

Zika in Pernambuco: rewriting the first outbreak

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Abstract

Introduction: A Zika virus epidemic was registered in 2015 in Northeast Brazil. In the State of Pernambuco, thousands of classical cases transpired, and in the following months, neurological disturbances in adults and microcephaly in newborns emerged as complications. After the peak of the epidemic, the official system reported only four cases of Zika virus but over 100,000 cases of dengue virus. The vigilance system was unable to retrospectively estimate cases or to issue an alert to officially notified cases with possible inconsistency concerning specific arbovirolosis diagnoses. **Methods:** To evaluate the frequency of different arbovirolosis diagnoses based on clinical-epidemiologic criteria, from January to April 2015, we conducted a hospital-based cross-sectional study retrospectively analyzing suspected cases of arbovirolosis. **Results:** Of 1,046 total suspected cases of arbovirus, 895 (86%) were classified as probable Zika virus cases, and 151 (14%) as probable dengue virus cases. The most frequent manifestations in probable Zika virus cases were exanthema (100%), pruritus (50.7%), fever (20.4%) and arthralgia (27.7%). **Conclusions:** In contrast to the official data, during the peak months of the arbovirolosis epidemic of 2015, most cases were compatible with Zika virus infections. Hospital-based studies, although retrospective and based on secondary data from clinical files, might provide a better estimate of the number of cases relative to currently available data, if derived from several urgent care units of representative areas of a city or state. This would partially retrospectively correct some inconsistencies regarding official notifications.

Keywords: Zika. Dengue. Outbreak. Arbovirus. Surveillance.

INTRODUCTION

The Zika virus (ZIKV) is an arbovirus of the *Flaviviridae* family. It was first identified in Uganda in 1947; however, occurrences of human infection were only sporadically reported in isolated situations until its epidemic potential was noticed in Micronesia in 2007. In 2013, in French Polynesia, a change in the pattern was observed, and the attack rate increased, with an estimated 11% of the population affected⁽¹⁾⁽²⁾.

In November 2014 and more so at the beginning of 2015, the State of Pernambuco and Rio Grande do Norte in Brazil noticed an outbreak of an exanthematic disease with a clinical pattern different from that of dengue virus (DENV). Shortly, the same disease was reported in other northeastern states. Based on its clinical pattern of an infectious disease with high incidence of sudden exanthema along with a lower incidence of arthralgia and conjunctivitis, it was hypothesized that this was an outbreak

of ZIKV infection. This was confirmed in April 2015 through polymerase chain reaction (PCR) tests using blood samples from patients who were being observed in Bahia⁽³⁾, and later in Rio Grande do Norte⁽⁴⁾.

In the following months, there was an increase of neurological incidents in different cities in northeast Brazil possibly related to the ZIKV; these incidents especially included Guillain-Barré syndrome. In Pernambuco, a single reference hospital neurological unit held 131 cases with suspected ZIKV involvement⁽⁵⁾. The virus was later detected in seven of these cases through PCR and virus isolation, confirming the association between ZIKV infection and neurological disorders, as suggested in French Polynesian studies⁽²⁾⁽⁶⁾.

In October 2015, suspicion arose regarding a relationship between ZIKV infection in mothers and newborns with microcephaly⁽⁵⁾⁽⁷⁾⁽⁸⁾. Until the last bulletin of the epidemiological week 51 of 2015, there were 2,975 suspected cases in Brazil and 1,153 in Pernambuco⁽⁹⁾. Around 60-70% of these newborns' mothers reported having experienced exanthema during the pregnancy, especially in the first trimester⁽¹⁰⁾⁽¹¹⁾.

In Pernambuco, despite confirmation of virus circulation and an impressive number of cases seen in health units,

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epidemiological surveillance in the state and the Ministry of Health did not have the tools to notify cases with a clinical-epidemiological suspicion of ZIKV infection. Therefore, instructions declared that every suspected case should be notified as DENV infection [*Sistema de Informação de Agravos de Notificação* (SINAN) Dengue *on line*], making the sentinel hospitals as the only ones capable of notifying suspected ZIKV cases⁽¹²⁾. After the critical stage of the ZIKV epidemic, the state's epidemiological bulletin reported 80,338 cases of DENV infection and four cases of ZIKV infection in the Ministry of Health report, only two ZIKV cases were notified by the sentinel units⁽¹³⁾.

