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Emerging Problems in Infectious Diseases

Co-infection with dengue, zika, chikungunya in a six-year-old patient in Bamako, Mali

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Abstract

Introduction: The burden of arboviral infections remains underestimated in sub-Saharan Africa due to the similarity of symptoms with malaria and other tropical febrile illnesses. Simultaneous infection with three arboviruses sharing the same vector is rarely reported.

Case presentation: We report here the case of a six-year-old girl diagnosed by multiplex real time-polymerase chain reaction for infection involving dengue, zika and chikungunya viruses with no severe symptoms and good clinical improvement with symptomatic treatment in Bamako, Mali.

Conclusions: Co-circulation of different arboviruses is possible in urban context where *Aedes* mosquito vectors are emerging. Further studies are needed to explore the epidemiology and the clinical features of these coinfections.

Key words: case report; dengue; zika, chikungunya; coinfection.

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Introduction

Arboviruses including dengue virus (DENV), chikungunya virus (CHIKV), and zika virus (ZIKV) pose a significant threat to global public health because of their potential for epidemics and fatal outcome [1,2]. DENV, ZIKV, and CHIKV are all positive-sense, single-stranded RNA viruses. DENV and ZIKV belong to the Flaviviridae family, but CHIKV belongs to Togaviridae family. Three organ systems play an important role in the pathogenesis of dengue fever: the immune system, the liver, and the endothelial cell linings of blood vessels. Chikungunya and zika have almost the same pathogenesis, but zika is moreover incriminated in neurological malformation in babies when the mother is infected during pregnancy [3–5]. All three arboviruses are transmitted by the same mosquito species, *Aedes aegypti* and *Aedes albopictus*; thus, increasing the possibility of the co-infection [6–8]. *Aedes aegypti* is the main vector that is reported in towns, villages and savannas across Mali. Female *Aedes* mosquitoes feed aggressively during the day, with peak activity at dawn and dusk [9]. The same actions taken for the control of this vector is thus important to prevent the occurrence of the infection by these three viruses. However, dengue is an urban/periurban disease, compared to other major arboviruses and malaria. The West African region emerges as a potential hotspot for arboviral disease transmission in a context of increasing urbanization, climate change, and enhanced international mobility [10,11]. The burden of arboviral infections remains underestimated due to the similarity of their symptoms with malaria and other tropical febrile illnesses. A review article concluded that in many settings in Africa, the diagnosis of dengue is less common than malaria. Rapid diagnosis tests for detecting NS1 Ag, IgM, and IgG are the most used diagnostic tools. But even when the test for malaria is negative, physicians often prescribe anti-malaria drugs [12]. This is true not just for dengue, but also for zika and chikungunya [13]. Moreover, the limited capacity of laboratories in low-income settings, and the low level of awareness of healthcare workers about arboviruses hinder the prompt detection and the timely reporting of cases. Serological studies have confirmed the circulation of DENV, CHIKV, and ZIKV in Mali with a prevalence of 77.2%, 31.2%, and 25.8% respectively [11,14,15]. We report a case of simultaneous triple infection with arboviruses that was diagnosed by real time polymerase chain reaction (RT-PCR) in a patient who was a resident in

Bamako, the capital city of Mali.

Case presentation

The case involved a six-year-old schoolgirl living in the peri-urban area of Bamako, Boulkassoumbougou, not far from the Niger river (Figure 1), with no history of known diseases, but had been in contact 2 weeks ago with a confirmed case of dengue fever living in the same house.

The symptoms began on 7 December 2023, with a fever of 40 °C, prompting her parents to take her to a local clinic where without any malaria testing—as reported in usual medical practice in many malaria endemic countries where the World Health Organization (WHO) recommendation for malaria "Test, Treat and track" is not well implemented—she received presumptive antimalaria treatment with artesunate. In response to the onset of a wet cough associated with persistent fever despite malaria treatment, the patient received probabilistic antibiotherapy (ceftriaxone) for pneumopathy. The patient was referred to the infectious disease ward of the University Hospital of Point G in Bamako for further investigation. The interview and clinical examination of the patient revealed only fever with temperature of 40.7 °C and normal vital signs. There was no sign of external or internal bleeding, and the tourniquet test was negative. Dengue fever, malaria, typhoid fever, and coronavirus disease 2019 (COVID-19) were hypothesized. A real-time polymerase chain reaction (RT-PCR) using the Center for Disease Control (CDC) Atlanta -Trioplex kit [16] was carried out at the University Clinical Research Center (UCRC) laboratory in Bamako coupled with a rapid diagnosis test (RDT) for dengue, and revealed the presence of 3 arboviruses: DENV, ZIKV, and CHIKV. Other causes including malaria, typhoid fever, and COVID-19 were disregarded using thick smear, blood culture, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) PCR on nasopharyngeal swab. An initial complete blood count (CBC) performed on 9 December 2023, showed normocytic anemia at 10.9 g/dL with increased transaminases and C-reactive-protein (CRP) (Table 1).

