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Zika virus-induced neurological critical illness in Latin America: Severe Guillain-Barre Syndrome and encephalitis



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ABSTRACT

Zika virus (ZIKAV) is classically described as causing minor symptoms in adult patients, however neurologic complications have been recognized. The recent outbreak in Central and South America has resulted in serious illness in some adult patients. We report adult patients in Latin America diagnosed with ZIKAV infection admitted to Intensive Care Units (ICUs).

Methods: Multicenter, prospective case series of adult patients with laboratory diagnosis of ZIKAV in 16 ICUs in 8 countries.

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Results: Between December 1st 2015 and April 2nd 2016, 16 ICUs in 8 countries enrolled 49 critically ill patients with diagnosis of ZIKAV infection. We included 10 critically ill patients with ZIKAV infection, as diagnosed with RT-PCR, admitted to the ICU. Neurologic manifestations concordant with Guillain-Barre Syndrome (GBS) were present in all patients, although 2 evolved into an encephalitis-like picture. 2 cases died, one due to encephalitis, the other septic shock.

Conclusions: Differing from what was usually reported, ZIKAV infection can result in life-threatening neurologic illness in adults, including GBS and encephalitis. Collaborative reporting to identify severe illness from an emerging pathogen can provide valuable insights into disease epidemiology and clinical presentation, and inform public health authorities about acute care priorities.

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1. Introduction

In March 2015, the first autochthonous transmission of Zika virus (ZIKAV) was described in continental South America [1,2]. This flavivirus likely originated in Uganda, and is presumed to have migrated eastward [3,4]. As of March 28, 33 countries in the region of the Americas have since reported confirmed cases of transmission [5].

Epidemics provide a crucial and time-sensitive opportunity to understand the epidemiology of a new or emerging infectious threat. Using prior experience with severe H1N1 influenza and Dengue outbreaks [6,7], we organized a network of 24 sentinel Intensive Care Units (ICUs) in 8 Latin American countries to detect critically ill patients with diagnosis of ZIKAV requiring admission to ICU.

Laboratory confirmation of the cases during an epidemic outbreak can be difficult, particularly in middle- or low-income countries. According to Pan-American Health Organization (PAHO), the majority of cases of ZIKAV are suspected cases (65,524 in the countries that report to our database) with only a minority having laboratory confirmation (1647) [8].

The best test to confirm infection is the Reverse Transcription Polymerase Chain Reaction (RT-PCR) in serum or cerebrospinal fluid, but it is not without disadvantages. Although first reports limited the usefulness of analyzing serum to 5–7 days after infection [9,10], recent data challenges this assertion and sets the median and 95th percentile for time until loss of positivity at 14 days (95% CI, 11 to 17) and 54 days (95th CI, 43 to 64) respectively. (Paz-Bailey G, Rosemberg ES, Doyle K et al. Persistence of Zika virus in body fluids – preliminary report. *N Engl J Med.* February 2017). Most cases are diagnosed on a clinical and epidemiological basis, using protocols and case definitions established in each country according to WHO definitions [11–15].

Clinical ZIKAV infection typically has a milder presentation when compared to other *Aedes*-related viral infections. However, it has been increasingly recognized to cause serious illness, particularly with cases identified during this epidemic. Evidence supporting the relationship between the ZIKAV infection and fetal microcephaly, Guillain-Barre Syndrome (GBS) and myelitis is increasing [16–19].

While microcephaly in the children of infected mothers has been the most dramatic manifestation of this neurotropic virus, various neurological disorders have been increasingly recognized in affected hosts [20,21]. In French Polynesia, a total of 42 cases of GBS were recorded during the ZIKAV outbreak (2013–14), an estimated risk of 0.24 cases per 1000 ZIKAV infections [22]. Cases of myelitis have been described during the acute phase of the infection, while GBS is more commonly a post-infectious complication [23].

