The 2014 chikungunya virus outbreak in the U.S. Virgin Islands: epidemiology, long-term health outcomes, and economic burden

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Abstract

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Background: Chikungunya virus (CHIKV), an emerging and acutely debilitating alphavirus transmitted by the *Aedes aegypti* and *Aedes albopictus* mosquito, was introduced into the Americas in December of 2013. As of April 2016, almost 2 million suspected or confirmed cases have been reported in 45 different countries in the Americas. Acute symptoms of the virus include high fever, severe polyarthralgia (incapacitating joint pain in two or more joints), headache and myalgia. Symptoms often resolve within 7-10 days. However, up to 79% of cases in previous outbreaks have reported persistent arthralgia, defined as joint pain lasting more than two weeks, resulting in decreased quality of life for up to 36 months following initial illness. Currently no cure or vaccine exists for infection, there are no effective therapeutic treatments for chronic symptoms, and disease prevention measures have proven to be insufficient. This dissertation sought to estimate the following: demographic risk factors and clinical manifestations associated with symptomatic CHIKV infection (Aim 1), prevalence of persistent arthralgia among CHIKV cases compared to similar healthcare seekers 1-2, 6 and 12 months after illness onset (Aim 2), the direct and indirect costs associated with the 2014-2015 CHIKV outbreak on the U.S. Virgin Islands (USVI) (Aim 3), and household characteristics and

individual behavioral practices of vector-control as potential risk factors for CHIKV disease (Aim 4).

Methods: All four aims were addressed using CHIKV surveillance data from the USVI Department of Health. Aims 2-4 were also addressed using data from a year-long prospective cohort study of laboratory-positive CHIKV cases and similar healthcare seekers. For Aim 1, descriptive statistics were used to summarize and compare laboratory-positive and suspected laboratory-negative cases from the surveillance data. For Aim 2, three separate regression models were fitted for self-reported presence of persistent arthralgia 1-2, 6 and 12 months following illness onset, adjusting for age, gender and self-reported history of arthritis. Generalized linear models using the binomial family with robust variance estimators were constructed to estimate prevalence differences of persistent arthralgia among cases and the comparison group using the identity link. For Aim 3, direct medical costs were estimated by calculating the mean cost of inpatient and outpatient visits associated with a suspected CHIKV case and indirect costs were estimated by multiplying the mean number of work days missed by the average annual wage in the USVI. For Aim 4, generalized linear models using the binomial family with robust variance estimators were constructed to estimate prevalence differences of household characteristics and personal-protective measures among cases and the comparison group using the identity link.

Results: CHIKV incidence was highest among individuals aged 55-64 years (13.06 per 1,000 cases) and lowest among individuals aged 0-14 years (1.77 per 1,000 cases). Incidence was higher among women compared to men (6.57 and 5.00 cases per 1,000, respectively). More than half of the reported laboratory-positive cases experienced fever lasting 2-7 days, chills/rigor,

myalgia, anorexia, and headache. No clinical symptoms apart from the suspected case definition of fever >38 °C and arthralgia were significantly associated with being a reported laboratory-positive case. One to two months after disease onset, the difference in prevalence of persistent arthralgia between cases and the comparison group was 42% (95% CI: 32%-52%), after adjusting for age, sex and self-reported history of arthritis. The difference in prevalence of persistent arthralgia between cases and the comparison group at 6 months was 32% (95% confidence interval [CI]: 23-40%) after adjustment for potential confounders; at 12 months after onset, the difference in prevalence was 19% (95% CI: 11-28%). Twelve months after illness onset, cases were 1.81 (95% CI: 1.08-3.02) times more likely to have difficulty walking, 1.96 (95% CI: 1.24-3.12) times more likely to have difficulty climbing stairs, and 2.63 (95% CI: 1.31-5.29) times more likely to have difficulty getting in and out of a car compared to similar healthcare seekers. The total estimated cost associated with the 2014-2015 CHIKV outbreak in the USVI ranged from $36.9 to $37.1 million, of which 13% was direct medical costs and 87% was indirect costs due to absenteeism from work. Household characteristics and individual-level behavior practices of vector-control did not differ between laboratory-positive CHIKV cases and similar healthcare seekers during the 2014-2015 CHIKV outbreak in the USVI.