The patient was isolated under a pyrethroid insecticide-treated net (ITN), and provided with antipyretics (paracetamol), hydration with oral rehydration solution, and vitamin therapy (vitamin C).

Figure 1. Map of the patient's residence in Bamako, Mali, West Africa.

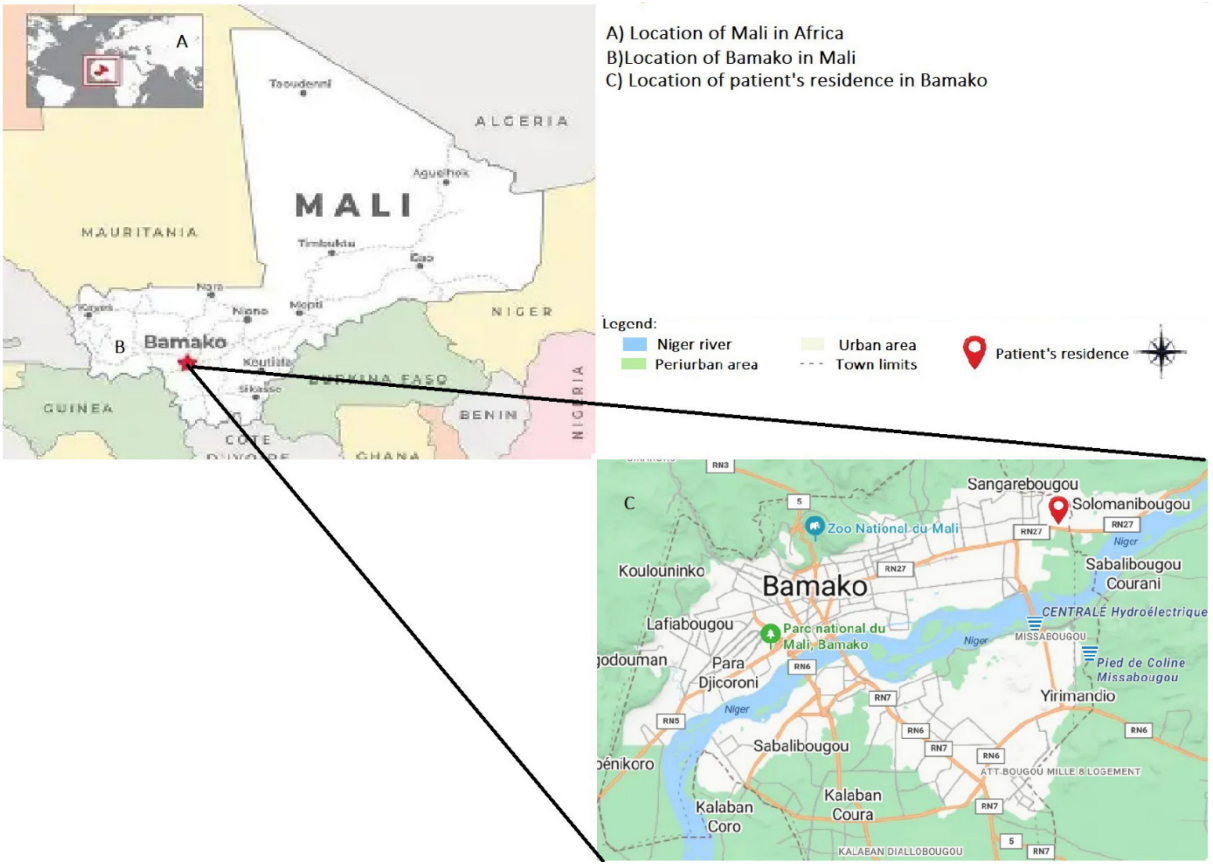

Table 1. Laboratory investigation results.

