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Epidemiology of the First Zika Virus Outbreak in the
United States Virgin Islands, 2016–2017

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Abstract

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By Jordan D. Peart

Zika virus was first identified in the Americas in Brazil in March 2015 and the first case of Zika virus in the United States Virgin Islands (USVI) was reported on January 19, 2016. This investigation describes the epidemiology of Zika virus in a susceptible island population, including clinical features, demographic characteristics, and geospatial patterns. Data were from the USVI Zika surveillance system; the study population consists of 4,139 persons, of which 1,251 were laboratory-positive Zika cases. Prevalence ratios were calculated using log-binomial regression to evaluate the association between Zika virus disease and several demographic characteristics and clinical features. The physical home addresses of laboratory-positive Zika cases were geocoded to identify estates with increased Zika virus transmission. Contact with a recently ill household member was associated with laboratory-positive Zika virus infection (adjusted PR= 1.39, 95% CI: 1.04, 1.86) and pregnancy was associated with not being a case (adjusted PR= 0.17, 95% CI: 0.11, 0.25). Rash (adjusted PR= 3.70, 95% CI: 3.33, 4.12), conjunctivitis (adjusted PR= 1.13, 95% CI: 1.04, 1.22), and arthralgia or arthritis (adjusted PR= 1.31, 95% CI: 1.19, 1.44) were associated with laboratory-positive Zika virus infection, whereas cold-like symptoms (adjusted PR: 0.85, 95% CI: 0.76, 0.94) and gastrointestinal symptoms (adjusted PR: 0.83, 95% CI: 0.74, 0.94) were associated with not being a case. Based on the geospatial patterns of Zika cases, increased transmission occurred in and around cities and seaports. These results enhance our knowledge of the effect of Zika virus in a susceptible island population, highlight the importance of timely public health intervention, and aid in public health planning for future Zika outbreaks in the USVI. Specifically, the USVI Department of Health can utilize these results to: (1) strengthen public health surveillance by implementing syndromic surveillance for increased rash, conjunctivitis, and arthralgia or arthritis, (2) target vector control efforts in areas with increased Zika virus transmission, and (3) increase messaging for personal protection against mosquitoes, especially among those who are ill.

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MANUSCRIPT

Zika virus is a flavivirus, in the family *Flaviviridae*, primarily transmitted by *Aedes* species mosquitoes (1). It was first isolated from a rhesus macaque in the Zika forest of Uganda in 1947 and the first human cases were reported in Nigeria in 1953 (2). In 2007, the first major Zika virus outbreak occurred on Yap Island, Federated States of Micronesia (3). Several other Pacific islands experienced outbreaks between 2013 and 2016, and there have been reports of sporadic cases of Zika virus in several Southeast Asian countries (2).

Zika virus disease typically presents as an acute febrile illness; symptoms include: maculopapular rash, arthralgia, myalgia, conjunctivitis, and headache. However, up to 80% of those infected with Zika virus are asymptomatic (2). Zika virus infection is also associated with Guillain-Barré syndrome and other neurologic complications (4). Infection during pregnancy is a cause of microcephaly and other adverse fetal outcomes (5). There is currently no vaccine or antiviral therapy for Zika virus infection, and treatment is symptomatic. Prevention and control measures focus on vector control and health education (2).

Introduction to the Americas

Zika virus was first identified in the Americas in Brazil in March 2015 (6) and Colombia reported the first autochthonous transmission of Zika outside of Brazil in October 2015. By March 2016, Zika virus was reported in at least 33 countries and U.S. territories in the Caribbean (2). In September 2015, Brazil reported an increase in cases of microcephaly in regions where Zika virus was previously reported (2). On February 1, 2016, the World Health Organization declared a Public Health

Emergency of International Concern due to the association between Zika virus and human birth defects (7).

Zika Virus in the United States Virgin Islands

The first case of Zika in the United States Virgin Islands (USVI) was reported on January 19, 2016. The USVI Department of Health (DOH) quickly ramped up its Zika response, which included community outreach and education, disease surveillance, strengthening laboratory capacity, and vector control. The USVI DOH, in collaboration with the Centers for Disease Control and Prevention, launched the Zika Emergency Operations Center and implemented free Zika testing for individuals with symptoms consistent with Zika virus disease and asymptomatic pregnant women in February 2016.

