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Epidemiology of occult hepatitis B and C in Africa: A systematic review and meta-analysis

Juliette Laure Ndzie Ondigui[a,b], **Sebastien Kenmoe**[c,*], **Cyprien Kengne-Ndé**[d], **Jean Thierry Ebogo-Belobo**[e], **Guy Roussel Takuissu**[f], **Raoul Kenfack-Momo**[g], **Donatien Serge Mbaga**[a], **Serges Tchatchouang**[h], **Josiane Kenfack-Zanguim**[g], **Robertine Lontuo Fogang**[i], **Elisabeth Zeuko'o Menkem**[j], **Ginette Irma Kame-Ngasse**[e], **Jeannette Nina Magoudjou-Pekam**[g], **Arnol Bowo-Ngandji**[a], **Nadège Mafopa Goumkwa**[b], **Seraphine Nkie Esemu**[c], **Lucy Ndip**[c], **Sara Honorine Riwom Essama**[a], **Judith Torimiro**[b]

[a]Department of Microbiology, The University of Yaounde I, Yaounde, Cameroon

[b]Molecular Biology Laboratory, Chantal Biya International Reference Centre for AIDS Research (CIRCB), Yaounde, Cameroon

[c]Department of Microbiology and Parasitology, University of Buea, Buea, Cameroon

[d]Epidemiological Surveillance, Evaluation and Research Unit, National AIDS Control Committee, Douala, Cameroon

[e]Medical Research Centre, Institute of Medical Research and Medicinal Plants Studies, Yaounde, Cameroon

[f]Centre for Food, Food Security and Nutrition Research, Institute of Medical Research and Medicinal Plants Studies, Yaounde, Cameroon

[g]Department of Biochemistry, The University of Yaounde I, Yaounde, Cameroon

[h]Scientific Direction, Centre Pasteur of Cameroon, Yaounde, Cameroon

[i]Department of Animal Biology, University of Dschang, Dschang, Cameroon

[j]Department of Biomedical Sciences, University of Buea, Buea, Cameroon

Abstract

* Correspondence to: Department of Microbiology and Parasitology, University of Buea, Molyko, Buea 00237, Cameroon. sebastien.kenmoe@ubuea.cm (S. Kenmoe).

CRediT authorship contribution statement

Kenmoe S, Ndzie Ondigui JL, and Torimiro J were responsible for conception and design of the study as well as project administration; Ndzie Ondigui JL, Kenmoe S, Kengne-Ndé C, Ebogo-Belobo JT, Takuissu GR, Kenfack-Momo R, Mbaga DS, Tchatchouang S, Kenfack-Zanguim J, Lontuo Fogang R, Zeuko'o Menkem E, Kame-Ngasse GI, Magoudjou-Pekam JN, Bowo-Ngandji A, Mafopa Goumkwa N, Nkie Esemu S, Ndip L, Riwom Essama SH, Torimiro J were responsible for the data curation and interpretation of results; Kengne-Nde C and Kenmoe S were responsible for statistical analysis; Kenmoe S and Ndzie Ondigui JL wrote the original draft; All authors critically reviewed the first draft and approved the final version of the paper for submission, and have read and approve the final manuscript.

Consent for publication

Not applicable.

Competing interests

None.

Background—Occult hepatitis B (OBI) and C (OCI) infections lead to hepatic crises including cases of liver cirrhosis and even hepatocellular carcinoma (HCC). OBI and OCI also pose a significant problem of their transmissibility. This study aimed to assess the overall prevalence of OBI and OCI in the African continent, a region highly endemic for classical hepatitis B and C viruses.

Methods—For this systematic review and meta-analysis, we searched: PubMed, Web of Science, African Journal Online and African Index Medicus for published studies on the prevalence of OBI and OCI in Africa. Study selection and data extraction were performed by at least two independent investigators. Heterogeneity (I^2) was assessed using the χ^2 test on the Cochran Q statistic and H parameters. Sources of heterogeneity were explored by subgroup analyses. This study was registered in PROSPERO, with reference number CRD42021252772.

Results—We obtained 157 prevalence data for this meta-analysis, from 134 studies for OBI prevalence; 23 studies on OCI prevalence, and a single study on the OBI case fatality rate. The overall estimate for the prevalence of OBI was 14.8% [95% CI = 12.2-17.7] among 18579 participants. The prevalence of seronegative OBI and seropositive OBI was 7.4% [95% CI = 3.8-11.8] and 20.0% [95% CI = 15.3-25.1] respectively. The overall estimate for the prevalence of OCI was 10.7% [95% CI = 6.6-15.4] among 2865 participants. The pooled prevalence of seronegative OCI was estimated at 10.7% [95%CI = 4.8-18.3] and that of seropositive OCI at 14.4% [95%CI = 5.2-22.1]. In Sub-group analysis, patients with malignancies, chronic hepatitis C, and hemodialysis had a higher OCI prevalence. While those with malignancies, liver disorders, and HIV positive registered highest OBI prevalence.

Conclusion—This review shows a high prevalence of OBI and OCI in Africa, with variable prevalence between countries and population groups.