The description of the clinical features of new emergent diseases is a challenge that might require gathering data concurrently with the epidemic outbreak. The present study had its focus on detecting and describing severe medical complications caused by ZIKAV infection in adults in a short period of incidence, through a multicenter, prospective and observational study of admitted patients in participating hospitals and intensive care units (ICUs) with diagnosis of ZIKAV.

1.1. Objectives

Describe the clinical presentation, demographic features, and evolution of critical ill adult patients admitted to ICUs with recent diagnosis of ZIKAV infection, through a surveillance network in 8 countries of Latin America.

2. Materials and methods

We developed a network of 24 sentinel ICUs in 8 participating Latin American countries to detect critically ill patients with diagnosis of ZIKAV between December 2015 and April 2016.

2.1. Eligibility criteria

We recruited all critically ill adult patients admitted to participant ICUs with recent diagnosis of ZIKAV infection. We established a confirmed diagnosis when the patient tested positive by RT-PCR against ZIKAV [24].

2.2. Exclusion criteria

We excluded patients without laboratory confirmation or with a plausible alternative diagnosis.

2.3. Data recollection

Clinical and demographic data were collected using an online case report form modified from the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) [22], with modifications relevant to critically ill patients, diagnosis and treatment of neurological complications. This case report form was made available to all 24 participating ICUs through Google Forms and data pooled in Google Drive.

2.4. Statistical analysis

Data were recorded in Excel and analyzed using Stata 11 v (College Station, Texas, USA). Quantitative variables are presented with measures of central tendency and dispersion, as appropriate for the data distribution. Categorical variables are presented as counts.

2.5. Ethical statement

International ethics guidelines for biomedical research on human beings were followed (WHO, CIOMS). As no intervention or purposeful modification of biological, physiological, psychological or social variables was intended, it is considered an exempt risk research and no informed consent was required. Data were obtained anonymously, assigning different codes for hospital records and never posing a risk to professional confidentiality agreement. The research occurred in the context of a ZIKAV outbreak. Protocol was defined and one Case Report Form (CRF) was the only information-gathering instrument.

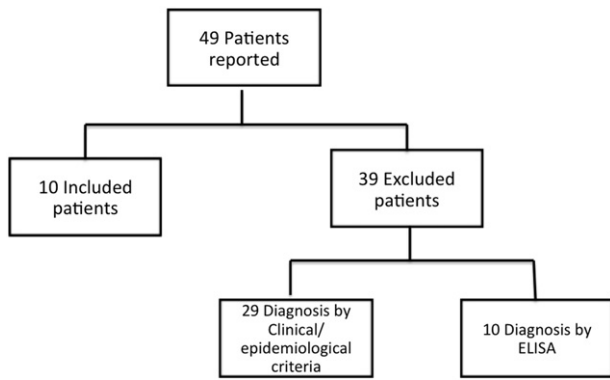


Fig. 1. Selection of reported patients with Zika virus infection in participating Intensive Care Units.

3. Results

Between December 1st 2015 and April 2nd 2016, 16 ICUs in 8 countries enrolled 49 critically ill patients with diagnosis of ZIKAV infection: Colombia 25, Venezuela 10, Salvador 6, Guatemala 2, Puerto Rico 2, Ecuador 2, Peru and Chile 1 each.

The diagnosis of ZIKAV was established through RT-PCR in 10 patients (9 from serum, 1 from Cerebrospinal Fluid), ELISA in 10 patients (Serum) and using clinical/epidemiological criteria in the remaining 29 patients. Only those patients with diagnostic confirmation by RT-PCR were included (Fig. 1). Baseline characteristics are described in Table 1.

ELISA detection of IgM was negative for dengue (55%), Human Immunodeficiency Virus (HIV) (46.9%), Cytomegalovirus (18.4%), hepatitis (14%), Epstein Barr virus (12%), Herpes Simplex virus (12%), with the exception of one case positive for Dengue. Other tests for Chikungunya, *Campylobacter jejunii*, *Mycoplasma pneumoniae*, were made with lesser frequency.