Conclusions: These findings highlight the long-term impaired physical functionality of CHIKV cases, the need for therapeutic and vaccine research to manage and prevent acute illness and long-term morbidity, and the significant economic burden of the first outbreak in the USVI. These results will aid policy-makers in creating informed decisions about prevention and control measures for inevitable future CHIKV outbreaks. Larger-scale seroprevalence and long-term cohort studies will further aid in determining the acute and long-term burden, as well as the public health impact of CHIKV and other arboviral outbreaks in the Americas.

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Chapter 1: Introduction

CHIKV is an emerging alphavirus transmitted by the *Aedes (Stegomyia) aegypti* and *Aedes (Stegomyia) albopictus* mosquitoes. Acute symptoms of the virus, which include high fever, severe polyarthralgia, headache and myalgia, often resolve within 7-10 days [1–3]. However, up to 79% of cases from previous outbreaks in the Indian Ocean Basin, including American and European travelers, have reported persistent arthralgia, resulting in decreased quality of life for up to 36 months following initial infection [2–13].

CHIKV was first identified in Tanzania in 1952 [14]. The word 'chikungunya' means 'to become contorted' in the Kimakonde language and graphically describes the stooped appearance of infected individuals suffering from extreme arthralgia [15]. Since 1952, outbreaks have been reported more than ten years apart in many Asian and African countries [16]. However, beginning in 2001, outbreaks began to occur more frequently in Asia, Africa, Oceania and Europe [16]. In December of 2013, the first case of CHIKV in the Americas was confirmed on the Caribbean island of Saint-Martin [17]. The virus spread rapidly through 45 countries in the Caribbean and Central, South, and North America, resulting in almost 2 million reported cases by April of 2016 [18,19].

Currently, there is no antiviral treatment or vaccine for the viral infection and there are no effective therapeutics for chronic symptoms. The only form of community-level CHIKV prevention is implementation of vector control measures including regularly removing larval habitats, applying larvacide to habitats that cannot be destroyed, and spraying insecticide indoors [20]. Vector control, however, is rarely sufficient and may not be a long-term solution due to the potential for the mosquito vector to build up resistance against insecticides [21]. On an

individual level, the only form of disease prevention is to avoid being bitten by a mosquito by using air conditioning, mosquito repellent, emptying uncovered water containers, and ensuring all windows and doors are screened [20]. Practicing individual-level vector-control is particularly difficult for CHIKV because both the *Ae. aegypti* and *Ae. albopictus* mosquito bite during the daytime [20]. Therefore, interventions used for other mosquito born infections, such as malaria, including the use of insecticide-treated bed nets are ineffective for prevention of CHIKV transmission. The CHIKV epidemic in the Americas is of significant public health importance due to the lack of sustainable and effective control and prevention strategies, the severe acute morbidity of the disease in a fully susceptible population, and the potential for persistent arthralgia to lead to long-term impaired physical functionality of infected individuals [22,23].

The U.S. Virgin Islands (USVI), one of the many regions in the Caribbean affected by the epidemic, identified four imported cases of CHIKV in January and February of 2014. On June 6, 2014 the USVI Department of Health (DOH) identified the first locally acquired case of CHIKV on the island of Saint Thomas. In response to the initial cases of CHIKV, the USVI DOH worked in collaboration with the Centers for Disease Control and Prevention (CDC) to establish and strengthen surveillance and diagnostic capacity for CHIKV and acute febrile illness, to educate healthcare providers and the public regarding CHIKV disease, and to provide recommendations for vector control and other mitigation efforts. Despite the swift response, almost 2,000 suspected cases of CHIKV were reported on the USVI, with the last laboratory-confirmed case reported on February 23, 2015.

