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Hepatitis E in Sub Saharan Africa – A significant emerging disease

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A B S T R A C T

Hepatitis E is an emerging endemic disease found across the African continent, but there are clear differences in epidemiology between North Africa and countries south of the Sahara. In this systematic review, Google scholar and PubMed databases were searched for peer-reviewed articles on HEV epidemiology. Publications meeting our inclusion criteria were critically reviewed to extract consistent findings and identify knowledge gaps. Hepatitis E has been reported in 25 of the 49 countries in Sub Saharan Africa.

Mortality rates of 1–2% in the general population and ~ 20% in pregnant women. Outbreaks were closely linked to refugees and Internally Displaced Persons in camps which accounted for 50% of reported outbreaks. There was very little research and concrete evidence for sources of contamination and transmission routes. There are indications of zoonotic transmission of Hepatitis E Virus infection but further research in these fields is required.

1. Introduction

Hepatitis E Virus (HEV) infection is a leading cause of acute viral hepatitis worldwide. It is transmitted through faecal contamination of drinking water and contact with infected animals and their products [1] . Global annual burden of infection is estimated at 20 million cases, with 3.4 million clinical cases, 70, 000 deaths (0.35% mortality rate) and 3000 stillbirths [2].

HEV was first identified in 1983 during an outbreak of non-A, non-B (NANB) hepatitis in Afghanistan [3]. Typical symptoms include fever, jaundice, anorexia, nausea, vomiting and hepatomegaly. Infections are mostly self-limiting except in Immunosuppressed people and pregnant women. Pregnant women with HEV are at high risk of developing acute liver failure, with high rates of mortality (15–25%), stillbirth and miscarriage. There is also high risk of vertical transmission to the foetus which contributes to pathology [2,4–7]. Immunosuppressed individuals, particularly organ transplant recipients with HEV are at high risk of complications such as chronic hepatitis and cirrhosis [8,9]. HEV infection is also a recognised contributing factor to liver cancers such as hepatocellular carcinoma [9].

HEV belongs to a single serotype but there are 4 main genotypes: genotypes 1 and 2 infect only humans while genotypes 3 and 4 are zoonotic in nature and infect several mammals such as pigs, rabbits, rats and deer, as well as humans [10–12].

Genotype 1 is predominantly found in North Africa and Central and South Asia; genotype 2 in West Africa and Mexico; genotype 3 has a worldwide distribution while genotype 4 is mainly found in Asia and Europe. HEV is generally considered a waterborne disease in developing countries, transmitted by poor sanitation and faecal contamination of water supplies [10,13–15]. In developed countries it is primarily a zoonotic disease and transmission is by consumption of undercooked infected meat, especially pork [16–18].

Over the past 30 years, clinical cases of HEV have been identified more frequently [10,15,19–21]. In developing countries this has manifested as large outbreaks of increasing frequency due to HEV 1 & 2. The majority of these outbreaks occur in Asia (59%) and Africa (39%) while Latin America accounts for the remaining 2% [15,22]. There is abundant evidence that Hepatitis E is an emerging zoonotic disease in developed countries. Epidemiology has shifted from travellers returning from endemic areas with acute HEV 1 & 2 to local zoonotic transmission of HEV 3 & 4, associated with eating undercooked or raw pork, wild boar or deer [23–25] [16,18,26–36]. A recent surveillance report recorded an increase in the number of confirmed HEV cases in Europe from 514 cases in 2005 to 5617 cases in 2015 [37]. It is unclear if this represents a true rise in HEV incidence or an increase in detection of cases due to growing awareness and testing for HEV.

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Despite its recognition as an emerging disease, HEV remains neglected in terms of public health awareness and funding. Both Hepatitis A virus (HAV) and HEV have been obscured by the precedence of hepatitis B and C infections at global, regional and national level. Despite significant gains in the fight against HBV and HCV, the global burden of liver disease caused by enteric hepatitis viruses has not subsided [38]. Unlike hepatitis B for which universal vaccination has been implemented by WHO, there is no recommended vaccine for HEV [39]. The recently developed HEV vaccine 'Hecolin' is only licensed in China and has not been recommended for routine use by WHO due to inadequate information on safety and efficacy in paediatric and geriatric populations [10].

In a previous systematic review of the epidemiology of HEV in Africa [13], a third of the publications were from North Africa. Results from North Africa dominated the narrative for several aspects of HEV epidemiology and may not accurately reflect the situation in Sub Saharan Africa (SSA). SSA accounts for 14–15% of all infections, clinical cases and deaths from HEV. However, SSA contributes a disproportionately high number of stillbirths at 29% with a low average age of infection (15.5 years) compared to the global average (17.7 years). Although the North Africa region also accounted for 14% of all global infections, it only contributed 8% of symptomatic cases and deaths with a very low average age of infection (8.1 years) [2]. These figures illustrate clearly that HEV infection profiles differ across the African continent and that the epidemiology and burden of HEV in SSA have not been fully described. SSA must, therefore, be considered separately to determine the current situation of the disease.

