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Research Article

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Seroprevalence and Associated Risks of Hepatitis E Virus Infection in An Epidemic Context in The Region of Kédougou, Southeast Senegal

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Abstract

Rapid proliferation of traditional gold mining sites in Kédougou a Southeast region in Senegal, led to mass population migration from the neighboring West African countries and rapid expansion of small mining villages with poor hygiene and sanitation conditions. An outbreak of hepatitis E was reported in 2014 with several cases of febrile jaundice among traditional mine workers. In this study, we analyzed both HEV IgM and IgG seroprevalence and the associated risk factors of infection by testing any suspected case and contacts collected from February 2012 to November 2014. RNA-negative sera from suspected cases and contacts were tested for anti-HEV IgM and anti-HEV IgG. A total of 799 sera were collected from 290 suspected cases, 470 contacts and 39 individuals with missing information. The median age of the cohort study was 19 years (1-88 years) with a male/female sex-ratio of 1.9. We found an overall prevalence of 43.68% (331/760) of anti-HEV IgM and 33.02% (251/760) of anti-HEV IgG sera. Our data provide new insights into the HEV epidemiology and point to the crucial need to estimate the disease's burden in Kédougou and assess the viral mechanisms driving the disease's severity in pregnant women.

Keywords: Hepatitis E Virus; seroprevalence; risk factors; mining gold villages; Southeastern Senegal

Background

Hepatitis E is a widespread disease worldwide and is a serious public health concern. Acute hepatitis E can cause febrile jaundice, asthenia, anorexia, and nausea-vomiting but regresses spontaneously within 4-6 weeks [1]. The disease can progress to fulminant and acute hepatitis infection therefore causing death. Every year there are an estimated 20 million hepatitis E virus (HEV) infections worldwide, leading to an estimated 3.3 million symptomatic cases of hepatitis E. The mortality rate of hepatitis E in humans ranges from 0.5 to 4% [2]. Pregnant women are more susceptible to complicated forms of the disease resulting in a 20% mortality rate in the last trimester[3]. Indeed, there is strong evidence that HEV is a major contributor to maternal morbidity and mortality in Southeast Asia, particularly in pregnant women in the third trimester. This makes HEV infection the most serious of all viral hepatitis in pregnancy [4–5-6].

Serological diagnosis of HEV infection rely on both IgG and IgM antibodies detection by ELISA. IgM antibodies, which indicate a recent

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disease, are detectable from the early symptomatic stages with a maximum peak after a month following the primary infection. This is followed by substantial IgM decrease of IgM from 2 to 6 months at most following the infections [7]. However, IgG antibodies, known to indicate a long-standing infection, become positive shortly after the appearance of IgM antibodies, and can persist for years or even a lifetime 8 . However, serological cross-reactivity has been described between the four HEV genotypes [8–9]. In Sub-Saharan Africa where access to sanitary facilities is limited, HEV is hyper-endemic. Previous HEV outbreaks reported in Chad and Sudan caused over a four-month period, 6861 suspected cases with 87 deaths in Sudan and 1442 suspected cases with 46 deaths in Chad [10] . Epidemics have also been reported in Algeria, Côte d'Ivoire, Ghana, Ethiopia and Somalia [11]. In 2014, an HEV epidemic linked to the rapid proliferation of traditional gold mining sites, was reported for the first time in the southeastern Senegal, with a high impact of the disease among pregnant women [12]. Herein, we investigated the HEV seroprevalence in an outbreak context using serum samples collected from patients with jaundice during the 2012- 2014 epidemic in the Kédougou region [12], to characterize the distribution patterns of serological markers of acute and old infections.

Methods

Ethical Statement

The Senegalese National Ethical Committee at the Ministry of Health and Social Action (MoHSA) has ap-proved our current surveillance protocol. Consent forms were obtained from all adults or parents for minors in-cluded in this study. Field investigations were regularly supervised by the authorities of the MoHSA in Senegal. Additional samples used in this study were collected in the frame of the national integrated surveillance program of fevers in Senegal and were available from the collection of the WHO Collaborating Centre for Arboviruses and Hemorrhagic Fevers at Institut Pasteur de Dakar. All methods including the use of human samples, were performed in accordance with the Declaration of Helsinki.

