### **ZIKA VIRUS SURVEILLANCE IN LOS ANGELES COUNTY, 2016**

### **ABSTRACT**

In 2014, an outbreak of Zika virus occurred in Brazil and rapidly spread to neighboring countries. The first Los Angeles County (LAC) resident became ill with this virus after returning from El Salvador in late 2015. In 2016, 101 Zika cases were investigated by the Acute Communicable Disease Control Program (ACDC) of the LAC Department of Public Health (DPH). Cases were identified with either Zika virus RNA (52%) or Zika acute phase antibodies (48%). Cases were primarily female (76%), Latino (71%), average age of 36.9 years (range: 9-66 years), and residence throughout the county. None were hospitalized. The annual disease rate was 1.1 per 100,000 and was highest among Latinos (12.1 per 100,000) followed by Whites (5.6 per 100,000). This rate was higher in females than males (1.6 vs. 0.6 per 100,000). All cases traveled to a Zikaendemic region prior to their illness (50% Central America, 27% Mexico), and most became ill in July and August (54%). No instances of local transmission of Zika virus, either vector or sexual transmission, were identified. A total of 11 infants were born to LAC residents with travel-associated Zika virus infection; all 11 appear healthy to date. Although the number of cases in LAC where relatively small, creating a surveillance system for any new emerging diseases is challenging, requiring the development of disease case definition, testing methods, and disease procedures and protocols while simultaneously assessing the disease impact to the community.

### **BACKGROUND**

Zika virus is an arbovirus primarily spread by the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*) [1]. Infection during pregnancy can result in severe fetal consequences including microcephaly and other birth defects. A large outbreak of Zika virus occurred in Brazil in 2015 and has spread across South and Central America and northward to the US. Local vector-borne transmission has been reported in Miami-Dade County, Florida [2] and Texas. Persons infected with Zika virus often have no symptoms or very mild symptoms, making detection and surveillance of cases challenging. Guillain-Barre syndrome, a more severe manifestation of Zika virus infection has been reported but is very rare. The primary burden Zika virus places on a community is measured through the impact the virus has on newborns.

In November 2015, a previously healthy resident LAC sought medical care for fever, rash, chills, conjunctivitis, headache, and joint pain after returning from El Salvador. An astute infectious disease specialist reviewed the patient's symptoms, travel history, and history of mosquito bites and suspected an arbovirus infection. The Centers for Disease Control and Prevention (CDC), Division of Vector-Borne Disease Laboratory, identified Zika virus antibodies in the patient's serum specimen. Dengue, Chikungunya, and West Nile testing results were all negative. The first case of Zika virus in LAC had been identified. By the end of 2016, over 100 cases were reported to LAC DPH for investigation.

With both imported human cases and the mosquito vector (*Aedes aegypti* and A. *albopictus* mosquitoes) present in LAC, Public Health officials became concerned that local vector-borne transmission of Zika in LAC was possible. A multi-agency, multi-disciplinary approach was developed to ensure that this new arbovirus did not establish itself in LAC. ACDC and Community Health Service (CHS) conducted interviews

with all reported cases to assess for Zika risk, pregnancy status, and Zika-like illness in other household members. The presence of *Aedes* mosquitos around cases' residences was assessed by local vector control programs. If any indication of local transmission was identified, the investigation was elevated.

DPH also monitored all participating pregnant Zika cases throughout their delivery. Newborns were tested for Zika virus at birth, and infants' development was assessed and documented at 2, 6, and 12 months of age. The mother's placenta may have also been collected and tested for Zika virus. These efforts required a coordinated effort with the LAC Public Health Laboratory (PHL), Maternal, Child and Adolescent Health (MCAH), and Children's Medical Services (CMS) Programs in LAC. In addition, DPH investigated any report of an infant born with microcephaly and tested those having a mother with Zika risk.

This report summarizes the Zika case investigations conducted in LAC in 2016 including the number and demographics of cases, infection rates, symptoms, exposure risk, laboratory tests performed, and instances where an elevated public health response was required to rule out local vector-borne transmission of Zika virus. The follow-up and testing of infants born to Zika cases and also infants born with microcephaly were reviewed. Zika reporting and investigation timeliness was also reviewed.