This review therefore seeks to answer the following research questions by a systematic review of literature on HEV in Sub Saharan Africa: (1) What is the evidence for the burden of HEV in SSA? (2) What are the gaps in our knowledge of HEV epidemiology in SSA? (3) What is the evidence for sources of infection?

2. Methods

2.1. Literature search and selection

This review was prepared according to "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines [40]. The search was focused on peer-reviewed journal articles specifically on HEV epidemiology. Individual countries were used in multiple searches rather than SSA because this proved to be much more efficient in retrieving publications. The search included papers in all three major languages in SSA i.e. English, French and Portuguese. "Sub-Saharan Africa" as used here refers to all countries of Africa lying south of the Sahara excluding the five north African countries, specifically Algeria, Egypt, Morocco, Tunisia and Libya. No search limits by any filter tool or year of publication was applied during the search carried out in December 2018.

2.2. Inclusion and exclusion criteria

Only peer-reviewed journal articles reporting HEV diagnostic testing, seroprevalence, outbreaks, genotype, risk factors or transmission routes in SSA were included. Studies on both human and animal populations were included. Case reports, review articles, studies on molecular genetics and mathematical models were excluded. These inclusion and exclusion criteria were applied to the titles, abstracts and full texts of all retrieved articles to arrive at the final set of articles from which data was extracted. There is a lot of information on outbreaks and surveillance in grey literature that is not included in peer-reviewed publications. Despite this wealth of information, grey literature is often difficult to access and access is not uniform across all countries. Therefore, the authors have chosen not to include it in this review. We acknowledge the fact that this exclusion may represent a bias of information in this review. Both Google Scholar and PubMed databases were searched using the following search terms ("Hepatitis E" OR "Hepatitis E virus" OR "HEV") AND ("Country name").

2.3. Data extraction

The following data were extracted from the selected articles: the country of origin of study; year in which the study was conducted (where this was not available the year of publication was used); study subjects; sample size; HEV diagnostic test; prevalence/seroprevalence of HEV the genotype of HEV involved; risk factors associated with HEV infection and direct evidence of sources of infection.

3. Results

3.1. Article selection

A total of **277** original research articles were retrieved from PubMed and Google Scholar after duplicates were removed. Titles and abstracts of these **277** records were screened based on the inclusion and exclusion criteria; **83** were included and **144** excluded. The full text of the **83** eligible articles were further screened applying the inclusion and exclusion criteria; **79** were included and **4** excluded. Data from the **79** eligible articles were then extracted into a structured form in excel and summarized in the main text. **Fig. 1** summarizes the steps involved in the literature search and selection process. (See Tables 1 and 2.)

3.2. Data sources

Data came from 79 publications in 25 out of 49 countries in Sub Saharan Africa. The publications were well distributed amongst countries in East and central Africa, but several countries in Southern and West Africa were not represented at all as shown in Fig. 2**.** The highest number of publications was from Uganda (9) followed by Sudan (8), Ghana (8) and Nigeria (8).

Publications included 58 (76%) surveys and 18 (24%) outbreak reports. The majority of the surveys were prospective studies (38) while 18 were retrospective studies on archived samples. There were equal numbers (7) of case-control and cohort studies amongst the surveys. Also, 4 case-control studies were reported during HEV outbreaks. Over a third of studies (28) were on patients with liver disease, mostly indicated by jaundice. There was also a heavy bias towards studies on specific populations such as pregnant women (13 studies), children (5), pig handlers (6), blood donors (6) and HIV patients (8). Most studies did not disclose whether samples sizes were calculated or not; only 10 studies reported details of their sample size calculation and 6 stated the use of a convenience sample.

Serological methods (ELISAs) were used in 73 studies to diagnose HEV infections by detection of anti-HEV antibodies IgG and/or IgM class. A named ELISA was used in 35 studies whereas others did not specify what test was used. Various commercial and proprietary were used with varying sentivity and specificity. However, the assay from Wantai Biological Pharmacy (12) was the most widely used, followed by Abbott Diagnostika (8), Diagnostic Bioprobes (5) and MP Diagnostics (5). Only two studies reported the use of a rapid detection test [41,42].

Molecular detection methods in addition to serology were used in 15 studies while molecular methods only were used in 5 studies [43–47]. Reverse -transcriptase PCR targeting HEV ORF 1 and 2 was the predominant method, with subsequent phylogenetic analysis. Molecular methods were mostly run on a subset of available samples as a confirmatory test.