Initial epidemiologic surveillance was rapidly expanded using USVI's existing ArboNET database. The database was later modified to provide additional surveillance information required to aid in the response to the Zika outbreak. The USVI Zika Pregnancy Registry was also established to monitor all pregnant women with laboratory-positive Zika virus infection throughout their pregnancy. Data from the Zika surveillance system have been used to guide public health action and program planning, but the epidemiologic characteristics of the outbreak have not yet been formally described.

Zika virus is a significant public health issue in the USVI. Major challenges include the fact that majority of cases are asymptomatic, sustainable vector control, and the uncertainty of the long-term effects for those with neurologic complications (8). This investigation describes the epidemiology of Zika virus in a susceptible

island population, including clinical features, demographic characteristics, and geospatial patterns, to inform public health program planning and enhance early detection of Zika virus transmission.

METHODS

Study setting and population

The USVI are a group of islands in the Caribbean, with a population of 106,405. The three main islands are St. John, St. Croix, and St. Thomas with populations of 4,170, 50,601, and 51,634, respectively. The islands are subdivided into estates, which are legally defined boundaries. There are 51 estates on St. John, 212 on St. Croix, and 73 on St. Thomas (9).

Zika virus surveillance in the USVI is passive; healthcare providers are required to report all suspected cases and asymptomatic pregnant women tested on a standardized form. A suspected Zika case is defined as an individual with at least two of the following symptoms: acute onset of fever ($>38^{\circ}\text{C}$), rash, conjunctivitis, or severe arthralgia or arthritis not explained by another medical condition (10).

Asymptomatic pregnant women are tested for Zika virus during their first prenatal visit, and again mid-second trimester. In some settings, such as health fairs, asymptomatic non-pregnant persons were also tested for Zika virus. The study population therefore consists of individuals who were tested for Zika virus in any public or private healthcare facility or health fairs in the USVI.

Data collection

This investigation received an exemption from Emory's Institutional Review Board. Data from the Zika surveillance system were de-identified, with each

individual represented by a unique reference identification code. The following information was collected: age, gender, pregnancy status, physical home address, clinical symptoms, travel 14 days before illness onset, and contact with recently ill household members. A laboratory-positive case was defined as an individual with either: 1) isolation of Zika virus or demonstration of Zika virus nucleic acid in serum, cerebrospinal fluid, or urine using reverse transcription polymerase chain reaction or 2) Zika virus-specific IgM antibodies in serum, or cerebrospinal fluid using enzyme-linked immunosorbent assay and Zika virus-specific neutralizing antibodies using plaque reduction neutralization test with a 90% plaque reduction cutoff. Individuals were confirmed negative if reverse transcription polymerase chain reaction did not detect Zika virus nucleic acid in serum, cerebrospinal fluid, or urine, or if individuals had no evidence of Zika virus-specific IgM antibodies in serum or cerebrospinal fluid (11).

Study design and analyses

The investigation is a cross-sectional study of the 2016–2017 Zika outbreak. We compared demographic and clinical data for all laboratory-positive Zika cases and laboratory-negative persons. Reported Zika cases per 1,000 population by island, age category, and gender (12) were calculated. We produced an epidemic curve of laboratory-positive Zika cases per 1,000 population by month. Data analyses were conducted using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2002–2012 SAS Institute Inc.

Demographic characteristics. Mean age of laboratory-positive Zika cases and laboratory-negative persons were compared using a two-sample t-test. Prevalence

ratios were calculated using log-binomial regression to evaluate the association between Zika virus disease and demographic characteristics including: age, gender, contact with a recently ill household member, travel before illness onset, and pregnancy status. These characteristics were examined separately, as well as combined in a multivariable model.

Clinical features. Prevalence ratios were calculated using log-binomial regression to evaluate the association between Zika virus disease and several symptoms. Each symptom was examined separately, as well as combined in a multivariable model.

Geospatial patterns. Physical home addresses of laboratory-positive Zika cases were geocoded to the estate level, using ArcGIS 10.5 (ESRI, Redlands, CA), to identify estates with increased Zika virus transmission.