A detailed description of demographic information, clinical manifestations and potential risk factors of reported laboratory-positive cases compared to laboratory-negative suspected

individuals in the USVI is essential to improving early identification of disease transmission and in identifying the most vulnerable populations for inevitable future outbreaks. Although CHIKV is now a reportable disease in the Americas, most countries, with the exception of Saint Martin, have not published epidemiological investigations of the outbreak [24].

The true prevalence of long-term persistent arthralgia attributable to CHIKV illness in the Americas and the associated outcomes of persistent arthralgia remain unknown. To date, the burden of persistent arthralgia associated with CHIKV illness has been assessed from outbreaks in only six countries (La Réunion, Italy, India, Malaysia, Mauritius and Singapore) [3,4,7–12]. Studies conducted in these countries followed CHIKV cases up to 36 months post-acute infection. One year after illness onset, prevalence of persistent arthralgia ranged from 7.0-78.6%, however some of these studies had small sample sizes and lacked a comparison group [3,4,7–11]. Furthermore, these study populations differ vastly from the USVI in demographics, geographical location and size. Estimating the long-term burden of CHIKV disease is of particular relevance. Due to the widespread distribution of the mosquito vectors, humans are likely to continue experiencing CHIKV and other arboviral outbreaks such as Zika and dengue in increasing frequency [25].

In addition to estimating persistent arthralgia, previous studies from CHIKV outbreaks in La Réunion, Colombia, and India identified high healthcare costs incurred by ill individuals, lost wages due to absenteeism, decreased quality of life for months following infection, and a large resource burden on unprepared healthcare systems [26–31]. To our knowledge, the economic impact of the first CHIKV epidemic in the Caribbean and years lived with disability (YLDs) associated with long-term sequelae of CHIKV illness have not been measured. This information

is essential for policy-makers to generate informed decisions about prevention and control measures for inevitable future CHIKV outbreaks.

Several studies in Thailand, Malaysia, and the Philippines have provided evidence that having garbage piles near homes and spending more than 8 hours per day outdoors were risk factors for acquiring CHIKV and DENV disease [32–35]. However, other personal protective measures and mosquito risk factors assessed by these studies, such as mosquito repellent use, screens on windows, and uncovered water containers in or near homes were not associated with CHIKV or DENV disease [32,33,35]. Assessing whether these personal protective measures are relevant and effective forms of disease prevention in the USVI is useful in aiding Departments of Health in providing updated personal protective guidelines to its residents.

Characterizing the first CHIKV outbreak in the USVI, estimating the long-term disease burden and cost of illness of the outbreak, as well as examining effectiveness of personal protective measures against CHIKV provide crucial information for stakeholders to implement policy that will mitigate and prevent future CHIKV and other relevant arboviral diseases.

This dissertation addresses several pressing questions regarding the 2014-2015 CHIKV outbreak in the USVI. The aims of the dissertations are as follows:

1) To test whether there are certain demographic risk factors associated with symptomatic CHIKV disease and to describe clinical manifestations associated with the outbreak.

2) To test whether the prevalence of persistent arthralgia is higher among subjects infected with CHIKV compared to similar healthcare seekers 1-2, 6 and 12 months after illness onset.

   a. Sub-aim: To test whether the prevalence of self-reported difficulty walking, climbing stairs, and carrying heavy objects is higher in infected subjects compared to similar healthcare seekers.

3) To calculate the total direct and indirect costs including inpatient and outpatient medical visits and average loss of wages for all symptomatic CHIKV cases to estimate the overall cost of illness of the 2014-2015 CHIKV outbreak in the USVI.

4) To test whether the prevalence of self-reported individual-level practices of vector-control and household characteristics differed between cases and similar healthcare seekers.