Seven patients still had eruption at the time of admission, as required by the WHO definition of ZIKAV infection case, and only one of them was pruritic, as seen in the convalescence period of other viral diseases like dengue (Table 1).

Nine patients came from urban areas, and 1 patient from rural area. Three reported Zika-like illnesses in family members. Eight patients were diagnosed with GBS, by an intensivist or a neurologist following the Brighton Criteria. Two patients diagnosed with encephalitis by neurologist according to clinically and radiologic criteria

Indications for ICU admission were: respiratory insufficiency due to neuromuscular weakness in 6, altered level of consciousness in 3, and one septic shock (Table 2).

The median time lapse between initiation of symptoms and admission was 5.5 days (IQR 9–2). The median stay at UCI was 6.5 days (IQR 9–6) and the median time between initiation of symptoms and neurologic nadir was 6 (IQR 8–4). The median hospital stay was 13 days (IQR 14–3) (Table 2).

A total of 6 patients required intubation and mechanical ventilation; all radiographs were described as normal, and the respiratory insufficiency had its origin in neuromuscular weakness; one required, additionally, nasal high flow oxygen during the stay. During the ICU stay, four confirmed patients received intravenous vasoactive drugs for shock; half required norepinephrine doses of >0.1 µg/kg/min (Table 2).

Table 1
Characterization of patients with Zika virus-related critical illness (n = 10).

Patients		1	2	3	4	5	6	7	8	9	10
Mean age (standard deviation) – years	42 (17)	60	60	24	37	26	36	25	67	40	18
BMI median	25.4	23.9	22.1	23.4	26.7	22.6	22.8		25.7	30.5	31.1
Female sex – no (%)	4 (40)			+	+			+		+	
State of departure											
Dead								+	+		
Symptoms at admission – no (%)											
Musculoskeletal symptoms											
Myalgia	9 (90)	+	+	+	+	+	+		+	+	+
Arthralgia	8 (80)	+	+	+	+	+	+		+		+
Central nervous system											
Headache	6 (60)		+			+	+	+	+		+
Motor dysfunction	7 (70)	+		+	+	+	+	+	+		
Confusion	3 (30)					+		+	+		
Behavioral changes	2 (20)							+	+		
Encephalopathy	2 (20)							+	+		
Ocular symptoms											
Conjunctivitis	5 (50)				+	+	+	+	+		
Photophobia	3 (30)		+			+		+			
Skin lesions											
Eruption	7 (70)		+	+	+	+	+	+	+		
Erythematous	6 (60)				+	+	+	+	+		
Pruritic erythema	1 (10)						+				
Maculopapular	1 (10)									+	
Ecchymosis	1(10)									+	
Exanthema	1 (0)		+								
Purpurae	0 (0)										
Bug stings	1 (10)										
Respiratory symptoms											
Difficulty breathing	4 (40)	+					+	+	+		
Chest pain	1 (10)		+								
Throat pain	1 (10)									+	
Cough	1 (10)		+								
Gastrointestinal symptoms											
Nausea	4 (40)	+				+	+			+	
Diarrhea	2 (20)	+								+	
Abdominal pain	1 (10)									+	

BMI: Body Mass Index. No: number. %: percent.

Table 2
Clinical characteristics of patients with Zika virus infection in intensive care.

