Epidemiology of Pediatric Zika Virus Infections

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abstract

BACKGROUND AND OBJECTIVE: In July 2016, local transmission of Zika virus (ZIKV) was announced in Miami-Dade County, Florida. In this report, we describe the epidemiology of pediatric ZIKV infections in locally acquired and travel-associated cases.

METHODS: All children aged 1 to 17 years tested for ZIKV between October 1, 2015, and March 29, 2017, were included. SAS 9.4 was used to analyze age, sex, race and/or ethnicity, origin of exposure, onset date, affiliation with a household cluster, clinical symptoms, hospitalizations, viremia, viruria, and antibody detection in specimens.

RESULTS: Among 478 confirmed ZIKV cases in Miami-Dade County, 33 (6.9%) occurred in children (1–17 years). Twenty-seven (82.3%) cases were travel-associated. The median age of a pediatric Zika case patient was 11 years. Seventeen (51.5%) case patients were boys, and 23 (69.9%) were Hispanic. Among 31 symptomatic cases, all reported having rash, 25 (80.6%) reported fever, 9 (29.0%) reported conjunctivitis, and 7 (22.6%) reported arthralgia. Sixteen (48.5%) cases reported 2 of 4 and 8 (24.2%) reported 3 of 4 main symptoms.

CONCLUSIONS: This report found that the majority of children identified during the 2016 ZIKV outbreak only presented with 2 of the 4 main symptoms. In addition, pediatric ZIKV cases were frequently associated with symptomatic household members.

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Ms Griffin and Dr Zhang conceptualized and designed the study, collected data, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Fernandez, Dr Cordero, Ms Logue, Dr Llau, Ms Thomas, Ms Moore, Dr Noya-Chaveco, Ms Etienne, Ms Rojas, Ms Goldberg, Ms Rodriquez, Dr Mejia-Echeverry, and Ms Rico collected data and critically reviewed and revised the manuscript; Drs Jean and Rivera critically reviewed and revised the manuscript; Mr White, Dr Gillis, and Mr Cone tested clinical specimens and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: In 2016, the first outbreak of the Zika virus (ZIKV) was identified in the continental United States. ZIKV is an emerging public health concern. However, there are limited data on the epidemiology of pediatric ZIKV infections.

WHAT THIS STUDY ADDS: The findings of this report reveal that the majority of children presented with only 2 of 4 main symptoms (fever, maculopapular rash, conjunctivitis, and/or arthralgia).

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Since the discovery of Zika virus (ZIKV) in Uganda in 1947, sporadic transmission has been reported in areas of Africa and the Pacific Islands; most recently, ZIKV was identified in the Americas with the 2015 Brazil outbreak and has since spread to the continental United States. ZIKV is a flavivirus spread primarily through the bite of an infected *Aedes aegypti* mosquito.[1] In June and August 2016, the Florida Department of Health (DOH) in Miami-Dade County (DOH–Miami-Dade), in partnership with the DOH Bureau of Epidemiology and Bureau of Public Health Laboratories (BPHL), identified the first travel-associated and locally acquired pediatric ZIKV cases.[2] The 2016 ZIKV outbreak in Miami-Dade County identified 27 (9.9%) pediatric case patients among 273 confirmed travel-associated case patients and 6 (2.9%) pediatric case patients among 205 locally acquired ZIKV cases, for a total of 33 pediatric ZIKV case patients included in this report.

During previous ZIKV outbreaks, the prevalence among pediatric populations has varied. A seroprevalence survey conducted during the 2007 ZIKV outbreak on Yap Island found that attack rates for children <19 years were lower than 10 per 1000 persons compared with attack rates for adults, which ranged from 10 to 56 per 1000 persons when stratified by age.[3] Similarly, during the 2015 ZIKV outbreak in Rio de Janeiro, Brazil, 11 (9.24%) of 119 confirmed ZIKV case patients were identified as children between the ages of 8 to 19.[4] A concurrent outbreak in Puerto Rico identified the highest incidence of laboratory-confirmed ZIKV cases among male patients and nonpregnant female patients in the age groups of 1 to 9 years (7.95 per 1000 persons) and 10 to 19 years (10.73 per 1000 persons). During this same outbreak, 7828 pediatric ZIKV case patients were identified between the ages of 1 and 19 years of the total 29 212 laboratory-positive cases (27.8%).[5] It is likely that these estimates varied in part as a result of differing methodologies of case identification within each affected country.