### **METHODS**

All LAC health care providers and laboratories are mandated to report any suspect Zika cases to DPH (Title 17, CCR). Zika reports are investigated by ACDC with the support from the CHS, PHL, Public Health Investigators (PHI), and local vector control programs (VCD). ACDC interviewed cases by phone to document travel history and symptoms and identify any recent illness in the household that may suggest local vector-borne transmission. CHS nurses interviewed cases at home that could not be reached by ACDC. PHI assisted when CHS was unable to locate a case or the case was uncooperative. Local VCDs assessed cases' neighborhoods for presence of *Aedes* mosquitoes and mitigated presence if identified.

The demographics of all cases investigated by LAC DPH were reviewed and demographic rates calculated. Zika risks such as travel country were reviewed. LAC DPH also reviewed the types of laboratory testing performed and timing of case notification as well as factors leading to prolonged notification. LAC DPH reviewed Zika testing results and follow-up assessment available for infants born to Zika cases in LAC. Zika testing results were also reviewed for newborns identified with microcephaly and a mother with a history of potential Zika risk.

All statistical calculations were performed in SAS version 9.3. LAC DPH utilized the case definition established by the Council of State and Territorial Epidemiologist (CSTE) [4] and included in Appendix B. LAC cases must have: 1) Zika RNA identified in a serum or urine specimen via RT-PCR laboratory technique, or 2) Zika IgM antibodies detected in serum via plaque reduction neutralization test (PRNT) technique.

#### **RESULTS**

A total of 101 LAC Zika virus cases were reported to and investigated by ACDC in 2016. All cases met the case definition as stated by the CSTE. The number of cases identified in 2016 was a substantial increase from those identified in late 2015 (N=6).

# **RESULTS** - Case Demographics

The overall annual rate of Zika cases in LAC was 1.1 per 100,000 residents (Table 1). The majority of cases were female (n=75, 74%) with a case-rate of 1.6 per 100,000. Females were 2.8 times more likely to be identified cases than males. The age of cases ranged from 9-66 years old (median=35 years, mean=36.9 years). Many cases were 15-34 years old (n=37, 37%); however, the case rate was highest in the 45-54 years old age group (1.5 per 100,000).

Latinos accounted for the majority of cases (n=71, 74%) and also had the highest case rate of the race ethnicity groups reviewed (1.5 per 100,000). By Service Planning Area (SPA), SPA 2 had the largest number of cases by residence (n=27, 28%); however, the case rate was highest in SPA 5 (2.0 per 100,000). A map of case residence by Health District is presented in Appendix A.

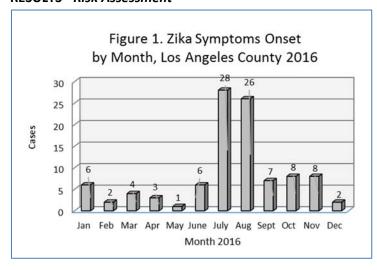
### **RESULTS** - Symptoms and Onsets

Nearly all Zika cases reported symptoms (91%), which included rash (78%), fever (56%), arthralgia (52%), and conjunctivitis (28%). A total of 78% of cases reported two or more symptoms, 55% reported three or more symptoms, and 13% reported all four symptoms. Only ten cases (10%) were asymptomatic. No cases were identified with Guillain-Barre syndrome. Zika cases reported by

Table 1. Demographic of Zika Cases									
Los Angeles County, 2016									
	n	%	Annual Rate* per 100,000	Relative Risk					
Total Cases	101	100	1.1	-					
Canadan									
Gender Female	75	74	1.6	2.8					
		26	1.6						
Male	26	26	0.6	Reference					
Age Group (years)									
<1	0	0	0.0	-					
1-4	0	0	0.0	-					
5-14	9	9	0.7	1.7					
15-34	37	37	1.3	3.0					
35-44	17	17	1.3	2.9					
45-54	20	20	1.5	3.5					
55-64	13	13	1.2	2.8					
65+	5	5	0.4	Reference					
Race -Ethnicity									
Latino	71	74	1.5	12.1					
White	19	20	0.7	5.6					
Asian	5	5	0.4	2.9					
Black	1	1	0.1	Reference					
Other	1	1							
SPA									
1- Antelope Valley	3	3	0.8	2.1					
2- San Fernando	27	28	1.2	3.4					
3- San Gabriel	6	6	0.4	Reference					
4- Metro	13	14	1.1	3.1					
5- West	13	13	2.0	5.4					
6- South	16	17	0.2	0.4					
7- East	14	14	1.1	2.9					
8- South Bay	6	6	0.6	1.5					
*Rates based on 2015 popu	lation da	ta							
Draft 6/12/2017									

month of symptom onset throughout 2016 is shown in Figure 1. The majority of cases reported symptoms occurring in July and August (54%). The specimen collection month was used for asymptomatic cases.