Even though the State of Pernambuco was affected by this substantial outbreak of ZIKV cases with typical presentation and complications, there were an insignificant number of case registrations in the surveillance system, and there was no established estimate regarding the number of cases based on regional data. In 2015, case samples notified as DENV infection by the State Secretary of Health were analyzed by laboratories of reference of the Ministry of Health: of 2,095 total cases, only 54 (2.6%) were positive for DENV, suggesting that a great number of notified cases were not truly cases of DENV, but could be associated with other arboviroses, such as Zika. In the State of Mato Grosso do Sul, which did not have a reported Zika epidemic, 75% of 1,365 suspected dengue samples were positive⁽¹⁴⁾.

The vigilance system was not able to make an retrospective estimative of cases or to alert for a possible inconsistency of cases of arbovirose officially notified, what may compromise analyzes of clinical-epidemiological patterns of this epidemic. Other countries have used different methodologies to estimate the number of cases as well as to adjust projections which contribute to the understanding of the epidemic pattern of the disease.

In virtue of the scarce information regarding the ZIKV epidemic in the State of Pernambuco in 2015, we conducted a hospital-based study retrospectively analyzing the probable cases accepted in urgent care, aiming to evaluate the frequency of arbovirus diseases. This rereading of cases contributes to an understanding of the epidemic and may serve as a potential model to evaluate epidemics with circulation of several arboviruses in different populations. Such information would also enhance knowledge concerning the epidemiology of these emerging diseases.

METHODS

Patients

A hospital-based retrospective cross-sectional study was conducted using individual medical records from patients admitted during the months of January until April of 2015 in the urgent care unit of Santa Joana Hospital, a general private hospital, which served as a reference for urgent care in the State of Pernambuco.

The study analyzed 100% of the admitted patients' medical records. Medical records registering acute febrile or exanthematic disease were selected. A standard simplified spreadsheet was applied to extract data from the medical records, which included signs, symptoms, and time (chronology) of the disease.

Initially, to investigate arbovirus diseases, symptoms and laboratory analysis that were not compatible with acute arboviral infection were excluded, such as patients with respiratory tract symptoms, gastroenteritis diagnosis, urinary tract symptoms, and localized infections (e.g., appendicitis, erysipelas, and acute pelvic inflammatory disease).

Case definition

Considering the confirmed viral circulation and ongoing epidemic, a clinico-epidemiological profile was used to define probable cases of arboviral diseases. Probable ZIKV cases were defined as those exhibiting pruriginous maculopapular exanthema, beginning up to two days after the first symptoms, with no fever, self-reported fever, or fever $\leq 38.5^{\circ}\text{C}$. Other signs and symptoms included conjunctival hyperemia (without secretion or pruritus), arthralgia, and articular edema.

As the chronology of exanthema helps differentiate between arboviruses, occurring prematurely with ZIKV infection and only after 3 or 4 days with DENV infection, cases with a history of exanthema up to 48 hours after the first symptoms were classified as probable ZIKV infection, and those with exanthema after 48 hours were classified as probable DENV infection.

In addition, the following were used to help determine cases of DENV infection: history of fever, usually lasting 2 to 7 days, with other symptoms such as nausea, vomiting, myalgia, arthralgia, headache, retro-orbital pain, petechiae, leukopenia, positive tourniquet test, and in some cases, warning signs, or shock.

Cases were classified as inconclusive if there was insufficient clinical data to be classified as either Zika or dengue virus infection.

RESULTS

Medical record evaluation and case classification

A total of 28,881 medical records from January to April 2015 were analyzed from the urgent care units of different medical specialties (surgery, orthopedics, neurology, pediatrics, internal medicine, and gynecology). Of the total records, 11,710 were from general medicine and 9,859 were from pediatrics.

We excluded 1,135 medical records that were not compatible with acute arboviral infections, 49 of which we excluded for lack of information such as time of the beginning of symptoms, time of exanthema, records stating nonspecific viral infections, and records without report of signs and symptoms. Forty records were also excluded for having insufficient data to indicate either Zika or dengue virus infection, such as being seen by a doctor only once in the first days of infection, having no history of fever or rash or only general symptoms such as headache and asthenia, being defined by the doctor as a *general viral infection*, or having fever as the only complaint without further evaluation. The remaining 1,046 cases were included for further analysis and case classification.