Chapter 2: The First Reported Outbreak of Chikungunya virus in the U.S. Virgin Islands, 2014-2015

2.1 Introduction

Chikungunya virus (CHIKV), an emerging alphavirus transmitted by the *Aedes aegypti* and *Aedes albopictus* mosquitoes, was newly introduced into the Americas in December of 2013 [36]. As of April 2016, almost 2 million suspected or confirmed cases have been reported in 45 different countries in the Caribbean, Central, South, and North America [18,19]. Acute symptoms of the virus, which include high fever, severe polyarthralgia, headache and myalgia, often resolve within 7-10 days [1–3]. However, up to 79% of cases from previous outbreaks in the Indian Ocean Basin, including American and European travelers, have reported persistent arthralgia, resulting in decreased quality of life for months following initial infection [2–13]. Currently, there is no antiviral treatment or vaccine for the infection, there are no effective therapeutics for chronic symptoms, and public health prevention measures, such as vector control, have proven insufficient in preventing its spread [1,21].

Between 1952 and 2000, CHIKV outbreaks had been reported in many Asian and African countries, typically with inter-epidemic periods of approximately ten years [16]. However, beginning in 2001, outbreaks began to occur yearly in Asia, Africa, Oceania and Europe [16,21]. In December of 2013, the first case of CHIKV in the Americas was confirmed on the Caribbean island of Saint Martin [17]. The U.S. Virgin Islands (USVI), one of the many regions in the Caribbean affected by the epidemic, identified four imported cases of CHIKV in January and February of 2014. On June 6, 2014 the USVI Department of Health (DOH) identified the first locally acquired case of CHIKV on the island of Saint Thomas. In response to the initial cases of CHIKV, the USVI DOH worked in collaboration with the Centers for Disease Control and

Prevention (CDC) to establish and strengthen surveillance and diagnostic capacity for CHIKV and acute febrile illness, to educate healthcare providers and the public regarding CHIKV disease, and to provide recommendations for vector control and other mitigation efforts. Despite the swift response, almost 2,000 suspected cases of CHIKV were reported in the USVI (population=103,574) [37]. The last laboratory-confirmed case was reported on February 23, 2015 and the last suspected case was reported on April 6, 2015.

The current CHIKV epidemic in the Americas is of significant public health importance due to the lack of sustainable and effective control and prevention strategies, the severe disease morbidity associated with a fully susceptible population, and the potential for persistent arthralgia leading to long-term impaired physical functionality of infected individuals [22,23]. Additionally, while the USVI has a total population of only 103,574, the Territory receive almost 3 million visitors per year by air travel and cruise ship, which could further contribute to global CHIKV transmission [37–39].

A detailed description of demographic information, clinical manifestations, and potential risk factors of laboratory-positive cases compared to laboratory-negative suspected cases, is essential to improving early identification of disease transmission for inevitable future outbreaks. In the present investigation, we describe the clinical epidemiology of the first CHIKV outbreak in the USVI during 2014-2015, as well as demographic risk factors associated with symptomatic CHIKV infection.

2.2 Methods

2.2.1 Study Setting and Subjects

The three main islands of the USVI are Saint Thomas, Saint Croix and Saint John with population sizes of 50,260, 49,255 and 4,059 people, respectively. Once the first confirmed case of CHIKV was recognized on June 6, 2014, all healthcare providers in the USVI were required to report suspected CHIKV cases to the USVI DOH using a standardized report form. As a result, residents of the USVI, who attended any of the three public hospitals or any public or private healthcare facility on Saint John, Saint Thomas or Saint Croix and met the definition of a suspected CHIKV case, were captured by the USVI DOH surveillance system. The USVI DOH defined a suspected case of CHIKV as a resident of any age with acute onset of fever (>38°C) and severe arthralgia or arthritis not explained by another medical condition. No active surveillance was conducted in the USVI during the outbreak; therefore the sample used for this analysis is one of convenience and excludes individuals who were infected with CHIKV but did not seek healthcare.