### **RESULTS - Risk Assessment**

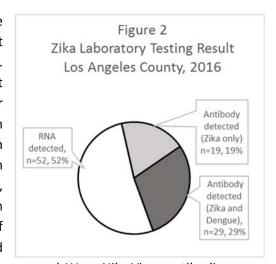


All Zika cases reported a history of travel to a Zika-endemic area within three months of seeking medical care and testing. Nearly all cases (99%) were exposed to Zika virus in areas of Central America (50%) and Mexico (27%). Only one case had no foreign travel history; this case traveled to Miami, Florida, which had local vector-borne Zika transmission. Only four case investigations identified an additional household member with Zikalike illness. In three of these households, the ill household member had also

traveled to a Zika-endemic region with symptoms onset consistent with exposure during travel. In one household, two ill family members were identified that did not travel with illness onsets concerning for local vector-borne transmission of Zika virus. The details and results of this investigation are presented in **RESULTS** - *Case Investigation 2 – Rule Out Vector-borne Transmission in a Household*. VCD staff mitigated any vector issues in the case neighborhoods of all four of these investigations.

### **Results - Laboratory Testing**

There were 2,500 patients who submitted specimens to the LAC PHL for Zika virus testing in 2016. This count does not include all patients tested through commercial laboratories. There were 101 patients with a positive Zika laboratory result that met the Zika virus case definition. All Zika cases either had Zika virus RNA detected in a serum or urine specimen (52%) or Zika virus acute phase antibodies detected in serum (48%), as shown in Figure 2. Many of those identified with Zika virus antibodies also had Dengue virus antibodies (29%), as identified by PRNT. Of interest, only one of the ten asymptomatic cases were identified with Zika virus RNA. Of the asymptomatic cases, seven of the ten cases also had



antibodies for Dengue, as identified via PRNT. No Chikungunya and West Nile Virus antibodies were detected with any of the Zika cases.

Of the 52 cases identified with Zika RNA in serum and or urine, 33 were positive on a serum specimen (34%), 28 were positive on a urine specimen (29%), and 10 were positive on both specimens (10%). There were 18 cases where Zika virus was detected in urine but not in blood (19%), and only 3 cases where Zika virus was detected in serum but not urine (6%).

A majority of cases were reported from a state or federal laboratory (68%) followed by commercial laboratory (20%) or the PHL in LAC (12%).

### RESULTS - Pregnant Zika Case and Infant Follow Up

DPH followed up on the progress of pregnant Zika cases in LAC by reviewing prenatal care records and ultrasound results from each patient's maternal health provider. In addition, collection of newborn specimens and birth products (placenta, umbilical cord, placental membrane) for Zika virus testing was discussed with the patient's delivery hospital. Information was collected on the newborn's health at birth such as Apgar score, head circumference, weight, and length as well as any birth abnormalities at time of delivery. DPH followed up with the patient's pediatrician to track the progress of the infant's health, recording head circumference, weight and length at 2, 6, and 12 months of age and monitored the infant's overall development.

In 2016, there were 11 infants born to LAC mothers infected with Zika virus while traveling outside of LAC. All 11 infants appear to be healthy and developing normally at the time of this report (January 1<sup>st</sup>, 2017). All infant mothers were identified with acute phase Zika antibodies in serum and none had Zika virus RNA (Table 2). A total of six of these mothers also had acute phase antibodies for Dengue virus. Another six mothers reported symptoms consistent with Zika virus infection, and the remainder were asymptomatic. During the DPH follow-up of the progress of pregnant mothers, one mother's fetal ultrasound revealed abnormalities on week 19 of gestation, increasing concern for the possibility of fetal infection and lag in brain development (#4). An amniocentesis was performed and amniotic fluid tested for Zika virus RNA. No evidence of Zika virus was identified. The fetus appeared normal on a follow-up ultrasound. All other mothers progressed to delivery without complication.