Overall seroprevalence of HEV in sub-saharan Africa ranged between 0.4% in a random community sample in Nigeria to 100% in displaced persons from Sudan and Chad. Generally, levels of IgG which indicates previous exposure to HEV were much higher than levels of IgM which indicates active or recent infection. However, very high seroprevalence of IgM was recorded in outbreaks in camps for refugees and internally

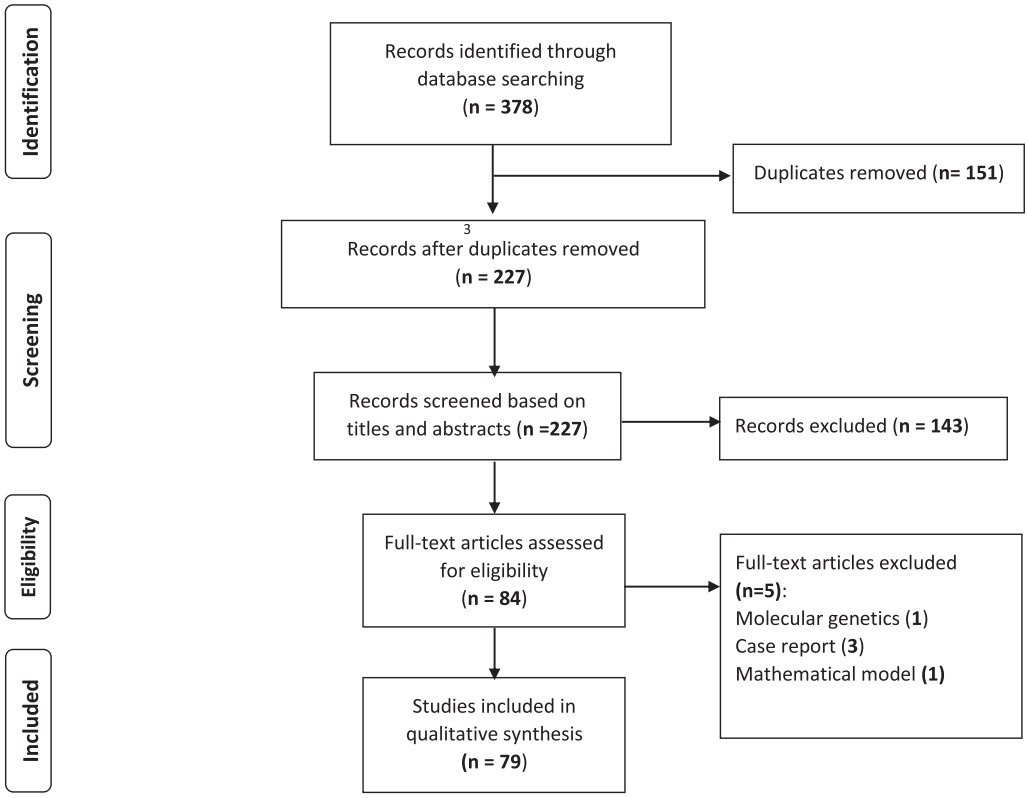

Fig. 1. literature selection process.

Table 1
Case Fatality Rates from Hepatitis E.

Country	Study	Population	Sample size	CFR	Citation
Chad	Outbreak Survey	HEV hospitalised patients	39	23%	[42]
		Pregnant women	15	20%	
Nigeria	Outbreak Survey	HEV case patients	148	1.40%	[41]
CAR	Outbreak Survey	HEV case patients	222	1.80%	[103]
		Pregnant women	5	20%	
Uganda	Outbreak Survey	Acute jaundice syndrome patients	347	2.00%	[84]
Uganda	Outbreak Survey	Jaundice cases	1359	2.20%	[85]
		Pregnant women	23	65.20%	
Uganda	Outbreak Survey	Jaundice cases	>10,000	1.50%	[105]
Kenya	Outbreak Survey	Acute Jaundice Syndrome patients	339	2.90%	[49]
Sudan	Outbreak Survey	Acute hepatitis E patients	147	6.80%	[98]
Sudan	Prospective Survey	Pregnant women with acute hepatitis	16	18.80%	[79]

Table 2
Seroprevalence rates in different groups.

Population	Seroprevalence (%)	Range (%)
Pigs	64.0	47–80
Pig-Handlers	30.5	15–76
Pregnant women	19.8	0–85
Blood donors	18.2	0–49
children	14.6	2–25
HIV	21.5	5–68
Jaundice/Hepatitis	55.9	3–100
Healthy	18.0	0–48

displaced persons from Somalia and Sudan [48,49]. Genotyping results from molecular studies reported genotypes 1, 2 and 3 in humans and genotype 3 in pigs as shown in Fig. 2. There were no reports of HEV genotype 4 in SSA.

3.3. Pigs and pig-handlers

HEV in pigs was investigated in 10 studies from 9 countries. High HEV seroprevalences between 47% - 80% was recorded in 5 studies [50–54]. Prevalence of active infection by RT-PCR was reported in 7 studies: very low levels (0.9–1.2%) in liver samples [43,51]; 2.5–77% in stool samples [44–46,52] and 12.5% in serum samples. Nigeria (77%), recorded a significantly higher prevalence than in all other countries. All genotyping studies reported HEV type 3 in pigs, clustering with either Asian [43,46,52] or European strains [44,45,55].

Pig handlers were investigated in 7 studies from countries with high pork production and consumption (Ghana, Burkina Faso, Uganda, Madagascar, Nigeria) [51,53,54,56–59]. Sero-prevalence in this population ranged from 15 to 76%. 3 studies recorded significantly higher seroprevalence in pig-handlers (37%, 67%, 76%) than in the general population (15%, 47.9, 48% respectively) as well as high seroprevalence in pigs (80%, 85%) [53,54,59]. Unfortunately, no molecular studies have been done in pig-handlers to confirm infection with zoonotic strains of HEV.