Keywords

Occult hepatitis B; Occult hepatitis C; Prevalence; Africa

Introduction

In the early 1980 s, a new form of clinical hepatitis B virus (HBV) infection was described, corresponding to the presence of HBV DNA in the liver and/or serum of patients in whom the HBs antigen (Ag) is undetectable by the usual serology tests. This was called occult hepatitis B (OBI) [1–3]. Based on the antibody profile of HBV, OBI can be distinguished into seropositive-OBI (anti-HBc and/or anti-HBs positive) and seronegative-OBI (anti-HBc and anti-HBs negative)[4]. A similar entity was studied in 2005, by Castillo et al., on the ability of hepatitis C virus (HCV) to replicate in peripheral blood mono-nuclear cells (PBMCs) of patients in the absence of viral RNA in serum and detectable anti-HCV antibodies, thus describing an occult HCV infection[5,6]. Two types of OCI are recognized: seronegative OCI (anti HCV antibody-negative and serum HCV RNA-negative) and seropositive OCI (anti HCV antibody-positive and serum HCV RNA-negative)[7]. These occult forms of hepatitis B and C can lead to hepatic crises including cases of chronic liver infection and liver cirrhosis [8]. It is known that OBI plays a role in the development of hepatocellular carcinoma [9]. These entities highlight

multiple concerns, including the potential for transmission of this form of infection through blood transfusion, hemodialysis, or from mother to child [10]. The OBI and OCI have been described in a variety of individuals, including hemodialysis patients, patients with sustained virologic response, immunocompromised individuals, patients with abnormal liver function, and apparently healthy subjects. Multiple meta-analyses on the prevalence of OBI and OCI have shown great variability in estimates according to population categories, regions, type of tests used, and the level of endemicity of the disease [9,11–17]. Two global meta-analyses with partial analyses for Africa reported the prevalence of OBI at 3.7% [15], seronegative OCI at 9.6% and seropositive OCI at 13.3% [17]. The highest prevalence of OBI was in countries with high endemicity of classical hepatitis B, including Africa, with prevalence of up to 35.6% in the general population in Uganda [15]. Similar to classical hepatitis C infection, which has the highest prevalence in Egypt, this meta-analysis showed that OCI had the highest prevalence in North Africa, represented only by Egypt [17]. Other meta-analyses have estimated the prevalence of OBI in Africa among people living with HIV at 11.2% [16] and in Sudan at 15.5% [12]. In a regional meta-analysis in the Middle East and Eastern Mediterranean countries the prevalence of OCI was estimated at 10.0% with the highest prevalence recorded in Egypt [14]. Estimates of a high OBI prevalence of 34% was reported in Western Europe and Northern America [18] and a lower OBI prevalence of 4% was observed in Asia [19]. Thus, there are no systematic syntheses for OBI and OCI for Africa which is a highly endemic region for classical HBV and HCV infections. In this meta-analysis, we compiled all available evidence for OBI and OCI in Africa with differences across populations and regions. The results of this review may help consider OBI and OCI in the WHO goal of eliminating viral hepatitis by 2030. It will also help to sound the alarm on the need to strengthen the diagnostic capacities of OBI and OCI in Africa which has limited access to molecular testing.

Materials and methods

Registration

This systematic review was conducted in full compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta - Analyses) guidelines (S1 Table) [20]. The protocol of this systematic review was developed and registered on PROSPERO (International prospective register of systematic reviews) on June 03, 2021 under the digital identifier: https://www.crd.york.ac.uk/pros-pero/display_record.php? ID = CRD42021252772.

Search strategy

In May 2021, an electronic literature search was performed and the following databases were used: PubMed, Web of Science, African Journal Online and African Index Medicus. A second update search was performed in July 2022 to search for additional articles. We used a combination of the keywords covering OBI, OCI, the names of African countries and regions as well as the boolean operators OR and AND as illustrated in detail in S2 Table. This search strategy was also adapted to identify relevant articles from other databases. To complement the bibliographic database search and identify potential additional data sources, we reviewed the reference list of all relevant articles. All search results were managed using

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Endnote X9 credential management software, and all duplicates were removed using this same software.

Inclusion and exclusion criteria

We considered published studies, without any restrictions in time, population category or detection assay. We classified populations for OBI as: 1) HBsAg negative 2) HBsAg negative and Anti-HBc positive, and 3) HBsAg negative and Anti-HBc negative [21,22], and for OCI as 1) seronegative OCI (anti HCV antibody-negative and serum HCV RNA-negative), 2) seropositive OCI (anti HCV antibody-positive and serum HCV RNA-negative), and 3) seropositive and/or seronegative OCI [7]. Only reports written in English and/or French were included. Exclusion criteria included all of the following: case reports, reviews and articles for which: studies were conducted outside Africa, sample size ≤ 10 participants, no baseline data for the longitudinal study, no data on OBI and/or OCI prevalence or case fatality rate, and no data on number of negative HBsAg tested.