Study area

The study was conducted in Kédougou, a region located in Southeastern Senegal (12°32’ N,12°11’ W). Insets are obtained from ArcGIS Desktop V10.8.1 (ESRI 2021, Redlands, CA: Environmental Systems Research Institute; https:// desktop. arcgis. com/ en/) and sampling sites are placed on base map using their respective XY coordinates and ArcGIS Desktop (Fig. 1a). The population of Kédougou is of 184,276, 5.1% of whom are under 18 years old, and the average population density is of 8 persons per km213. Kédougou shares borders with the Republic of Guinea and Mali. The climate is Sudano-Guinean with a single rainy season from May to October. Temperatures are gener-ally high with an annual average of 28.4 °C. Agriculture is the main economic activity in the region, but hunting and logging are also source of contact between humans and wildlife [13]. The Gambia River flows through the region and creates during the dry season temporary pools with dense vegetation. Recently, gold mining has become one of the most important economic activities in the region.

Data collection

Following the 2012-2014 HEV outbreak in Kédougou, a retrospective sero-surveillance study was carried out using the previously collected sera [12]. All patients included in this study were working in the three main traditional mining gold villages (Kharakhena, Bantaco, Tenkoto) which are supervised by the health districts of Kédougou and Saraya, respectively. Twelve samples from suspected individuals from the health district of Salemata, a non-gold mining area were included in our study. Epidemiological data retrieved from the database of the virology depart-ment of the Institut Pasteur de Dakar in Senegal, were analyzed in addition to both anti-HEV IgM and anti-HEV IgG serological data. Out of the 1617 sera analyzed by RT-PCR, a total of 1045 tested positive for HEV viral RNA [12]. Of the 906 RT-PCR-negative sera, 799 including both suspected cases and contacts, were selected for evaluation of the sero-prevalence study based on the available volume of sample.

Serological testing

Sera were tested using the IgM ELISA 3.0 (ref: 2P35-01(23160-096) and MP Diagnostics IgG ELISA (ref: 2F09-02(21150-096T) kits according to the manufacturer's procedures (MP DIAGNOSTICS), for the detection of IgM HEV and IgG HEV antibodies. All samples were processed in duplicates.

Statistical analysis

Statistical analyses were performed using R version 4.0.3 (R Corporation). The age distribution by sex was rep-resented by a boxplot showing the age distribution in the two groups, as well as the geographical distribution of the patients. The 95% confidence intervals (CI) were calculated using analysis of variance. Univariate comparison of proportions between groups (age, sex, status, and geographic location) was performed using analysis of variance. To estimate the strength of association, odds ratios (ORs) and associated 95% CIs were used. Variables with signifi-cant univariate associations at a P value < 0.05 were entered into a multivariate binomial regression model. $P<0.05$ or a 95% CI not spanning 1.0 was considered statistically significant for all analyses.

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Results

Study population

Senegal is a West African country where mining activities have emerged over the last years particularly in Kédougou. The large number of undeclared migrants working in the traditional gold mining villages continue to increase (Figure 1-a). The majority among the included patients lived in the Kédougou district (n= 641), followed by the Saraya district (n= 146) and the non-mining gold sanitary district of Salemata (n= 12) (Figure 1-b). Out of the 799 patients included in our study, we identified 470 contacts and 290 suspected cases with 39 patients for whom information was missing concerning these two categories. The median age was 19 years (1-88 years) with a male/female sex ratio of 1.9 (Figure 1-c).

