Seroprevalence and Symptomatic Attack Rate of Chikungunya Virus Infection, United States Virgin Islands, 2014–2015

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Abstract. When introduced into a naïve population, chikungunya virus generally spreads rapidly, causing large outbreaks of fever and severe polyarthralgia. We randomly selected households in the U.S. Virgin Islands (USVI) to estimate seroprevalence and symptomatic attack rate for chikungunya virus infection at approximately 1 year following the introduction of the virus. Eligible household members were administered a questionnaire and tested for chikungunya virus antibodies. Estimated proportions were calibrated to age and gender of the population. We enrolled 509 participants. The weighted infection rate was 31% (95% confidence interval [CI]: 26–36%). Among those with evidence of chikungunya virus infection, 72% (95% CI: 65–80%) reported symptomatic illness and 31% (95% CI: 23–38%) reported joint pain at least once per week approximately 1 year following the introduction of the virus to USVI. Comparing rates from infected and noninfected study participants, 70% (95% CI: 62–79%) of fever and polyarthralgia and 23% (95% CI: 9–37%) of continuing joint pain in patients infected with chikungunya virus were due to their infection. Overall, an estimated 43% (95% CI: 33–52%) of the febrile illness and polyarthralgia in the USVI population during the outbreak was attributable to chikungunya virus and only 12% (95% CI: 7–17%) of longer term joint pains were attributed to chikungunya virus. Although the rates of infection, symptomatic disease, and longer term joint symptoms identified in USVI are similar to other outbreaks of the disease, a lower proportion of acute fever and joint pain was found to be attributable to chikungunya virus.

INTRODUCTION

Chikungunya virus is a mosquito-borne alphavirus that causes large outbreaks of acute febrile illness with polyarthralgia. Chikungunya virus is primarily transmitted to humans by *Aedes aegypti* and *Aedes albopictus* mosquitoes. When introduced into a naïve population, chikungunya virus generally spreads rapidly with humans serving as the main reservoir for the virus.¹ In past outbreaks, the seroprevalence rate has ranged from 10% to 75% of the population.^{2–10} Most of the infected persons are thought to develop clinically apparent disease, with estimates ranging from 50% to 85%.^{4,6,9–11} Symptoms of chikungunya virus disease include acute onset of fever and polyarthralgia which generally resolve within 7–10 days.^{12–14} Although increased mortality rates have been reported following chikungunya outbreaks, deaths caused by chikungunya virus are rare.^{15–19} However, the joint pains can be debilitating, and some patients have reported persistent joint pains for months to years.^{19–29} There is presently no vaccine or medication to prevent or treat chikungunya virus infection, although infection is believed to confer lifelong immunity.^{14,30}

In December 2013, the World Health Organization reported the first local transmission of chikungunya virus in the Western Hemisphere, with autochthonous cases identified in Saint Martin. The virus then spread throughout much of the Caribbean, South America, and Latin America. In June 2014, the U.S. Virgin Islands (USVI) Department of Health identified the first locally acquired case of chikungunya virus disease in the territory, on the island of St. Thomas. By the end of 2014, ≥ 1,700 chikungunya virus disease cases, almost 2% of the

total population, were reported among USVI residents across all three islands in the territory.³¹ We conducted a population-based household survey to estimate the seroprevalence, symptomatic attack rate, risk factors for becoming infected, and the proportion of the population still experiencing joint symptoms because of their chikungunya virus infection approximately 1 year after the first cases of local chikungunya virus disease were identified in USVI.

METHODS

U.S. Virgin Islands is a U.S. territory located in the Caribbean Ocean. The territory comprises three main islands with a total population of 106,405 persons according to the 2010 U.S. census.³² We conducted a population-based household serosurvey using a stratified, one-stage cluster sampling design. The three islands of St. Thomas, St. Croix, and St. John served as the strata, and households were clusters within strata. A database of property tax records for all land parcels in USVI was obtained from the Geographic Information System (GIS) Division of the Office of the Lt. Governor, USVI. Land parcels with no individual legal owner, such as a trust or a government-owned property, parcels whose legal owner was not a USVI resident, and subdivisions (i.e., estates) with ≤ 5 parcels were excluded. Land parcels were then selected using simple random sampling within stratum. GIS shapefiles of randomly selected parcels were superimposed onto Google Earth (Google, Inc., Mountain View, CA) and parcels without a visible structure were removed from the database. The remaining parcels were assigned a study identification number.