2.2.2 Data Collection

The data provided by the USVI DOH were de-identified, and each individual was represented by a unique reference identification code. The following information was collected using a standardized questionnaire for all suspected cases: age, sex, clinical symptoms, international travel 14 days before onset of illness, and contact with recently ill household members. A laboratory-positive case was defined as a suspected case with either: 1) isolation of CHIKV or demonstration of CHIKV nucleic acid in blood using reverse-transcriptase polymerase chain reaction (RT-PCR); or 2) CHIKV virus-specific IgM antibodies in serum using enzyme-linked immunosorbent assay (ELISA) with confirmatory chikungunya virus-specific neutralizing

antibodies using plaque reduction neutralization test (PRNT) and a 90% plaque reduction cutoff [40,41]. Individuals were confirmed negative if RT-PCR did not detect CHIKV nucleic acid in blood within the first five days of illness onset, or if individuals had no evidence of CHIKV virus-specific IgM antibodies in serum after the first five days of illness onset [41,42].

2.2.3 Study Design and Analysis

The investigation is a cross-sectional study, examining the demographic and clinical differences between laboratory-positive CHIKV cases and laboratory-negative suspected cases. Descriptive statistics were used to summarize and compare these data. Reported CHIKV cases per 1,000 population were calculated by island, age category and gender during the 2014-2015 outbreak. We generated an epidemic curve of laboratory-positive CHIKV cases per 1,000 population by month. All data analyses were conducted using STATA 12 and R 3.2.2 [43–45].

2.2.4 Demographic Characteristics

To examine the association between CHIKV disease and individual demographic risk factors including: age, gender, contact with a recently ill household member, prior travel and pregnancy status, prevalence ratios were calculated using Poisson regression with robust variance estimators [46]. These risk factors were first examined separately and then together in a multivariate model.

2.2.5 Clinical Manifestations

To determine additional clinical manifestations most strongly associated with CHIKV disease other than fever >38°C and arthralgia/arthritis, prevalence ratios were calculated for each symptom separately and together in a multivariate model using Poisson regression with robust variance estimators [46].

2.3 Results

2.3.1 Study population

A total of 1,929 suspected cases of CHIKV were reported to the USVI DOH between January 1 2014 and April 6 2015. Due to limited healthcare capacity and cost of laboratory testing, only 912 (47%) of the suspected cases had blood specimens that were tested for CHIKV. Of all suspected cases with a tested blood specimen, 275 (30%) were laboratory-negative and 637 (70%) were laboratory-positive (6.15 positive cases per 1,000 population during January 2014 to April 2015). Of the laboratory-positive cases, 469 (74%) were residents living on Saint Thomas (9.33 positive cases per 1,000 population during January 2014 to April 2015), 143 (22%) were living on Saint Croix (2.90 positive cases per 1,000 population during January 2014 to April 2015) and 25 (4%) were living on Saint John (6.16 positive cases per 1,000 population during January 2014 to April 2015). Based on the epidemic curve, Saint Thomas experienced the outbreak more severely and earlier in the year than the islands of Saint Croix and Saint John (Figure 2.1). Peak incidence of reported laboratory-positive cases was 2.56 per 1,000 population and occurred during August of 2014.

2.3.2 Demographic Characteristics

Of those presenting at a hospital or healthcare clinic, the median age of laboratory-positive cases was 46 years, whereas the median age of laboratory-negative suspected cases was 41 years (Table 2.1). The mean difference in age between laboratory-positive cases and laboratory negative suspected cases was 3.9 years (p-value=0.03). CHIKV incidence was highest among individuals aged 55-64 years and >65 years (13.06 and 11.71 cases per 1,000 population) and lowest among individuals aged 0 to 14 years and 25 to 54 years (1.77 and 2.39 cases per 1,000 population, respectively, Table 2.2). A larger percentage of laboratory-positive cases was female

(60%) compared to male (40%) and this was consistent when stratifying by island. Overall, incidence was higher among females compared to males (6.57 and 5.00 cases per 1,000 population, respectively). CHIKV incidence, however, was slightly higher among males aged 0-24 years than females of the same age (Table 2.2). Laboratory-positive cases were 14% (95% CI: 2-27%) more likely than laboratory-negative suspected cases to have contact with a household member who was recently ill (Table 2.1). After adjusting for age and gender, the percentage increased to 18% (95% CI: 5-32%). Traveling outside of the country 14 days before onset of illness was not associated with being a laboratory-positive case.

