

A case series of suspected dengue-like illness in Pakistan

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ABSTRACT

Dengue is an arbovirus endemic to Pakistan, with frequent outbreaks reported nationwide. We report a case series of 11 patients who presented during an outbreak of dengue-like illness in Karachi between November and December 2021. Although initial dengue testing was negative in most patients, further molecular testing identified Zika virus in two patients, including one patient with dengue and Zika virus co-infection. Neither patient had a recent travel history; however, absence of travel history alone does not establish local transmission. This case series highlights the diagnostic challenge of distinguishing Zika virus and dengue virus infection in patients presenting with dengue-like illness and supports consideration of broader molecular testing during unexplained arboviral outbreaks.

Keywords: Arboviruses; Coinfection; Dengue; Outbreaks; Zika Virus

BACKGROUND

Pakistan has diverse climates and ecosystems contributing to the spread of vector-borne diseases (VBDs), hence posing significant public health challenges.¹ Since the first reported epidemic of dengue fever in Pakistan in 1994, the dengue virus (DENV) has become increasingly prevalent, with cases documented across all five provinces.²

Dengue is caused by viruses belonging to the family Flaviviridae. The typical clinical presentation includes fever, joint pain, retro-orbital headache, and rash; however, in severe cases, complications can lead to organ failure and hemorrhages.³ However, the Zika virus (ZIKV), belonging to the same family, is transmitted by *Aedes* spp. mosquitoes. ZIKV infection is generally self-limiting. 1983 marks the first identification of ZIKV infection in Pakistan through serological evidence. Although ZIKV was previously suspected to circulate in the region, subsequent molecular and sequencing studies have now confirmed ZIKV infection in patients from Karachi.^{4,5}

Here, we report an outbreak of dengue-like illness in Pakistan. The emergence of these cases caused significant concern among both the public and health

care professionals in Pakistan. Additionally, the media referred to the illness as a "new mysterious virus," further fueling panic within a population already distressed by the ongoing COVID-19 pandemic and DENV infection epidemics.⁶ Further investigation into this unidentified illness led to the identification of DENV-ZIKV co-infection in one patient; subsequent sequencing of samples from the same outbreak identified ZIKV in a second patient.⁵

CASE SERIES:

We present a case series of 11 patients admitted to two tertiary care centers in Karachi, Pakistan, between November and December 2021. These patients had symptoms of fever and generalized body aches suggestive of a dengue-like illness. The cases were identified based on their shared clinical presentation and common outbreak setting. We describe the clinical and laboratory characteristics of all 11 patients while highlighting the two patients in whom ZIKV was identified, including one with DENV-ZIKV co-infection.

Table-I summarizes the clinical and biochemical profiles of the 11 cases with ages ranging from 15 to 59 years, with a mean age of 33.5 ± 15.27 years. Fever and generalized body aches were common in all the 11 patients. The two pregnant women had similar clinical courses and were followed up later, both with uncomplicated pregnancies and healthy births. Among the 11 patients, Case 6 was managed on an outpatient basis, while the remaining ten required hospitalization, with a mean hospital stay of 3.7 ± 1.25 days. The etiology of virus was not known, and molecular diagnosis (qRT-PCR) was performed later.

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As presented in Table-II, initial testing for dengue virus antigen (NS1) and dengue-specific IgM was negative in all 11 patients, except for Case 5, which demonstrated a positive IgM result on day 7 of illness. Pan-Dengue PCR was positive in Cases 1–6. Zika PCR was positive in Case 5 and initially equivocal in Case 6 on duplex PCR. Subsequent sequencing of samples from this outbreak confirmed ZIKV in Cases 5 and 6.⁵

Notably, this analysis identified DENV-ZIKV co-infection in Case 5 using qRT-PCR. Subsequent sequencing of samples from this outbreak also identified ZIKV in Case 6.⁵ The clinical presentation of Case 5 and 6 closely resembled that of the other patients, with common symptoms including fever, body aches, nausea, and vomiting. No additional or unique symptoms were noted. Laboratory investigations revealed normal hemoglobin, hematocrit, and white blood cell (WBC) counts. However, marked thrombocytopenia was noted, with a platelet count of 26

$\times 10^9/L$. In comparison, confirmed dengue cases also demonstrated significantly reduced platelet counts, with a mean of $38 \pm 8.52 \times 10^9/L$. Furthermore, none of the cases had a significant history of recent travel. While this is compatible with possible local exposure, it does not by itself confirm local transmission. In the ZIKV-negative cases, an alternative viral etiology, including chikungunya or another arboviral infection, cannot be excluded because additional pathogen-specific testing was not uniformly performed during the outbreak evaluation. At this time (2021), no outbreak of Chikungunya was recorded in Karachi. All 11 patients affected by the dengue-like illness were retrospectively interviewed regarding environmental and household risk factors for arboviral transmission using a structured questionnaire in the households of identified cases. The most frequently reported risk factor was lack of bed net use, reported in five of the 11 cases.

Table-I: Demographics and presenting complaints of eleven cases.