Randomly preselected households were visited by investigation teams between June 8 and June 30, 2015. All eligible household members were invited to participate, with eligibility defined as a USVI resident who 1) resided in USVI for ≥ 8 months of the previous year and 2) spent an average

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of ≥ 2 days per week sleeping in the home. Infants aged < 6 months were excluded to avoid the possibility of maternal antibodies causing a false-positive test result.³³ Households were classified as either a participant, refused, or not available. A participant household was a household in which at least one household member met the eligibility criteria and agreed to fully participate in the study by completing a survey and providing a blood sample. A refused household was a household where a person answered the door but was unwilling to provide a blood sample. Not available households were households that appeared to be occupied and a study information sheet placed at the residence during the first visit had been removed but either an adult was not present or no one answered the door during three visits. Households where no one in the household met the inclusion criteria or was unoccupied (i.e., vacant or information sheet was still present after three visits) were considered not eligible for the study.

Verbal consent was obtained from all who met the eligibility criteria and agreed to participate. For minors aged < 18 years, parental permission was obtained from the parent or legal guardian. We administered a standardized questionnaire which collected information on demographics, any symptoms consistent with chikungunya virus disease, and risk factors for becoming infected or having more severe or prolonged disease (e.g., underlying joint disease). For persons aged < 12 years, their parent or guardian completed the survey questions on behalf of the minor. The head of the household answered all survey questions related to household characteristics on behalf of the household.

A venous blood sample was obtained from all participants in a serum separator tube. Blood samples were kept cold at 4°C until they could be spun down and the serum removed. The serum sample was then frozen at -20°C until they could be shipped for testing at CDC's Arbovirus Diagnostic and Reference Laboratory in Fort Collins, Colorado. All samples were tested for chikungunya virus immunoglobulin (Ig) G antibodies by enzyme-linked immunosorbent assay (ELISA), as previously described.³⁴ Any sample testing chikungunya virus IgG positive was confirmed by plaque reduction neutralization test.³⁵ If a person reported having fever and joint pain in the week before their interview, reverse transcriptase-polymerase chain reaction (RT-PCR) and IgM ELISA were also performed.^{35,36}

Participants were considered to have recent or previous chikungunya virus infection if their serum had evidence of 1) chikungunya viral RNA by RT-PCR or 2) chikungunya virus IgM or IgG antibodies with confirmatory neutralizing antibodies. Those without evidence of chikungunya viral RNA and antibodies were classified as chikungunya virus noninfected. A participant who reported an acute illness with fever and joint pain within the last year was considered symptomatic. Participants who reported having joint pain at least once a week at the time of interview were considered to have current or persistent joint pains.

Data were entered into REDCap (Research Electronic Data Capture), an online data collection and management tool,³⁷ and were analyzed with Epi Info version 7 (CDC, Atlanta, GA) and R version 3.2.0 (R Core Team, Vienna, Austria). All estimates were calibrated to age and gender of USVI 2010 population and incorporated design weights. Missing observations were excluded and proportions with 95% confidence intervals (CIs) were computed. All inferential analysis excluded three participants from whom age was not

available. Comparisons were made by computing relative risk based on survey regression coefficient and variance estimates. The attributable risk percent (i.e., attributable proportion) was calculated by taking the difference of the adjusted probability of that outcome in those who were infected and those who were not infected over the adjusted probability outcome for those who were infected. Population attributable risk percent (i.e., attributable proportion in the entire population) was calculated by taking the overall adjusted probability of an outcome minus the adjusted probability of that outcome in those who were not infected divided by the overall adjusted probability of the outcome.

RESULTS

A total of 913 eligible households were visited by teams during the study period. Of these, 338 (37%) agreed to participate, 363 (40%) refused participation, and 212 (23%) were not available after three visits. There were 509 individuals in the 338 participating households who answered the questionnaire and provided a blood sample. The median age of participants was 52 years (range: < 1 –91 years) and 56% were female. Compared with the population of USVI, participants were older (Table 1).

Among the 509 participants, 171 had laboratory evidence of previous chikungunya virus infection; after weighting appropriately for the study design and age and gender of the population, the estimated infection rate was 31% (95% CI: 26–36%). When demographic and household characteristics and mosquito-borne prevention measures were compared between those who were infected with chikungunya virus and those who were not, most factors were not significantly associated with infection (Table 2). However, not wearing insect repellent all the time, a lack of a septic tank, and low household income were each found to be significantly associated with chikungunya virus infection on univariate analysis.