Patients	1	2	3	4	5	6	7	8	9	10	
ICU characterization											
Mean APACHE II (standard deviation)	12 ± 7										
Reason for ICU admission – no (%)											
Risk of respiratory insufficiency caused by neuromuscular weakness	6 (60)	+	+		+	+	+			+	
Progressive neurological deterioration (motor/sensitive)	0 (0)			+							
Mental status compromise	3 (30)						+				
Other (septic shock/thrombocytopenia)	1 (10)							+		+	
Indicators of stay. Median-IQR (days)											
Time: Begging of symptoms-ICU admission	5.5 (9–2)	1	0	18	4	6	2	8	5	22	9
Time: Hospital stay	13 (14–3)	36	3	10	9	14	25	7	9	11	10
Time: ICU stay	6.5 (9–6)	0	3	6	6	16	27	7	9	9	6
Time: Begging of symptoms – Neurological nadir	6 (8–4)		4		3	7	8	5	8	14	5
Rankin at discharge	1 (6–1)	5		1	1			6	6	1	1
Hemodynamic support n (%)											
Need for ventilatory support	6 (60)	+				+	+	+	+		+
Need for hemodynamic support	4 (40)	+				+		+	+		
Plasmapheresis	1 (10)				+						
Immunoglobulins	6 (60)	+		+		+	+		+		+

PCR: Polymerase Chain Reaction, IgM: Immunoglobulin M, APACHE = acute physiology and chronic health examination, ICU: Intensive Care Unit, IQR: Interquartile range.

Six patients were treated with immunoglobulin and 1 with plasmapheresis (Table 2).

Lumbar puncture (LP) was performed in 6 patients, with a mean time lapse between onset of symptoms and procedure of 13.4 ± 7.4 days. Cerebrospinal fluid (CSF) analysis revealed pleocytosis in 4, two of those also had increased proteins, and glucose was normal in all of them.

Table 3
Neuro conduction study of sensory and motor nerve of a confirmed patient with diagnosed Guillain-Barre Syndrome associated with Zika virus infection (case 3).

A. Wave studies										
NR	F-Lat (ms)		Lat norm (ms)		L-R F-Lat (ms)		L-R F-Lat norm			
Left median (Mrks) (Abd Poll Brev)	23.57		<33		4.74		<2.2			
Right median (Mrks) (Abd Poll Brev)	28.31		<33		4.74		<2.2			
Left tibial (Mrks) (Abd Hallucis)	40.00		<61		7.97		<5.7			
Right tibial (Mrks) (Abd Hallucis)	47.97		<61		7.97		<5.7			
B. Study of the right and left ulnar nerve										
Left ulnar motor (Abd Dig Minimi)										
Wrist	1.3	<4.2	5.4	>3	B elbow	Wrist	4.1	20.0	49	>53
B elbow	5.4		5.7		A elbow	B elbow	1.2	8.0	67	>53
A elbow	6.6		3.6							
Right ulnar motor (Abd Dig Minimi)										
Wrist	2.1		8.5	>3	B elbow	Wrist	3.4	20.0	59	>53
B elbow	5.5		8.2		A elbow	B elbow	1.2	7.0	58	>53
A elbow	6.7		8.3							
C. H reflex studies										
NR	H-Lat (ms)		L-R-H-Lat (ms)		L-R Lat norm					
Left median (Flex Car Rad)	18.12		0.39		<1.0					
Right median (Flex Car Rad)	17.73		0.39		<1.0					
Left tibial (Gastroc)	30.14		0.47		<2.0					
Right median (Flex Car Rad)	29.67		0.47		<2.0					

Three patients underwent electromyography (EMG). Findings were consistent with demyelinating polyneuropathy in one, axonal polyneuropathy in the other and mixed in the last (Table 3). Fig. 2 shows this patient's EMG.

Eight patients underwent brain imaging; three magnetic resonance images (MRI) and six Computed Tomographic (CT) images. One MRI was reported pathological with hyperintense lesions in frontal and temporal cortical regions bilaterally, and subcortical involvement that persisted in axial flair, rendering the sequence compatible with inflammatory lesions "characteristic of encephalitis/rhombencephalitis" (Fig. 3). One CT scan showed signs suggestive of brain swelling. All the other imaging studies were normal.