Placenta, umbilical cord, and/or membranes were collected and tested from 8 of the 11 mothers at delivery. Only one mother (#1) was identified with Zika virus RNA present in an umbilical cord specimen. All other tissue testing results found no evidence of Zika virus infection for this mother and the other seven mothers. Eight of the 11 newborns were tested for Zika virus. No evidence of Zika infection was identified in any of the eight, including the infant of the mother with a questionable ultrasound (#4) and the infant of the mother with umbilical cord positive for Zika RNA (#1). Only one infant was admitted to the NICU (#8) for four days with respiratory distress and low birth weight (4.9 lbs.). This newborn was discharged home after four days. All other infants had a normal hospitalization stay.

Figure 3 displays each infant's head circumference (HC) measurements at 2, 6, and 12 months of age plotted against a line representing the third percentile of HC measurement for age and gender. Microcephaly is a birth defect defined as a newborn or infant with a smaller than expected HC (<3<sup>rd</sup> percentile) when compared to babies of the same sex and age. Only two infants were identified with a small HC at birth (#6, #8). Infant #6 had a HC well below the 3<sup>rd</sup> percentile at birth and was diagnosed with microcephaly by the patient's pediatrician at that time. The HC measurement at birth was verified at one week of age (30.1 cm). However, this infant's HC measurement was within normal HC range by two months of age (36.8 cm) and remained normal at 12 months of age. A cranial ultrasound performed at three months of age did not reveal any abnormalities, and the microcephaly diagnosis has been dropped for infant #6. The HC measurement for infant #8 also measured slightly below the 3<sup>rd</sup> percentile (31.0 cm); however, this was an overall small infant, with short length (47 cm) and low weight (4.9 lbs.), born at week 38 of gestation. This infant was not given a microcephaly diagnosis. The infant's head size continued to grow to normal size by 12 months of age (44.5 cm).

A total of two pregnant Zika cases chose to discontinue participation in the DPH infant follow up program after their infants were born healthy and with normal HCs (#3, #5), so no further information on these infants could be obtained. There were two pregnant Zika cases identified in 2016 that chose not to participate in the DPH infant follow up, so the outcomes of these births, or possible terminations, remains unknown.

Table 2. Zika Case and Infant Testing and Infant Follow-up, Los Angeles County 2016

		Zika Case									Infant						
-		Serum Testing			Н	etal ealth cators	Tissue Testing		Serum Testing			Infant H Indica		Follow-up Month Completed			
	Symptomatic	Zika IgM	Zika RNA	Dengue IgM	Cranial Imaging CT	Amniotic Fluid Zika RNA	Central Placenta Zika RNA	Umbilical Cord Zika RNA	Placental Membrane Zika RNA	Zika IgM	Zika RNA	Apgar Score	Small Head Circumference	Admitted to NICU	Cranial Imaging CT	Month Completed	
1	+	+	-	-	-	NT	-	+	-	-	-	9	-	-	-	0,2,6,12	
2	+	+	-	+	-	NT	-	-	-	NT	NT	9	-	-	NT	0,2,6,12	
3	-	+	-	-	-	NT	NT	NT	NT	NT	NT	9	-	-	NT	0, NP	
4	-	+	-	-	+	-	-	-	-	-	-	9	-	-	NT	0,2,6,12	
5	-	+	-	+	-	NT	-	NT	-	-	-	9	-	-	-	0, NP	
6	+	+	-	+	-	NT	-	-	-	-	-	9	+	-	-	0,2,6,12	
7	+	+	-	+	-	-	NT	NT	NT	-	-	9	-	-	NT	0,2,6,12	
8	+	+	-	+	-	NT	-	NT	NT	-	-	9	+	+	-	0,2,6,12	
9	+	+	-	-	-	NT	-	-	-	-	-	9	-	-	NT	0,2,6,12	
10	-	+	-	+	NT	NT	NT	NT	NT	NT	NT	9	-	-	NT	0,2,5,12	
_11	-	+	-	+	-	NT	-	-	-	-	-	9	-	-	NT	0,2,6,12	

NP - Not participating

NT - Not Tested

<sup>6 -</sup> Dx microcephaly at birth

<sup>7 -</sup> Infant urine also with PCR negative result

<sup>8 -</sup> Admitted to NICU for 4 days for respiratory distress and low birth weight. Born at 38 weeks gestation. Discharged home.