Of the 171 chikungunya virus-infected individuals, 121 reported having an acute illness with fever and joint pain in the last year for an adjusted prevalence of symptomatic disease of 72% (95% CI: 65–80%). However, 68 (20%) of the 338 noninfected persons reported acute fever and polyarthralgia in the previous year. Using the symptom rates from infected and noninfected participants, we estimate that 70% (95% CI: 62–79%) of acute fever and joint pain in chikungunya virus-infected individuals was due to their infection. Furthermore, we estimate that 43% (95% CI: 33–52%) of the symptomatic

TABLE 1
Demographics of study population compared with the population of USVI

	Participants, N = 509	USVI population, N = 106,405
	n (%)	n (%)
Female gender	285 (56)	55,538 (52)
Age group (in years)		
0–19	78 (15)	29,697 (28)
20–39	90 (18)	24,682 (23)
40–59	162 (32)	30,267 (28)
60+	176 (35)	21,759 (20)
Resident Island		
St. Thomas	259 (51)	51,634 (49)
St. Croix	239 (47)	50,601 (48)
St. John	11 (2)	4,170 (4)

USVI = United States Virgin Islands.

TABLE 2

Demographic and household characteristics and mosquito-borne prevention measures for chikungunya virus-infected and noninfected participants

Characteristics and measures	Chikungunya virus-infected participants (%)	Chikungunya virus noninfected participants (%)	aRR	(95% CI)
Male gender	41	47	0.83	(0.63–0.91)
Age group (in years)				
0–19	18	20	0.90	(0.50–1.63)
20–39	22	21	Ref	–
40–59	28	34	0.86	(0.53–1.40)
≥ 60	31	24	1.17	(0.75–1.85)
Employment status				
Working	42	49	0.82	(0.63–1.07)
Retired	24	18	1.27	(0.94–1.73)
Not working	17	13	1.22	(0.84–1.76)
School	16	19	0.90	(0.60–1.34)
Time per day outside				
1 hour	15	15	Ref	–
1–4 hours	35	36	0.98	(0.61–1.55)
5–8 hours	24	25	0.96	(0.55–1.67)
8 hours	26	24	1.04	(0.61–1.79)
Repellent usage				
All the time	1	5	Ref	–
Some of the time	29	25	7.25	(1.01–1.52)
Never	71	71	6.59	(0.92–47)
Air conditioning				
Central	5	5	0.97	(0.64–1.46)
Local (one to two bedrooms)	31	32	0.94	(0.41–2.17)
None	64	63	Ref	–
Presence of water-holding container in yard				
Water cistern	45	48	0.91	(0.70–1.19)
Potted plants	41	40	1.02	(0.78–1.35)
Buckets	28	26	1.06	(0.80–1.42)
Septic tank	24	35	0.68	(0.50–0.92)
Trash	9	12	0.80	(0.50–1.28)
Used old tires	5	8	0.73	(0.40–1.34)
Windows open				
All times	73	79	0.66	(0.36–1.22)
During the day	14	14	0.71	(0.33–1.54)
During the night	3	2	0.88	(0.27–2.83)
Never	10	5	Ref	–
Annual household income				
≤ \$25,000	28	23	3.97	(1.14–13)
\$26,000–\$50,000	19	20	3.36	(0.93–12)
\$51,000–\$75,000	14	16	3.16	(0.84–12)
≥ \$76,000	4	17	Ref	–
Declined to answer	36	24	–	–

CI = confidence interval; aRR = adjusted relative risk ratio.

illness, with acute fever and joint pain, that was experienced in the population of USVI was likely attributable to chikungunya virus infection. No demographic features were significantly associated with developing symptomatic disease. Of preexisting medical conditions, only respiratory disease was significantly more common in persons who developed symptoms compared with persons who were infected but did not become symptomatic (Table 3).

Of the 121 symptomatic infected participants, 48 sought care for their acute illness for an adjusted prevalence of 43% (95% CI: 33–53%). In comparison, 28 (41%) of the 68 noninfected persons with reported acute fever and polyarthralgia sought care for their illness. The duration of illness also was similar with symptomatic persons infected with chikungunya virus reporting being ill for a median of 7 days (interquartile range: 4–14 days) and uninfected persons with fever and arthralgia reporting symptoms for a median of 7 days (interquartile range: 3–14 days).