3.4. General population

Overall, 21 studies reported HEV seroprevalence in healthy members of the general population, mostly comprising the control group in case-control or cohort studies. IgG seroprevalence was 2.7–47.8%, while IgM ranged from 0 to 34% (studies which did not differentiate IgG from IgM

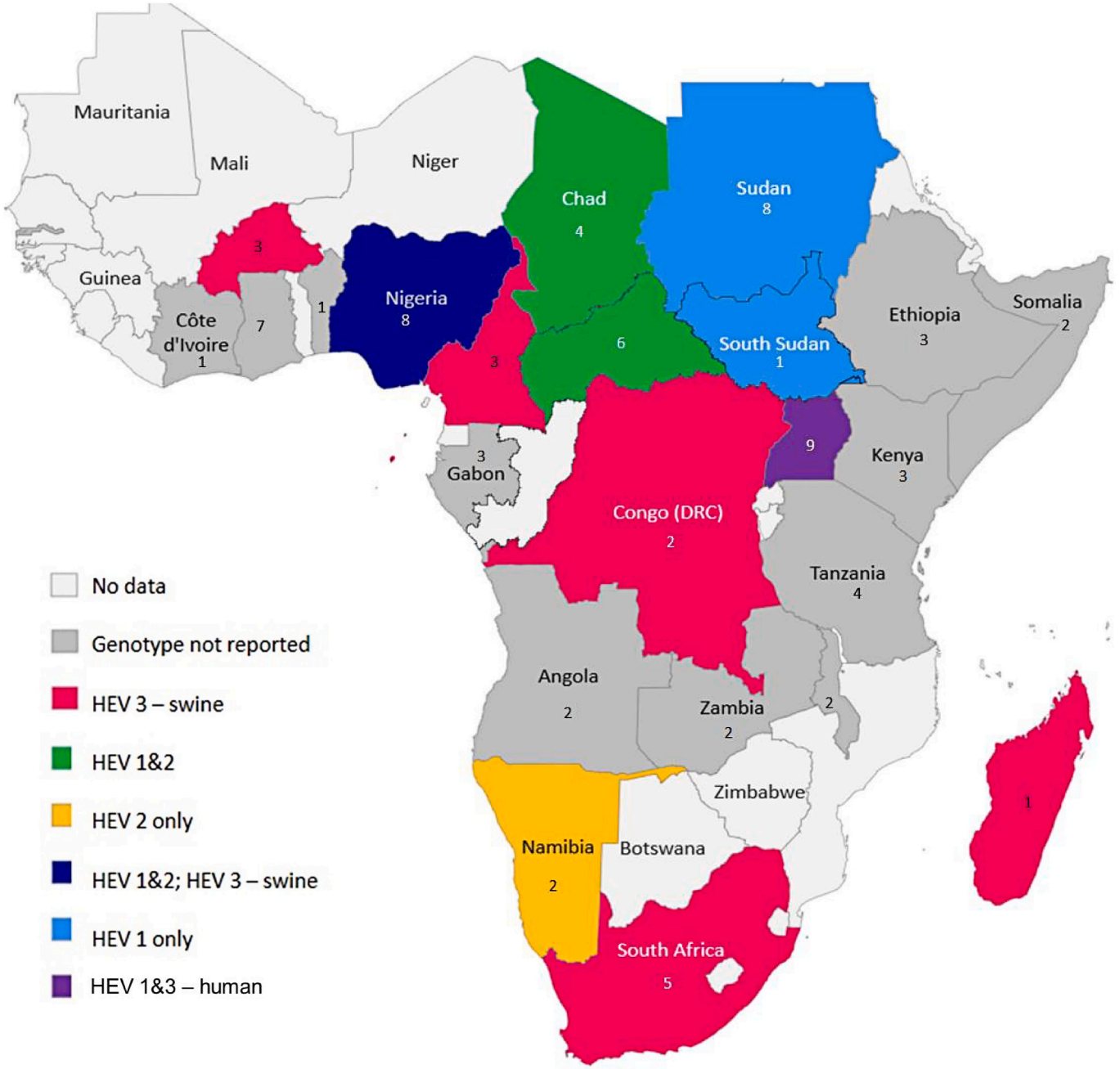

Fig. 2. Distribution of HEV publications and genotypes and in Sub Saharan Africa.

were excluded from this analysis). Exposure to HEV has been recorded in all studies indicating that HEV is endemic in SSA. Active infection was not recorded in all studies.

Of the studies in the general population, 7 were on blood donors with IgG seroprevalence ranging from 4.6–47.8%. IgM seroprevalence and therefore risk of HEV contaminated donor blood was 3.1–5.9% [53,60–64]. Also, 3 of the studies were from Burkina Faso which showed a significantly higher prevalence than other countries increasing over time (19% in 2012 to 40% in 2014).

