemei *et al*[28]	2020	Kenya	Populations with high risk of HBV infection	18.7	Cohort	Real-time PCR	ND	99	
Rusine *et al*[80]	2013	Rwanda	HIV patient	42.9	Prospective study	PCR	ND	218	
Ahmed *et al*[112]	2022	Sudan	Patients with chronic renal failure	22	Cross-sectional	Nested PCR	ND	188	
Mustafa *et al*[101]	2020	Sudan	Renal Transplant Patients	51.4	ND	Real-time PCR	ND	100	A, D, E
Bashir and Hassan[33]	2019	Sudan	Febrile malaria Patients	18.2	ND	Real-time PCR	ND	88	
Sahr Hagmohamed *et al*[111]	2019	Sudan	Haemodialysis	15.9	Cross-sectional	PCR	ND	88	
Majed *et al*[100]	2018	Sudan	Haemodialysis	0	Cross-sectional	PCR	ND	88	
Hassan *et al*[55]	2017	Sudan	Blood donors	7.9	ND	Nested PCR	ND	177	
Mohammed *et al* [110]	2015	Sudan	Haemodialysis	3.3	ND	PCR	ND	91	
Mudawi *et al*[84]	2014	Sudan	HIV patient	11,07	Cross-sectional	Real-time PCR	ND	316	
Yousif *et al*[39]	2014	Sudan	HIV patient	55.5	ND	Real-time PCR	ND	18	D, E, A, D/E
Abd El Kader Mahmoud *et al* [46]	2013	Sudan	Blood donors	38	ND	Real-time PCR	ND	100	
Mahgoub *et al*[56]	2011	Sudan	Blood donors	4.6	ND	Nested PCR	ND	129	
Meschi *et al*[34]	2010	Tanzania	Febrile patient	7.7	Cross-sectional	Real-time PCR	ND	13	

OBI: Occult hepatitis B infection; HBV: Hepatitis B virus; PCR: Polymerase chain reaction; HIV: Human immunodeficiency virus; ND: Not defined; ART: Antiretroviral therapy.

Studies have shown that patients with CHC are at a high risk of developing OBI, with reported prevalence rates ranging from 3.2% to 90.9%[42,86,92,93]. However, the wide range of reported prevalence rates may be attributed to differences in study design, patient population, and diagnostic methods used. Patients with CHC who have OBI face a greater risk of liver cirrhosis, HCC, and reactivation of HBV infection during immunosuppressive therapy.

Furthermore, haemodialysis and thalassemia patients are also at a high risk of developing OBI due to the frequent blood transfusions required. Prevalence rates of OBI in these patient populations range from 2.2% to 90.9% and 13.6% to 32.5%, respectively[8,62,116,120]. A study showed a similar prevalence of 31.4% among thalassemia patients who had received multiple blood transfusions in India[120].

Table 5 Distribution of occult hepatitis B infection prevalence in the western region of Africa

Ref.	Year	Countries	Patients	OBI prevalence, *n* (%)	Types of studies	Methods	DNA limit of detection	Effective	HBV genotype
Ky/Ba *et al* [25]	2021	Burkina Faso	Blood donors	4	Cross-sectional	Real-time PCR	ND	300	
Diarra *et al* [26]	2018	Burkina Faso	General population	7.3	ND	Real-time PCR	ND	219	E and A3
Somda *et al* [24]	2016	Burkina Faso	Blood donors	32.8	Prospective study	Real-time PCR	ND	160	
Ndow *et al* [27]	2022	Gambia	General population	18.3	Case-control study	Nested PCR	5 IU/mL	82	
Gouas *et al* [97]	2012	Gambia	Patient with Cirrhosis and HCC	15% cirrhosis et 24% with HCC	Case–control study	PCR	ND	34 et 88	E, D, A
Attiku *et al* [77]	2021	Ghana	HIV/HBV co-infected patients	30.8	Longitudinal purposive study	Real-time PCR	2 copies/mL	13	
Attia *et al* [78]	2012	Ivory Coast	HIV patient	21.3	Cross-sectional	COBAS Amplicor HBV	6 UI/mL	188	
Fasola *et al* [60]	2021	Nigeria	Blood donors	1	Cross-sectional	Nested PCR	1 IU/mL	100	
Akintule *et al*[52]	2018	Nigeria	Blood donors	8.7	ND	Nested PCR	ND	206	83.3% A 11.1% no A
Olotu *et al* [53]	2016	Nigeria	Blood donors	5.4	Cross-sectional	Real-time PCR	20 IU/mL	354	
Oluyinka *et al*[61]	2015	Nigeria	Blood donors	17	ND	Real-time PCR	ND	492	
Nna *et al* [54]	2014	Nigeria	Blood donors	8	ND	Nested PCR	ND	100	
Opaleye *et al*[79]	2014	Nigeria	HIV patient	11.8	ND	PCR	ND	188	

