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First report of epidemic dengue fever and malaria co-infections among internally displaced persons in humanitarian camps of North Darfur, Sudan

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Abstract

Objectives: This study aimed to investigate an outbreak of a non-malaria, undifferentiated febrile illness, among internally displaced persons (IDPs) living in humanitarian camps in North Darfur, Sudan, in 2019.

Methods: An investigation team was deployed to North Darfur to identify suspected cases and collect blood samples, and clinical and demographical data. Blood samples were examined microscopically for *Plasmodium spp* and tested for dengue (DENV) and yellow fever viruses by reverse transcriptase-quantitative polymerase chain reaction.

Results: Between September 7 and December 18, 2019, we clinically identified 18 (24%), 41 (54%), and 17 (22%) cases of dengue fever, dengue with warning signs, and severe dengue, respectively. Blood samples were collected from 22% of patients, and 47% of these tested positive

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Author contributions

Conceptualization, A.A. and Y.A.; methodology, A.A., Y.A., M.E., and AE, formal analysis, A.A. and Y.A.; investigation, Y.A., and T.B.; writing—original draft preparation, A.A.; writing—review and editing, A.A. M.E., A.E., T.B., I.D., Y.A., and S.C.W.

Conflicts of interest

The authors declare no conflict of interest.

for DENV-1 RNA. We confirmed 32 malaria cases with 5 co-infections with DENV. This outbreak of dengue was the first among IDPs in the humanitarian camps.

Conclusions: Our findings indicate that dengue has become endemic or that there has been a new introduction. Further epidemiological, entomological, and phylogenetic studies are needed to understand disease transmission in the area. An early warning and response system and an effective health policy are crucial for preventing and controlling arboviruses in Sudan.

Keywords

Dengue with warning signs (DWWS); Severe dengue fever (SD); Arboviruses; outbreak; Epidemic; Sudan

Introduction

Dengue fever (DF) is caused by 1 of 4 closely related but antigenically distinct serotypes of dengue virus (DENV), DENV-1–4 (Simmons et al., 2012). The global health risk of arthropod-borne viral diseases such as DF is growing rapidly (Ahmed et al., 2020a; Elduma et al., 2020). DF, in particular, is one of the most widespread infectious diseases, with annual infections estimated to be approximately 390 million globally (Bhatt et al., 2013). The clinical presentation of DENV infections ranges from self-limiting or flu-like symptoms to severe and fatal forms of the disease, including dengue with warning signs (DWWS) and severe dengue (SD) (WHO, 2011). However, most DENV infections are inapparent, showing no symptom or clinical presentation (Endy et al., 2011). Nevertheless, asymptotically infected persons are still capable of infecting insect *Aedes* (*Stegomyia*) spp. mosquito vectors, specifically *Aedes aegypti* and *Ae. albopictus*, the primary vectors of DENV (WHO, 2011; Duong et al., 2015).

Several vector-borne diseases are endemic in Sudan, including malaria, onchocerciasis, leishmaniasis, and many human and zoonotic arboviral diseases (Ahmed et al., 2020b, 2020c; Mohamed et al., 2019, 2021). More importantly, the frequency of arboviral diseases outbreaks is steadily increasing, with recent epidemics of arboviruses emerging and re-emerging throughout the country, including the Rift Valley fever in the North (Ahmed et al., 2020d), Chikungunya in the East (Ahmed et al., 2020b), Dengue, Crimean–Congo hemorrhagic fever (CCHF), and West Nile virus in the West of the country (Ahmed et al., 2019a). Although the current evidence does not show a positive association between the *Aedes*-borne arboviral diseases and socioeconomic status (Whiteman et al., 2020), some studies have suggested a link between dengue transmission and some socioeconomic risk factors, namely living in densely populated houses, housing conditions, and the use and storage conditions of water (Ahmed et al., 2019a; Elaagip et al., 2020; Ahmed et al., 2019b).

