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Factors associated with dengue fever IgG sero-prevalence in South Kordofan State, Sudan, in 2012: Reporting prevalence ratios

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Summary
Background: Dengue fever (DF) is a vector-borne virus transmitted to humans by infected Aedes mosquitoes. In this study, we identified the most important factors associated with the prevalence of IgG antibodies in a border state between Sudan and the new republic of South Sudan.
Objectives: To quantify the association of specific factors with the prevalence of DF IgG antibodies in Lagawa among subjects aged 16—60 years in 2012.
Methodology: Analytical cross-sectional community-based study conducted in Lagawa in 2012.
Results: Indoor mosquito breeding was the most significant predictor affecting DF IgG serology. Household water storage was also strongly associated with the presence of IgG antibodies. Residence in urban areas, younger age and a history of travel to the Red Sea State were significant predictors of DF IgG seroprevalence in South Kordofan state.

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Conclusion: Indoor (household) behaviors associated with DF infection should be modified to mitigate the infection risk in the study area. Awareness should be raised regarding DF in Lagawa to ensure community participation in all control measures, and the surveillance system at the border between Sudan and the republic of South Sudan should be strengthened.

Introduction

Dengue fever (DF) is a vector-borne virus transmitted to humans by infected *Aedes* mosquitoes. It is an endemic disease of tropical and sub-tropical areas [1]. There are four known DF viral serotypes. The disease varies in presentation from asymptomatic infections to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS), which are the most serious forms of the disease [2].

DF has been rising in prevalence in recent years and has become a public health problem of global importance that necessitates the notification of public health authorities per International Health Regulations (IHR 2005). The World Health Organization (WHO) estimates that two-fifths of the world's population is at risk of DF infection and that DF is now endemic in more than 100 countries [3,4]. Many factors influence the propagation and spread of DF, and the most recent evidence suggests that DF infection is usually associated with indoor behaviors, including water-storage methods that offer media for mosquito breeding. The mosquitoes are also thought to rest indoors. The spread of disease is due to the expansion of urban populations, increased vector density due to unsustainable control programs, climate change and the increase in commercial air travel, which has facilitated he rapid movement of viremic humans and the spread of the disease around the globe [5]. The virus has been circulating throughout the African continent since the early 20th century. Outbreaks of the four serotypes have increased dramatically since 1980 [6]. In particular, Sudan had been affected by repeated outbreaks of DF, including at Port Sudan, which is located in the eastern part of the country and in the west coast of Red Sea. According to the annual report of the Sudan Medical Service in 1928, DF infections have been occurring in Port Sudan since 1908 as reported by Lewis in 1945 [7]. DF outbreaks attributed to serotypes 1 and 3 were reported in Sudan in 1986 and 2005, respectively. Moreover, serotypes 1, 2 and 3 have been reported in the port city of Jeddah, Kingdom of Saudi Arabia, which is across the Red Sea from and connected to Sudan [8].

In 2008, 2009 and 2010, repeated outbreaks of DF were reported in Sudan, with the most cases (more than 4000) reported in 2010.

In 2011/2012, an outbreak of non-specific symptoms was detected though the national surveillance systems in Lagawa, South Kordofan, along the border between Sudan and the new republic of South Sudan. Initial investigations confirmed the presence of DF and chikungunya viruses, along with sporadic cases of West Nile virus.

Except for yellow fever, no proper epidemiological studies had been conducted to estimate the prevalence of VHFs in the border states between Sudan and South Sudan; however, DF in eastern Sudan has been more closely studied, and many achievements have been documented in DF control there.

Sustainable interventions, such as breeding source reduction and other targeted interventions, are key to controlling DF. In this study, important factors associated with DF IgG prevalence were identified to improve understanding and facilitate the development of strategies for disease control.

Materials and methods

Study design

An analytical cross-sectional community-based study was conducted to study important factors associated with DF IgG prevalence.

Study setting (area)

Southern Kordofan is a border state between Sudan and the Republic of South Sudan. It has an area of 79,470 km^2 and a population of 1,406,000. Its climate is associated with the savannah zone, in which rainfall ranges from 350 mm in the north to 850 mm in the south; the vegetation density varies from the north to the south based on the levels of rainfall and soil types. According to the Sudan National Metrological Authority, the average temperature ranges between 30 °C and 40 °C throughout the year [9,10].

Study population

The total population of South Kordofan state aged 15—60 years was the target population; the population of Lagawa aged 15—60 years was considered the source population. We included both sexes and anyone who gave consent for an interview and blood sampling. We excluded people visiting the area for less than 14 days, immunocompromised patients (e.g., patients with HIV, transplants, malignancies or chronic kidney disease or those taking immunosuppressant medications) that may alter the immunological response to infections and pregnant women or women in the puerperal period due to their altered immune responses.