RESULTS

A total of 4,158 persons were identified in the Zika virus surveillance system between January 19, 2016 and May 12, 2017. Nineteen persons were excluded because there was no confirmatory laboratory test for Zika virus. The study population therefore consists of 4,139 persons, of which 1,251 (30%) were laboratory-positive Zika cases (11.8 cases per 1,000 population). Of the laboratory-positive Zika cases, 101 (8%) were reported from St. John (24.2 cases per 1,000 population), 301 (24%) were reported from St. Croix (6.0 cases per 1,000 population), and 849 (68%) were reported from St. Thomas (16.4 cases per 1,000 population).

Based on the epidemic curve, St. Thomas experienced the outbreak earlier than St. Croix and St. John (Figure 1). Peak incidence of laboratory-positive Zika cases occurred in August in St. Thomas and in October in St. Croix and St. John. St. John experienced the outbreak most severely, followed by St. Thomas then St. Croix.

Demographic Characteristics

Zika virus incidence was highest among individuals aged 25–54 (18.4 cases per 1,000 population) and individuals aged 15–24 (17.0 cases per 1,000 population), and lowest among individuals aged 65 and older (4.0 cases per 1,000 population) and individuals aged 14 and younger (4.9 cases per 1,000 population) (Table 1). When pregnant women were excluded, incidence in the 25–54 and 15–24 age groups decreased but the general trend remained the same. The majority of laboratory-positive Zika cases occurred in females (72%) (Table 2), and was consistent when pregnant women were excluded (65%). Incidence was higher among females compared with males (16.0 cases per 1,000 population and 6.9 cases per 1,000 population, respectively) (Table 1). When pregnant women were excluded, incidence among females decreased but still remained higher when compared with males (11.9 cases per 1,000 population and 6.9 cases per 1,000 population, respectively).

The median age of laboratory-positive Zika cases was 35 years compared with a median age of 30 years for laboratory-negative persons (Table 2). The mean difference in age between laboratory-positive cases and laboratory-negative persons was 4.9 years (95% CI: 3.8, 5.9). Laboratory-positive cases were more likely than laboratory-negative persons to have contact with a recently ill household

member (unadjusted PR= 2.22, 95% CI: 1.71, 2.87) and to have traveled 14 days before illness onset (unadjusted PR= 1.69, 95% CI: 1.32, 2.15). Laboratory-positive cases were less likely than laboratory-negative persons to be female (unadjusted PR= 0.60, 95% CI: 0.54, 0.66) (Table 2). However, when pregnant women were excluded there was no association between Zika virus and gender (unadjusted PR= 1.03, 95% CI: 0.94, 1.13). Pregnancy was associated with not being a case (unadjusted PR= 0.26, 95% CI: 0.23, 0.30) (Table 2). This association remained but was attenuated when asymptomatic individuals were excluded (unadjusted PR= 0.41, 95% CI: 0.28, 0.60). When demographic characteristics were examined together in a multivariable model, contact with a recently ill household member remained associated with laboratory-positive Zika virus infection (adjusted PR= 1.39, 95% CI: 1.04, 1.86) and pregnancy remained associated with not being a case (adjusted PR= 0.17, 95% CI: 0.11, 0.25). Age, gender, and travel 14 days before illness onset were not associated with being a laboratory-positive case.

Clinical Features

Of the laboratory-positive Zika cases, 80% (1001) were symptomatic. In general, a larger proportion of laboratory-positive cases experienced each symptom when compared with laboratory-negative persons. However, a similar proportion of laboratory-positive cases and laboratory-negative persons experienced the symptoms 'abdominal pain or tenderness' and 'unable to walk during illness' (Table 2). Only one Guillain-Barré case was reported. When all clinical features were examined together in a multivariable model, rash (adjusted PR= 3.70, 95% CI: 3.33, 4.12), conjunctivitis (adjusted PR= 1.13, 95% CI: 1.04, 1.22), and arthralgia or

arthritis (adjusted PR= 1.31, 95% CI: 1.19, 1.44) were associated with laboratory-positive Zika virus infection. Cold-like symptoms (adjusted PR: 0.85, 95% CI: 0.76, 0.94) and gastrointestinal symptoms (adjusted PR: 0.83, 95% CI: 0.74, 0.94) were associated with not being a case.

