

Outbreak

Concomitant outbreaks of yellow fever and hepatitis E virus in Darfur States, Sudan, 2012

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Abstract

Introduction: Yellow fever (YF) is a vector-borne disease transmitted to humans by infected *Aedes* mosquitoes, while hepatitis E virus (HEV) is a waterborne disease that is transmitted through the fecal-oral route. Both diseases have very close clinical presentation, namely fever, jaundice, malaise, and dark urine; they differ in severity and outcome.

Methodology: In this cross-sectional, laboratory-based study, an attempt was made to measure the correlation of concomitant YF and HEV infection in Darfur States during the previous YF outbreak in 2012.

Results: Results found concomitant outbreaks of YF and HEV at the same time with very weak statistical correlation between the two infections during the outbreak period, with Cramer's V correlation 0.05 and insignificant p value of 0.86.

Conclusions: This correlation indicates that clinicians and care providers in tropical areas have to deal with clinical case definitions used for disease surveillance very carefully since prevalence of HEV infection is relatively common and this increases the possibility of misclassification and missing YF cases, particularly initial index cases, in a season or outbreak.

Key words: yellow fever; hepatitis E virus; co-infection; Darfur.

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Introduction

Yellow fever (YF) virus is one of zoonotic *Flavivirus* that is endemic in the tropics of Africa and South America [1]. Its clinical presentation varies from mild flu-like illness to hemorrhagic fever and may lead to death, with a case fatality rate ranging between 20% and 50% [2]. The disease is transmitted by *Aedes* mosquito species and maintained in enzootic cycles, infecting non-human primates (*e.g.*, monkeys). Humans usually acquire the infection accidentally when they are visiting or working in the jungle [1,3]. On the other hand, its urban cycle occurs with the presence of relatively large population living in close proximity to mosquito species (*Aedes aegypti*) capable of virus transmission and outbreak propagation [1,3].

YF is known to have occurred in West, East, and Central Africa, including Sudan, since the 1940s when an outbreak was reported from the Sudan-Ethiopia border. Subsequently, YF spread along the Omo River valley, causing a major epidemic between 1960 and 1962 [2]. In 1989, a serological survey in Merwie and Karima towns in North Sudan that involved patients

with acute febrile illness documented the presence of disease-specific antibodies with possible immunological cross-reaction with Sandfly fever Napels virus [4]. In 2003 and 2005, other outbreaks took place in Imatong, southern Sudan, and South Kordofan State of Sudan, with considerable morbidities and mortalities [5,6]. More recently in 2012 and 2013, a major outbreak occurred in the Darfur region in the western part of Sudan, a region that had never been covered by YF vaccination before [7].

Hepatitis E virus (HEV) is a waterborne disease that transmitted through the oral-fecal route, generally presents with mild to moderate clinical severity, and even passes unnoticed in the majority of cases. HEV infection is only considered as a serious health event when it selectively affects pregnant women; then, disastrous outcomes for both mother and fetus are usually anticipated in terms of miscarriage, prematurity, and maternal mortality [8,9]. HEV outbreaks have occurred in Sudan during the last couple of years in different areas of the country [10].

During last YF outbreak in Darfur states, simultaneous co-existence of both YF and HEV infections was observed in affected localities. This co-existence had further complicated the outbreak interpretation since the clinical manifestations of the two infections are almost identical. It was impossible to distinguish between the two infections without specific laboratory serological tests. One of the most important tools for communicable disease outbreak investigation and containment is the establishment of standard operational cases definition for case finding, reporting, and treatment [11]. Co-existence of such infections with shared cardinal clinical features is believed to affect both sensitivity and predictive power of a case definition, with a direct effect on hindering outbreak control dynamics. The nationally recommended operational case definition of YF during that outbreak was any case of fever, vomiting with or without jaundice, or bleeding tendency in the absence of positive blood film for malaria or any other obvious cause of fever [12]. According to that case definition, the total suspected cases that had been reported to the national disease surveillance system was 844, with 171 deaths, resulting in a case fatality rate (CFR) of more than 20%. During that outbreak, large-scale containment interventions were carried out, including mass vaccination campaigns that covered more than two million people, vector surveillance/control, and case management activities. Laboratory capacity was strengthened during the outbreak; all required materials and equipment were made available. Technical laboratory support was provided by different partners, namely the Institute Pasteur in Dakar (PID) and the Naval American Medical Research Unit 3 (NAMRU-3). That support and strengthening of laboratory capacity enabled the national public health laboratory and national surveillance system to thoroughly investigate as many as possible of the reported suspected YF cases during the outbreak period. Interesting findings were obtained from the analysis of outbreak samples that confirmed concomitant dual outbreaks of YF and HEV in the same population. This study reports the co-existence of YF and HEV infections in Darfur region during the last YF outbreak season and highlights the potentiality of clinical misclassifications when referring to a clinical standard case definition.