Sampling techniques

Multi-stage cluster sampling was used [11]. In the first stage, clusters (popular administrative units [PAU]) were selected using a probability-proportionate-to-size technique (PPS). Households were selected using the ''spinning the pen'' technique, which is often used to avoid costly and time-consuming listing of all households (EPI technique) [12]. Within the household, a list of all eligible residents present at the time of the survey was prepared, and we randomly selected one individual for the blood collection and interview.

Sample size to assess risk factors

The sample size has 80% power to detect an anticipated odds ratio (OR) of 2 with a 95% confidence interval (CI), assuming exposure levels between 11% for mosquito repellent and 80% for water storage among non-infected individuals. The minimum required sample size to assess risk factors was 599, assuming 5% missed data at the time of analysis.

Lab analysis and quality assurance

The samples were analyzed using Panbio ELISA kits (DF IgG indirect). Positive- and negative-control serum specimens were used, and the ELISA kits were tested before the serum samples were analyzed. This test has high sensitivity (99.72%) and specificity (99.62%) and is recommended for serological studies [13]. All serological tests were conducted at Sudan National Public Health Laboratory, which has considerable experience in the detection and confirmation of arboviruses and a continuous program for validation and quality control.

Data analysis

The frequencies for general descriptions were computed using SPSS-19 and STATA-12 software. The Breslow modified Cox proportional hazards model assuming a fixed time variable was run along with robust variance method to estimate the adjusted prevalence ratios (PRs). We reported the associations as PRs rather than ORs because the study design was cross sectional and ORs tend to overestimate the strength of association when the prevalence of the outcome is high (>10%) [14—17].

Results

Descriptive statistics (basic characteristics)

We interviewed 615 individuals and received 600 responses with complete information. Of these 600%, 51% were female. The age of the participants was normally distributed, with a mean of 37 years and a standard deviation of 12.6 years. In addition, 15.5% of the participants reported having traveled to South Sudan, whereas 13.2% reported a history of traveling to the Red Sea State. Their medical histories revealed that 38.2% of participants had been affected by fever in the three months before the interview, whereas only 7.8% had experienced fever with hemorrhagic manifestations during their lives. In addition, 77.8% of participants were vaccinated against yellow fever. The main characteristics of the study participants are presented in Table 1. Regarding entomological indicators, 90.7% of participants stored water at home, but only 67% were properly covering their water containers at the time of the interview. Although we confirmed indoor mosquito breeding in only 9% of visited households, 90.8% reported using mosquito nets at night, but only 2% reported also using the nets during the day. Although 24.8% of visited households had window screens, only 14.7% were intact. Additionally, 79.3% of visited households kept domestic animals indoors.

DF IgG prevalence

The overall prevalence of DF IgG in Lagawa was 27.7% (95% CI 24.1—31.3%).

Inferential statistics (associated factors) entomological indicators

Indoor water storage (the main exposure variable) was one of the most important risk factors for DF IgG serology (PR = 2.1, 95% CI: 1.1, 4.5). Indoor

Table 1 Distribution of basic characteristics in the study population.

Characteristic	(*N* = 600)	
	N	%
Age	M ± SD 37 ± 12.6 years	
Younger than 35 years	141	23.5
35—39 years	139	23.2
40—44 years	167	27.8
45 years and older	153	25.5
Sex		
Male	294	49
Female	306	51
Occupation		
Farmer	212	35.3
Animal keeper	45	7.5
Shop keeper	51	8.5
Government employee	73	12.2
Unemployed	219	36.5
Education level		
Illiterate	214	35.7
Traditional religious education (Khalwah)	102	17
Basic education	192	32
Secondary education	77	12.8
University or higher	15	2.5
Duration of continued residence in South Kordofan	M ± SD 33.6 ± 15 years	
Residence Cluster (locality)		
Lagawa	250	41
Alsunut	161	27
Jangaru	120	20
Shingil	69	12
History of		
Fever during the last 3 months	229	38.2
Fever with bleeding	47	7.8
Yellow Fever vaccination	467	77.8
Travel to Red Sea State	79	13.2
Travel to South Sudan	93	15.5
Indoor water storage	544	90.7
Indoor breeding of mosquitoes	54	9
Use of mosquito nets	545	90.8
Timing for Mosquito nets		
At night	522	87
During the day	11	1.8
Both day and night	12	2
Use of mosquito repellant	45	7.5
Intact screens	88	14.7
Regular use of an indoor insecticidal spraying	55	9.2
Keeping domestic animals at home	476	79.3
Type of animals		
Sheep	81	13.5
Goats	291	48.5
Cows	104	17.3

Table 2 Summary results of regression analysis for DF IgG seropositivity with risk factors among the study population.