Of the 121 persons with reported fever and polyarthralgia and laboratory evidence of previous chikungunya virus infection, 43 reported having current joint pain at least once a

week at the time of the interview for an adjusted estimated prevalence of 33% (95% CI: 24–43%). In addition, 15 chikungunya virus-infected persons who did not report acute symptoms in the previous year also reported having joint pain at least once a week at the time of the interview. Therefore, 58 participants who were infected reported having current joint pain at the time of interview for an estimate of 31% (95% CI: 23–38%). In comparison, 87 (26%) of the 338 noninfected individuals reported having joint pain at least once per week at the time of the interview. Therefore, an estimated 23% (95% CI: 9–37%) of continued joint pain in patients infected with chikungunya virus was due to their infection. Overall, 12% (95% CI: 7–17%) of the joint pains reported in the population of USVI roughly 1 year after chikungunya virus was first introduced into the territory was attributable to infection with the virus.

DISCUSSION

Our investigation at approximately 1 year following the initial identification of chikungunya virus in USVI identified infection

TABLE 3
Demographic and selected medical conditions for symptomatic and non-symptomatic chikungunya virus-infected participants

Characteristics and measures	Chikungunya virus-infected symptomatic participants (%)	Chikungunya virus-infected non-symptomatic participants (%)	aRR	(95% CI)
Male gender	38	46	0.92	(0.74–1.12)
Age group (in years)				
0–19	18	18	0.92	(0.62–1.35)
20–39	24	16	Ref	–
40–59	29	28	0.91	(0.67–1.24)
≥ 60	39	38	0.82	(0.62–1.11)
Medical conditions				
High blood pressure	34	21	1.17	(0.98–1.42)
Chronic joint pain	20	25	1.09	(0.90–1.31)
Diabetes	13	11	1.06	(0.83–1.35)
Respiratory disease	6	0	1.40	(1.25–1.57)
Heart disease	5	2	1.20	(0.90–1.60)
Neurologic disease	3	1	1.18	(0.86–1.64)

CI = confidence interval; aRR = adjusted relative risk ratio.

and symptomatic disease rates similar to those reported with previous outbreaks. However, when the background rates of acute and longer term symptoms in noninfected individuals were accounted for, we estimated only 70% of fever and polyarthralgia, and 23% of joint pain reported roughly 1 year following the outbreak in chikungunya virus-infected individuals was attributable to their infection. Finally, we estimated that 44% of acute fever and polyarthralgia occurring following the introduction and spread of the virus and 12% of the continuing joint pain reported among residents of USVI roughly 1 year following the outbreak was likely attributable to chikungunya virus infection.

Previous studies have reported that from 10% to 75% of populations can be infected during an outbreak of chikungunya virus. The variation of infection rates among studies are likely because of several factors, such as when the survey is conducted relative to the introduction of the virus, who was included in the survey, the likelihood of previous circulation of the virus in an area and the potential for cross-reactive antibodies being detected, when the virus was introduced relative to the peak transmission season of vector-borne disease, and living conditions of the residents in the area surveyed. At 1 year following the introduction of the virus into USVI, we estimated our infection rate in the population to be 31% (95% CI: 26–36%). This is higher than the three previous infection rates estimated for other locations in the Americas (Saint Martin at 17%, Nicaragua at 12%, and Puerto Rico at 24%), but all of these estimates come from surveys conducted < 1 year after the first reported autochthonous case and the Puerto Rico survey included only blood donors.^{8–10} However, we did not obtain travel histories from participants, so cannot exclude that our higher rate was secondary to participants becoming infected during travel to other epidemic areas. Our rate is slightly lower than the rates estimated in La Reunion (38% [95% CI: 36–41%]) and Mayotte (37% [95% CI: 34–41%]), where both surveys were conducted > 18 months following the first case and after two seasons of transmission.^{6,7} Much higher seroprevalence rates were detected in Grande Comore Island (63%) and Lamu Island (75%).^{4,5} However, there was much higher rates of IgG antibodies in older individuals, particularly in Lamu, which the authors suggested could represent previous circulation of chikungunya virus or another alphavirus, such as O'nyong nyong.⁵ Finally, the chikungunya virus seroprevalence rate was found to be 10% in Italy at 3–5 months after the outbreak started.² Both the timing of the

outbreak relative to the end of the transmission season in a temperate area and extensive vector control efforts were felt to curb the size of the outbreak.^{2,38} Overall, the infection rate estimated by our survey is similar to that in other locations, particularly islands, suggesting that the outbreak in the Americas has caused similar infection rates as previous outbreaks seen in the Indian Ocean.