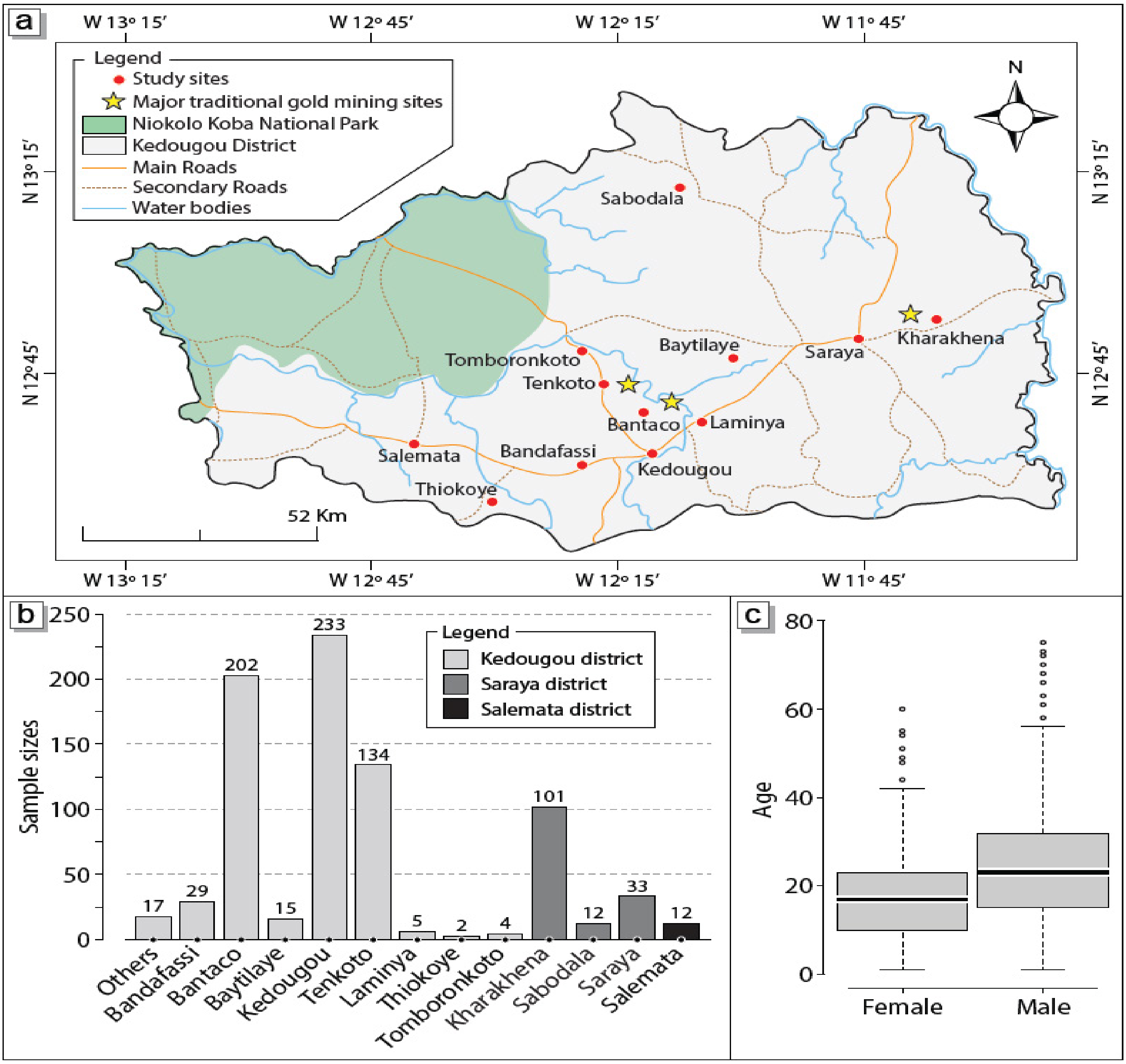

Figure 1: Geographical distribution of included patients. **a)** Kédougou's map is represented. The mining gold villages are highlighted (stars). This work was done in collaboration with the three health districts of Saraya, Kédougou (town) and Salemata. Kharakhena. **b)** 233 individuals residing in the city of Kédougou, 437 gold miners from the three traditional mining sites: Bantaco (n=202), Tenkoto (n=134), and Kharakhena (n=101) were included, while the other patients came from the surrounding villages. **c)** The median age based on the sex ratio (1.9) shows a population with a median age of 19.4 for women versus 24.4 for men.