3.5. Pregnant women

There were 17 studies on pregnant women from 11 countries across SSA, reporting seroprevalence of 0–85%; 5 also reported RT-PCR prevalence of 0–100% [65–68]. In healthy pregnant women, a seroprevalence of 0–43.3% was reported in 12 studies and RT-PCR prevalence of 0% in only 1 [59,60,65,69–77]. In pregnant women with hepatitis, a seroprevalence of 10–85% was reported in 5 studies and RT-PCR prevalence of 28.6–100% in 2. However, sample sizes in these studies were quite small, ranging from 2 to 39 [65–68,77–79].. Amongst pregnant women with HIV, HEV seroprevalence of 7–8% was recorded in 3 studies while RT-PCR prevalence of 0% was recorded in 2 [66,68,72].

3.6. Age

There were four studies investigated HEV in children [68,80–82]. Seroprevalence ranged from 1.1% in Malawi [68] to 25.4% during an outbreak in Uganda [81]. The various age ranges quoted as risk factors for HEV are consistent with young adults being at highest risk of HEV [55,69,70,74,75,83–85]; [86] [53].

4. HIV patients

Investigations in people living with HIV were conducted in 9 studies in 8 countries [59,66,68,72,87–91]. Seroprevalence ranged between 2% in Cameroon [87] and 68% in Central African Republic [88]. All subjects were negative by RT-PCR except for a single case of zoonotic HEV type 3 in Uganda. In 2 cohort studies, no significant difference was reported in HEV prevalence between people with and without HIV [90,91]. In contrast, both Furukawa et al. [64] and Jacobs et al. [82] found that HIV infection significantly increased the likelihood of HEV infection. Caron et al. [72] found that HIV viral load was significantly higher in pregnant women testing positive for anti-HEV IgG (1.3E+05 vs 5.7E+04 copies per ml; $p \leq 0.02$).

4.1. Outbreaks

A total of 20 outbreaks were recorded in 9 countries across SSA: Chad, Nigeria, Central African Republic, Ethiopia, Kenya, Uganda, Namibia, Sudan, and Somalia. East Africa had the highest number of outbreaks with 8 from Uganda and 4 from Sudan. Of all the outbreaks reported, 50% occurred in refugee/IDP camps from countries with significant conflicts: Angolan, Sudanese and Somalian refugees in Namibia, Chad and Kenya respectively as well as IDPs from Sudan, Uganda and Nigeria [41,48,49,55,83,84,86,92,93].

Of the 20 outbreaks reported, only 3 investigated the source of infection. During an outbreak in Uganda caused by HEV 1, Teshale [55] tested both pigs and water sources. Water sources were negative and pigs tested positive only for HEV 3. However, infection patterns at household levels pointed strongly to person-person transmission. Other studies found HEV1 in surface water and hand rinses [47,83].

4.2. Clinical cases and mortality

HEV in people with hepatitis or febrile jaundice was investigated in 28 studies. The number of hepatitis cases attributed to HEV (based on IgM) ranged from 5.4–100% in sporadic cases [65,77–79,94–102] and 14–100% in outbreaks.

HEV is clearly responsible for a significant proportion of hepatitis cases in SSA. However, there are several other infectious agents that could cause outbreaks of febrile jaundice, including Yellow fever and Hepatitis A, B and C viruses. Gadia et al. screened cases of febrile jaundice for viral pathogens in CAR and found no cases of yellow fever. The predominant pathogens were hepatitis B (30.9%), hepatitis E (20.2%), hepatitis C (12.3%) and malaria (8.2%). A similar study in DRC [101] also found no Yellow Fever but several cases of HBV (24.6%), HAV (16.7%), HEV (10.4%) and HCV (2.3%). A third study found that HEV was responsible for 38% of febrile jaundice cases while Yellow Fever caused 64% during an outbreak in Darfur [102].

Data on mortality from HEV was sparse, reported only in outbreaks and studies on pregnant women. A mortality rate of 1–2% was recorded in the general population [41,49,67] and 20% mortality in pregnant women [42,79,85,103]. Notable exceptions were a general mortality rate of 23% during an outbreak in Chad [42], 65% mortality in pregnant women [85] and 13% mortality in children under 2 years [104] in outbreaks in Uganda.

4.3. Risk factors

Multivariate analysis was conducted in 32 studies to determine risk factors associated with HEV infection. The majority of studies cite increasing age [59,64,82], particularly young adults between the ages of 15 and 35 as having the highest risk of HEV infection [53,75]. Teshale et al. [104] reported that children 0–2 years old had a high risk of mortality from HEV despite being generally asymptoamtic.

Several water and sanitation issues were cited as risk factors for HEV infections, including drinking untreated water [85,86,106], river/surface water [55,59,97], well water [59,107] and even piped water where it is prone to contamination [56].

Issues of hygiene such as not washing after toilet use [75], communal hand washing [83], storing water in open mouth vessels [83], not washing utensils [85], open defaecation [59], eating road side food [85] and not washing vegetables before consumption [59] were also risk factors for HEV.