Based on clinico-epidemiological criteria, of these 1,046 cases, 895 (86%) were classified as probable ZIKV infection and 151 (14%) as probable DENV infection. Cases of arbovirus

infection represented 48.5 cases per 1,000 medical visits (general care and pediatrics). The peak number of probable dengue and Zika virus cases occurred in March 2015 and represented 41% of the total arboviral related visits (434/1,046) for an overall rate of 69 cases per 1,000 visits (**Table 1**). Seventy-five percent of cases were recorded in the adult emergency sector (789/1,046) and 25% in the pediatrics sector (257/1,046; **Table 2**). In the analysis of probable Zika cases, the results were similar for the total sample, with 75% of cases over 14 years of age (670/895). The peak month for this age group was March, with a rate of 81 cases per 1,000 visits. Among probable cases of the new epidemic, 41% (368/895) were male, and 59% (527/895) were female. The median age was 31 years old (range, 5 months and 85 years).

The time between the beginning of symptoms until the hospital visit was a minimum of 10 hours and maximum of 8 days, with an average of 3.4 days and median of 3 days.

The most frequent manifestation of cases classified as probable Zika was exanthema, which was present in 100% of cases, followed by pruritus, present in approximately half (50.7%) of cases. Fever was reported in only 183 (20%) patients and was positively measured at the time of consultation in 13 (1.5%) of the cases (**Table 3**). Arthralgia was reported in 215 (27.7%) patients, articular edema was reported in 41 (4.5%) patients, and conjunctivitis was reported in only 27 (3%) patients.

DISCUSSION

Historically, DENV epidemics occur in Pernambuco during the first half of the year, when *Aedes aegypti*, the main type of mosquito that spreads the ZIKV, reaches its highest spread. The following retrospective chart review from an urgent care hospital identified that 86% of suspected arboviral diseases occurring during the first four months of 2015 were classified as probable ZIKV infection, whereas only 14% were classified as probable DENV infection. These data are in disagreement with Pernambuco's epidemiologic surveillance, which took into consideration suspected case notifications. According to the official data, it was registered as a major dengue outbreak, although the presence of the ZIKV had already been confirmed and medical assistance professionals alerted epidemiologic surveillance regarding the low number of DENV cases and the high number of ZIKV cases. The latest epidemiologic bulletin from the Brazilian Ministry of Health in 2015 registered 1,649,008 probable cases of DENV infection and 20,661 of Chikungunya virus (CHIKV) infection, with no reference to the total number of ZIKV cases; presence of autochthonous cases was mentioned in just 19 federative units⁽¹⁴⁾.

In Pernambuco, which was the state with the highest occurrence of ZIKV infection, data distortion worsened due to an official note orientating the notification of all cases as DENV infection (SINAM dengue *on line*), with only hospitals belonging to the sentinel network being able to notify suspected cases of ZIKV infection⁽¹²⁾; this official note also pertained to other federal states. According to Ministry of Health records, on October 2, 2015, only two cases of ZIKV infection had been reported from sentinel units in Pernambuco, demonstrating the fragility of this system regarding ongoing epidemic diseases⁽¹³⁾.

TABLE 1
Arboviral related visits including adults and children.

Month	Jan	Feb	March	April	Total
Arboviral cases	103	228	434	281	1,046
Total visits	4,175	4,340	6,269	6,785	21,569
Cases/1,000 visits	25	53	69	41	48

TABLE 2
Distribution of arbovirolosis by age group.

Age group (years)	Probable Zika cases		Probable dengue cases	
	n	%	n	%
0-4	105	11.7	14	9.3
5-9	63	7.0	12	7.9
10-14	57	6.4	6	4.0
15-19	54	6.0	13	8.6
20-39	350	39.1	64	42.4
40-59	201	22.5	34	22.5
>60	65	7.3	8	5.3
Total	895	100.0	151	100.0

TABLE 3
Clinical manifestations in 895 cases classified as probable Zika virus infection.