Study selection and data extraction process

Duplicates identified in the full list of studies were removed. The titles and abstracts of articles retrieved from the electronic literature search were independently reviewed by four researchers, and the full texts of potentially eligible articles were obtained and further assessed for final inclusion. Articles were selected based on the availability of data needed to calculate the prevalence of OBI and/or OCI in the study. Data from the included studies were extracted using a Google Form by 18 of the study authors and verified by SK. Data extracted were first author name, year of publication, design of study, WHO region, UNSD region, country, country's income level, sampling method, time of data collection, period of study, age of study participants, recruiting framework, population categories, OBI and/or OCI diagnostic method, and prevalence of OBI and/or OCI in Africa. We considered as the high-risk groups of OBI: HIV-positive patients, patients with chronic liver disease, patients on hemodialysis, patients with hematological disorders, patients with malignancies, organ recipients, healthcare workers, patients who inject drugs and men who have sex with men [12,19,23]. We grouped apparently healthy individuals, blood donors, the general population, and pregnant women as the low-risk group for OBI.

Disagreements observed during study selection and data extraction were resolved by discussion and consensus.

Quality assessment

The tool developed by Hoy et al. for cross-sectional studies was used to assess the methodological quality of the included studies (S3 Table) [24]. Discussion and consensus were used to resolve disagreements.

Statistical analysis

Study-specific estimates were pooled using DerSimonian and Laird's random-effects model meta-analysis [25]. This model provided the overall prevalence, the 95% confidence interval and the prediction interval which informs about the values of future studies. Heterogeneity was assessed by the Cochrane statistical test, and the p value of the Q

test (< 0.05) was used to indicate significant heterogeneity and quantified by I^2 values, assuming I^2 values of 25%, 50% and 75% represent respectively low, moderate and high heterogeneity[26,27]. Publication bias was assessed using Egger's test and funnel plot [28]. Subgroup analyses were performed based on study design, sampling approach, setting, timing of sample collection, countries, WHO region, UNSD region, country income level, age range, population categories, and OBI and/or OCI diagnostic assays. We considered p values < 0.05, to be statistically significant. R software version 4.1.0 was used to perform the analyses[29,30].

Results

Selection of studies

As of 07/18/2022, 496 studies were analysed with no additional studies added from the manual search. After removing the duplicates (152), 344 articles were screened. The full text evaluation led to the elimination of 78 studies for several reasons, including lack of data on OBI and/or OCI prevalence or case fatality rate, or small sample size (S4 Table). In all, a total of 109 articles reporting the prevalence and/or case fatality rate of OBI and/or OCI in Africa were included in this synthesis (Fig. 1) [3,31–138].

Study characteristics

Overall, we obtained 157 prevalence data for this meta-analysis, including 133 studies for OBI prevalence; 23 studies for OCI prevalence, and a single study for OBI case fatality rate (S5, S6, and S7 Tables). The OBI case fatality rate study reported a total of 6 deaths among 72 OBI and HIV infected patients in Botswana [108]. The studies were published between 2006 and 2022 in general and respectively from 2006 to 2022 and 2010-2022 for OBI and OCI. Participants were registered from 1997 to 2021. The majority of studies were cross-sectional (84.7%) with non-probability sampling (88.5%). The study setting was mainly in the hospital (93.6%). The studies were carried out in 21 African countries, mainly in Egypt (44.6%) and South Africa (13.4%). The largest number of studies were from lower-middle-income countries (68.2%). Most of the studies recruited adults (61.8%). Of the included studies, 39 (24.8%) were carried out in HIV infected patients, 27 (16.6%) in patients with chronic hepatitis C infection, 19 (12.1%) in blood donors, and 19 (12.1%) in hemodialysis patients. The diagnosis of OCI was either performed using conventional RT-PCR (5.7%) or real-time RT-PCR (8.3%). OBI diagnosis was made using conventional PCR (46.5%) or real-time PCR (39.5%). The type of sample used was blood for OBI (100%) and peripheral blood mononuclear cells (PBMCs) for OCI (100%). Most of the prevalence data were at moderate risk of bias (59.2%).

The prevalence of occult C infection

In total, the twenty-three studies reporting OCI prevalence data in Africa were conducted only in Egypt. The pooled OCI prevalence was estimated to be 10.7% [95% CI = 6.6-15.4] on a sample of 2865 participants with substantial heterogeneity (I^2 = 90.7% [95% CI = 87.4-93.2], p < 0.001) (Table 1, Figs. 2 and 3). Two studies presented the prevalence of seropositive and/or seronegative OCI without distinction with an estimated at 5.8% [95% CI = 0.8-13.9] in a total of 100 participants. There was a total of 14 studies reporting

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seronegative OCI prevalence. The pooled seronegative OCI prevalence was estimated to be 10.7% [95% CI = 4.8-18.3] in a sample of 908 participants. There was a total of 7 studies reporting seropositive OCI prevalence. The overall seropositive OCI prevalence was estimated to be 14.4% [95% CI = 5.2-22.1], with a total of 1857 participants.