OBI: Occult hepatitis B infection; HBV: Hepatitis B virus; PCR: Polymerase chain reaction; HIV: Human immunodeficiency virus; ND: Not defined; HCC: Hepatocellular carcinoma.

The high prevalence rates of OBI in these populations may be attributed to the residual risks of HBV transmission through blood transfusions. To minimize this risk, strategies such as HBV nucleic acid testing and vaccination of patients and healthcare workers must be implemented in African countries.

This study suggests a risk of OBI reactivation in patients undergoing chemotherapy and suffering from sickle cell disease[113-115]. HBV reactivation is most commonly reported in patients with lymphoma, but it is unclear whether lymphoma itself increases the risk of HBV reactivation because there are no studies comparing the risk in patients with other diseases receiving similar chemotherapeutic regimens. The frequent association between lymphoma and HBV reactivation might be related to the intensity of the chemotherapy regimen, resulting in marked immunosuppression [121]. Thus, identifying and monitoring OBI in these patient populations is crucial to prevent the risk of reactivation. Because current therapies do not eliminate cccDNA, which serves as a model for HBV replication, thus preventing the eradication of the virus[122,123]. Lymphoid cells that present as a sanctuary can archive cccDNA[124,125].

Our research underscores the importance of hepatitis B vaccination in preventing OBI. For example, a study conducted on diabetic children and adolescents in Egypt found no instances of OBI after vaccination, demonstrating the vaccine's effectiveness in preventing OBI[20]. Similarly, the introduction of vaccination in South Africa[119] led to a reduction in the prevalence of OBI. These findings underscore the importance of vaccination in preventing OBI in high-risk populations.

Finally, this review identified a high prevalence of OBI in patients with HCC, ranging from 3.2% to 59.4%[41,97]. Notably, the presence of OBI in HCC patients has been associated with more aggressive tumors and a poorer prognosis[9,98], emphasizing the critical need for routine screening for OBI in HCC patients.

It should be noted that the HBV DNA detection methods used in the studies selected for this literature review greatly influence the reported results, due to their variable sensitivity as well as their heterogeneity in the different analytical steps[86,116]. This methodological variability results in observed OBI prevalences that vary widely across studies. This is an important limitation to consider when interpreting the OBI prevalence data from this literature review.

Table 6 Distribution of hepatitis B virus genotypes involved in occult hepatitis B infection