Symptoms	Number	Percentage
Rash	895	100.0
Pruritus	454	50.7
Headache	266	29.7
Myalgia	288	32.2
Asthenia	248	27.7
Arthralgia	215	24.0
Fever	183	20.4
Retro-orbital pain	109	12.2
Articular edema	41	4.6
Adenomegaly	24	2.7
Conjunctivitis	27	3.0
Sore throat	79	8.8
Diarrhea	19	2.1
Vomit	14	1.6

Because of the notification regarding all cases as DENV infection, on epidemiologic week 41 in Pernambuco, there were 80,338 DENV cases and only four ZIKV cases. On December 10, 2015, an official note was issued allowing the notification of suspected ZIKV cases by all health units. Within 21 days, 1386 cases had been notified diseases⁽¹³⁾⁽¹⁵⁾. Prior data from the first 11 months of the year were maintained without any official record regarding the number of rectifications or indications of incorrect data. On February 17, 2016, compulsory notification was officially required regarding ZIKV infection⁽¹⁶⁾.

The use of currently available data as an information source may lead to misinterpretation by the national and international scientific community. A practical example is the analysis of dengue virus-related deaths. According to the bulletin of epidemiologic week 51, Pernambuco had 10,488 probable dengue cases and 32 confirmed deaths in 2014, with 102,721 probable cases and 23 confirmed deaths in 2015. Mortality in 2014 was higher than that in 2015, although the number of probable cases in 2014 was 10 times lower than that in 2015⁽¹⁴⁾. These data could suggest a DENV epidemic with an important change in the virus pattern: despite the higher number of cases in 2015 (which in absolute numbers would be the largest DENV epidemic in Pernambuco since 2002), a lower number of deaths was registered. However, the majority of these cases were probably associated with the ZIKV but were equivocally notified as DENV, a hypothesis which this study reinforces, that most of the epidemic cases must have been caused by ZIKV, that is not associated with lethality.

In the present study, the peak number of cases occurred in March, with the suspected ZIKV cases comprising 41% of visits. These data are compatible with reports that the peak epidemic and virus exposure in the state was in March. Regarding the 40 first cases of microcephaly that occurred in October, 67% of the women presented with exanthema⁽¹⁰⁾⁽¹¹⁾, 58% of whom reported that the symptoms had taken place in March (personal note from the author).

The most common clinical manifestation present in probable ZIKV cases was exanthema, which was present in all cases. In contrast, articular involvement and conjunctivitis were registered in only 24% and 3% of cases, respectively. Currently, there are few studies in the literature describing the frequency of ZIKV infection symptoms during the acute phase, with some reported differences in the frequency of the symptoms. The primary report, which described 31 confirmed cases on Yap Island (in the Micronesian islands) in 2007, reported rash in 90% of cases, fever in 65%, arthralgia in 65%, and conjunctivitis in 55%⁽¹⁷⁾. In a study in Rio de Janeiro of 262 patients with a history of rash, with or without fever, 119 (45%) patients had laboratorial confirmation of ZIKV infection. Rash was the most frequent symptom and was present in 97% of cases; however, there was no report concerning the timing or pattern of the rash. In addition, conjunctivitis was observed in 56% of cases, arthralgia in 63%, articular edema 29%, and persistent fever 36%⁽¹⁸⁾. In 115 cases of ZIKV infection in the USA, only 37% presented conjunctivitis⁽¹⁹⁾. The lower frequencies of these manifestations in the current report may reflect missing information in the

registry or in the clinical file regarding other symptoms related to exanthema. The presence of exanthema is often the reason why the patient seeks urgent medical care and, accordingly, is the main complaint registered by the doctor. Unlike the more severe articular symptoms that occur with CHIKV infection, articular symptoms with ZIKV infection are relatively mild. In addition, as patients often seek medical care owing to the presence of exanthema, others symptoms may have not have yet been present.

Zika virus-related conjunctivitis is not purulent⁽¹⁸⁾. It is asymptomatic, leading to a mild hyperemia, which is many times only noticed by family members and doctors. At the beginning of the epidemic, before its presence was undetected, it may have passed unnoticed as a symptom. In prospective cohort studies of patients, the researchers, being aware of what symptoms to seek, tend to register and notice other associated symptoms⁽¹⁸⁾.