The incubation period of ZIKV is estimated to be 3 to 14 days.[6] The 4 main clinical symptoms of ZIKV are a maculopapular rash, fever, conjunctivitis, and arthralgia, although it is believed that 80% of ZIKV infections are asymptomatic.[1] Clinical features of ZIKV infection may resemble common childhood illnesses, which complicates the diagnosis of ZIKV infections in children.[1] The authors of a systematic review of 6 publications in which pediatric ZIKV case studies were addressed cumulatively described 10 children between the ages of 3 and 16. From these case reports, the authors noted that 70% of children exhibited gastrointestinal symptoms, but it was unclear whether this was ZIKV infection related.[7] In the United States, among 158 children who acquired ZIKV infection while abroad, 53 (33%) children exhibited 3 or more symptoms, whereas 111 (70%) children exhibited 2 or more.[8] The most frequently reported symptoms within this population were rash (82%) and fever (55%).[8] The authors of a seroprevalence survey conducted in French Polynesia found that the proportion of asymptomatic infections was substantially lower among 312 cases identified in school children (29%) compared with 154 cases among the general population (53%).[9]

The association between ZIKV infection and the development of Guillain-Barré syndrome (GBS) is still under investigation; however, of the 38 GBS cases identified during the French Polynesia outbreak, none occurred among children.[7] In addition, ZIKV-associated deaths among children were not reported during outbreaks in Micronesia or French Polynesia.[3]

To date, no studies have been published regarding the epidemiology of locally acquired ZIKV infections in pediatric populations in the United States. This is the first report in which the epidemiology of travel-associated and locally acquired pediatric ZIKV infections in Miami-Dade County is described.

METHODS

Data were obtained from Merlin, an electronic surveillance database used by the DOH staff to report, investigate, and manage cases of reportable diseases. Pediatric ZIKV cases between October 1, 2015, and March 29, 2017, were identified through both passive and active surveillance methods: (1) provider reports of suspected ZIKV in symptomatic patients, (2) routine screening of asymptomatic pregnant women, and (3) epidemiologic investigations of ZIKV clusters by DOH–Miami-Dade (urosurveys). Clinical and epidemiologic data from these sources were entered into and managed in Merlin by DOH–Miami-Dade and used during the 2016 ZIKV outbreak to classify pediatric ZIKV cases according to national case definitions. Congenital ZIKV infections were excluded from analysis.

During the 2016 ZIKV outbreak, DOH–Miami-Dade initiated active surveillance in the presumed area of exposure for all new locally acquired cases. Epidemiologic investigations of local transmission (cluster investigations and urosurveys) included testing all household members, regardless of the presence of symptoms.[10] As local transmission was identified, testing of all household members, regardless of standard clinical testing criteria, became part of routine investigations for all local ZIKV case patients who had not traveled to active transmission zones. All children were interviewed by a parent and/or

guardian proxy, and parental consent for specimen collection of children under epidemiologic investigation was obtained.

A confirmed pediatric ZIKV case patient was defined as a child aged 1 to 17 years at the time of infection, with laboratory evidence of ZIKV infection by real-time reverse transcriptase polymerase chain reaction (RT-PCR) in specimens of serum, urine, and whole blood, and/or Zika immunoglobulin M antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) detection with confirmation by plaque reduction neutralization testing (PRNT).[11] Specimens were tested at the BPHL in Miami, Tampa, and Jacksonville.

Testing recommendations in Florida were based on clinical symptoms and travel history.[12] Travel-associated persons under investigation for suspected ZIKV infection met testing criteria at BPHL with 2 of 4 main symptoms and recent travel history to an area outside of the United States experiencing ZIKV activity. Locally acquired persons under investigation, in the absence of travel outside of Miami-Dade County, met testing criteria with 3 of 4 symptoms.