Ref.	Year	Countries	Patients	OBI prevalence, *n* (%)	Types of studies	Methods	Effective	HBV genotype
Mbangiwa *et al* [67]	2018	Botswana	Pregnant women with/without HIV	6.6	Prospective study	COBAS AmpliPrep	622	D3, A1, E
Diarra *et al*[26]	2018	Burkina Faso	General population	7.3	ND	Real-time PCR	219	E and A3
Esmail *et al*[40]	2016	Egypt	Haemodialysis without HCV	8.3	ND	Real-time PCR	144	B, C, D
Kishk *et al*[58]	2015	Egypt	Blood donors	22.7	ND	Real-time PCR	343	D
Kishk *et al*[88]	2014	Egypt	CHC patient	7.5	ND	Real-time PCR	162	D
Elkady *et al*[113]	2013	Egypt	Hematological malignant patients	5.66	ND	Real-time PCR	18	D1
Taha *et al*[42]	2013	Egypt	HCV patients with/without hepatocellular carcinoma	22.5 (17.5 with CHC 5 without CHC)	Cross-sectional	Nested PCR	40	D, B, C, A
Youssef *et al*[36]	2013	Egypt	Children with acute HBV	29,16	ND	Real-time PCR	24	D (D1, D2)
Hassan *et al*[41]	2011	Egypt	Hepatocellular carcinoma patient	22.5	ND	Nested PCR	40	D, B, A, C
Youssef *et al*[43]	2009	Egypt	Patient with elevated transaminases	64.8	ND	Nested PCR	119	C (C2), D (D1)
Meier-Stephenson *et al* [38]	2020	Ethiopia	Pregnant women	20.3	Prospective	Nested PCR	182	D, C
Patel *et al*[44]	2020	Ethiopia	HIV patient	19.1	Cross-sectional	Nested PCR	291	D, E, A, C
Bivigou-Mboumba *et al* [76]	2016	Gabon	HIV patient	8	Cross-sectional	Real-time PCR	762	A, E
Gouas *et al*[97]	2012	Gambia	Patient with Cirrhosis and HCC	15% cirrhosis et 24% with HCC	case–control study	PCR	34 et 88	E, D, A
Aluora *et al*[37]	2020	Kenya	Blood donors	2.3	Cross-sectional	Nested PCR	300	A
Akintule *et al*[52]	2018	Nigeria	Blood donors	8.7	ND	Nested PCR	206	83.3% A 11.1% no A
Ibrahim *et al*[102]	2020	Sudan	Renal transplant patients	18	Cross-sectional	Nested PCR	100	D, A, E
Mustafa *et al* [101]	2020	Sudan	Renal Transplant Patients	51,4	ND	Real-time PCR	100	A, D, E
Yousif *et al*[39]	2014	Sudan	HIV patient	55.5	ND	Real-time PCR	18	D, E, A, D/E

OBI: Occult hepatitis B infection; HBV: Hepatitis B virus; PCR: Polymerase chain reaction; HIV: Human immunodeficiency virus; ND: Not defined; HCV: Hepatitis C virus; CHC: Chronic hepatitis C; HCC: Hepatocellular carcinoma.

CONCLUSION

Studies on the prevalence of OBI are limited. However, our review highlights the significant burden of OBI in various high-risk populations, including patients with CHC, haemodialysis patients, patients with HCC, and thalassemia patients. The high prevalence of OBI in these studied populations underscores the need to increase HBV screening in order to vaccinate non-infected patients and monitor those who are positive or have an OBI. Further studies are required to better understand the transmission and pathogenesis of OBI and to develop effective prevention and treatment strategies.