Laboratory parameters	Unit	12/09/2023	12/14/2023	12/19/2023	Reference limits
Hemoglobin (Hb)	g/dl	10.9	10.6	11.2	11.5–15.0
Total white blood cells count	cells/ml	6,500	12,500	7,400	4,100–10,900
Differential leukocyte count					
Neutrophils	cells/ml	2,990	5,000	3,600	2,000–7,500
Lymphocytes	cells/ml	2990	7100	3,400	1,500–4,000
Monocytes	cells/ml	520	250	350	400–1200
Eosinophils	cells/ml	0	125	40	40–500
Basophils	cells/ml	0	0	10	0–100
Platelets	cells/ml	430 000	429 000	405000	150000–450000
Blood prothrombin	%	95	86	90	70–100
Creatinine	mmol/L	59	69.7	62.4	50–100
Transaminases					
Aspartate aminotransferase (AST)	UI/L	69.03	194.73	58.27	< 40.0
Alanine aminotransferase (ALT)	UI/L	66.74	99.17	46.22	< 40.0
C-reactive protein (CRP)	mg/L	12	72	10	< 5
Blood smear for malaria		Negative	-		–
PCR DENV*		Positive	Negative	Negative	–
PCR ZIKV*		Positive	Negative	Negative	–
PCR CHIKV*		Positive	Negative	Negative	–
NS1 Ag DENV (RDT)**		Positive	Positive	Negative	–
Ig M DENV (RDT)**		Negative	Positive	Positive	–
Ig G DENV (RDT)**		Negative	Negative	Positive	–

PCR: polymerase chain reaction; DENV: dengue virus; ZIKV: zika virus; CHIKV: chikungunya virus; NS1 Ag: non-structural antigen; IgM: immunoglobulin M; IgG: immunoglobulin G; RDT: rapid diagnostic test. Follow up of patient's biological parameters upon diagnostics shows abnormalities on day 5 then improvement on day 10: decrease in hemoglobin level; leukocytosis mainly lymphocytosis, increase of CRP, and increase of transaminases (mainly of AST reaching 5 times the normal value on day 5). Platelets, blood prothrombin, and creatinine remained normal. PCR showed rapid negativity on day 5. Serology indicated sequential positivity of NS1 Ag, and IgM and IgG antibodies against the dengue virus.

A follow-up laboratory investigation carried out for 5 days was consistent with no severe symptoms but found a normal platelet count, an increase in white blood cell (WBC) counts, with lymphocyte predominance in transaminases and in CRP (Table 1). Moreover, the test for Epstein Barr virus was negative for IgM and IgG, and the clinical presentation did not show any abnormality in favor. There was no lymphadenopathy, and ultrasound or clinical evaluation of liver and spleen was normal. The patient recovered with a negative PCR on day 7 after the diagnosis, improvement of biological parameters (Table 1), and no sequelae.

Discussion

Although serological studies have described the potential risk of exposure to the 3 arboviruses in Mali [11,14,15], this report provides, for the first time, evidence of simultaneous co-infection with DENV, CHIKV, and ZIKV in a single patient in Bamako. The coinfection may be due to a simultaneous transmission by *Aedes* mosquito vectors, both *A. aegypti* and *A. albopictus* [17,18]. Despite the simultaneous coinfection with the 3 arboviruses, the clinical symptoms were mild, and no severe symptoms were observed. Coinfection with arboviruses could reduce the virulence of each virus and attenuate the clinical signs, though higher death rate was also reported among co-infected patients [19–21]. This has been explained in recent articles which have demonstrated, both in vitro and in vivo, antibody-dependent potentiation in patients with anti-DENV antibodies who acquire the ZIKV infection or vice versa [22,23]. In this report, the mild clinical symptoms were consistent with limited abnormalities observed in laboratory. This case also raises the issue of diagnosis of non-malarial fevers in endemic areas, with the patient being overtreated with antimalarial drugs and antibiotics at the local clinic due to the persistence of fever associated with cough. This is a common practice in low-income settings where limited laboratory capacity contributes to the overuse of antibiotics [24]. Investigation of viral etiology (arboviruses) could avoid unnecessary antimicrobial treatment. The rationale of our approach of testing for arbovirus was based on a recent study which found that dengue accounted for 23.4% of fever cases outside an epidemic period in Bamako, Mali [25].

Conclusions

This clinical case highlights co-circulation of different arboviruses in the urban context where *Aedes* mosquito vectors are emerging. Given the difficulty of distinguishing these infections clinically, we recommend systematic seroprevalence studies on these 3 arboviruses to evaluate their frequency. In addition, the need of strengthening laboratory capacity with rapid multiplex diagnostics should be considered. This clinical presentation emphasizes the need for understanding the clinical impact of infection with multiple arboviruses and the need for preventive and control measures that cover these infections together.

Ethical considerations

The patient's father gave his informed consent for the anonymous publication of the case

Authors' contributions

YC: manuscript draft; EAA: patient follow-up and obtaining inform consent; AK: trioplex RT-PCR; BD: lab tests; YD: SID: MS: patient examination; IKI: SD: SoD. manuscript review.

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Conflict of interest

No conflict of interest is declared.

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