The real-time RT-PCR Lanciotti assay and the Centers for Disease Control and Prevention (CDC) Trioplex real-time RT-PCR assay were used at BPHL.[13,14] Zika MAC-ELISA was used to detect ZIKV antibodies in serum specimens. PRNT was performed on serum and urine at the CDC to confirm ZIKV and/or dengue virus infection; case patients with unspecified flavivirus infections (individuals who tested positive for both ZIKV and dengue virus neutralizing antibodies) were excluded from this analysis. As commercial laboratories were often used by health care providers when cases did not meet clinical and/or epidemiologic criteria for ZIKV testing at BPHL, confirmatory testing for all positive cases identified through commercial laboratories was performed at BPHL and the CDC. Negative results from commercial laboratory testing were not required to be reported to the DOH and were therefore not included in this analysis.

Variables of interest included testing trends, age, sex, race and/or ethnicity, clinical symptoms, distribution of cases by date of onset, travel status, household clusters, hospitalizations, cross-sectional observations of viremia and prolonged viremia in serum and whole blood, viruria in urine specimens, and detection of ZIKV antibodies in serum. Prolonged viremia was defined as the presence of ZIKV RNA detected by RT-PCR 14 or more days after symptom onset for symptomatic pediatric Zika case patients or the presence of ZIKV RNA in serum 21 or more days after last possible exposure within an area of active ZIKV transmission for asymptomatic ZIKV cases.[14,15] Antibody detectability was examined through MAC-ELISA results after symptom onset. Descriptive statistics and frequencies were calculated for pediatric ZIKV infections by travel status (travel-associated versus locally acquired). All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 245 children were tested for ZIKV at BPHL from Miami-Dade County between October 1, 2015, and March 29, 2017. Testing of children peaked when active areas of transmission were announced during the months of July, August, and September, with 42 (17.1%), 86 (35.1%), and 39 (15.9%) children tested in the respective months. Children residing in 48 of 79 zip codes in Miami-Dade County were tested. The greatest number of children tested for ZIKV by zip code of residence occurred in areas in which either a urosurvey was conducted or where active transmission was announced during the outbreak.

A total of 33 confirmed pediatric ZIKV case patients were identified (Table 1). Thirty (91.0%) case patients were identified by health care providers, 1 (3.0%) by asymptomatic screening of pregnant women, and 2 (6.0%) through epidemiologic investigations. The median age for all pediatric ZIKV case patients was 11 years (mean 11.1, range 1–17). When stratified by age group, 4 (12.1%) were between the ages of 1 and 5 years, 14 (42.4%) between 6 and 12 years, and 15 (45.5%) were between the ages of 13 and 17 years. Seventeen (51.5%) case patients were boys. Twenty-three (69.7%) case patients were Hispanic. One (6.2%) female case patient was pregnant.

Twenty-seven (81.8%) pediatric ZIKV case patients had travel-associated infections and 6 (18.2%) case patients locally acquired their infection in Miami-Dade County (Table 2). Among the 27 travel-associated case patients, the top 3 countries of origin and presumed exposure were: Nicaragua (9, 33.3%), Dominican Republic (6, 22.2%), and Puerto Rico (5, 18.5%). All ZIKV cases in patients within the 1 to 5 age group were travel-associated. Six (22.2%) case patients with travel-associated infections occurred in 3 pairs of siblings within households, including 1 set of twins who presented with the same onset date and symptoms of fever, rash, diarrhea, nausea, and vomiting. The twins were both RT-PCR positive in urine 14 days after symptom onset.

Household cluster investigations identified 3 (50.0%) pediatric case patients whose infections were locally acquired. Two (33.3%) case patients with locally acquired infections lived in active ZIKV transmission zones at the time of

TABLE 1 Characteristics of Pediatric ZIKV Case Patients, Miami-Dade County, October 1, 2015 to March 29, 2017 ($N = 33$)