Risk factor	Univariate analysis			Multivariate analysis		
	Prevalence ratio	95% CI	*P* value*	Adjusted Prevalence ratio	95% CI	*P* value*
Younger than 35 years	1.3	(1.1, 1.7)	0.04	1.4	(1.1, 1.9)	0.02
35 years and older	1	—	—	1	—	—
Male	1.2	(0.9, 1.6)	0.13	0.7	(0.5, 0.9)	0.03
Female	1	—	—	1	—	—
Lagawa	1.5	(1.2, 1.9)	0.002	1.4	(1.1, 1.8)	0.04
Outside Lagawa	1	—	—	1	—	—
Fever in the last 3 months	1.6	(1.2, 2.0)	<0.001	1.4	(1.1, 1.9)	0.01
No fever in the last 3 months	1	—	—	1	—	—
Travel to Red Sea State	1.5	(1.1, 2.1)	0.01	1.4	(1.1, 1.9)	0.04
No travel to Red Sea State	1	—	—	1	—	—
Indoor water storage	3.3	(1.4, 7.7)	0.01	2.1	(1.1, 4.4)	0.04
No indoor water storage	1	—	—	1	—	—
Indoor mosquito breeding	3.1	(2.5, 3.9)	<0.001	2.9	(2.2, 3.8)	<0.001
No indoor mosquito breeding	1	—	—	1	—	—
Use of mosquito nets	0.6	(0.4, 0.8)	0.001	0.2	(0.1, 0.4)	0.003
No use of mosquito nets	1	—	—	1	—	—
At night	2.2	(1.2,3.8)	0.01	2.5	(1.1,5.5)	0.03
Both day and night	1	—	—	1	—	—
Every day	0.5	(0.3, 0.7)	<0.001	0.5	(0.4, 0.8)	0.002
Interrupted use	1	—		1		
Indoor insecticidal spraying	2.5	(1.9, 3.1)	<0.001	1.8	(1.3, 2.5)	<0.001
No indoor insecticidal spraying	1	—	—	1	—	1

* The cutoff point for statistical significance for univariate analysis is 0.2; the cutoff point for multivariate analysis is 0.05.

mosquito breeding at the time of the household visit was the factor most strongly associated with DF IgG (PR = 2.9, 95% CI: 2.2, 3.8). Mosquito nets were found to have a protective effect (PR = 0.2, 95% CI: 0.1, 0.4), and individuals who used nets only at night were at higher risk of developing DF than those who used the nets both at night and during the day (PR = 2.5, 95% CI: 1.1, 5.5). The frequency of mosquito net use was found to play a significant role in the DF serological outcome because the daily use of a net had a protective effect compared with intermittent use (PR = 0.5, 95% CI: 0.3, 0.8). The regular use of indoor insecticidal spray was a risk factor for DF IgG (PR = 1.8, 95% CI: 1.3, 2.5).

Medical predictors of DF IgG

A history of fever during the three months preceding the interview was strongly associated with the DF IgG (PR = 1.4, 95% CI: 1.1, 1.9). A history of travel to the Red Sea State was also a risk factor (PR = 1.4, 95% CI: 1.1, 1.9). The history of traveling to South Sudan and YF vaccination were not statistically significant risk factors.

Socio-demographic factors

Participants who reside in greater Lagawa popular administrative units are at higher risk of DF IgG than those who are living outside of Lagawa (PR = 1.4, 95% CI: 1.1, 1.8), and younger participants are at greater risk than those aged 35 years or older (PR = 1.4, 95% CI: 1.1, 1.9). The male gender also has a protective effect (PR = 0.7, 95% CI: 0.5, 0.9) (Table 2).

Discussion

The obtained results strongly support the theory that the source of DF infection is almost always associated with indoor behaviors [18—20].

Indoor water storage was associated with DF IgG seropositivity in Lagawa; the prevalence of DF IgG among participants who store water at home is double that among those who do not store water at home (PR = 2.1, 95% CI: 1.1, 4.5). This behavior provides breeding sites for *Aedes aegypti* [21,22]; recent and older mosquito surveys throughout Sudan have found indoor water storage to be strongly associated with the presence of *A. aegypti*. Indoor mosquito breeding at the time of the household visit was the strongest risk factor for DF IgG seropositivity in this study (PR = 2.9, 95% CI: 2.2, 3.8). This result is coherent and consistent with many studies around the world [21]; *A. aegypti* lay infected eggs and can transmit the disease immediately after maturation, usually during the female mosquito's first blood meal. Studies in the Red Sea and Kassala states in the eastern part of Sudan had shown that water jars and other small water containers are the key breeding sites preferred by *A. aegypti* [23].