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In Kédougou district, the villages of Thiokoye (100%, n= 1), Laminya (60%, n= 3), Baytillaye (53.3%, n= 8) and Tenkoto (29.8%, n= 40) had the highest seroprevalences for IgG (p-value= 1.88x10-6). In Saraya district, the highest seroprevalences for IgG were observed in Sabadola village (81.8%), Saraya town (60.6%) and Kharakhena village (47.5%) (p-value= 0.043). In Saraya district and Kédougou district, there was an anti-HEV IgG positivity rate of (53.1%) and (26.3%), respectively. However, in Salemata district, we found that 8 out of 12 suspected patients (66.6%) tested positive for anti-HEV IgG (Table 1). For IgM seroprevalence, the highest seroprevalence was recorded in Kédougou district (220/620). This overall 35,5% recent HEV infections were distributed in Baytilaye (11/15), Thiokoye (1/2), Tenkoto (60/134), Laminya (2/5) and the city of Kédougou (86/233) (p-value= 1.88x10-6). In Saraya district, the highest seroprevalence rates were observed in the villages of Sabadola (91.7%), Saraya (75.8%) and Kharakhena (52.5%) (p-value= 0.043). As for IgG, we found also a high rate of IgM seroprevalence in the Salemata district 10/12 (83.3%) (Table 1). Overall, an anti-HEV igG seroprevalence of 53.1% and 26.3% was recorded in the Saraya and Kédougou districts, respectively while anti-HEV igM prevalence rates of 70% and 35% were found in the Saraya and Kédougou districts, respectively. Of the 8 deaths recorded among the included patients with positive IgM serology, 3 were from the Kédougou district and 5 from the Saraya district. In addition, 50% of these patients included pregnant women (n= 4) (Table 1).

Gender and age distribution of IgM and IgG HEV positive cases

Out of the 331 IgM-positive cases, the active population aged from 16-30 years-old group show the (47.9%) highest recent HEV infections rate, followed by the 15 years old population, the 31-45 years-old group and the age group above 45 years with 25%, 19.6% and 7.5%, respectively (p-value = 0.05592). Table 2 displays the same pattern for old HEV infections rates. Indeed, out of the of 251 IgG-positive cases, the highest rate was recorded in the 16-30 years-old group with 48.2%, followed by the 31-45 years-old group, the age group under 15 years and the and the age group above 45 years with 22.7%, 19.5% and 9.6%, respectively (p-value = 0.05592) (Table 2). Moreover, if we consider gender balance, we found that HEV infections were affecting most likely men than women also see that men with 68.6% vs. 31.4% of IgM-positive and 75.3% vs. 24.7% of IgG positive cases p-value = $4.496x10^{-6}$ (Table 2). Next, we sought to map out the overall distribution of HEV infections.

Table 1: Seroprevalence of IgM and IgG antibodies as well as the number of deaths due to HEV in the normal population and in pregnant women in the districts of Kédougou, Saraya and Salemata

District	Village	Total number of analysed samples	IgG Seroprevalence n (%)	Total number of analysed sample	IgM Seroprevalence n (%)	Death (n = 8)	Pregnant women (n= 4)	P-value
Kédougou	**Bandafassi**	**29**	**8 (27.6)**	**29**	**08 (27.6)**	-	-	$1.88x 10^{-6}$
	Bantaco	202	54 (26.7)	202	52 (25.7)	-	-	
	Baytilaye	15	8 (53.3)	15	11 (73.3)	-	-	
	Kédougou	233	49 (21.0)	233	86 (36.9)	3	2	
	Laminya	5	3 (60.0)	5	02 (40.0)	-	-	
	Tenkoto	134	40 (29.8)	134	60 (44.8)	-	-	
	Thiokoye	1	1 (100.0)	2	01 (50.0)	-	-	
Total		619	163(26.3)	620	220(35.5)	3	2	
Saraya	Kharakhena	101	48 (47.5)	101	53 (52.5)	2	1	0.043
	Sabodala	11	9 (81.8)	12	11 (91.7)	1	-	
	Saraya	33	20 (60.6)	33	25 (75.8)	2	1	
Total		145	77(53.1)	146	89(70.0)	5	2	
Salemata	Salemata	12	8(66.7)	12	10 (83.3)	-	-	
Total		12	8(66.7)	12	10 (83.3)	-	-	
Missing		23		21				
Total		799		799				