Child Characteristics	Total ($N = 33$), *n* (%)	Travel Associated ($n = 27$), *n* (%)	Locally Acquired ($n = 6$), *n* (%)
Sex			
Male	17 (51.5)	14 (51.9)	3 (50.0)
Race or ethnicity			
Non-Hispanic white	3 (9.0)	2 (7.4)	1 (16.7)
Non-Hispanic African American	2 (6.0)	1 (3.7)	1 (16.7)
Hispanic	23 (69.6)	21 (77.7)	2 (33.3)
Other	5 (15.4)	3 (11.1)	2 (33.3)
Age			
Mean, median (range)	11.1, 11 (1–17)	10.7, 11 (1–17)	13.2, 14 (7–17)
Age groups, y			
1–5	4 (12.1)	4 (14.8)	0 (0.0)
6–12	14 (42.4)	11 (40.8)	3 (50.0)
13–17	15 (45.5)	12 (44.4)	3 (50.0)

TABLE 2 Characteristics of Clinical Illness Among Pediatric ZIKV Case Patients, Miami-Dade County, June 4, 2016 to September 18, 2016 ($N = 33$)

Clinical Characteristics	Total ($N = 33$), *n* (%)	Travel Associated ($n = 27$), *n* (%)	Locally Acquired ($n = 6$), *n* (%)
Symptom status			
Asymptomatic	2 (16.5)	0 (0.0)	2 (33.3)
Symptomatic[a]	31 (83.5)	27 (100.0)	4 (66.7)
Symptoms			
Rash	31 (100.0)	27 (100.0)	4 (100.0)
Fever	25 (80.6)	22 (81.5)	3 (75.0)
Conjunctivitis	9 (29.0)	6 (22.2)	3 (75.0)
Arthralgia	7 (22.5)	6 (22.2)	1 (25.0)
Sore throat	7 (22.5)	6 (22.2)	1 (25.0)
Diarrhea	5 (16.1)	5 (18.5)	0 (0.0)
Myalgia	2 (6.4)	2 (7.4)	0 (0.0)
Nausea	2 (6.4)	2 (7.4)	0 (0.0)
Retro-orbital pain	2 (6.4)	2 (7.4)	0 (0.0)
Vomiting	2 (6.4)	2 (7.4)	0 (0.0)

[a] The main symptoms of ZIKV infection include a maculopapular rash, fever, conjunctivitis, and/or arthralgia.[12]

onset and/or specimen collection. There was no correlation found between a positive ZIKV result and location of residence within an active area of ZIKV transmission versus a nonactive area. Because of small sample sizes, statistically significant differences by travel status in sex, age, race and/or ethnicity, and testing trends between active and nonactive transmission areas could not be examined.

Among 33 confirmed ZIKV case patients, 31 (93.9%) were symptomatic. Three (9.6%) case patients reported having all 4 main symptoms, 8 (25.8%) reported only 3 of 4, 16 (51.6%) reported only 2 of 4, and 4 (12.9%) reported only 1 of 4. Among symptomatic case patients, all reported having rash, 25 (80.6%) reported fever, 9 (29.0%) reported conjunctivitis, and 7 (22.5%) reported arthralgia (Table 2). Among the 31 confirmed case patients, 25 (80.6%) reported having both fever and rash. Additionally, 5 (18.5%) case patients with travel-associated infections reported diarrhea in addition to fever and rash, a clinical observation worth noting. Symptom onsets ranged from June 4, 2016, to September 18, 2016 (Fig 1). Among case patients with only 2 of 4 symptoms, all infections were travel-associated; no case patients with travel-associated infection identified were asymptomatic.

A difference was observed in the distribution of symptoms between travel-associated and locally acquired cases. The most likely explanation for this observation is the difference in testing criteria and methods of case identification. Case patients with locally acquired infection who reported being asymptomatic (33.3%), and those who reported only 1 of 4 symptoms (16.7%) and only 2 of 4 symptoms (0.0%) were identified through passive surveillance screening of pregnant women or active surveillance of household cluster investigations. There were no ZIKV-associated hospitalizations, reported instances of GBS, or deaths as a result of ZIKV infection.

Real-time RT-PCR testing performed on paired specimens of serum and urine identified 30 confirmed ZIKV cases (Table 3). ZIKV was detected in 9 paired serum and urine specimens, with a mean of 2.4 ± 1.4 days (median 2, range 0–5) after symptom onset. Among 13 children with ZIKV detection by RT-PCR in serum only, ZIKV RNA was detected, with a mean of 3.2 ± 2.7 days (median 3, range 0–11) after symptom onset. Among 8 children with ZIKV detection by RT-PCR in urine only, ZIKV RNA was detected, with a mean of 6.8 ± 6.6 days (median 3, range 1–15) after symptom onset. ZIKV RNA was not detected in the 6 whole blood specimens that were collected.