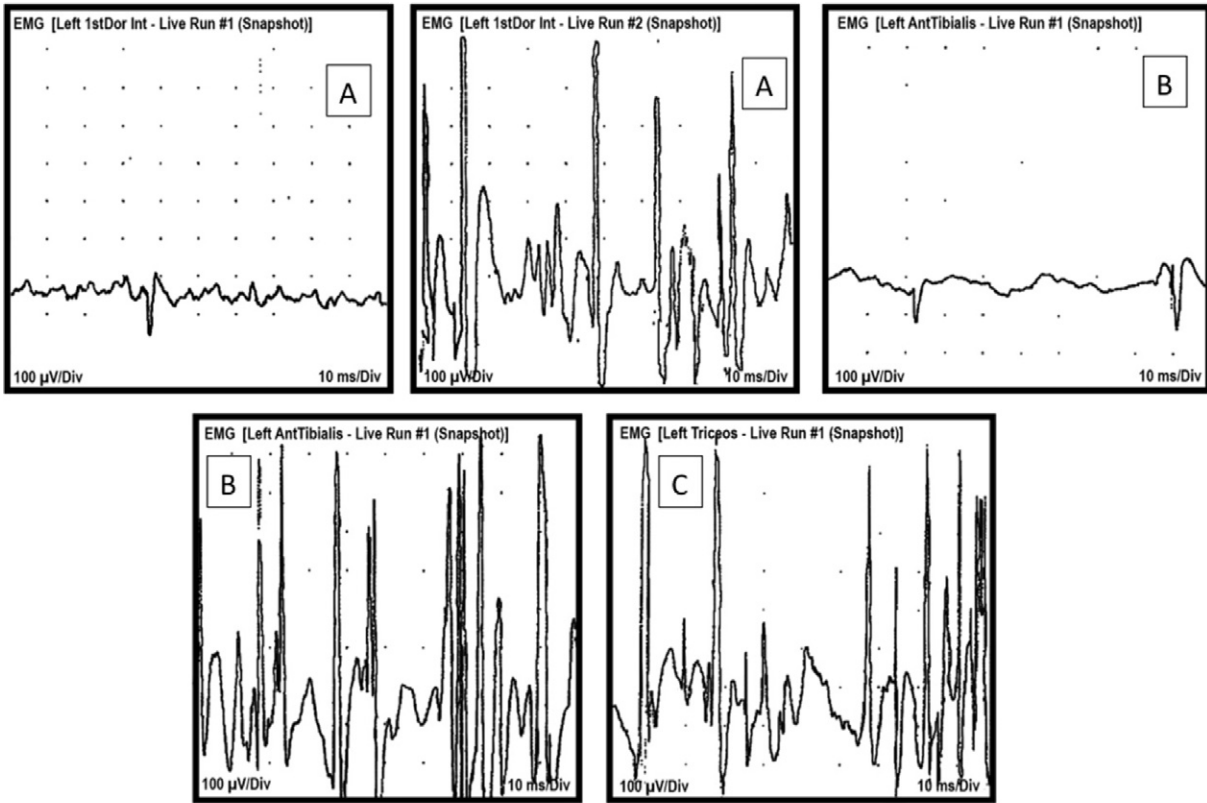
Two patients had a clinical picture compatible with encephalitis. One patient was diagnosed after showing suggestive findings on MRI (as described above), a LP with 34 lymphocytes/mm³, elevated proteins and normal glucose with a positive RT-PCR for ZIKAV in the CSF. After an eleven-day stay in the ICU, the patient was discharged with no neurological disability. The other, admitted with a diminished level of consciousness, had the abnormal CT described above and died after less than a week in the ICU.

The median Rankin scale at discharge was 1 (IQR 6–1), meaning no significant disability. Two patients died, one diagnosed with GBS (and subsequent multisystem organ failure), the other with encephalitis. The neurologic deficit responsible for ICU admission persisted at discharge in only one of all the cases. Nevertheless, this one patient suffered severe disability (bedridden, incontinent and requiring constant nursing care) (Table 2).