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Figures 2a and 2-b showed the risk factors of HEV infection including both suspected and confirmed cases. For both IgM and IgG seroprevalence, we found a similar pattern with patients over 45 years-old, showing a higher risk of developing the disease of 88.8% (n= 24) and 96.15% (n= 25), respectively. However, the 31-45 years-old, 16-30 years-old and under 15 years groups exhibited prevalence of (n= 57) 74.02%, (n= 121) (51.05%) and (n= 49) (24.13%), respectively (Figure 2-a, b). In terms of geographical distribution, the villages of Kharakhena, the 2014 HEV epidemic epicentre, Bantaco and Tenkoto, which are all villages hosting the largest traditional gold panning sites, had more cases developing both IgG and IgM antibodies indicating that the virus was present in the population from 2012 to 2014. This is also the case for Kédougou, which hosts the reference center for the entire Kédougou region (Figure 2-c). Table 3 indicates that out of the 290 suspected cases included in our study, 42.4% (n= 123) tested positive for IgG antibodies. However, the rate of IgM-positive cases was significantly higher (63.8% (n= 185)), (p-value = $2.2x10^{-16}$). The overall prevalence of suspected cases developing both IgM and IgG antibodies at the same time was 37.2% (n= 108). In addition, the same trend was observed among contacts. Among the 470 contacts, 25.3% (n=119) were positive for IgG antibodies (p-value = $2.2x10^{-16}$) while 30% (n= 141) of them were positive for IgM (p-value = $2.2x10^{-16}$) (Table 3). The overall prevalence of contacts developing both IgM and IgG antibodies at the same time had an antibody rate of 14.25% (n= 67).

Table 2: Seroprevalence of IgM and IgG antibodies according to age and sex

	IgM		IgG	
	n (%)	**p-value**	**n (%)**	**p-value**
Age group (years old)				
<15	83(25)	0.05976	49(19.5)	0.05592
16-30	159(47.9)		121(48.2)	
31-45	65(19.6)		57(22.7)	
>45	25(7.5)		24(9.6)	
Total	**331(100)**		**251(100)**	
Sex distribution				
M	227(68.6)	0.01907	189 (75.3)	$4.496x10^{-6}$
F	104(31.4)		62 (24.17)	
Missing	1			
Total	**332(100)**		**251(100)**	

Overlapping IgM and IgG distribution and evolution pattern from 2012 to 2014

The comparative analysis of individuals developing IgM type antibodies as well as those developing IgG type antibodies came from Kharahena (considered the epicenter of the epidemic), Tenkoto and Bantako which are villages that host the largest traditional gold panning sites in the region (Figure 3-a). The commune of Kédougou recorded a significant number of patients with both HEV IgM and IgG antibodies (Figure 3-a). The comparative study of individuals developing both IgM and IgG antibodies over the years showed there was a discrete/silent HEV evolution loci from 2012 to 2013. However, in 2013 there was a rapid expansion of HEV infections in the Kégoudou region leading to the outbreak previously declared from January 2014[20]. Figure 3-b showed that both old and recent HEV infections increased from 2013 with two peaks of infection recorded in February and May 2014, respectively.

Age and gender as risk factors for increased seroprevalence

Statistical analysis has shown that both age and gender are risk factors associated with increased seroprevalence. We can thus observe that the risk is greater in men than in women, with men almost 2 times more likely than women to develop the disease (Supplementary material Figure S1). We can also see that as age increases, so does the risk of contracting the disease. Adults over 45 are the most vulnerable, followed respectively by individuals aged 31-45, 16-30 and children aged 0-15 (Supplementary material Figure S1).

Discussion

In our study, 799 HEV RNA-negative samples were tested for IgM and IgG antibodies which are indicating recent and old infections. With 332 IgM-positive cases versus 251 IgG-positive cases we found despite negative PCR detection a significant IgM/IgG ratio in Kédougou from 2012 to December 2014 as previously reported12. Our IgG

Table 3: recapitulative of the seroprevalence of suspected cases and contacts according to IgM and IgG antibodies and cases positive at the same time for IgM and IgM.

Suspected cases (n= 290)	Number of positive individuals n (%)	p-value
IgG+	123 (42.4)	$2.2x10^{-16}$
IgM+	185 (63.8)	
IgM+/ IgG+	108 (37.2)	
Contacts (n= 470)		
IgG+	119 (25.3)	
IgM+	141(30)	$2.2x10^{-16}$
IgM+/ IgG+	67 (14.25)	