The prevalence of occult B infection

A total of 133 studies reporting prevalence data on OBI were conducted in 5 UNSD regions of Africa: Central Africa, Eastern Africa, West Africa, Northern Africa, and Southern Africa (Fig. 2). The OBI prevalence was estimated at 14.8% [95% CI = 12.2-17.7] in a sample of 18579 participants with significant heterogeneity (I^2 = 96.2% [95% CI = 95.8-96.5], p < 0.0001) (Table 1, Figs. 2, 4, and S1 Fig). The pooled prevalence of seropositive OBI was estimated at 20.0% [95% CI = 15.3-25.1] among 6873 participants. Prevalence data on seronegative OBI were obtained from 32 studies and the prevalence was estimated at 7.4% [95% CI = 3.8-11,8] with 2896 participants. A total of 44 studies reported on seropositive and/or seronegative OBI with an estimated prevalence of 14.3% [95% CI = 10.1-19.2] in 8810 participants. Few studies provided data on the variation of seropositive or seronegative OBI with anti-HBs (only 9 studies). The distribution of OBI prevalence according to anti-HBs was as follows: 17.32% [4.37; 35.69] for anti-HBc negative/ anti-HBs negative, 30.95% [17.10; 46.62] for anti-HBc positive/ anti-HBs negative, 27.41% [8.89; 50.70] anti-HBc positive/ anti-HBs positive, and 0% for anti-HBc negative/ anti-HBs positive (S3 Fig).

Subgroup analyses

Occult hepatitis C infection—The OCI prevalence was statistically different (p = 0.005) according to the population categories with an estimated prevalence of 34.9% in patients with malignancies, 12.3% in those with chronic hepatitis C, 7.2% in hemodialysis patients, and 1.1% in apparently healthy individuals (S8 Table). OCI prevalence did not vary significantly by study design (p = 0.380), sampling approach (p = 0.460), type of OCI (seropositive or seronegative) (p = 0.819), and diagnostic method (p = 0.067).

Occult hepatitis B infection—Variation of OBI prevalence was statistically significant by country (p < 0.001), categories of population (p < 0.001), and type of OBI (seropositive or seronegative) (p < 0.001) (S8 Table). The highest OBI prevalence rates were in Morocco (42.8%), Gabon (22.6%), and South Africa (20.2%). Patients with malignancies, patients with liver disorders, and HIV positive patients were the three population categories with the highest OBI prevalence, 41.9%, 33.1%, and 17.0% respectively. The seropositive OBI prevalence (20.1%) was significantly higher than that of seronegative OBI (8.0%). The OBI prevalence did not vary significantly by study design (p = 0.360), sampling approach (p = 0.117), setting (hospital or community-based) (p = 0.360), timing of data collection (p = 0.875), WHO region (p = 0.544), UNSD region (p = 0.384), country income level (p = 0.395), age range (p = 0.799), and diagnostic method (p = 0.659).

Publication bias—Egger's tests were significant for the OCI prevalence (P < 0.001) and OBI prevalence in Africa (P = 0.014), suggesting the presence of a publication bias. Funnel plots confirmed the results of publication bias obtained by Egger's test (S2 and S4 Figs).

Discussion

We performed a meta-analysis to provide an estimate of the prevalence and case fatality rate of OBI and OCI in Africa. A total of 109 studies were reviewed and a total of 18579 and 2865 participants were assessed for OBI and OCI respectively. There was only one study that reported deaths (6/72) in HIV-positive subjects with OBI in Botswana. The prevalence of OBI ranged from 0% to 100% and the prevalence of OCI ranged from 0% to 60%. An estimated prevalence of OCI (10.7%) and OBI (14.8%) was obtained in relevant articles published between 2010 and 2022 in Africa. Overall, we found a higher prevalence of OCI in patients with malignancies, in patients with chronic hepatitis C, and in hemodialysis patients. Patients with malignancies, patients with liver disorders, and HIV positive patients were the population groups with the highest OBI prevalence.

Our results show that apart from Egypt, studies on OCI in Africa are very rare. Although Egypt has the highest prevalence of HCV in the world [139], many other African countries also have significant HCV prevalence, including Cameroon, Burundi and Morocco [140]. From this observation, it is therefore necessary to conduct additional studies on OCI in other African countries outside of Egypt. Studies have shown risks of reactivating the presence of OCI in subjects with a sustained virological response to HCV [17]. With the arrival of new direct-acting HCV treatments [141], OCI studies on those patients with a sustained virologic response are needed. Our systematic review found that the combined prevalence of OCI was 10.7% (14.4% for OCI seropositive and 10.7% for OCI seronegative). Related studies have reported similar prevalence of OCI at 10% in Middle Eastern and Eastern Mediterranean countries [14]. In a global review, the prevalence of seropositive OCI was estimated at 13.3% and seronegative OCI at 9.6%. [17]. These related reviews suggest that the prevalence of OCI is high in subjects with chronic liver disease, subjects who inject drugs, HIV positive subjects and patients on hemodialysis. [14,17]. We also found similar results in the present work, with a higher prevalence in patients with malignancies, patients with hepatological disorders, HIV positive patients and patients on hemodialysis. So far, no studies were found on OCI in people at high risk of HCV, such as people who inject drugs or men who have sex with men, so these studies are needed in Africa.