4. Discussion

The authors studied a population of patients whose illness was sufficiently severe to merit ICU admission. Forty-nine patients were identified in 24 ICUs in Latin America, however only the 10 cases diagnosed were confirmed with RT-PCR, presumably due to technological limitations in the different countries. These patients were admitted over a period of 25 epidemiological weeks. All presented with GBS according to Brighton criteria; two of them died one due to encephalitis and one with septic shock.

The WHO/PAHO reported a peak of incidence in ZIKAV infection between epidemiological weeks 3 and 9 of 2016 [6]; consistent with what was observed in Micronesia, our cases began to occur 2 weeks later. When comparing demographical data, recent data from Pernambuco, Brazil show similarities to what we report. Although the age group most



EMG: Electromiography

Fig. 2. Electromyography of a confirmed patient with diagnosed Guillain-Barre Syndrome associated with Zika virus infection (case 3), compatible with an asymmetrical mixed axonal and demyelinating polyneuropathy, showing: A) Activity increased insertion and few signs of instability membrane left dorsal interosseous muscles and triceps first left. B) Tibial and paraspinal bilateral L5 engine with morphologically normal motor units and recruitment slightly decreased from the distal. C) In other muscles motor activity units insertion, spontaneous activity and recruitment pattern showed normal.

frequently affected by ZIKAV-related GBS was patients in their fourth decade, the attack rate was higher in the patients over the age of 60 [5].

Flaviviruses, including dengue virus, have previously been shown to occasionally develop neurological complications [25–28]. In our 10

patients confirmed with RT-PCR, the most common presentation was ascending weakness with hyporeflexia/arreflexia, consistent with the Brighton criteria for GBS [29]. The time between the appearance of symptoms to neurologic deterioration was 5 days and the neurologic

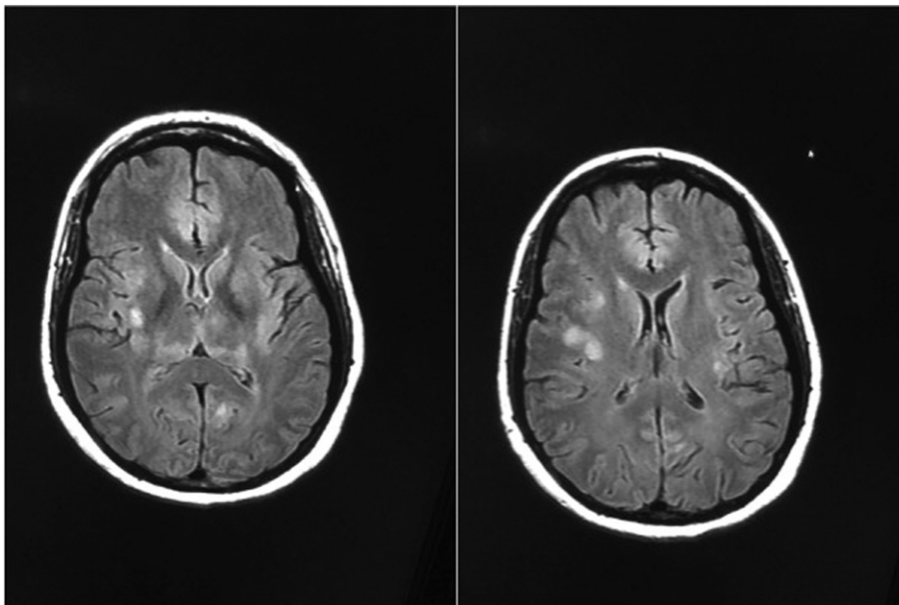


Fig. 3. Magnetic resonance brain of a confirmed patient (case 4) with diagnosed with encephalitis associated with Zika virus infection showing: hyperintense lesions in frontal and temporal regions bilaterally, additionally subcortical damage can be found predominantly in the right side. These findings are compatible with a diagnosis of encephalitis.

nadir was reached in a median of 5 days, consistent with GBS reports of 12 h to 28 days [20,30]. Nevertheless, the CSF analysis showed 4 patients with pleocytosis, and none with albumin-cytologic dissociation (an increase in CSF protein levels without a corresponding increase in cellular content characteristic of GBS). Previous reports on ZIKAV-GBS showed similar time between onset of viral symptoms and neurological deterioration (6 days). In spite of this, no patient with such presentation was still viraemic at admission, as established by RT-PCR [9,10]. Whether we are looking at a subset of patients with a different presentation from GBS, is still far from settled [31].