Several studies demonstrated zoonotic links to HEV, citing contact with pigs and their carcasses [54,56,58,59,107]; and eating pork [107,108] as significant risk factors for infection.

Predisposing conditions such as Hepatitis B [90], alcohol consumption [56] and alchoholism [59] which have negative effects on liver health were cited as risk factors for HEV infection along with HIV [64,82]. In pregnant women, being in the third trimester of pregnancy [70], being over 25 [69,74] and having 2–3 children already [74] were significant risk factors for HEV.

During outbreaks, contact with patients and attending patient funerals [55,84]' [42] significantly increased chances of contracting Hepatitis E. Location and gender were context-specific risk factors for HEV infection. Both urban [73] and rural residents [59,75,106] were considered at high risk for HEV infection in different settings; Similarly, depending on the context, males [88,90,109] and females [55,64,98] had the highest risk of HEV infection.

5. Discussion

Data is missing from ~50% of counties in SSA. It is not clear whether or not HEV is endemic in these countries or simply not diagnosed/reported. It is possible that data on HEV exist in these countries in grey literature. However, this review did not include grey literature, therefore these results may be biased against countries where HEV reports have not been published in peer-reviewed journals.

Despite these gaps, research and publications on HEV have increased steadily over the past decade in SSA (Fig. 3). There were several retrospective studies on archived samples from past non-A/non-B hepatitis outbreaks. As HEV tests become more widely available, researchers are applying them to these archived samples and making retrospective HEV diagnoses. However, there are some limitations to the available literature. Firstly, the majority of studies were done on specific groups, with a great deal of variety in the settings and selection criteria. This may have introduced significant bias to the results of this review. However, a good number of these were case-control or cohort studies which also present data on the general public. Therefore we believe that this review provides balanced information on at-risk groups as well as the general population. Secondly, as there is currently no diagnostic gold standard for HEV, several different commercial and proprietary diagnostic tests were used. Thirdly, different criteria were used in the definition of clinical hepatitis cases. This makes it difficult to make direct comparisons between the different studies and countries within the region. Finally, several of the surveys lacked clearly stated, robust sample sizing and selection.

HEV is generally considered a waterborne disease in developing countries and a zoonosis in developed countries. However, there is little concrete evidence for either transmission pathway in SSA as sources of infection were rarely investigated. Numerous studies in Asia provide concrete epidemiological and molecular evidence implicating contaminated water, contact with swine and consumption of undercooked pork as the source of HEV cases/outbreaks [14,15,110–112]. More studies on identifying sources of infection will add to our knowledge of HEV transmission in SSA and build capacity for fast and effective intervetions during outbreaks.

HEV is mostly diagnosed by serological means in Sub Saharan Africa. Molecular methods were used in less than 20% of studies, for confirmation and phylogenetic analysis rather than surveillance of circulating genotypes. Anti-HEV IgG is a marker of past exposure to infection while the presence of IgM indicate recent or current infection [64]. However,