Geospatial Patterns

Of the 1,251 Zika cases, 1,023 (82%) had identified addresses that were geocoded. Zika cases on St. Croix were mostly concentrated in and around the cities of Christiansted and Frederiksted, and in the central region of the island. Zika cases on St. John were mostly concentrated in the western region of the island. Zika cases occurred throughout St. Thomas but were mostly concentrated in the central and eastern regions of the island (Figure 2).

DISCUSSION

The USVI was one of many islands in the Caribbean to experience the first documented Zika outbreak in the Americas. As of August 22, 2017, Zika cases are still being reported in the USVI. It is still uncertain whether Zika outbreaks will reoccur in the USVI. Reports of recurrent outbreaks of dengue and chikungunya, diseases also transmitted by *Aedes* species mosquitoes, indicate that Zika outbreaks might also reoccur (13). This investigation is important for understanding the characteristics of the first Zika outbreak in the USVI and informing public health program planning for potential future outbreaks.

The largest proportion of Zika cases was reported from St. Thomas followed by St. Croix and St. John, likely due to the variation in population density between the islands (1,614 persons per square mile, 602 persons per square mile, and 209

persons per square mile, respectively) (14). The larger proportion of cases on St. Thomas may also be attributed to greater number of visitors when compared with St. Croix. St. Thomas received four times the number of air passenger arrivals and fourteen times the number of cruise ship passenger arrivals than St. Croix in 2016 (15, 16). The increased population density and greater number of tourists, and thus additional human movement, may have increased transmission of Zika virus on St. Thomas (14, 17). St. Thomas experienced the outbreak earlier than St. Croix and St. John, reaching peak incidence in August 2016. This is consistent with the trend that occurred during the 2014–2015 chikungunya outbreak in the USVI (14) and may also be associated with increased Zika virus transmission due to higher population density on St. Thomas. Zika virus incidence was much higher on St. Thomas and St. John when compared with St. Croix. This could be explained by the relative ease of travel between St. Thomas and St. John when compared with travel to St. Croix. St. Thomas and St. John are relatively close in distance (11 nautical miles) and travel between the two islands is inexpensive, with a ferry traveling between the two islands multiple times per day. Both St. Thomas and St. John are further in distance to St. Croix (38 nautical miles on average) and up until April 2017, travel between the islands was limited to more expensive air travel (18).

Zika virus incidence was highest among individuals aged 15–54, and much higher among females when compared with males. This was also observed when pregnant women, who received free Zika virus testing at prenatal visits, were excluded from analyses. These findings are consistent with reports of Zika outbreaks in other countries but different from patterns observed during the

chikungunya outbreak in the USVI. During the 2014–2015 chikungunya outbreak, incidence was highest among individuals aged 55 and older, and incidence was only slightly higher among females when compared with males (14). Similar observations of higher Zika virus incidence in females and those of reproductive age have been made in Yap, Federated States of Micronesia and Puerto Rico (3, 19). When pregnant women were excluded, females accounted for 65% of Zika cases. Other countries have also reported a larger proportion of Zika cases among females. In one study, this was hypothesized to be due to: more exposure to *Aedes* mosquitoes in the home, more severe symptoms at certain ages, differences in health care-seeking behavior, and reporting biases by health care workers because of risk of infection during pregnancy (20). In the USVI, females were more likely to get tested for Zika virus regardless of pregnancy status. A study in Rio de Janeiro, Brazil indicated that sexual transmission from men to women might also be a factor (21). These observations might explain the distribution of Zika cases in the USVI. Serological studies of Zika virus infection will be useful to estimate the true incidence among gender and all age groups in the USVI.

Contact with a recently ill household member was associated with laboratory-positive Zika virus infection. This was also observed during the 2014–2015 chikungunya outbreak in the USVI and in a study of Zika virus in Brazil. In Rio de Janeiro Zika cases were clustered within households, which the authors stated could be attributed to high vectorial capacity and, to a lesser extent, possible sexual transmission (22). It has also been shown that the restricted flight range and frequent blood-feeding behavior of *Aedes aegypti* mosquitoes have contributed to

clustering of dengue infections (23). The finding that contact with a recently ill household member was associated with being a case is consistent with these observations. Pregnancy was associated with not being a Zika case. A small study found low rates of maternal Zika infection among pregnant women traveling to countries with local Zika transmission (24). In the USVI, this could indicate that the DOH has been effective in targeting Zika virus prevention messaging and materials to pregnant women. However, a recent study in the USVI found low prevalence of protective behaviors against Zika virus among a sample of pregnant women (25). More studies on the risk of Zika virus infection in pregnant women in areas of local Zika transmission are needed.