Historically, DF, as a major public health concern in Sudan, was confined to the eastern region of the country (Elduma et al., 2020; Hamid et al., 2019). However, DF has grown into a country-wide public health problem (Ahmed et al., 2020b; Elduma et al., 2020). In 2014/15, DENV emerged in humanitarian and refugee camps in the Darfur area, West Sudan (Ahmed et al., 2019b). The region of Greater Darfur consists of 5 large states, and its population has become internally displaced persons (IDPs) continually moving around

the region or fleeing to one of the neighbor countries to escape the war that started in the early 2000s (Ahmed et al., 2019a, 2019b; Gayer et al., 2007). DF was first documented in Al Fashir, the capital city of North Darfur State, and it did not take long before the virus caused the first outbreak in the region in 2016, with infections reported by 4 out of the 5 states (Ahmed et al., 2019a).

Here we report an outbreak of DF between September and December 2019 among IDPs living in a humanitarian camp setting of the post-conflict environment in North Darfur State, West Sudan.

Materials and methods

The outbreak investigation

In response to a report of non-malaria undifferentiated febrile illness among IDPs living in humanitarian camps in North Darfur, an investigation team was assembled and deployed by the Sudan Federal Ministry of Health during the first week of September 2019. The team identified suspected cases by active surveillance and collected blood samples, and clinical and demographical data. A 2-ml venous blood sample was drawn using a sterile syringe. From each blood sample, 2 drops were placed on a microscope slide and examined for *Plasmodium species* to confirm the presence or lack of malaria infection. The rest of the blood was collected in EDTA tubes that were placed in an icebox and shipped to the National Public Health Laboratory in Khartoum, Sudan, where they were stored in a –80 °C freezer until later use. Based on the epidemiological history of the study area, clinical presentations of the suspected cases, and limited laboratory capacity, instead of testing for all the major human arboviruses in the country (Ahmed et al., 2020b), the blood samples were tested for DENV only. However, later, when additional resources became available, retesting for yellow fever virus was prioritized and performed. Following the national ethical guidelines for outbreaks investigations and response, blood sampling, and data collection, the need for ethical approval and informed consent were waived by the North Darfur State, Ministry of Health.

Molecular analysis

Total RNA was extracted from the blood samples using the QIAamp viral RNA mini kit (QIAGEN Inc. Germany) according to the manufacturer's guidelines. Testing for DENV with a Multiplex Assay to identify the serotypes and testing for yellow fever were performed using the RealStar® Dengue RT-PCR Kit 2.0 and RealStar® Yellow Fever Virus RT-PCR Kit 1.0 (Altona Diagnostics GmbH, Hamburg) real-time qPCR kits, respectively, following the manufacturer's instructions. The confirmation of malaria infection was performed using Giemsa stain and microscope.

Results

The DF outbreak continued for 14 weeks between September 7 and December 18, 2019, with a total of 76 cases, including 2 related deaths. The outbreak peaked on November 28 with 5 new cases (Figure 1).

The outbreak was confined to North Darfur State, with cases reported from 7 localities. The majority of cases (86%) were reported from the Al Fashir locality, the capital city of North Darfur State (Figure 2).

The demographic analysis of the cases revealed that the male-to-female ratio was 1.1:1. Most cases (57%) were young adults between 16 and 30 years old, while other age groups were represented almost equally (Figure 3).

The majority of the patients (48%) were students, followed by 22% and 17% who were homemakers and day laborers, respectively (Figure 4).

Eight (47%) DENV infections were polymerase chain reaction (PCR)-confirmed out of the 17 collected blood samples obtained from 22% (17/76) of the suspected cases. Serotype analysis revealed that all cases involved DENV-1. The microscopic examination confirmed 32 malaria infections with *Plasmodium falciparum*. Five cases of malaria-dengue co-infection were confirmed. Eighteen (24%), 41 (54%), and 17 (22%) cases of DF, DWWS, and SD, respectively, were identified clinically. Patients presented with fever (89%), 68% with headache, and 4% suffered from neurological disorders (Figure 5).