The prevalence of OBI is known to be very variable according to population categories. The high-risk groups reported by the authors included HIV-positive patients, patients with chronic liver disease, patients on hemodialysis, patients with hematological disorders, patients with malignancies, organ recipients, healthcare workers, patients who inject drugs and men who have sex with men [12,19,23]. The geographical context is also an important source of variability in the prevalence of OBI. The main factors of this variability include the endemicity of circulation of classic hepatitis B (low, intermediate or high level), the socio-demographic index and the rate of vaccination coverage for infection due to the hepatitis B virus [15,23]. Diagnostic factors such as the type of samples (blood, peripheral blood mononuclear cells or liver tissue) and the sensitivity and specificity of diagnostic techniques for the targets (DNA, HBsAg, anti-HBc, anti-HBs) are also associated with a significant influence of the prevalence of OBI [18,23]. Because of all these variability factors, objective comparisons between estimates from studies with different methodological approaches are difficult. Similar prevalence to the one found in our review were reported in a national

review in Sudan (15.5%) and in a second review conducted in Africa among HIV-positive patients (11.2%) [12,16]. The prevalence of HBV in HIV-positive patients in Africa is known to be high due to the high endemicity of these two diseases and their common route of transmission [142]. Therefore, the high prevalence of OBI also found in HIV-positive subjects in this study suggests the need for HBV DNA testing in these high-risk patients in Africa. Africa is a highly endemic area for classic HBV. So, hoping for the elimination of HBV as recommended by the WHO, strengthening vaccination policies against HBV is necessary and more particularly in patients with malignancies and HIV-positive patients [143]. Compared to the prevalence of OBI in this work, Xie et al., estimated a lower pooled prevalence of 4% from 70 studies conducted in Asia [19]. Surprisingly, the highest prevalences have been estimated for areas of the world with the lowest endemicity, notably 36% and 25% for Western Europe and North America, respectively [18].

Our study is mainly limited by the representativeness of the included studies. All OCI prevalence studies were conducted in Egypt and OBI prevalence data were usually collected in certain regions, which might not represent national prevalence and due to unavailability of data from OCI. Only 15/55 African countries were represented in this review. Therefore, the data may not be sufficient to represent the whole continent for the OBI and the OCI. In addition, substantial residual statistical heterogeneity in prevalence measures was identified in the overall and subgroup meta-analyses for OBI and OCI. Despite these limitations, the main strength of our review is that we identified a very large number of studies, which covered multiple categories of symptomatic, apparently healthy populations at high risk of HCV and HBV infection. We also took into account in our estimates the variability of prevalence according to anti-HCV serological status as well as that of anti-HBc.

Conclusion

This review presents a summary of the prevalence of OBI and OIC in Africa. It shows that despite the great variability of prevalence according to population category and geographic region, in general, the prevalence of OBI and OCI in Africa are high and patients with malignancies, hemodialysis patients and HIV patients are groups at high risk for these infections. This highlights the need to include more appropriate OCI and OBI screening programs to target those at high risk of infection. In addition, the lack of data in several African countries shows the need for researchers to investigate this field, particularly in countries with high endemicity for HBV/HCV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

Ag	antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
OBI	occulthepatitis B
OCI	occulthepatitis C
PBMC	peripheral blood mononuclear cells