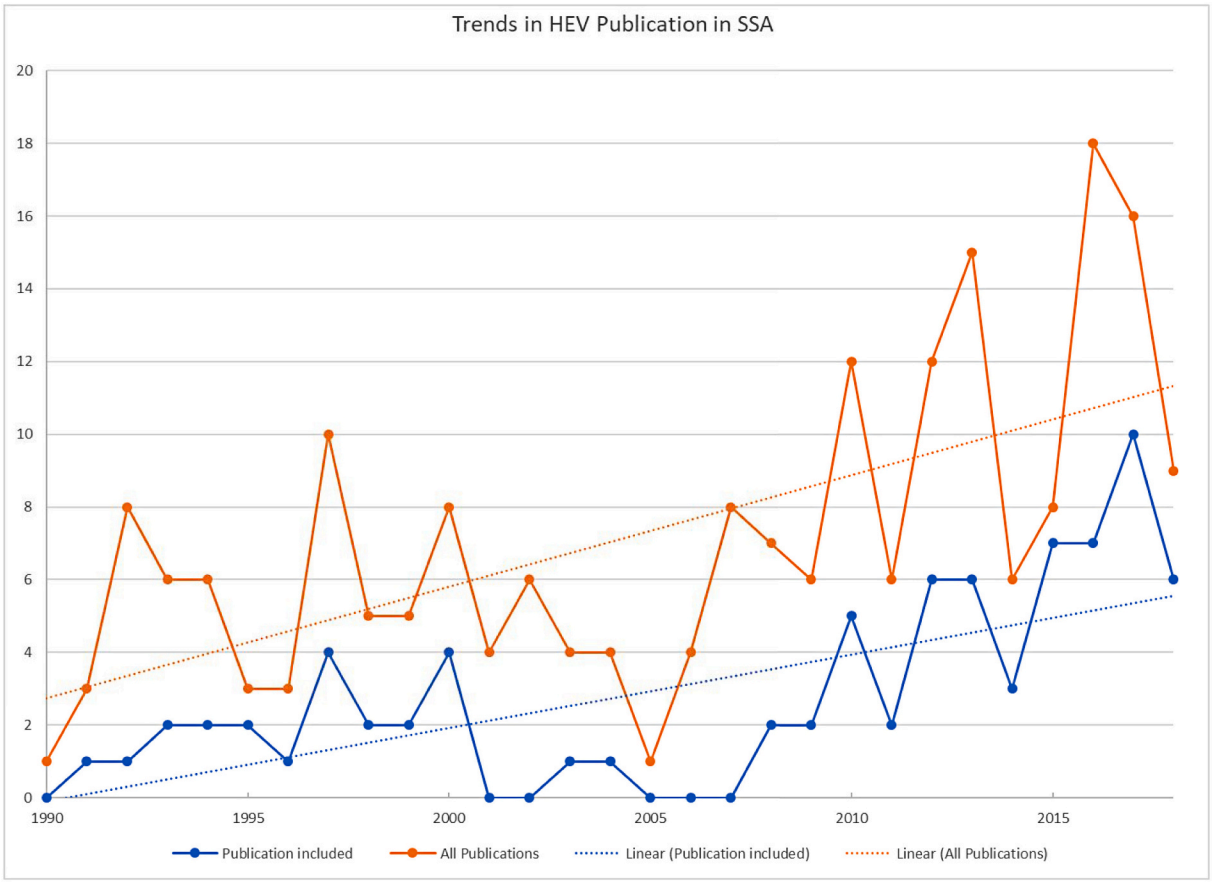

Fig. 3. HEV publications in Sub Saharan Africa.

in many instances ELISAs measuring IgG only were used, giving an estimate of previous exposure to HEV only. Determination of actual prevalence of active infection relies on the use of IgM or molecular methods to detect the presence of the virus. In several instances, ELISAs measuring total immunoglobulin were also used, which are difficult to interpret.

The differences in sensitivity and specificity of the various assays used leads to significant differences in HEV seroprevalence. Thus reported HEV seroprevalences may be inaccurate and direct comparison between different studies, countries and settings is not possible [113–115]. A validated gold-standard method is required to standardise HEV diagnosis [116]. The 'Beijing Wantai' assay was the most commonly used in HEV studies in SSA. It has been validated in several studies and shows a higher sensitivity compared to most other commercial assays without any loss of specificity [117–119] [120] [121–123] and remained positive for longer post infection [121] [124,125].

IgM rapid test kits for Hepatitis E have been developed by Beijing Wantai and MP Diagnostics and show high sensitivity (92.6%, 96.1% respectively) and specificity (100%) [126] comparable to ELISAs [127]. They are easy to use and give rapid results for ongoing HEV infections. Only two studies in this review mentioned the use of rapid test kits. Although they are not yet widely used in Sub Saharan Africa, they would be very useful for point of care testing, particularly for pregnant women and during outbreaks [127].

Results show significant risk (up to 6%) of HEV contaminated donor blood and subsequent transfusion-transmission of HEV in certain countries. Donor blood is routinely tested only for HIV and Hepatitis B & C in most African countries [61]. So far, the presence of the Hepatitis E virus in donor blood has not been confirmed by RNA detection. This needs to be done to more accurately assess the risk of blood transfusion as a transmission route for HEV in SSA. Donor blood could be routinely screened for Hepatitis E virus and other transfusion-transmitted infections using minipool Nucleic acid testing (NAT) [128].

Intrauterine foetal deaths, maternal deaths and preterm deliveries, stillbirths were common outcomes of acute HEV hepatitis in pregnant women in SSA [67,78,79]. Pregnant women had almost ten-fold mortality rate compared to other populations. This is consistent with findings in other endemic regions. However, despite the danger there is quite low awareness and clinical suspicion of HEV at primary health care facilities in SSA. It would be advisable to include increased awareness and diagnostic kits for Hepatitis E in routine ante-natal care in high-risk settings. This will ensure early detection and better management of infection, consequently reducing foetal and maternal mortalities.

HEV seroprevalence was low in children and increased with age acros SSA, consistent with epidemiological trends in other regions [129]. Unusually high mortality (13%) was reported in children below the age of two during a large outbreak in Uganda. A similar occurence has been reported previously in a large 1985 HEV outbreak in Uzbekistan [130].

It has been clearly demonstrated that immunosupressed individuals with conditions such as solid-organ transplants, auto-immune hepatitis and HIV are at significant risk of chronic Hepatitis E infection [124,131,132]. This review presents evidence both for and against HIV infection as a significant risk factor for HEV in Sub Saharan Africa. However, the only reported case of zoonotic HEV type 3 from Africa was in an HIV positive individual. It is thus possible that HIV is a predisposing factor for zoonotic HEV infections [90].