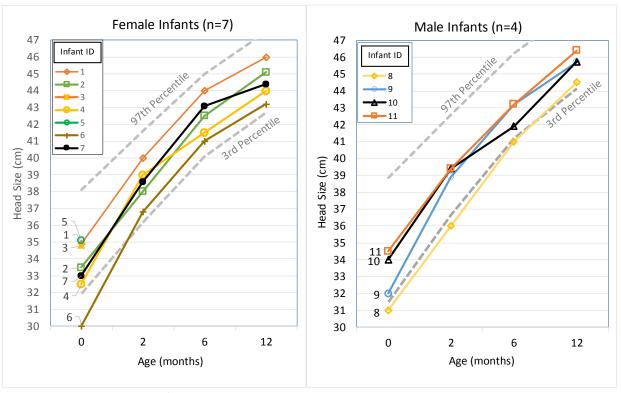


Figure 1. Infant Head Circumference, Los Angeles County 2016 (N=11)

### **RESULTS - Newborns Identified with Microcephaly**

In 2016, there were 11 newborns identified with microcephaly and born to a mother with Zika risk, but had no positive Zika lab test or chose not to test. No evidence of Zika infection was identified with any of these infants. All 11 were tested for the presence of Zika virus RNA in serum, and all were negative. There was one fatality who died shortly after delivery due to severe brain malformation. In addition to the negative Zika RNA test result obtained for this infant, a negative Zika virus RNA test result was obtained on mother's placenta and a pathology review revealed no evidence of infection. All other infants are stable as of last update, but many have very complicated health issues. Only 2 of the 11 infant mothers were also tested for Zika virus at time of delivery, and both had a negative test result. The remaining nine infant mothers were either outside the three-month time period of detectable acute phase antibodies for Zika or declined testing. One newborn was later identified with a gene deletion (4.22q11 deletion) that has been associated with microcephaly. All 11 infants were transferred to CMS for further investigation.

### **RESULTS - Case Reporting and Investigations**

All Zika cases were evaluated and tested by a clinician in an outpatient setting, and none were hospitalized. The majority of cases were tested through a private LAC health care provider (90%) followed by DPH health clinics (8%) and facilities outside of LAC (3%). Cases were primarily reported to DPH by the performing laboratory via a faxed laboratory report (49%) or as an electronic laboratory report (48%) with a few cases reported from another public health jurisdiction (3%). Only one case was reported by a health care provider. Cases were primarily interviewed by ACDC staff (83%) followed by CHS staff (19%).

For symptomatic cases (n=91), the average time from the case's symptom onset to the DPH notification date (T1) was 38 days (range: 4 to 195 days, median: 24 days). The average T1 measure was much shorter

for cases with a PCR test result notification (18 days, median=15 days, n=52) than cases with a PRNT test report notification (67 days, median=61 days, n=39) (p<0.01, T-test, unequal variances). In addition, the average T1 value for cases that were reported by Electronic Laboratory Reporting (ELR) were shorter (14 days, median=11 days, n=26) than those reported via fax transmission (56 days, median=30 days, n=29) (p<0.01, T-test, unequal variances). All ELR reports were also PCR reports.

# RESULTS - Case Investigation 1 - Rule out Vector-Borne Transmission in a Neighborhood

In August 2016, DPH received a positive Zika result (Zika IgM- and PRNT-positive, Zika PCR-negative) from a governmental laboratory for an LAC patient. This patient met the CSTE case definition for a Zika case., The patient was uncooperative with public health and refused to provide a complete travel history. Because the patient's travel history was unclear, the possibility of local vector-borne transmission of Zika virus needed to be ruled out. VCD assessed the case's residence and the nine surrounding properties. No Aedes were identified, and no obvious sources for mosquito breeding were found in the patient's yard such as overgrowth of brush, trash, or standing water.