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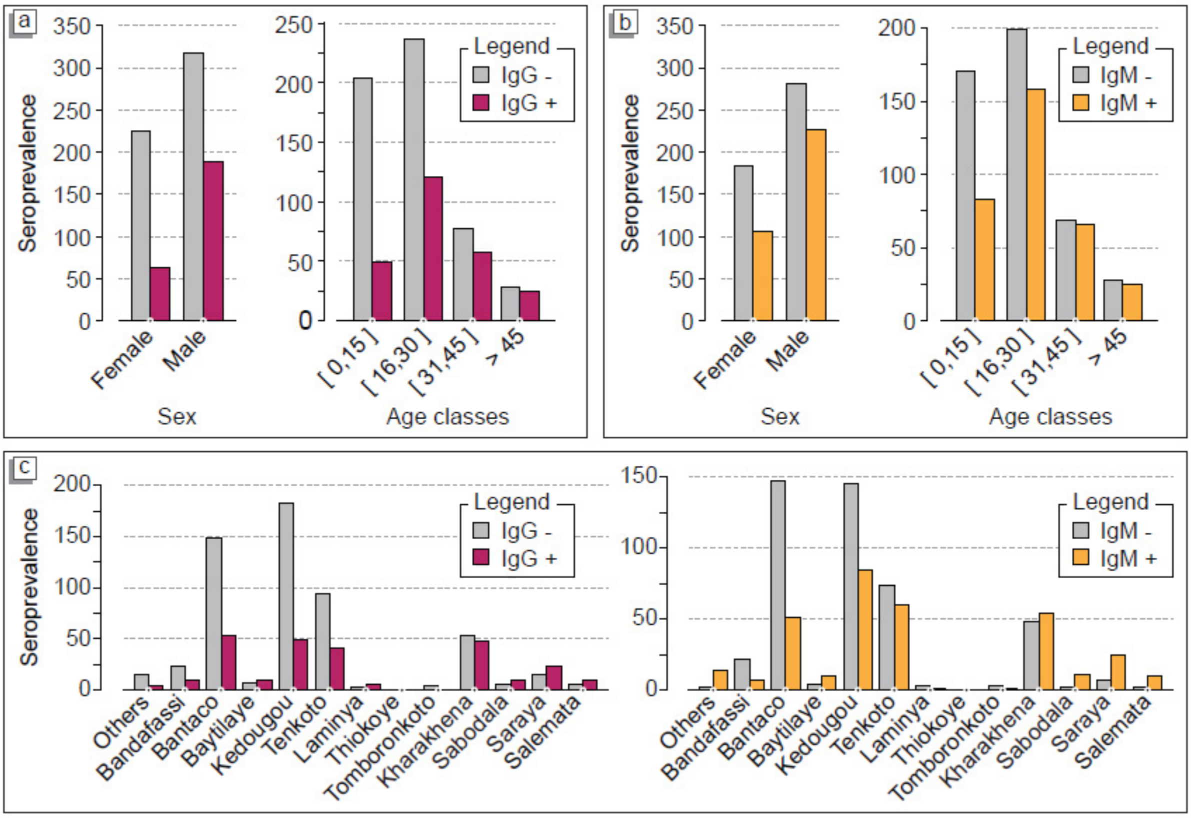

Figure 2: seroprevalence by sex and age and the geographic distribution of IgM and IgG antibodies in the general population (n=799).

serological data shows that HEV was circulating in the region since 2012. This shows that the classical PCR detec-tion method alone is not sufficient to assess the HEV surveillance. ELISA must be coupled with routine PCR detec-tion methods to prevent HEV outbreaks. Our work has shown the impact of human movements from traditional mining gold villages where sanitation, precarious hygienic conditions and access to drinking water are often chal-lenges on HEV expansion. In fact, the highest seroprevalence recorded in the Salemata district could be related to the return of patients from gold mining sites such as Kharakhena, Tenkoto and Bantaco. Seroprevalence and HEV risk associated were found to directly impact males than females with 68.6% versus 31.4% IgM+ and 75.3% versus 24.7% IgG+. These data are similar to those previously reported from Asia14. However, we found that pregnant women are highly susceptible to HEV infection as previously reported4. Thus, training of clinicians and healthcare workers in the Kédougou region in the appropriate management of this disease whose signs in terms of jaundice are reminiscent of yellow fever, could be needed to avoid high mortality rate in this vulnerable group in the future. In addition, clinical monitoring of Senegalese women for HEV during pregnancy and postpartum, especially in high-risk settings as Kédougou, is critical during the last trimester of pregnancy15,16. The fact that the 16-30 years old group was significantly affected by the disease could be due to the routine activities as workers in the traditional gold panning mines as previously reported in Nepal17. In addition, the risk of contracting HEV in people over the age of 45 years may be related to their fragile immunity, which can rapidly deteriorate over the years18. Given the seriousness of hepatitis E, particularly in pregnant women, in Senegal, and more particularly in Kédougou, the hep-atitis E virus must be suspected in the presence of any unexplained acute hepatitis, even if it does not involve travel to an endemic zone and especially if it occurs in a patient over 40 years of age. Although there is no etiological treatment for this disease, vulnerable populations such as pregnant women and the elderly should be particularly vigilant regarding detection and early management in order to avoid high mortality. Although a low seropreva-lence was found in children under 15 years in our study (25% IgM+ and 19% IgG+), more seroprevalence studies could be promoted in children across Sub-saharan Africa, particularly those under 2 years as an unusual high mor-tality (13%) has been previously reported in Uganda19. However, their possible involvement as disease vector to pregnant women could be also assessed. The non-negligible rate of IgM antibodies in contacts could be explained by the asymptomatic nature of the majority of hepatitis E cases in an outbreak20,21 , symptomatic cases