MAC-ELISA testing performed on serum specimens identified 5 ZIKV case patients, all of which were locally acquired (Table 3). Among these 5 case patients, 3 were identified only by positive immunoglobulin M (IgM) serology results (confirmed by PRNT performed at CDC); for the other 2, both IgM serology and serum RT-PCR tests yielded positive results. Two case patients were asymptomatic, 1 of whom was pregnant and the other associated with a household cluster; both were identified only by positive IgM serologic test results. Among

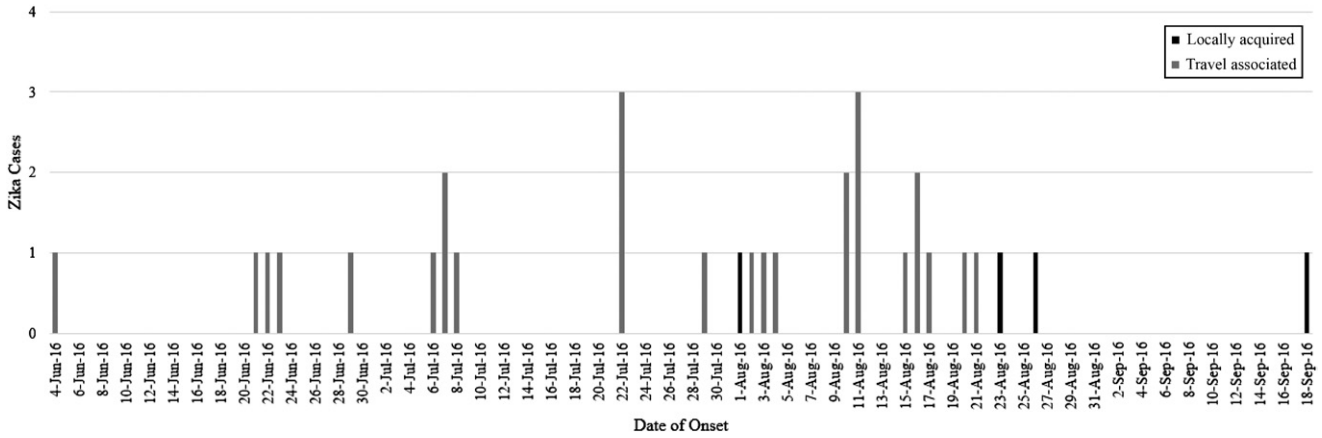

FIGURE 1
Epidemic curve of symptomatic pediatric ZIKV case patients by date of onset, Miami-Dade County, Florida, 2016 ($N = 31$).

TABLE 3 Summary of Laboratory Results for Pediatric ZIKV Case Patients Reported by Miami-Dade County, June 4, 2016 to September 18, 2016 ($N = 33$)

Specimen or Test	Total ($N = 33$), *n* (%)	Travel Associated ($n = 27$), *n* (%)	Locally Acquired ($n = 6$), *n* (%)
Positive RT-PCR specimen type[a]			
RT-PCR: serum, urine	9 (30.0)	9 (33.3)	0 (0.0)
RT-PCR: urine only	8 (26.6)	8 (29.6)	0 (0.0)
RT-PCR: serum only	13 (43.4)	10 (37.0)	3 (100.0)
Total cases with a positive RT-PCR result[b]	30 (90.9)	27 (100.0)	3 (50.0)
Total IgM-positive results among cases[c]	3 (9.1)	0 (0.0)	3 (50.0)
Total Zika cases with IgM only (confirmatory positive Zika PRNT result)	3 (9.1)	0 (0.0)	3 (50.0)
RT-PCR specimen type and IgM-positive results			
Serum and IgM-positive results	2 (100.0)	0 (0.0)	2 (100.0)
Zika and PRNT	4 (12.1)	0 (0.0)	4 (66.7)