Rash, conjunctivitis, and arthralgia or arthritis were associated with laboratory-positive Zika virus infection. The clinical features of laboratory-positive Zika cases were consistent with those reported in Zika outbreaks in other countries (3, 22, 26). Surprisingly, fever was not associated with Zika virus in the USVI. This could be due to how fever is reported in the Zika surveillance system, either as a fever $> 38^{\circ}\text{C}$ or a fever lasting 2–7 days. A study in Rio de Janeiro, Brazil found that among confirmed Zika cases, fever was low-grade and short-termed, not lasting longer than one day (22).

Based on the geospatial patterns of Zika cases in the USVI, increased transmission of Zika virus occurred in and around cities on all three islands. This is likely explained by increased population density in these areas. There was also increased transmission of Zika virus near seaports and marine facilities (27), which may be explained by additional human movement in these areas (17) and

transportation of mosquitoes in ships (28). Vector control efforts targeting these areas could reduce Zika virus transmission.

Strengths and Limitations

Zika virus surveillance in the USVI is passive and data may not accurately reflect the actual distribution of Zika virus. The sample only represents individuals who sought health care for their symptoms, women who received prenatal care, and those who requested Zika virus testing at a health fair. It is possible that the analysis over represents individuals who exhibited more severe symptoms, women who are more likely to receive prenatal care, and individuals most concerned about Zika virus infection, including partners of pregnant women and those considering conception. However, the wide availability of free Zika virus testing throughout the USVI may have mitigated this limitation.

Surveillance data quality depends on providers to accurately and completely report demographic and clinical data. Providers were routinely educated about the importance of capturing data and were familiar with the Zika case report form, as it is also used to report dengue and chikungunya. However, in many cases data were missing and it is possible that some data were reported inaccurately. Data were manually entered into the Zika surveillance system by USVI DOH staff, with majority of records double-checked by another individual to ensure data accuracy.

Despite these limitations, this investigation describes the demographic risk factors and clinical features associated with the first Zika outbreak in the USVI. These results enhance our knowledge of the effect of Zika virus in a susceptible island population, highlight the importance of timely public health intervention, and

aid in public health planning for future Zika outbreaks in the USVI. Specifically, the USVI DOH can utilize these results to: (1) strengthen public health surveillance by implementing syndromic surveillance for increased rash, conjunctivitis, and arthralgia or arthritis, (2) target vector control efforts in areas with increased Zika virus transmission, and (3) increase messaging for personal protection against mosquitoes, especially among those who are ill.

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TABLES

Table 1. Laboratory-positive Zika Cases per 1,000 Population by Age Category and Gender, United States Virgin Islands, January 2016–May 2017.

Age Category, years	Cases per 1,000 Population		
	Females	Males	Total
≤ 14	5.8	4.1	4.9
15–24	27.0	6.5	17.0
25–54	24.7	11.1	18.4
55–64	10.5	5.7	8.3
≥ 65	5.5	2.2	4.0
Total	16.0	6.9	11.7

Table 2. Proportion of Laboratory-positive Zika Cases and Laboratory-negative persons by Demographic Characteristics and Clinical Features, and Unadjusted Estimated Prevalence Ratios and 95% Confidence Intervals Comparing Laboratory-positive Zika Cases and Laboratory-negative Persons, United States Virgin Islands, January 2016–May 2017.