Methodology

Study design

This cross-sectional study included demographic, clinical, and laboratory data obtained from the national

communicable disease surveillance database for the recent YF outbreak that took place from September to December 2012 in Darfur states.

Study area

Darfur region is located in the western part of Sudan and composed of five administrative states (provinces); it borders Northern State, North/South Kordofan States, and has international borders with neighboring countries Libya, Chad, the Central African Republic, and the new Republic of South Sudan [13]. Darfur region covers almost 20% of Sudan's land space. Since 2003, the region has witnessed several events of turmoil such as conflicts, political complications, and humanitarian crises [14]. This passively influenced the socio-demographic dynamics in the region, resulting in the current agony of population displacement, fragile health system, security instability, and inaccessibility to the civil service.

Study population

All reported suspected YF cases throughout outbreak period were included in this analysis, particularly those who had been tested for both YF and HEV. Cases with missing data or incomplete clinical records were excluded.

Data collection tools

Data were collected through the standard Sudanese national surveillance system reporting format, including the standard YF case investigation form and outbreak line list.

Laboratory analysis

The total number of samples that were tested for YF and other viruses was 134, while 80 samples were tested for both YF and HEV. Enzyme-linked immunosorbent assay (ELISA) technique was performed to confirm the presence of both YF and HEV by detecting IgM antibodies, which is usually an indicator for recent infection [15,16]. The reagent kits used were obtained from MP Diagnostics from Geneva, Switzerland and the Centers for Disease Control and Prevention IgM capture assay for HEV and YF, respectively [17,18].

Results

A total of 80 cases were investigated and analyzed; males represented 84% of the study population. The mean age of participants was 25 years (standard deviation of 11 years). A total of 38.8% of the cases

resided in urban settlements: 32.5% were from North Darfur State, 22.5% from Central Darfur State, 20% from South Darfur State, and the rest from different areas of Darfur region. More than 48% of the cases had temporal jobs (mainly daily wage laborers), while 20% were mine workers (mainly traditional gold mining in Darfur region), and 12% were shepherds. Medical review history showed that 97.5% of cases had fever during the current illness, 62.5% were found to have hemorrhagic manifestations, and more than 58.8% had developed clinical manifestations of jaundice. Main characteristics of the study participants are presented in Table 1.

With respect to serological virology, 37 (64%) of cases were positive for YF, and 10 (27%) of them died as a result of the disease; details of YF patients are summarized in Table 2. Thirty patients (38%) were found to be positive for HEV, of which more than 60% were males and in the younger age group. Mine workers and farmers were the most affected by HEV, and there were no mortalities reported among those people who had only HEV. Thirteen (16.3%)

participants were concomitantly positive to both YF IgM and HEV IgM. Cramer's V statistical correlation value was found to be 0.05 and with a p value of 0.86, which indicates very weak statistical correlation between YF and HEV; interestingly, the mortality in patients who had both YF and HEV group was lower than the mortality among patients with YF only (7.7% and 37%, respectively). Details of patients with concomitant YF and HEV infections and statistical correlation are summarized in Tables 3 and 4.

Discussion

This is the first study that attempts to measure the correlation between YF and HEV infection among outbreaks in Darfur region. The study reveals that the most affected age group was the 14–39 year group because people in this group move more, usually looking for work; in this context, traditional gold mining is a considerable factor. This was also observed in Kenya in 1992–1993, where researchers reported that more than 70% of cases between 10–39 years of age were found to have higher YF prevalence

Table 1. Distribution of basic characteristics of study population.

Characteristic		Count (n)	Percent (%)
Outcome	Lived	60	75
	Died	20	25
Gender	Male	67	84
	Female	13	16
Age group (years)	< 14.9	13	16
	15–29.9	49	61
	30–44.9	11	14
	> 45	7	9
	Mean age (years)	25	SD = 12
Occupation	Butcher	1	1
	Driver	1	1
	Farmer	9	11
	Housewife	1	1
	Mine worker	16	20
	No specific work	35	44
	Shepherd	10	13
	Soldier	2	3
	Student	5	9
State	Central Darfur	18	23
	East Darfur	2	3
	North Darfur	31	39
	South Darfur	16	20
	West Darfur	13	17
Complaint	Fever	78	98
	Jaundice	47	59
Diagnosis	Bleeding tendency	50	63
	Yellow fever	37	64
	Hepatitis E	30	38
	Both YF & HEV	13	16

SD: standard deviation

[19]. Males had higher YF positive serological outcome compared to females in this study, which suggests high exposure to infected jungle mosquitoes (> 70% had unfixed jobs or were mine workers). Knowing that YF is transmitted to humans through the *Aedes* mosquito while HEV infection is one of the waterborne diseases that has been known to be circulating in Darfur region since 2004 [10], it is not surprising in this analysis to find that 16% of the study

population had both YF and HEV infections at the time of outbreak. The statistical correlation between YF and HEV was demonstrated in this study by applying Cramer's V correlation statistic, which is used to quantify the correlation between two nominal variables. Cramer's V value was 0.05, which shows a very weak relationship between having concomitant infection with both YF and HEV, and it is generally not statistically acceptable according to the cutoff

Table 2. Characteristics of patients with yellow fever.