Case	Age (years)	Gender	Presenting complaints							Duration of hospital stay (in days)	
			Fever	Body ache	Headache	Nausea and vomiting	Cough and sore throat	Joint pain	Petechiae		Dysuria
Case 1	47	F	Y	Y	Y	Y			Y		4
Case 2	16	M	Y	Y	Y		Y				2
Case 3	15	F	Y	Y	Y	Y		Y			4
Case 4*	33	F	Y	Y	Y					Y	5
Case 5	59	M	Y	Y		Y					4
Case 6	27	F	Y	Y		Y	Y	Y	Y		N/A
Case 7	22	F	Y	Y		Y					4
Case 8	58	F	Y	Y	Y	Y					6
Case 9	32	M	Y	Y			Y				3
Case 10*	34	F	Y	Y	Y		Y				2
Case 11	25	F	Y	Y						Y	3

This table summarizes patient demographics, presenting complaints, and length of hospital stay.

(*) denote patients who were pregnant at the time of presentation—Case 4 at 23 weeks and 3 days, and Case 10 at 31 weeks and 2 days of gestation.

Table-II: Overview of initial diagnostic results for eleven cases.

Case	Dengue NS1 antigen	Dengue Ig M	Dengue Ig G	Pan Dengue PCR	Zika PCR	Zika Duplex PCR	Platelet Count ($\times 10^9/L$)
Case 1	negative	negative	negative	positive	negative	negative	N/A
Case 2	negative	negative	positive	positive	negative	negative	39
Case 3	negative	negative	positive	positive	negative	negative	46
Case 4	negative	negative	N/A	positive	negative	negative	41
Case 5	negative	negative *	N/A	positive	positive	negative	26
Case 6	negative	negative	N/A	positive	negative	equivocal †	268
Case 7	negative	negative	N/A	negative	negative	negative	200
Case 8	negative	negative	N/A	negative	negative	negative	347
Case 9	negative	negative	N/A	negative	negative	negative	204
Case 10	negative	negative	N/A	negative	negative	negative	208
Case 11	negative	negative	N/A	negative	negative	negative	148

This table presents the initial laboratory investigations for all eleven cases. An asterisk (*) indicates a case that initially tested negative but subsequently tested positive on day 7 of illness. The dagger symbol (†) denotes a case with equivocal Zika PCR results on the initial duplex assay. Case 6 was subsequently confirmed as ZIKV-positive by sequencing.⁵ The cut-off value for standard Zika PCR is 40 cycles (Ct); values >40 is considered negative. For Zika duplex PCR, the cut-off is 38.5 cycles (Ct) for both amplicons; values >38.5 are considered negative.

DISCUSSION

To the best of our knowledge, this is the first documented case of DENV-ZIKV co-infection identified during the 2021 dengue-like illness outbreak in Karachi. Sequencing work published in Emerging Infectious Diseases identified ZIKV in two patients from this outbreak, including one DENV-ZIKV co-infection, providing additional support for the inclusion of these cases within a case series.⁵ The similar clinical presentations of dengue and ZIKV underscore the diagnostic challenge and the value of considering ZIKV testing when dengue testing is negative during an arboviral outbreak. This study focuses on the clinical and diagnostic findings of the outbreak-associated cases rather than estimating the prevalence or extent of ZIKV transmission.

Although fatal cases of ZIKV infection are rare in otherwise healthy individuals, the virus is associated with significant morbidity and mortality in patients with underlying comorbidities.⁷ One of the most alarming outcomes is congenital Zika syndrome, characterized by microcephaly and other neuro-developmental abnormalities.⁸

In the context of molecular diagnostics, Pan-Dengue PCR and Zika duplex PCR are employed to detect the presence of these viruses in patients with dengue-like illness. These findings highlight the need for more comprehensive diagnostic strategies to accurately identify arboviral infections.⁷ The remaining cases were not confirmed to have ZIKV; however, because additional pathogen-specific testing was not uniformly performed, other viral etiologies cannot be excluded. The presence of competent Aedes vectors in their living areas remains relevant to the potential for arboviral transmission in Pakistan.⁵

Strengthening diagnostic capacity, vector control programs, and public awareness may help address the diagnostic and public health challenges posed by overlapping arboviral illnesses. Given the presence of ZIKV and DENV in the same outbreak setting, clinicians should consider ZIKV in the differential diagnosis of dengue-like illness when routine dengue testing is negative.^{5,9}

This was not a formal ZIKV surveillance study or a population-based outbreak investigation, so the extent of viral spread and transmission cannot be estimated. The eleven cases were obtained from patients presenting to the participating hospitals and therefore do not

represent all individuals affected by the outbreak. The findings should consequently be interpreted as an outbreak-associated clinical case series, with emphasis on the diagnostic identification of two ZIKV infections rather than estimation of transmission.

CONCLUSION

Viral fever of unknown origin is not a new phenomenon in Pakistan and has previously been observed during dengue outbreaks. This case series describes 11 patients with dengue-like illness identified during a 2021 outbreak in Karachi, including two patients subsequently confirmed to have ZIKV infection and one with DENV-ZIKV co-infection.⁵ The findings highlight the diagnostic challenge of overlapping arboviral illnesses and the importance of considering ZIKV when dengue testing is negative. Further investigation is needed to define the broader epidemiologic significance of these findings.

DISCLOSURES

None

CONFLICT OF INTEREST

None

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AUTHOR CONTRIBUTION

Haleema Sadia: Conceptualization, study design, final approval, accountable for all aspects of publication

Kumail Ahmed: Manuscript drafting, final approval, accountable for all aspects of publication

Syed Faisal Mahmood: Reviewing it critical, final approval, accountable for all aspects of publication

Erum Khan and Najeelha Talat Iqbal: Manuscript drafting, final approval, accountable for all aspects of publication

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