2.3.3 Clinical Manifestations

A larger proportion of laboratory-positive cases had fever lasting 2 to 7 days, myalgia, headache, chills/rigor, anorexia, and were unable to walk compared to laboratory-negative suspected cases (Table 2.1). A larger proportion of laboratory-negative cases had a sore throat, nasal congestion, cough, rash and diarrhea. When examining all reported clinical manifestations together (aside from fever over 38 °C and arthralgia) in a multivariate model, no symptoms were associated with reported CHIKV infection. Only one symptom remained significantly associated with not being a case; laboratory-positive cases were 25% (95% CI: 4-41%) less likely to have diarrhea compared to laboratory-negative suspected cases.

2.4 Discussion

In 2014, the USVI was one of many island regions in the Caribbean to experience the first documented CHIKV outbreak in the Americas. A total of 1,929 suspected cases were reported to the USVI DOH. Although the last laboratory-positive case of CHIKV in the USVI was reported in February of 2015, it is unclear whether CHIKV transmission will reoccur in subsequent years.

Re-emergence is of particular concern, given that CHIKV transmission is still ongoing in many neighboring countries and could become endemic in the region along with other important arboviruses such as Zika and dengue. It is therefore imperative to learn from the 2014 outbreak to enhance early surveillance efforts and strengthen public health prevention methods against arboviral diseases.

Despite similar sized populations, Saint Thomas had a larger proportion of CHIKV cases than Saint Croix, likely in part due to the higher population density, (1,649.1 compared to 607.3 persons per square mile, respectively). The larger proportion of cases may also be due to the fact that Saint Thomas received almost three times the number of air passenger arrivals and almost 16 times more cruise ship passengers than Saint Croix in 2014 [38,39]. The relative hyper-mobility of the Saint Thomas population as well as the increased population density due to both visitors and residents may have helped facilitate the spread of CHIKV [47].

Overall, laboratory-positive cases were older than laboratory-negative suspected cases. Individuals aged 55 years or older had the highest reported CHIKV incidence, which is consistent with findings from previous outbreaks in other countries where increased age was associated with symptomatic infection and severe atypical disease [5,48]. Older individuals may have been more likely to seek healthcare for CHIKV infection and more likely to have experienced symptomatic or severe disease than younger individuals.

Aside from having fever >38 °C and arthralgia or arthritis, no other clinical symptoms were significantly associated with CHIKV infection. Clinical manifestations of laboratory-positive cases from the USVI outbreak were consistent with symptoms reported in prior outbreaks among

confirmed cases in Singapore, India, Malaysia and La Reunion [4,6,12,42,49,50]. Of note, a larger proportion of laboratory-positive cases in the USVI reported myalgia (93%) and eye pain (35%) compared to cases from previous outbreaks in other regions of the world [4,6,12,42,49,50].

Contact with a recently ill household member was associated with being a laboratory-positive case. This is typical for diseases spread by *Ae. aegypti* and *Ae. albopictus* mosquitoes which tend to be domestic/peridomestic in nature with limited flight ranges (78 - 230 meters) [51,52]. Mosquitoes breeding near one household are capable of infecting persons living within a certain distance of that house. The greater number of people living within that range, the greater opportunity the mosquito has to transmit CHIKV to a human. It is therefore not surprising that contact with a previously ill household member was associated with being a case [53].

Several limitations of this study should be highlighted when considering the results. The sample was one of convenience because only cases who sought healthcare for their symptoms were included in the analysis. As a result, the true incidence of CHIKV remains unknown. Large-scale serological studies capable of detecting the seroconversion rates of these populations will be useful in capturing true incidence. Additionally, the quality of the surveillance data was dependent on the providers' ability to consistently and accurately report suspected cases and their clinical symptoms. Although providers were educated on the importance of capturing this data, monitoring of the reporting was not conducted. Laboratory-negative suspected cases may not be the optimal comparison group for this analysis, because although they are similar to cases in regard to healthcare seeking behavior, they may not be representative of the larger USVI population. Lastly, only 47% of suspected reported cases received laboratory testing for CHIKV

because either the healthcare facilities ran out of resources to continue laboratory testing or because suspected cases refused to be laboratory-tested. Refusal was likely due to the cost of the test or fear of needles. Because the sample tested was not a random sample of all suspected cases, the results may not accurately represent the demographic characteristics of the CHIKV outbreak in the USVI.