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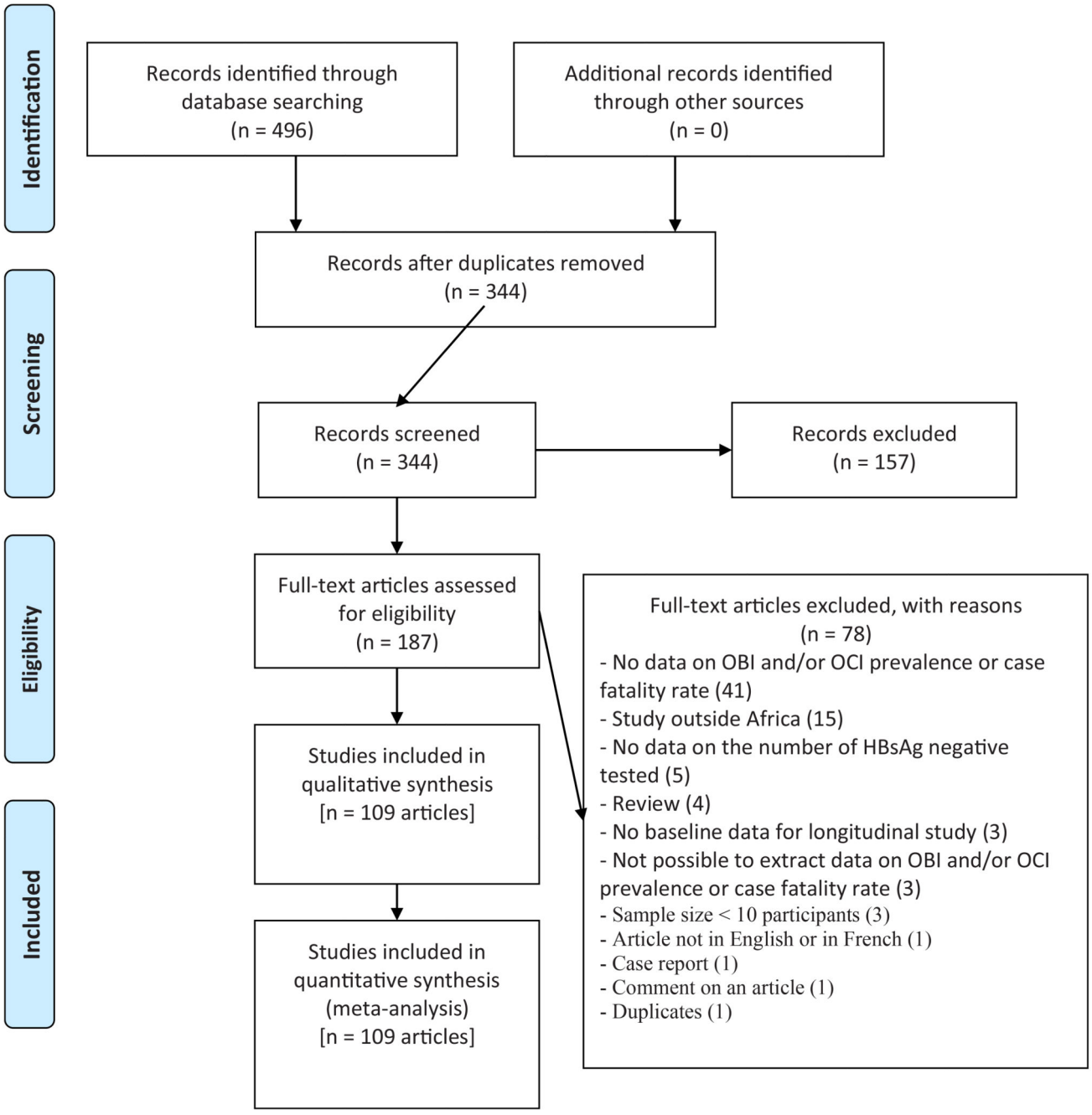

Fig. 1. PRISMA flow diagram demonstrating the literature search and screening process.

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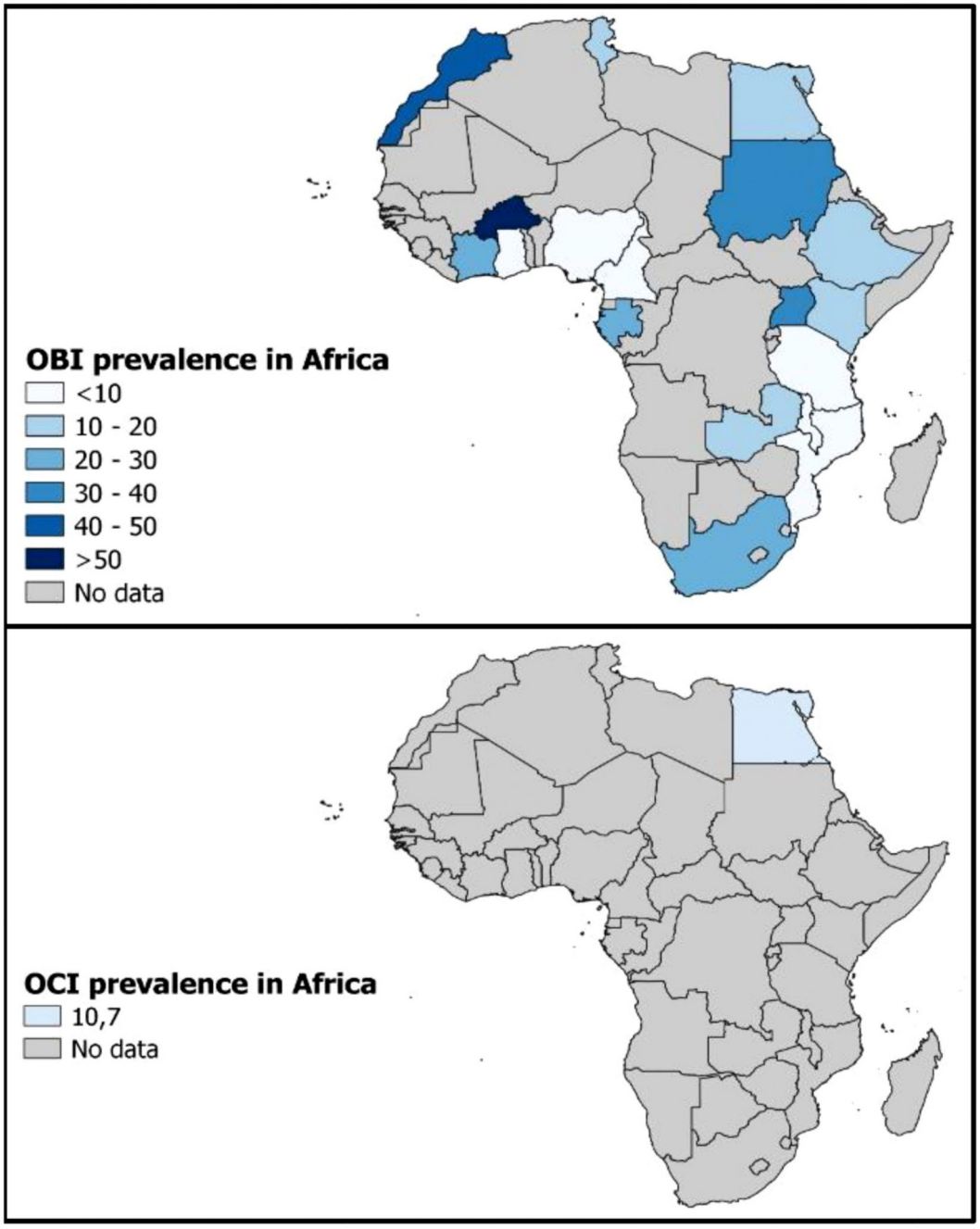