The Infectious Disease (ID) specialist that oversaw the care of this patient stated that this patient presented with fever, vomiting, and headache and was hospitalized and diagnosed with viral meningitis. The ID physician felt that the patient's meningitis was due to herpes simplex virus 1 (HSV1) infection, not Zika virus. The examination of the patient's cerebrospinal fluid (CSF) revealed mild pleocytosis with lymphocyte predominant as well as identification of HSV1 in CSF via PCR. In addition, the governmental reference laboratory repeated the Zika testing on the patient's original serum specimen, and no Zika virus antibodies were identified. The findings of this investigation indicate that this patient had a false positive Zika result.

### RESULTS - Case Investigation 2 - Rule Out Vector-Borne Transmission in a Household

In October 2016, DPH received a positive Zika PCR result for an LAC resident from a private clinical laboratory. This patient met the CSTE case definition for Zika virus. Upon interview, the case reported being symptomatic after returning to the US from Guatemala (Zika-affected area). The case also reported two adult household contacts (HHC) ill with Zika-like symptoms eight days after the case's return to the US. HHC1 reported symptoms of conjunctivitis, cough, sneezing, and sore throat. HHC1 also reported having unprotected sexual contact with the case in the week prior to onset, suggesting possible sexual transmission of Zika. HHC2 reported symptoms including conjunctivitis, fever, chills, and sore throat and had no sexual contact with the case. The symptoms reported by both HHCs were suggestive of a number of illnesses including Zika virus. Neither HHC had traveled to a Zika-affected area, prompting concerns of local vector-borne Zika transmission. Adding to this concern was the identification of *Aedes aegypti* mosquitoes within five miles of the case's residence earlier in the year.

To rule out local vector-borne transmission in this household, ACDC requested VCD staff to assess for the presence of *Aedes* mosquitoes in the case's neighborhood and a CHS staff to obtain urine specimens from the HHCs for Zika testing. VCD inspected 86 properties and 30 businesses and placed mosquito traps (ova cups) around the case's residence. No *Aedes* were observed at any stage of growth. The urine specimens collected from the HHCs by CHS and tested by LAC PHL were both negative for Zika virus RNA. Overall, the investigation found no evidence suggesting local transmission of Zika virus in this household. The investigation was closed within one week of the original DPH laboratory notification of the case.

#### DISCUSSION

Female residents in LAC were more likely to be identified as Zika cases than males in 2016. This difference likely reflects gender-specific screening criteria and not a true difference in risk by gender. The 2016 Zika virus testing protocol recommends testing of all pregnant females with Zika risk, whereas all other persons had to present with a Zika symptom in order to be tested. Latinos were also more likely to be identified as Zika cases compared to other race-ethnicities in LAC. This may reflect the difference in travel patterns by race-ethnicity. Latinos are more likely to travel to Zika-affected areas to visit family for longer durations and visit more rural areas than other race-ethnicities. Mexico and Central American countries were likely travel locations for most LAC cases. Only two cases traveled to Brazil where the Latin American Zika virus outbreak was originally identified in 2015.

Interpretation of Zika laboratory results can be complicated [5]. Dengue virus antibodies identified via PRNT were 29% of LAC Zika cases. It is unclear whether this represents a Dengue infection with antibodies that cross-react to Zika antigens resulting in a false Zika result, a Zika infection with antibodies that cross-react to Dengue antigens resulting in a false-positive Dengue result, or infection with both viruses. Dengue virus also circulates in many of the same regions as Zika virus and is also transmitted by the *Aedes* mosquito.

Zika RNA detection in urine via RT-PCR appears to be more sensitive than serum—10 of 52 cases (19%) were identified with RNA in urine and not in serum. Collection of urine as compared to serum is simpler, does not require a phlebotomist, and patient compliance is generally higher. However, 3 of 52 cases (6%) were identified with RNA in serum but not in urine, and these cases would have been missed if urine were collected alone. Similar results were found with a review of cases identified in Florida in 2016 [2].