Discussion

In this study, we report the first outbreak of DF among IDPs living in humanitarian camps in the war-torn North Darfur State of Sudan. These camps are characterized by limited health, education, and stable water supply services (Ahmed et al., 2019a). The population lives in a very crowded situation with high dynamicity between camps and borders crossing to the neighbor countries (Ahmed et al., 2019b, 2019a). Our investigation identified DENV-1 as the causative agent of this outbreak, and no co-infection or circulation of another serotype of DENV or different arbovirus was detected, unlike previous outbreaks of arboviral diseases (Ahmed et al., 2019b, 2019a). However, 5 out of the 8 (63%) DENV PCR-confirmed cases were co-infected with *P. falciparum*, highlighting the high burden of malaria in this endemic area (Bhatt et al., 2013). The detection of only *P. falciparum* and DENV-1 in our research participants does not exclude the possibility of other DENV serotypes and/or arboviruses circulating in the area. It is likely that the limitations of our study, including insufficient resources and small sample size, meant we were not able to detect other serotypes or arboviruses (Elduma et al., 2020; Ahmed et al., 2019a,b).

Following the new World Health Organization (WHO) guidelines for the diagnosis, treatment, prevention and control of DF and considering the clinical manifestations of the patients, we clinically identified 18 (24%), 41 (54%), and 17 (22%) cases of DF, DWWS, and SD, respectively, these included 2 deaths (WHO, 2011, 2009). DENV infection was molecularly confirmed in 47% (8/17) of blood samples, suggesting the involvement of other hemorrhagic fever agents. However, due to limited resources, samples were only further tested for yellow fever virus as the second most likely causative agent, and all were negative (Ahmed et al., 2020b). This diagnostic challenge underscores the need for more comprehensive and sensitive diagnostic tools such as sequencing; however, this would

require greater resource mobilization and international partnerships because it exceeds the local capacity (Ahmed et al., 2020b).

Sudan suffers from a relatively high burden and frequent outbreaks of arboviral diseases, including Rift Valley fever, Chikungunya, and dengue viruses (Ahmed et al., 2020a,b,d). DENV has emerged recently in the war-torn region of Darfur (Ahmed et al., 2019a,b). However, this is the first outbreak among IDPs and the local community, healthcare providers, and public health operators are not yet fully aware of the ongoing risk of DF in the area. This lack of awareness could be due to the limited sharing of health information (Ahmed, 2020). The lack of community awareness of the public health risk affected this investigation by limiting the submission of blood samples for molecular testing, similar to previous investigations of arboviral epidemics in the area (Ahmed et al., 2019a; Soghaier et al., 2013). Because of the lack of health policy for preventing and controlling arboviral diseases in the country, and the limited surveillance system in Sudanese regions affected by war, DF has developed into a challenging health problem (Ahmed et al., 2019a,b; Elduma et al., 2020).

The case fatality rate of 3% (2/76) is relatively low compared to previous outbreaks of DF in the area, possibly due to the circulation of a single serotype, DENV-1, limiting secondary infection with a different serotype associated with severe and fatal forms of the disease (Ahmed et al., 2019a,b). Considering that approximately 22% and 54% of the cases were clinically identified as DWWS and SD, respectively, this indicates that our surveillance was not sensitive enough and only identified the severe cases (Figure 5) (Ahmed et al., 2019a). As expected, most cases were reported from the Al Fashir locality, where the disease first appeared in the region (Ahmed et al., 2019b). Similar to the previous outbreak of DF in the area, most (74%) of the DENV infections were detected among children and young adults, and there was no difference in infection rate between males and females (Ahmed et al., 2019a). The recent increase in the frequency and intensity of arboviral diseases epidemics underscores the urgent need for national health policy to prevent and control arboviral diseases (Ahmed et al., 2019a,b,d).

The Darfur region has recently suffered from a long, armed conflict that has affected the socioeconomic structure of the local community and increased the vulnerability of the population to infectious diseases, including DF (Elaagip et al., 2020; Gayer et al., 2007; Whiteman et al., 2020). All of the patients we identified were IDPs living in humanitarian camps without adequate public health services. Further, their living conditions in densely populated camps are a major risk factor for DENV transmission (Gubler, 2011). Also, the lack of a sustainable water supply forces the IDPs to store water in containers inside the camps, which has created ideal larval habitats for the major mosquito vector, *Ae. aegypti* (Ahmed et al., 2019a).