Fig. 2. Prevalence of occult hepatitis B and C virus infection in Africa.

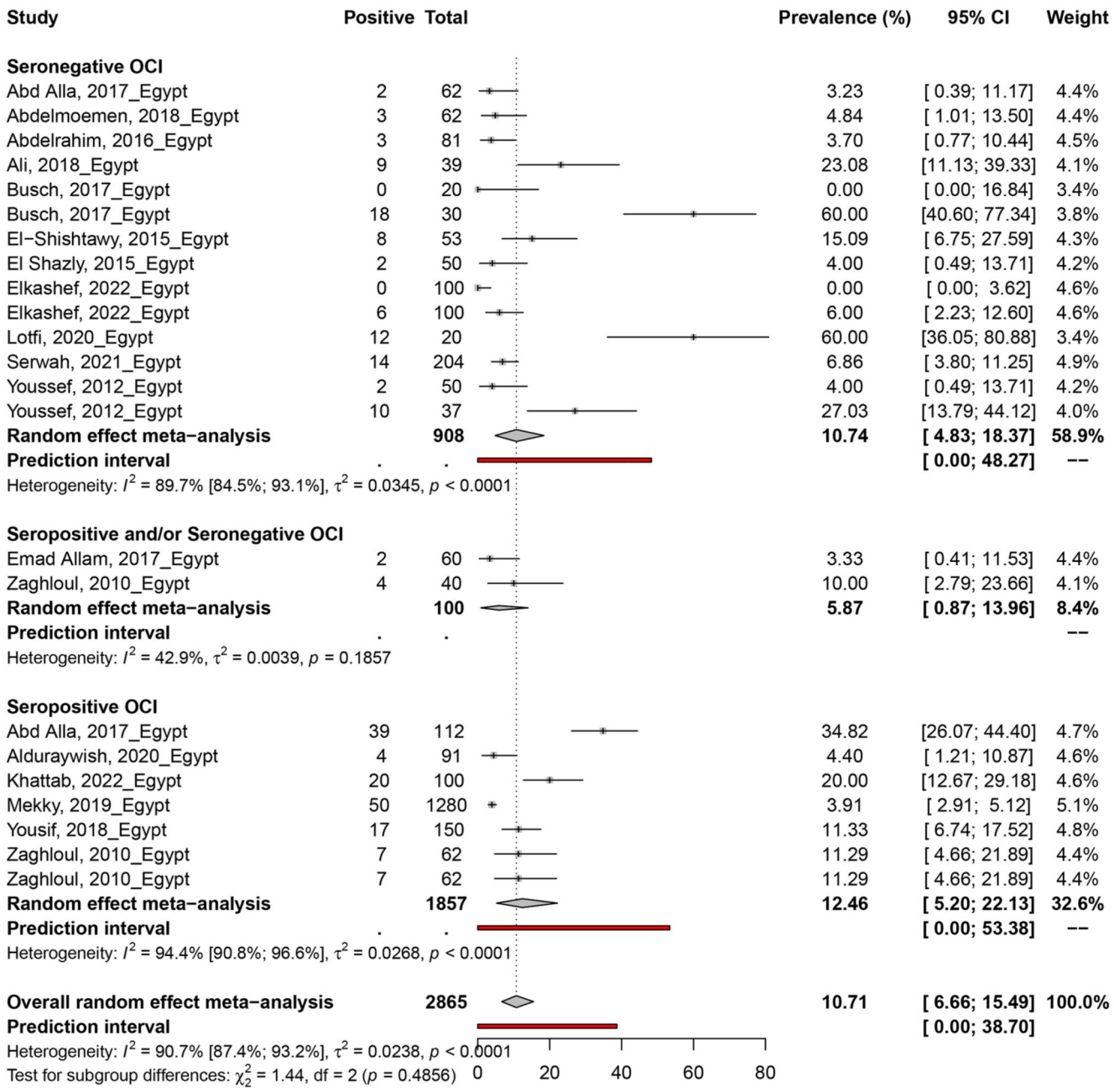

Fig. 3. Prevalence of seronegative and seropositive occult hepatitis C virus infection in Africa.