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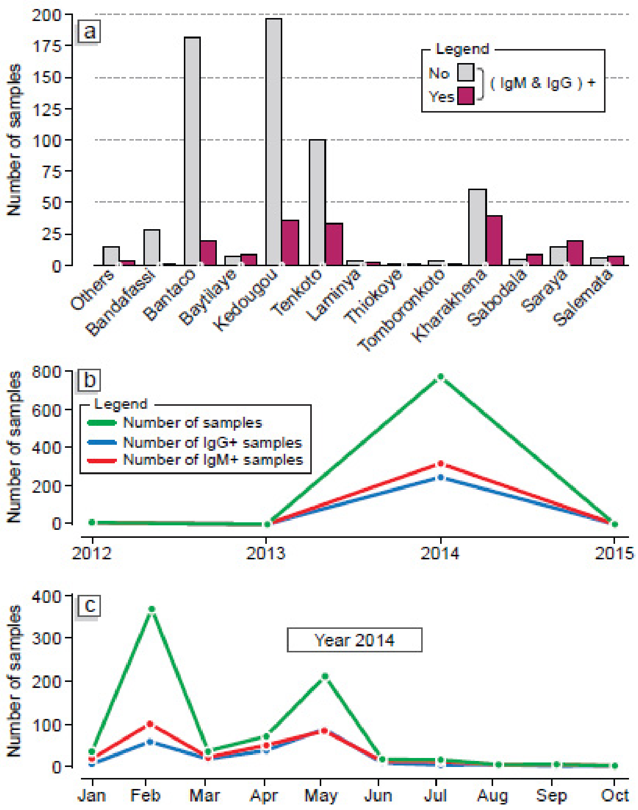

Figure 3: Geographical (a) and Temporal (b and c) distributions of IgM/IgG positive cases from 2012 to 2014 and monthly distribution of IgM/IgG positive cases in 2014.

could have also participated to the progressive spread of the disease in Kédougou from 2012 to 201412, in contrast to the brutal and massive circulation generally reported in HEV epidemics22,23. To evaluate the real burden of future hepatitis E epi-demics, dual testing of suspected cases using both serology testing and real-time PCR could be considered. Given the similarity of HEV to yellow fever in terms of signs, HEV testing should be used as differential diag-nosis. In addition, it is necessary to sensitize the population on the modes of HEV transmission and the usual hy-giene measures such as systematic hands washing after leaving the toilets, before preparing the meal, after contact with live animals or products of animal origin, using clean latrines, covering wells16 Next, it is necessary to supply the population with drinking water in the gold mining sites by installing new boreholes and water purification sys-tems at the household level. Finally, improvement of sanitation and wastewater management systems in gold min-ing sites could be prioritized.

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Data availability

All data were presented in this manuscript. The manuscript was previously presented online in preprint at the following source: https://www.preprints.org/manuscript/202308.1423/v1.

Author Contributions

B.D.S., M.F., A.S., Ous. F., and A.A.S., designed and conducted the study; B.D.S performed the laboratory analyses; B.D.S., A.S., and A.A.S. performed the field investigations; A.G., A.M., B.D.S., M.F., C.T.D., A.S and B.S analyzed and interpreted the data, all authors reviewed the manuscript and accepted the latest version. First authors: B.D.S. and MF. Third authors A.G and C.T.D. Last authors: AM, N.D, A.A.S, AS.

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