We identified very few factors that were significantly associated with chikungunya virus infection during the USVI outbreak. Similar to others, we found that wearing insect repellent was protective but it had to be worn all the time by our participants.^{39,40} Only 6% of our surveyed participants reported doing this, suggesting that, particularly in an area with active virus circulation, this measure might be challenging to implement. Lower socioeconomic status was identified as a risk factor for chikungunya virus infection in our study and others and has been previously identified as a risk factor for other mosquito-borne infections, such as dengue and St. Louis encephalitis viruses.^{6,10,39–43} Finally, it is unclear why participants who were infected with chikungunya virus were less likely to have septic tanks than participants who were not infected, as a previous study performed during a dengue virus outbreak in Puerto Rico found septic tanks with unscreened vent pipes or open, broken, or improperly closed to be one of the containers responsible for a large production of *A. aegypti* mosquitoes.⁴⁴ However, having a septic tank in USVI was not correlated with socioeconomic status.

In our study, an estimated 72% (95% CI: 65–80%) of persons with laboratory evidence of previous chikungunya virus infection reported fever and joint pain in the past year; however, once rates in uninfected persons were accounted for, approximately 70% of the fever and joint pain in infected individuals could be attributed to chikungunya virus. Our overall symptomatic attack rate was the same as what was reported in Mayotte, where 72% of infected persons reported symptoms and was slightly lower than the symptomatic attack rates reported in Italy (82%), Malaysia (83%), La Reunion (83%), and Grand Comore (86%).^{2,4,6,7,45} Our rate was higher than what was reported in Thailand (53%) and Lamu (55%), where chikungunya virus or a related virus was suspected as having previously circulated in the affected regions,^{5,11} and for other studies performed in the Americas, namely, St. Martin (61%) and Nicaragua (35% for those aged ≥ 15 years and 42% for those aged 2–14 years),^{9,10} where the virus is unlikely to have previously circulated. Most of the previous studies that

reported the symptomatic attack rate, however, either lacked a control group or failed to account for the rate of similar symptoms in noninfected persons.

We found that 43% of symptomatic individuals sought health care, which again was similar to the rate reported in Mayotte of 52%.⁶ We also found that 31% of infected individuals reported having current joint pains at least once per week at roughly 1 year following the start of the outbreak. Overall, this rate falls within the 7–79% of patients with either symptoms consistent with chikungunya or laboratory-confirmed chikungunya who have been reported to have persistent arthralgia following their acute disease.^{2,7,19–29} However, after we adjusted for the background rates of joint symptoms in the controls, only 23% of the joint pains occurring approximately 1 year after the start of the outbreak in infected individuals and only 12% of ongoing joint pains in the population were likely attributable to chikungunya virus infection. These rates are lower than those of most previous studies and suggest that background rates of joint symptoms in a population need to be accounted for when assessing the long-term impact of chikungunya virus disease.

This study was subject to several limitations. First, a lower than expected number of blood samples were obtained, which might impact the precision of our estimates. Second, our case definition required both fever and joint pain for symptomatic disease; therefore, we might have underestimated the symptomatic disease rate as not all symptomatic patients with chikungunya will have both of these symptoms. Furthermore, lack of specificity of these symptoms for chikungunya compared with other diseases, including other arboviral diseases that occur in USVI such as dengue, might have impacted the estimate of the symptomatic attack rate and the proportion of symptoms attributable to chikungunya virus. Third, we only assessed persistent joint pain and did not assess other signs and symptoms that have been reported to occur following the acute infection (e.g., neuropsychological or tendon pain) and thus have likely underestimated the longer term burden caused by chikungunya virus infection. Fourth, interviewing participants up to 1 year out from potential infection could have introduced recall bias and also might have impacted our symptomatic disease rate, particularly if a person acquired the infection and became symptomatic in another epidemic area before June 2014. Finally, exclusion of government-owned properties prevented roughly 3,500 low-income government-subsidized housing units from being included in the study, which might have underestimated the infection rate.

Overall, our study found similar rates of infection, symptomatic disease, and longer term joint symptoms following the introduction of chikungunya virus in USVI as has been reported previously from other outbreaks in naïve populations including the most recent outbreaks in and around the Indian Ocean. However, when we adjusted the rates based on the background rates in the control population, the amount of symptomatic disease and longer term joint symptoms that was truly attributable to chikungunya virus infection is much lower but still suggested that chikungunya virus when introduced into a naïve population can cause a notable amount of acute disease and longer term symptoms in the population. Given this, the public should continue to be educated regarding risks of mosquito-borne diseases and ways to prevent them, such as using mosquito repellent when outdoors, ensuring that people have intact screens or use air-conditioning

to keep mosquitoes out of their homes, and supporting local vector control measures. Further research is needed to better quantify the economic and public health impact of chikungunya virus disease. Larger comparative studies are needed to better define the long-term consequences of chikungunya virus disease.

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