Table 7 DNA limit of detection in included studies

Ref.	Year	Countries	Patients	OBI prevalence, *n* (%)	Types of studies	Methods	DNA low limit of detection	Effective	HBV genotype
Abdel-Maksoud *et al*[104]	2019	Egypt	Haemodialysis	7.3	Cohort	Nested PCR	30 copies/mL	150	
Elbedewy *et al*[114]	2015	Egypt	Patient with malignant tumors of the lymphatic system	13.89	Cross-sectional	Real-time PCR	12 IU/mL	72	
Kishk *et al* [58]	2015	Egypt	Blood donors	22.7	ND	Real-time PCR	100 copies/mL	343	D
Elrashidy *et al*[20]	2014	Egypt	Diabetic children and adolescents following hepatitis B vaccination	0	ND	Nested PCR	100 copies/mL	170	
El-Ghitany *et al*[86]	2013	Egypt	Blood donors with hepatitis C	4,16 (3,2 HVC+ et 5,1 HCV-)	Case–control study	Real time PCR	45 copies/mL	504	
Elkady *et al* [113]	2013	Egypt	Hematological malignant patients	5.66	ND	Real-time PCR	20 IU/mL	18	D1
Said *et al*[48]	2013	Egypt	Blood donors	1.64	Cross-sectional	Real-time PCR	3.8 IU/mL	3167	
Abu El Makarem *et al*[105]	2012	Egypt	Haemodialysis with/without HCV	4.1	ND	Real-time PCR	6 IU/mL	145	
Selim *et al* [89]	2011	Egypt	HCV patients	38.3	ND	Real-time PCR	45 copies/mL	60	
Emara *et al* [90]	2010	Egypt	HCV patients	3.9	Cross-sectional	Real-Time PCR	12 IU/mL	155	
El-Sherif *et al* [91]	2009	Egypt	HCV patients	16	ND	Real-Time PCR	30 copies/mL	100	
Gissa *et al* [99]	2022	Ethiopia	Patients with chronic liver disease of unidentified cause	5.56	Prospective	Real-Time PCR	15 IU/mL	36	
Bivigou-Mboumba *et al*[75]	2018	Gabon	HIV patient	17.5	Cross-sectional	Real-time PCR	50 IU/mL	137	
Bivigou-Mboumba *et al*[76]	2016	Gabon	HIV patient	8	Cross-sectional	Real-time PCR	100 IU/mL	762	A E
Ndow *et al* [27]	2022	Gambia	General population	18.3	Case-control study	Nested PCR	5 IU/mL	82	
Attiku *et al* [77]	2021	Ghana	HIV/HBV co-infected patients	30.8	Longitudinal purposive study	Real-time PCR	2 copies/mL	13	
Attia *et al*[78]	2012	Ivory Coast	HIV patient	21.3	Cross-sectional	COBAS Amplicor HBV	6 UI/mL	188	
Salyani *et al* [70]	2021	Kenya	HIV patient ART naïve	5.3	Cross-sectional	COBAS AmpliPrep	20 UI/mL	208	
Mabunda *et al*[51]	2020	Mozambique	Blood donors	0.98	Cross-sectional	PCR	20 UI/mL	1435	
Fasola *et al* [60]	2021	Nigeria	Blood donors	1	Cross-sectional	Nested PCR	1 IU/mL	100	
Olotu *et al* [53]	2016	Nigeria	Blood donors	5.4	Cross-sectional	Real-time PCR	20 IU/mL	354	
Powell *et al* [81]	2015	South Africa	HIV patient	13.5	ND	Real-time PCR	250 copies/mL	394	
Hoffmann *et*	2014	South Africa	Pregnant women with	1.71	Case-control	Real-time	20 IU/ mL	175	

al[65]			HIV		study	PCR		
Bell *et al*[68]	2012	South Africa	ART naive HIV	3.79	Cohort	Real-time PCR	20 IU/ mL	79

OBI: Occult hepatitis B infection; HBV: Hepatitis B virus; PCR: Polymerase chain reaction; HIV: Human immunodeficiency virus; ND: Not defined; HCV: Hepatitis C virus; ART: Antiretroviral therapy.

ACKNOWLEDGEMENTS

The researchers of the associated laboratories and all those who contributed to improving this manuscript. We thank the researchers at the Transmissible Diseases Laboratory, the Molecular Biology and Genetics Laboratory, and all those who contributed to improving this manuscript.

FOOTNOTES

Author contributions: Bazie MM, Sanou M, Djigma FW and Kabamba B conceived and designed the study; Bazie MM, Sanou M and Djigma FW were involved in independent research of relevant articles; Bazie MM, Sanou M, Djigma FW and Compaore TR were involved in full text review of relevant articles; Bazie MM, Sanou M and Djigma FW were involved in data extraction, analysis and interpretation; Bazie MM, Sanou M, Djigma FW, Compaore TR, Obiri-Yeboah D, Kabamba B, Nagalo BM were involved with drafting or revising the manuscript; Sanou M, Djigma FW, provided administrative, technical and material support; Supervision of the study was made by Sanou M, Kabamba B, Simpore J and Ouedraogo R; all authors critically revised and approved the final version of this publication.

Conflict-of-interest statement: No potential conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Qu XL
L-Editor: A
P-Editor: Zhao YQ

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