Conclusions

This outbreak, the third detected in the area, however, it is the first that occurred exclusively among IDP communities. DENV-1 and -3 were previously detected in the area, but only DENV-1 was detected in this outbreak, which could be attributed to: an unintentional

sampling bias due to the small sample size, only DENV-1 has managed to establish endemic transmission, or there has been a new introduction of DENV-1 in the area. Additional information on disease dynamics in the area, as well as entomological, epidemiological, phylogenetic, and socioeconomic studies, are critically needed to understand DENV transmission in the area. Additionally, establishing routine surveillance and preventative health policies to control arboviral diseases in the area is urgently needed to reduce morbidity and mortality. Preventive measures, including intensive vector surveillance and control activities, health education sessions, and community engagement, are essential in the IDP camps to prevent cases and outbreaks of infectious diseases.

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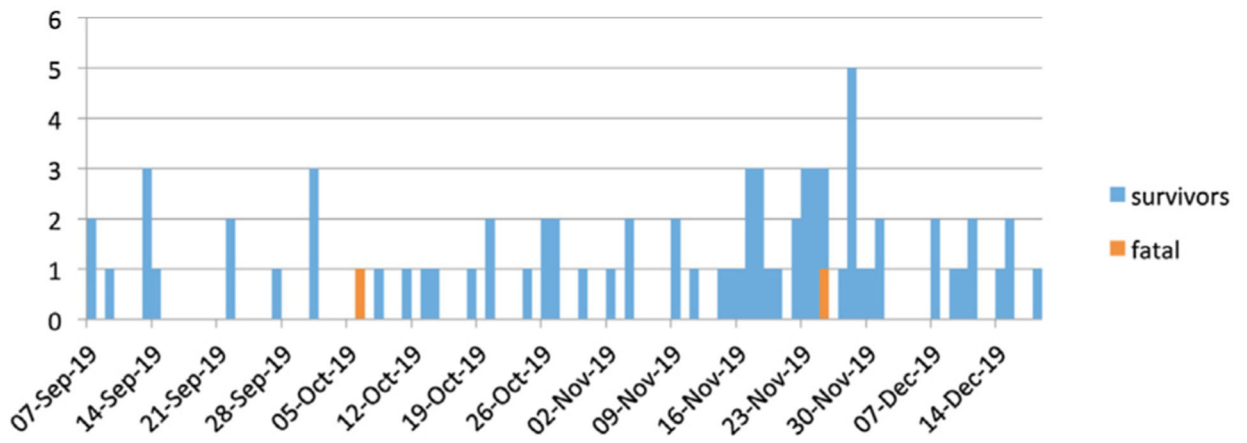


Figure 1. Epidemic curve showing the distribution of the 76 dengue cases and deaths identified in North Darfur State between September 7 and December 18, 2019.