Exanthema may be the only Zika virus-related symptom with a pattern different from that of other arboviral diseases. Exanthema occurs in 90-100% of ZIKV cases and first appears within the first 72 hours of disease onset. This differs from dengue virus-related exanthema, which emerges after 3 to 4 days of illness, when the fever is fading⁽²⁰⁾.

Although many countries have registered Zika epidemics, many questions regarding the clinical manifestations of the disease, including patients presenting mild symptoms, still remain unanswered. This includes the lack of an internationally accepted and consistent case definition of ZIKV infection⁽²¹⁾. From the initial case series description on Yap Island⁽¹⁷⁾, countries have adopted diverse criteria⁽¹⁹⁾⁽²²⁾⁽²³⁾⁽²⁴⁾⁽²⁵⁾; this reinforces the importance of conducting descriptive studies to standardize the case definitions and therefore allow better comparisons.

It is a challenge to define a model to estimate the number of cases in a new epidemic. Only epidemiologic serologic population studies are suitably able to address this issue with high accuracy. Nonetheless, to be considered representative, the number of cases required in field research on a large population would be substantially high and, thus, expensive. Moreover, specific serologic tests for ZIKV are not yet available for such large-scale use. Accordingly, the use of clinical criteria in health care units for estimating the number of cases might be a feasible alternative.

With regards to the epidemiology of epidemics, it is an internationally shared concept that during emerging cases, efforts must be focused on a laboratory-based diagnosis. However, once viral transmission has been established, not all patients need laboratory-based confirmation, and the case can be confirmed as a suspected infection based on the clinical and epidemiologic criteria⁽²⁶⁾, with laboratory-based diagnoses reserved for severe or atypical cases.

French Polynesia uses suspected case definitions based on clinical aspects to estimate the number of cases all over the country. The evaluated network comprises 40 to 50 health care units, localized on 25 islands from five archipelagos. Of these units, 40% are private clinics and 60% are hospitals and public health centers. Between October 2013 and February 2014, 8,262

suspected cases of Zika infection were reported by the syndromic surveillance sentinel network of French Polynesia⁽²⁾⁽²⁴⁾. Only 746 blood samples were sent for laboratorial confirmation using real-time PCR, of which 396 (53.1%) were positive. From the clinically identified and posteriorly notified cases, a projection was made for the whole country. The number of patients with ZIKV infection was estimated to be more than 29,000, about 11.5% of the French Polynesia population. However, as many people do not seek medical assistance, it was argued that the actual number of cases may have been even higher.

The Ministry of Health published an estimated number of ZIKV infection cases in 2015, but proper methodology was not applied and local information was not collected. The estimate was made based on the international literature, and only states with autochthonous cases of ZIKV infection were considered. The estimated number of cases ranged from 497,593 to 1,482,701 in Brazil and between 34,579 and 81,303 in Pernambuco⁽²⁰⁾.

By the end of 2015, the State of Pernambuco had officially notified 146,089 suspected dengue cases, most of which were probable ZIKV cases⁽¹⁵⁾. If the results from other hospitals are similar to the current findings, 85% (124,175) of cases notified as DENV were likely ZIKV, whereas only 15% (21,913) were of cases notified as DENV were likely dengue virus-related cases, which is still higher than the previous year when the same dengue serotypes were circulating.

Despite being retrospective and relying on secondary data from clinical files, hospital-based studies such as the one presented herein, if conducted in conjunction with other urgent care units of representative areas of a city or state, might improve estimates regarding the number of cases than estimates based on currently available data; this may partially correct some inconsistencies in official notifications. Following the pattern followed in French Polynesia, which was established as a global standard, this approach would use selected hospitals to generate more representative data, thus improving regional estimates of the attack rate.

In addition to not reflecting the reality of the ZIKV epidemics, the official data from Pernambuco and other states that followed the Ministry of Health recommendation regarding notifications also distorted the analysis concerning DENV behavior. Therefore, despite the inherent challenges, there is a need to retrospectively rewrite the epidemiologic history of ZIKV infection in 2015, using estimates of frequency and behavior that are closer to actual numbers. The choice of methodology must be exhaustively discussed to achieve the most applicable and feasible actual numbers.

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Conflict of interest

The author declares there is no conflict of interest.

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