Of the three cases that underwent electromyography, two of them were reported as suffering acute demyelinating polyneuropathy and one axonal motor polyneuropathy, in contrast to what has been reported in recent publications in Colombia and French Polynesia where axonal motor neuropathy was the predominant [32–37]. This could be due to an earlier acquisition in those studies, that could have later shown different results, as previously reported by Cao-Lormeau VM et al.

Although variable, the median ICU stay was 6.5 (IQR 9–6). Although there is no data regarding ZIKAV-related GBS in particular, it was shorter than the two or three weeks described for other patients with GBS [20,30]. The need for ventilator support was higher, as 60% required intubation and mechanical ventilation due to muscular failure. This is higher than what has been previously reported both for ZIKAV and other types of GBS [38–43]. Also, more patients received intravenous vasoactive medication (40%) for hypotension, a greater proportion than the 20% that has been described for GBS [37,40].

It is worth noting the outcome heterogeneity, attributable to some extent to the limited sample. Of the surviving GBS patients, the degree of motor incapacity was minimal at the time of departure for all except one; similar to previous publications [37–39]. Mortality in this group was 12.5% similar to previous reports 6 to 15% [44–46]. Two patients were suspected to have encephalitis; one was discharged without disability while the other died.

Our study benefited from the establishment of the Latin American Critical Care Trials Investigators Network (LACTIN) which provided a platform for collaboration amongst investigators in geographically dispersed areas, and from the International Forum for Acute Care Trialists (InFACT) which provided methodological support and mentorship for the study. Indeed, large investigator-led research consortia have proven to be important in the initial characterization of novel infectious threats such as H1N1 influenza, MERS-CoV, Ebola, and ZIKAV. The availability of validated and ready-to-use case report forms through the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) facilitated the rapid launch of data collection.

The study here presented has a number of limitations. Of the 49 cases reported, 39 were discarded due to the lack of RT-PCR confirmation. The scarcity of resources and technological limitations in certain countries, especially during an epidemic, play a major role in determining diagnostic protocols. In addition, the workup for GBS was insufficient, undermining the certainty of diagnosis in some cases. Some data had to be collected retrospectively and even then, key elements may be missing due to the complexity of this nascent international collaboration. Participation in the study was voluntary and unfunded. As such, we do not claim to establish the regional burden of severe ZIKAV infection during the period reported. Furthermore, we lack reliable prevalence data, so we cannot estimate the risk of severe illness amongst infected patients.

In summary, we show that ZIKAV has uncommon neurologic complications that are severe enough to warrant ICU admission. We present a really heterogeneous population, some patients concordant with ZIKAV-GBS as described previously by Cao-Lormeau VM et al., while other patients were still viraemic at presentation, something not previously reported, warranting further investigation. Encephalitis is a much rare, but also more lethal, presentation of this emerging infection.

5. Implications and conclusions

It is important to understand the spectrum of presentations of ZIKAV infection as the current outbreak expands. In this study we report 10 adults critically ill patients with diagnosis of ZIKAV confirmed that required admission to ICU due to life-threatening complications. In our series, ZIKAV was associated with a spectrum of neurological presentations: most commonly a GBS-like syndrome, but also encephalitis, suggesting more than one potential pathophysiological mechanism. This is important in clinical follow-up of patients suspected with ZIKAV, and when considering etiologies amongst patients presenting with neurologic symptoms. Larger population-based observational studies of patients with ZIKAV are needed to help identify risk factors for severe illness so that we may better counsel patients and prepare the health care system.

Conflict of interest

The authors declare having no conflict of interest.

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