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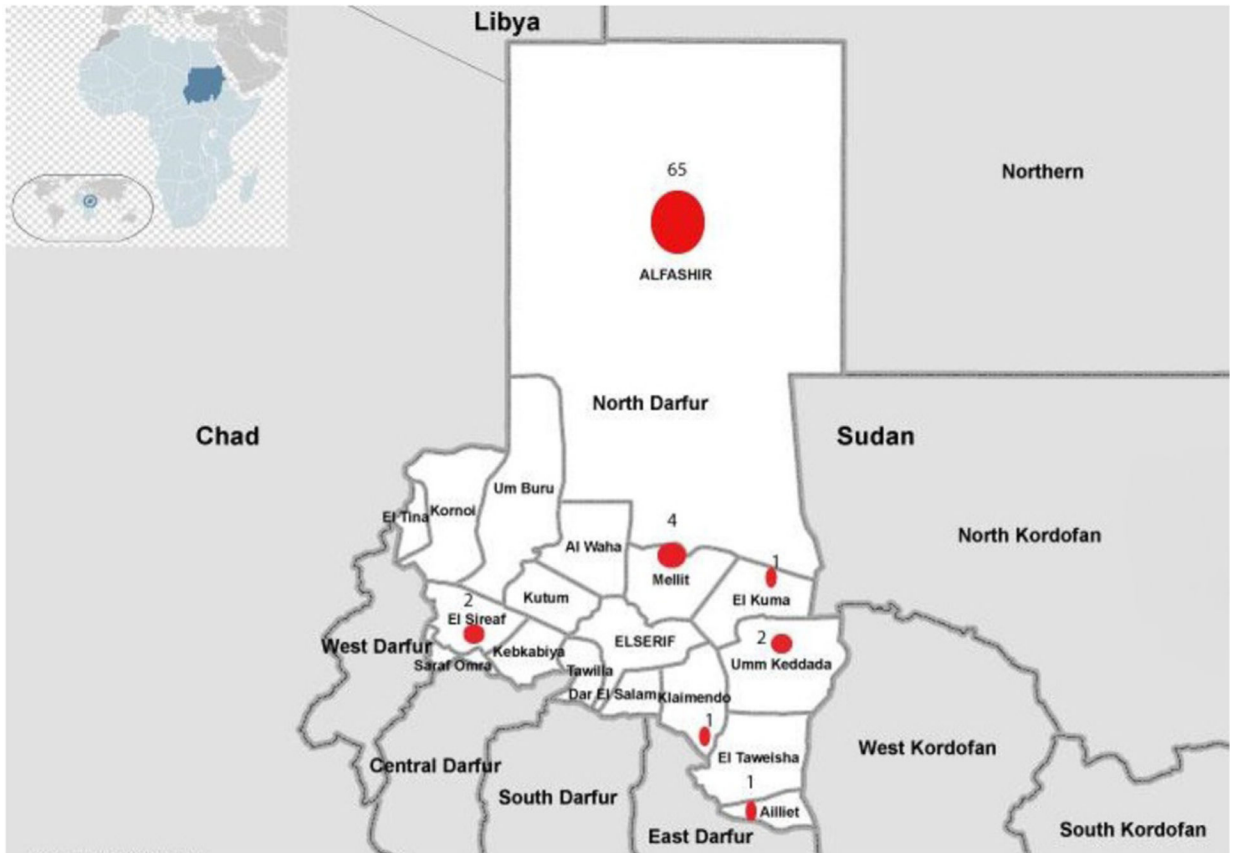


Figure 2. Distribution of the 76 dengue cases identified in North Darfur State between September 7 and December 18, 2019. Red circles represent the number of cases per camp in the relevant localities.

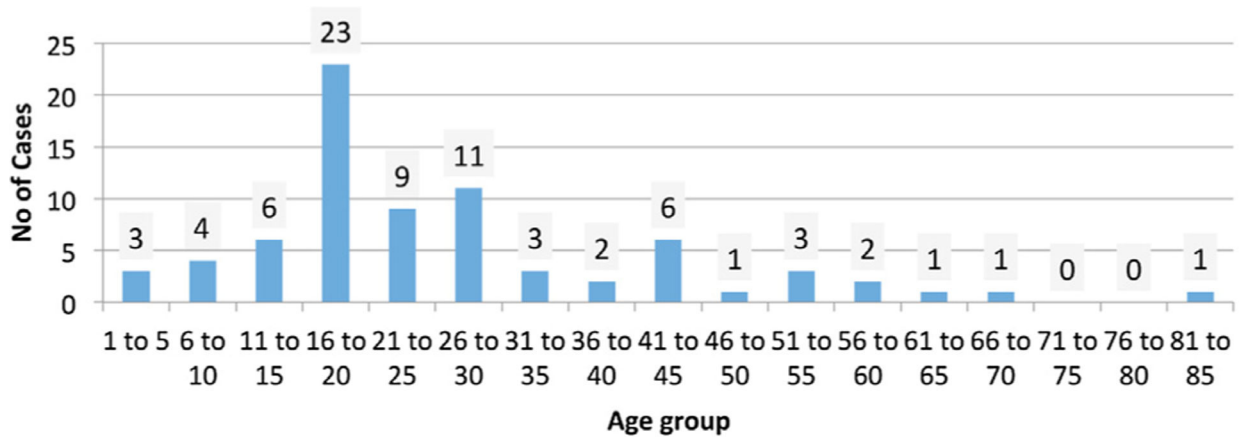


Figure 3.
Age distribution of the 76 dengue cases identified in North Darfur State between September 7 and December 18, 2019.