Mosquito nets were found to have a protective effect (PR = 0.2, 95% CI: 0.1, 0.4); individuals who used nets only at night were at higher risk of developing DF than those who used the nets both at night and during the day (PR = 2.5, 95% CI: 1.1, 5.5). The frequency of mosquito-net use was found to play a significant role in serological outcome because the daily use of a net had a protective effect compared with intermittent use (PR = 0.5, 95% CI: 0.3, 0.8). These findings are fully consistent with the existing knowledge regarding the DF and *A. aegypti* ecology as the mosquito is mainly day-biting and prefers the hours after sunrise and before sunset [24—26]. In addition, long-lasting insecticide-impregnated mosquito nets were recently distributed in the study area and might have helped to protect against all types of mosquito. The use of mosquito repellents and intact window screens were not associated with the DF serology in our study, possibly because the repellents were being applied incorrectly and because the participants often kept doors open during the day, allowing mosquitoes to rest indoors and feed from the participants. Some other studies have drawn similar conclusions [27]. The regular use of an indoor insecticidal spray was a risk factor for DF IgG seropositivity (PR = 1.8, 95% CI: 1.3, 2.5). The regular use of an indoor insecticide spray is believed to protect against DF if a residual effect insecticide is used according to standard operational procedures [28]. However, in our study, this result may be distorted by an unmeasured residual confounder. For example, the vector density in the home was not measured because we did not perform a concomitant entomological estimation at the time of blood sampling; normally, people start spraying their own homes when they notice high mosquito densities. Efficacy and resistance to the insecticides used were not properly evaluated.

The studied socio-demographic factors in this study also support the theory of an indoor source of DF infection. In our study, we found that females in the study area were at greater risk of DF seropositivity compared with males, suggesting high exposure to the infected mosquito in the household [18,19]. In this rural and conservative community, most women spend the majority of their time at home. Younger participants were at greater risk of DF IgG seropositivity, with an adjusted PR of 1.4. Younger adult (particularly 30—35 years) populations tended to be more reactive to the majority of serological tests [29]. Residence in the PAUs in Lagawa town was significantly associated with DF IgG. This finding is coherent and consistent with the current knowledge of DF etiology because the vector is an urbanized mosquito. We also found some medical indicators to be consistent with the current knowledge of DF. A history of fever during the three months preceding the interview was highly predictive of DF IgG seropositivity (PR = 1.4, 95% CI: 1.1, 1.8), and up to 20% of febrile illnesses were due to DF under similar conditions, suggesting that these fevers were the result of DF infection. However, a history of fever and bleeding was not associated with DF IgG seropositivity, which is consistent with the current knowledge of DF; only 3.1% of DF cases in some countries are severe and hemorrhagic according to the WHO DF fact sheet (2012). A history of yellow fever vaccination was not associated with DF IgG seropositivity, although many studies have suggested and confirmed cross-immunity between flavivirus groups [30—32]. Interestingly, participants with a history of travel to the Red Sea State in eastern Sudan were at greater risk of developing a DF IgG serological outcome. RSS is known to be a DF-endemic area and has recently experienced repeated DF and DHF outbreaks [33]. Population movements between South Kordofan and RSS have also been documented as many people who live in RSS are originally from South Kordofan and return to their homeland for the rainy season each year to cultivate and harvest their crops. In contrast, travel to South Sudan was not associated with DF IgG. This finding is consistent with current knowledge as the disease is endemic in the eastern part of the country and has not been reported in the south. Analyses and studies of other arboviruses such as RVF and CCHF are expected to show a reverse association from that seen here as the other arboviruses are expected to be endemic to South Sudan.

Strength and study limitations

This study is the first to identify factors associated with DF in Lagawa, South Kordofan state, which is the border state between Sudan and the Republic of South Sudan. The prevalence ratios for the associated risk factors are a better measure than the odds ratio of the strength of the association. The sampling technique and adequate, representative sample size are strengths of this study. Despite the logistic efforts expended, our study is still subject to many limitations. The EPI methodology for household sampling does not ensure full probability samples because the sampling frames are not updated. The design of this study would have been stronger if it had been integrated with a simultaneous entomological survey in the study area.

Conclusion

The current study results support the theory that the source of DF infection is usually associated with indoor behaviors. Thus, community awareness campaigns should target indoor behaviors that support *A. aegypti* breeding.

Ethical considerations

Ethical clearance was obtained from the ethical review committee in November 2011. Permission from the Sudan Federal Ministry of Health (FMOH) was issued in July 2011. Signed, informed consent was obtained in Arabic from all study participants.

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