Pigs had very high HEV seroprevalence rates in SSA as found in other regions [18]. Genotyping results reported only HEV genotype 3, with no occurrence of HEV 4. Several studies employed RT-PCR for detection of Hepatitis E virus in pigs. However, several different samples were used

(stool, serum, liver tissue) making the prevalence results difficult to interprete or compare. A small number of studies also investigated HEV in people with occupational exposure to pigs and pork. These were from countries with high pork production and consumption (Ghana, Burkina Faso, Uganda, Madagascar, Nigeria) and showed clear evidence of increased HEV in pig handlers compared to the general population suggesting zoonotic transmission in SSA. However, as with the case of water-borne outbreaks, there is scant molecular evidence to prove that transmission of HEV from pigs to humans occurs. This was investigated in just one (1) study [55] which demonstrated that the HEV outbreak was due to genotype 1 and not genotype 3 which was circulating in local pigs.

In Uganda, there is a rapid increase in pig production as a result of increasing pork consumption. Total pork consumption has increased more than 20 times in the past 50 years [133] and is estimated to increase by 185% over the next 30 years from 2000 [134]. Likewise, in Ghana pig production has increased at a rate of 10.5% annually over the last 15 years, however demand still exceeds domestic production by 20% [135,136]. Total annual consumption is projected to increase by more than 1000% across SSA between 2000 and 2030 [134]. As contact with pigs and consumption of pork increase subsequent studies should address this limitation to establish the risk of zoonotic transmission associated with these occupationally exposed groups in SSA.

HEV outbreaks seem to occur irregularly, focused on a few countries, mostly in East Africa. Conflict zones and refugee and IDP settlements play a significant role in the epidemiology of HEV outbreaks, accounting for 50% of reports in this review. Such settlements tend to be overcrowded with limited water and sanitation facilities. Outbreaks are associated with a breakdown in sanitation facilities and contaminated water supplies, often related to flooding or drought. Additionally the impaired health status of residents as a result of poor nutrition make them vulnerable to disease [92].

HEV outbreaks also spread with displaced populations: In 2004 there was a large outbreak of Hepatitis E in Darfur with over 4000 cases [86,92]; A substantial population of Darfur residents fled to Chad which subsequently experienced outbreak of over 1000 cases amongst Sudanese refugees [48]. In 2017, a widely dispersed outbreak of HEV was reprted across the Lake Chad region comprising parts of Niger, Nigeria, Chad and Cameroon. The area shares the common wetlands resource of Lake Chad and surrounding communities in all four countries are linked by trade routes, conflict and displacement related to cattle rustling and the Boko Haram terrorist group. The region is dotted with refugee camps, some with tens of thousands of people [137–140]. The outbreak was first noted in Niger in January 2017 and was still in progress in June. By this time, Nigeria also reported an outbreak close to the borders with Niger and Cameroon [41]. These twin outbreaks involved over 1300 cases, with new cases still being recorded in December 2017 [140]. These outbreaks take a massive toll on some of the world's most deprived people. The emergency response community feel that the response is inadequate and reflects the shortage of global research into HEV, particularly in humanitarian settings [140]. This view is supported by calls for HEV to be recognised as a neglected tropical disease. The burden of the disease, combined with relative neglect by the public health, research, and clinical communities and limited options for treatment and control, fulfill all the requirements for inclusion in the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases list of recognised NTDs [141]. This classification would bring additional dedicated public health and research resources in addition to increasing general awareness in the health community and beyond.

Urban settings were also implicated in HEV transmission and outbreaks [42,54,73,82]. Slum areas suffer equally from overcrowding and poor water, sanitation and hygiene (WASH), mostly due to unplanned urban expansion and inadequate infrastructure. SSA currently has the highest annual urban population growth rate (4.1% compared to the global average of 2.0%). As of 2014, 55% of the SSA urban population were living in slums. When rapid urbanization is poorly planned and occurs in the context of existing widespread poverty, it has negative effects on all aspects of health, but particularly diseases related to WASH. Proper urban planning can be a valuable source of achieving sustainable economic growth and urban health [142].

6. Conclusion

These data show clearly that HEV is endemic in Sub Saharan Africa and is responsible for a significant proportion of hepatitis cases and a high rate of poor outcomes (including mortality) in pregnant women. The true burden of active infection is difficult to estimate as most studies focused on serological evidence of exposure. There is still little concrete evidence for sources of contamination and the risk of zoonotic HEV transmission in SSA. This data is of great importance in developing effective intertervention strategies against Hepatitis E.

Hepatitis E is currently considered an emerging disease by many in the public health community. It is very likely that it will continue to rise in both prevalence and distribution across sub saharan Africa.

Contributing factors include conflict and displacement, urbanization and increasing demand for pork across the continent.

HEV epidemiology in SSA raises concerns considering the low priority of the disease as a public health threat and the complexities of transmission [19].

We recommend that the risk factors emphasised in this review be used to develop information and educational programs in the relevant high risk areas to increase awareness of HEV. Secondly, that routine screening and surveillance for Hepatitis E be established for blood donors and and pregnant women as an integral part of blood donation and ante-natal clinics.

Authors contributions

Conceptualisation: HB, AOM, SCW; Data collection and analysis: HB, AOM; Manuscript preparation: HB, AOM; Manuscript review and editing: AOM.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.onehlt.2020.100186.

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