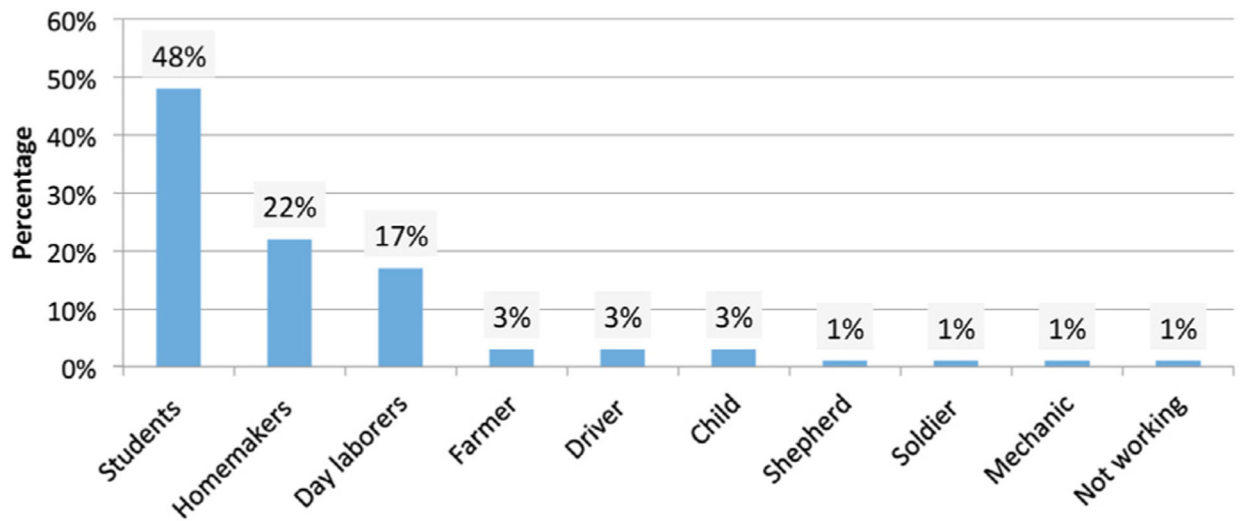


Figure 4.
Distribution of the 76 dengue cases identified in North Darfur State between September 7 and December 18, 2019, by occupation.

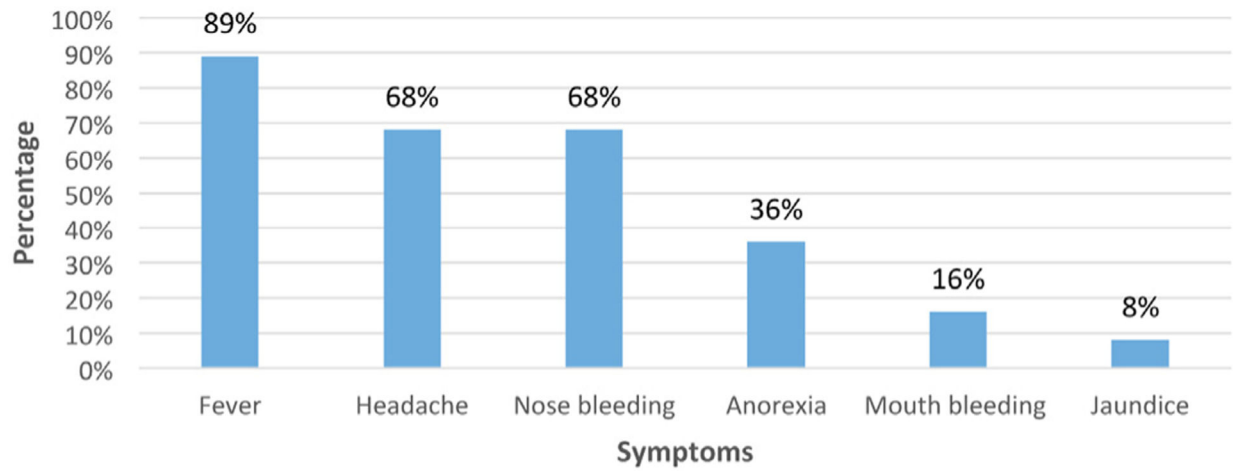


Figure 5.
The clinical manifestations of the 76 dengue cases identified in North Darfur State between September 7 and December 18, 2019.