Infants born to Zika cases and identified with Zika-related birth defects have been reported in California [3]; however, the impact of Zika virus on newborns in LAC appears to be minimal with only 1 of 11 newborns presenting with a questionable Zika-related birth defect diagnosis. In addition, 11 LAC infants with a suspect Zika-related birth defect tested negative for Zika virus. It is not clear whether any virus or antibody could be detected in these newborns, limiting any conclusion drawn from these findings. Additional causes of microcephaly such as toxoplasmosis, cytomegalovirus, and other infections should also be assessed in these newborns, which requires additional follow up. Future studies should assess any change in newborn microcephaly trend with the introduction of Zika virus in LAC. A review of hospital discharge data suggests a newborn microcephaly rate of 4.2 per 10,000 live births in LAC prior to the introduction of Zika virus, or an average of 55 per year.

Local vector-borne transmission of Zika virus had been identified in Florida [6] and possibly Texas in 2016 [7]. As a large metropolitan county with known *Aedes* mosquito populations, LAC was also at risk for local vector-borne Zika transmission. However, no instances of local vector-borne transmission in LAC were identified in 2016. The introduction of Zika virus among LAC travelers highlights many of the surveillance challenges posed by any new emerging diseases. Laboratory tests were initially not widely available nor were testing protocols, case definitions, and survey tools for this disease. As these tests and guidelines became available, they required constant review and modification to keep them up-to-date with the best science available for this disease. In addition to the Zika case activities, Zika virus surveillance required follow up of newborns associated with pregnant cases for testing and birth defects surveillance.

LAC DPH is continually working to refine Zika surveillance and work with local VCDs to optimize agency collaboration. This collaboration will improve utilization of resources to prevent Zika virus from becoming endemic in LAC. Many lessons were learned from Zika surveillance in 2016, which will help improve efforts to minimize Zika disease risk to LAC residents in the future.

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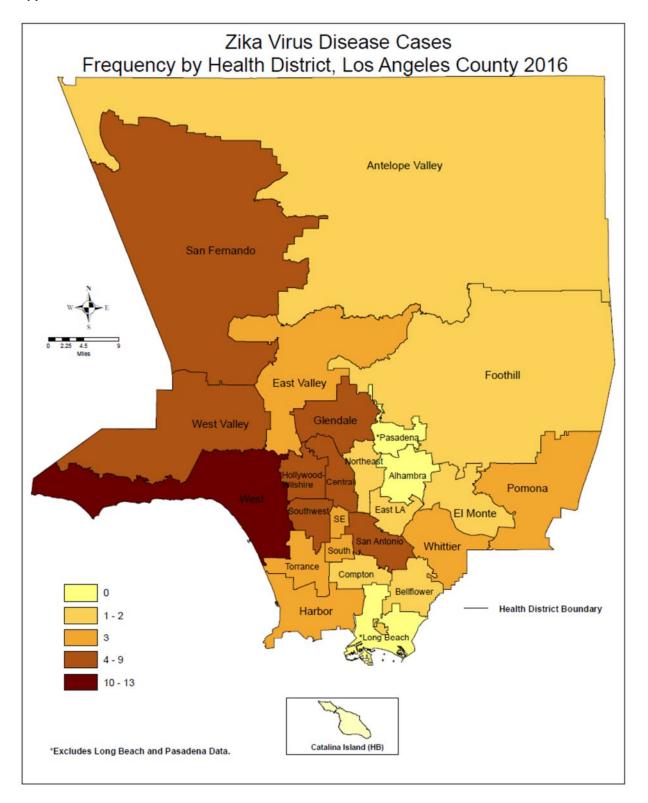
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# Appendix A



# Appendix B

### **ZIKA CASE CLASSIFICATION**

**Confirmed:** A clinically compatible case and confirmatory laboratory results, OR a person who does not meet clinical criteria but has an epidemiologic linkage and confirmatory laboratory results.

**Probable:** A clinically compatible case and presumptive laboratory results, OR a person who does not meet clinical criteria but has an epidemiologic linkage and presumptive laboratory results.

**Flavivirus infection of undetermined species:** A clinically compatible case and evidence of recent infection with a flavivirus where the neutralizing antibody test results on a single specimen are insufficient to determine the identity of the infection virus, OR a person who does not meet clinical criteria but has an epidemiologic linkage and evidence of recent infection with a flavivirus where the neutralizing antibody test results on a single specimen are insufficient to determine the identity of the infection virus.