Demographic Characteristic/Clinical Feature	Positive (no.)	Negative (no.)	PR	95% CI
Median Age, years	35.00 (1241)	30.00 (2863)		
Female	0.72 (896)	0.85 (2439)	0.60	0.54, 0.66
Pregnant	0.18 (222)	0.58 (1652)	0.26	0.23, 0.30
Contact with recently ill household member	0.22 (47)	0.08 (68)	2.22	1.71, 2.87
Travel 14 days before illness onset	0.23 (58)	0.13 (109)	1.69	1.32, 2.15
Fever ^a	0.33 (411)	0.17 (495)	1.74	1.59, 1.91
Rash	0.61 (757)	0.12 (341)	4.25	3.88, 4.65
Conjunctivitis	0.18 (226)	0.05 (147)	2.22	2.02, 2.45
Arthralgia or arthritis	0.52 (655)	0.23 (660)	2.36	2.16, 2.58
Myalgia	0.40 (499)	0.20 (570)	1.91	1.74, 2.08
Chills or rigor	0.21 (267)	0.12 (360)	1.52	1.37, 1.69
Headache or eye pain	0.46 (573)	0.21 (602)	2.13	1.95, 2.33
Any hemorrhagic manifestation	0.06 (72)	0.04 (107)	1.35	1.12, 1.63
Fatigue or malaise	0.10 (120)	0.06 (160)	1.46	1.27, 1.69
Gastrointestinal symptoms ^b	0.11 (132)	0.09 (254)	1.15	0.99, 1.33
Cold-like symptoms ^c	0.16 (199)	0.13 (379)	1.17	1.03, 1.32
Abdominal pain or tenderness	0.03 (32)	0.04 (106)	0.76	0.56, 1.03
Unable to walk during illness	0.04 (56)	0.04 (114)	1.09	0.88, 1.36

PR, prevalence ratio; CI, confidence interval

^a Fever includes fever >38°C and fever lasting 2–7 days^b Gastrointestinal symptoms include nausea, vomiting, and diarrhea^c Cold-like symptoms include cough, sore throat, and nasal congestion

FIGURES

Figure 1. Epidemic Curve of Laboratory-positive Zika Cases per 1,000 Population by Month of Illness Onset and Island, United States Virgin Islands, January 2016–May 2017.

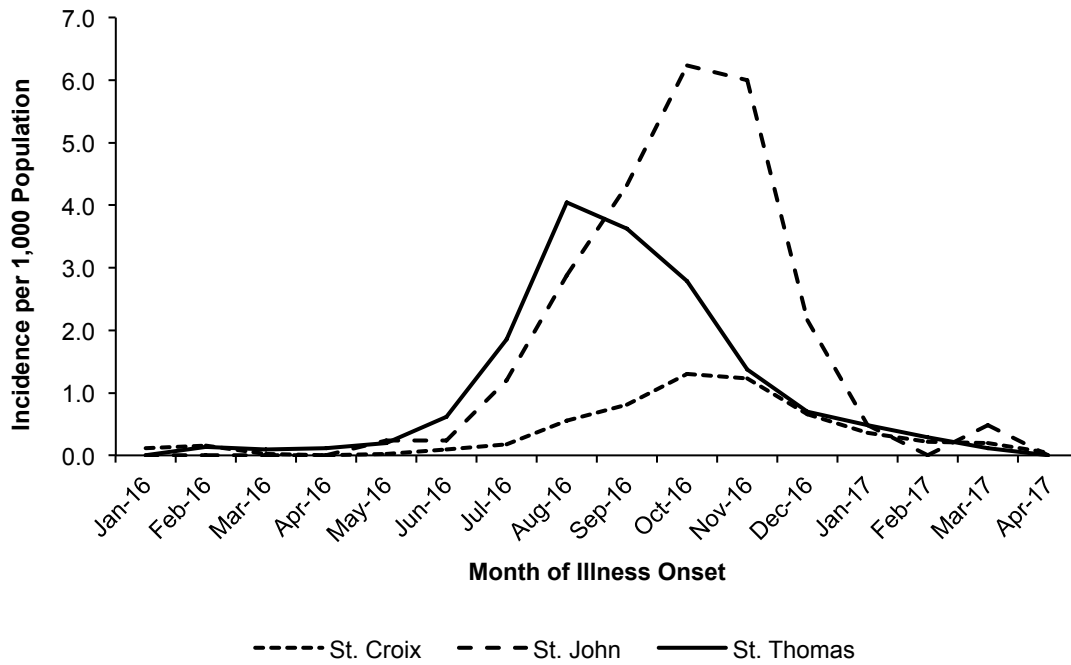


Figure 2. Geographic Distribution of Laboratory-positive Zika Cases, United States Virgin Islands, January 2016–May 2017.