Characteristic		Count (n)	Percent (%)
Outcome	Lived	27	73
	Died	10	27
Gender	Male	31	84
	Female	6	16
Age group (years)	< 14.9	6	16
	15–29.9	22	60
	30–44.9	7	19
	> 45	2	5
Occupation	Butcher	1	3
	Farmer	4	11
	Mine worker	6	16
	Shepherd	5	14
	Student	2	5
	No fixed job	19	51

Table 3. Yellow fever and hepatitis E virus cross-tabulation and correlation.

Cross-tabulation	YF positive	YF negative	Total
HEV positive	13	17	30
HEV negative	24	26	50
Cramer's V value	0.05*		
P value	0.86		

*Cutoffs: < 0.15: very weak correlation; 0.16–0.3: weak to moderate correlation; 0.3–0.5: strong to very strong correlation; 0.5–.9: redundant and perfect correlation

Table 4. Characteristics of participants who had concomitant yellow fever and hepatitis E virus.

Characteristic		Count (n)	Percent (%)
Outcome	Lived	12	92
	Died	1	8
Gender	Male	12	92
	Female	1	8
Age group (years)	15–29.9	8	62
	30–44.9	4	31
	> 45	1	8
	Butcher	1	8
Occupation	Farmer	2	15
	Mine worker	6	46
	Shepherd	1	8
	Student	1	8
	No fixed job	2	15
Complaint	Fever	12	92
	Jaundice	12	92
	Bleeding tendency	4	31

values [20] (Table 3). This supports the hypothesis and the current state of knowledge regarding both YF and HEV. No biological plausibility is currently known that links these two types of viruses, though they were clinically and concomitantly found in this outbreak, which suggests that there was an ongoing outbreak of HEV along with the YF during that particular time. The co-existence of YF and HEV infection outbreaks in Darfur might be explained by the fact that the YF outbreak occurred immediately after the rainy season. Usually in many parts of Sudan, including Darfur States, nomadic people and animal keepers store water in large ground ponds (hafeers), and they use this water for drinking, cooking, and other domestic purposes, which might be the source of contamination and HEV infection [10]. In addition, when someone takes water from hafeer, some water leaks behind and it fills the footprints of their animals (small, deep, and dark holes), which offers a very suitable environment for mosquito breeding, particularly *Aedes* mosquito, the responsible vector for YF and some other hemorrhagic fevers; this finding was observed in several entomological surveys [21,22]. Moreover, the circulation of both YF and HEV in Sudan and some neighboring countries is well known, particularly in Ethiopia [23]. Based on this summary, it is reasonable to assume that the HEV outbreak started before YF and that the majority of HEV cases went unnoticed by the surveillance system since the disease is of mild severity, particularly among the young people who were affected by YF initially [7]. In addition, increasing sensitivity of the surveillance system during the outbreak led to HEV cases being reported to the health facilities as well. The same phenomenon was reported from Port Sudan, the capital city of the Red Sea State, during 2010, which had been affected by a dual outbreak of HEV and dengue fever according to the disease surveillance system, Sudan Federal Ministry of Health [24,25]. Both dengue and YF are from the same virological family and are transmitted by the same means [1]. Moreover, during the South Kordofan YF outbreak in 2005, investigators confirmed the co-existence of chikungunya; both YF and chikungunya are transmitted to humans by the same mosquito [6]. On the other hand, concurrent infection of mosquito-borne disease with another waterborne disease, such as dengue fever and hepatitis A infection or malaria with typhoid fever, is quite often reported from different developing countries [26]. Also, co-infections due to *Leptospira* and HEV were reported from some tropical countries, but this is

the first time the co-existence of YF with HEV as outbreaks in our African region was reported [27].

Conclusions

This study has reported the concomitant outbreaks of YF and HEV infection in Darfur States during 2012. This demonstrates how important it is that clinicians, epidemiologists, and other healthcare providers carefully set the operational case definitions and management planning, particularly during health emergencies and disease outbreaks. Further studies should be carried out to explore the severity of concomitant infections and their relationship with clinical outcomes.

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