[a] RT-PCR positive results were combined regardless of originating laboratory. IgM-positive results were combined regardless of originating laboratory. Indeterminate and equivocal results were not considered confirmed ZIKV cases and were excluded from this report.
[b] None of the children tested positive for ZIKV by using the following combinations: RT-PCR in serum, urine, and whole blood; RT-PCR in serum and whole blood; RT-PCR in urine and whole blood; RT-PCR in whole blood only; RT-PCR in serum, urine, whole blood, and IgM; RT-PCR in serum, whole blood, and IgM; RT-PCR in serum, urine, and IgM; RT-PCR in urine and IgM; RT-PCR in whole blood and IgM.
[c] IgM results may reflect multiple positive IgM (including already collected convalescent samples) for the same individual pediatric Zika case.

the 3 symptomatic case patients, 1 had a positive IgM test result 39 days after onset of symptoms; the other 2 were associated with positive results both for IgM and for RT-PCR testing performed on serum collected 4 and 11 days after onset of symptoms, respectively. The symptomatic case patient who tested IgM-positive 39 days after symptom onset reported rash as the sole symptom. Although ZIKV IgM was detected in this patient within the presumed time frame of ZIKV-IgM detectability (ie, up to 12 weeks), noting that the patient did not receive medical attention at the onset of his symptoms (rash), it is possible that the reported rash was ascribable to a rash-associated illness other than ZIKV.

DISCUSSION

During the 2016 ZIKV outbreak in Miami-Dade County, pediatric cases accounted for 6.9% of all confirmed cases; this proportion is lower than those identified in concurrent outbreaks in Brazil and Puerto Rico. According to the 2014 American Community Survey, 66.5% of our population in Miami-Dade County is Hispanic; as such, the proportion of Hispanic cases (23, 69.7%) was ethnically-representative of our population.[16] The 4 main symptoms of ZIKV were observed among pediatric cases in Miami-Dade County, with the majority of case patients reporting only fever and rash. The findings of this analysis reveal that the majority of pediatric ZIKV cases (51.6%) presented solely with 2 of 4 symptoms.

Researchers have shown that the *A aegypti* mosquito can bite several individuals during a single blood meal.[1] In this study, we identified ZIKV clustering among children in households with confirmed ZIKV cases. Particular emphasis must be placed on the investigation of household clusters to include the testing of pediatric populations, in particular those within households with symptomatic adults or in residential areas of active transmission. The results of this analysis suggest that individuals seek medical attention and discuss ZIKV testing with their health care providers if a household member is infected with ZIKV. The identification

of sibling clusters reiterates the need for families to take mosquito bite prevention measures when traveling to areas of active ZIKV transmission.

Individuals tested for ZIKV and associated with negative test results are not reportable to DOH–Miami-Dade; thus, unavailable data on children who received negative test results for ZIKV through commercial laboratories or never sought testing is a limitation of this analysis. As such, denominator data were unavailable, and we were unable to evaluate risk factors associated with overall infection. However, all positive ZIKV test results are required to be reported to the DOH; thus, we capture in this report all pediatric ZIKV cases in Miami-Dade County that were associated with positive test results. Lastly, several surveillance methods (which differed by testing criteria) were used to identify the 6 locally acquired cases; as such, there are limitations in making generalizations about the epidemiology of locally acquired pediatric cases.

CONCLUSIONS

Throughout the outbreak, key messaging for health professionals emphasized the importance of testing individuals with ZIKV-like symptoms who had an epidemiologic link to an area of active ZIKV transmission. Although ZIKV cases peaked in the summer months of 2016, the climate of Miami-Dade County remains optimal for mosquito breeding and disease transmission year-round.

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ABBREVIATIONS

BPHL: Bureau of Public Health Laboratories
CDC: Centers for Disease Control and Prevention
DOH: Florida Department of Health
GBS: Guillain-Barré syndrome
IgM: immunoglobulin M
MAC-ELISA: immunoglobulin M antibody capture enzyme-linked immunosorbent assay
PRNT: plaque reduction neutralization testing
RT-PCR: reverse transcriptase polymerase chain reaction
ZIKV: Zika virus

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