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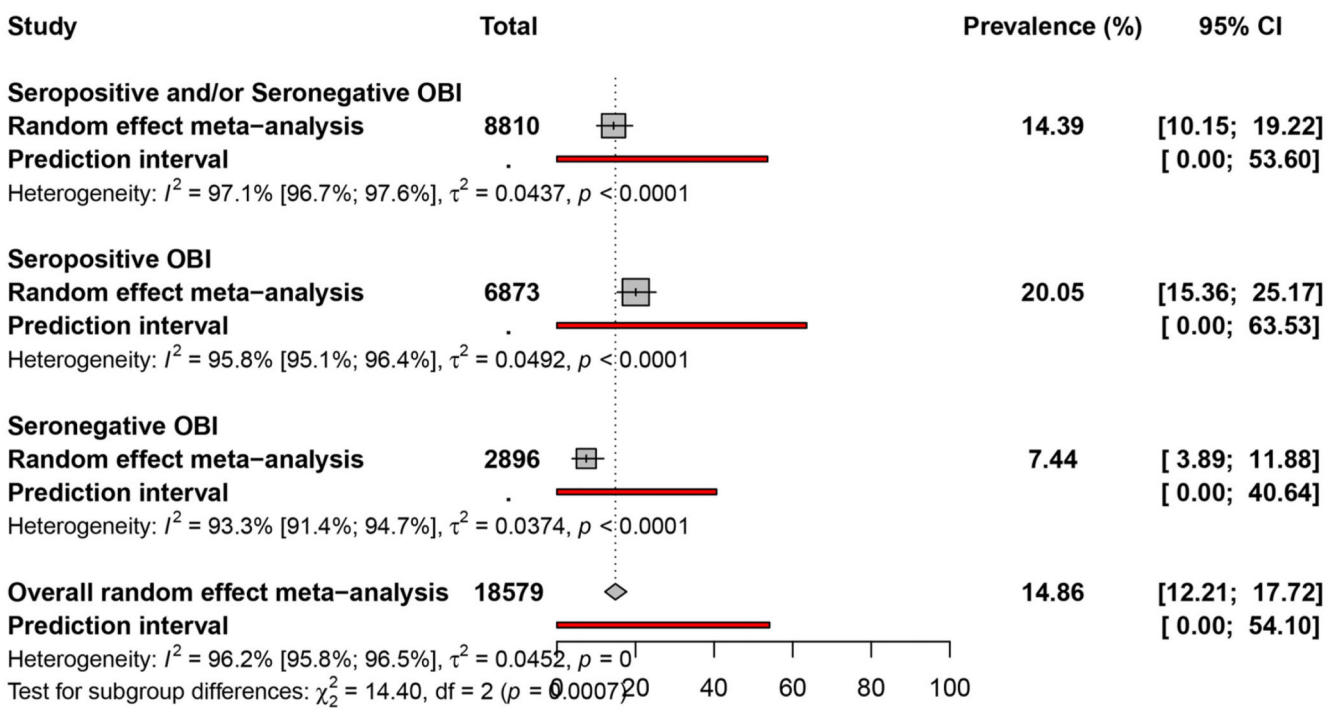

Fig. 4. Prevalence of seronegative and seropositive occult hepatitis B virus infection in Africa.

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Table 1

Summary of meta-analysis results for the prevalence of occult hepatitis B and C in in Africa

	Prevalence. % (95%CI)	95% Prediction interval	N Studies	N Participants	¶H (95%CI)	§I² (95%CI)	P heterogeneity
OBI prevalence in Africa							
Overall	14.9 [12.2–17.7]	[0–54.1]	133	18579	5.1 [4.9–5.4]	96.2 [95.8-96.5]	< 0.001
Cross-sectional	15.7 [12.7–18.9]	[0-56.1]	116	15443	5.1 [4.8–5.3]	96.1 [95.7-96.5]	< 0.001
Low risk of bias	15.7 [11.6–20.1]	[0–53.5]	51	7535	4.9 [4.6–5.3]	95.9 [95.2-96.5]	< 0.001
OCI prevalence in Africa							
Overall	10.7 [6.7–15.5]	[0–38.7]	23	2865	3.3 [2.8–3.8]	90.7 [87.4-93.2]	< 0.001
Cross-sectional	8.9 [5.1–13.5]	[0–32.1]	17	2451	2.9 [2.4–3.5]	88.2 [82.7-92]	< 0.001
Low risk of bias	12.2 [6–20.2]	[0–49]	12	2141	4 [3.3-4.9]	93.8 [90.9-95.8]	< 0.001

CI: confidence interval; N: Number; 95% CI: 95% Confidence Interval; NA: not applicable.

¶H is a measure of the extent of heterogeneity, a value of H = 1 indicates homogeneity of effects and a value of H > 1indicates a potential heterogeneity of effects.

§I2 describes the proportion of total variation in study estimates that is due to heterogeneity, a value > 50% indicates presence of heterogeneity