A variety of other factors including human mobility/behavior, population density, herd immunity, mosquito abundance, climate, and socio-economic conditions are responsible for the CHIKV patterns observed in the US Virgin Islands and Caribbean [54]. A more detailed understanding of the true incidence and recent epidemic dynamics will be valuable in understanding differences in morbidity between countries, prediction of future outbreaks, and potential consequences of human-driven change including urbanization, globalization, and climate change.

Despite certain limitations, the present investigation describes the clinical manifestations associated with the first CHIKV outbreak in the USVI and identifies the most vulnerable populations for CHIKV disease. These results contribute to our knowledge of CHIKV disease and may aid in mitigating future CHIKV outbreaks in the Caribbean.

2.5 Tables and Figures

Table 2.1: Proportion of suspected (but not tested), laboratory-positive and negative CHIKV cases by demographics risk factors and clinical manifestations, as well as univariate prevalence ratio estimates comparing laboratory-positive cases and laboratory-negative suspected cases.

Demographic risk factor/clinical manifestation	Suspected* (n)	Positive (n)	Negative (n)	Prevalence Ratio (95% CI)
Median age (years)	43.25 (880)	45.99 (572)	41.04 (248)	-
Female	0.58 (551)	0.60 (364)	0.63 (165)	0.96 (0.88-1.05)
Traveled 14 days before illness onset	0.05 (35)	0.07 (32)	0.11 (21)	0.83 (0.66-1.04)
Contact with ill household member	0.25 (166)	0.25 (103)	0.17 (29)	1.14 (1.02-1.27)
Pregnant	0.02 (5)	0.06 (12)	0.02 (1)	1.27 (1.06-1.51)
****Fever over 38 °C**	0.65 (460)	0.77 (404)	0.69 (152)	1.14 (1.01-1.28)
Fever (2-7 days)	0.71 (476)	0.80 (362)	0.75 (148)	1.08 (0.95-1.24)
Arthralgia	0.94 (826)	0.94 (562)	0.86 (214)	1.45 (1.14-1.84)
Arthritis	0.43 (317)	0.44 (246)	0.40 (94)	1.06 (0.96-1.16)
Nausea/vomiting	0.24 (141)	0.21 (92)	0.25 (46)	0.93 (0.81-1.06)
Rash	0.42 (274)	0.33 (144)	0.39 (74)	0.93 (0.83-1.04)
Myalgia	0.86 (622)	0.93 (441)	0.84 (165)	1.46 (1.13-1.88)
Diarrhea	0.16 (92)	0.12 (54)	0.25 (48)	0.72 (0.60-0.87)
Fatigue/malaise	0.22 (118)	0.27 (117)	0.35 (64)	0.89 (0.79-1.00)
Headache	0.70 (458)	0.70 (316)	0.67 (130)	1.03 (0.92-1.15)
Chills/rigor	0.57 (335)	0.67 (299)	0.58 (108)	1.12 (1.00-1.25)
Eye pain	0.35 (197)	0.35 (140)	0.35 (62)	1.01 (0.90-1.13)
Anorexia	0.36 (180)	0.56 (231)	0.50 (88)	1.07 (0.96-1.20)
Unable to walk	0.39 (263)	0.44 (222)	0.34 (72)	1.14 (1.03-1.25)
Cough	0.16 (103)	0.11 (51)	0.19 (40)	0.78 (0.65-0.94)
Nasal congestion	0.13 (78)	0.07 (31)	0.14 (27)	0.74 (0.58-0.95)
Sore throat	0.15 (96)	0.10 (47)	0.16 (33)	0.83 (0.68-1.00)

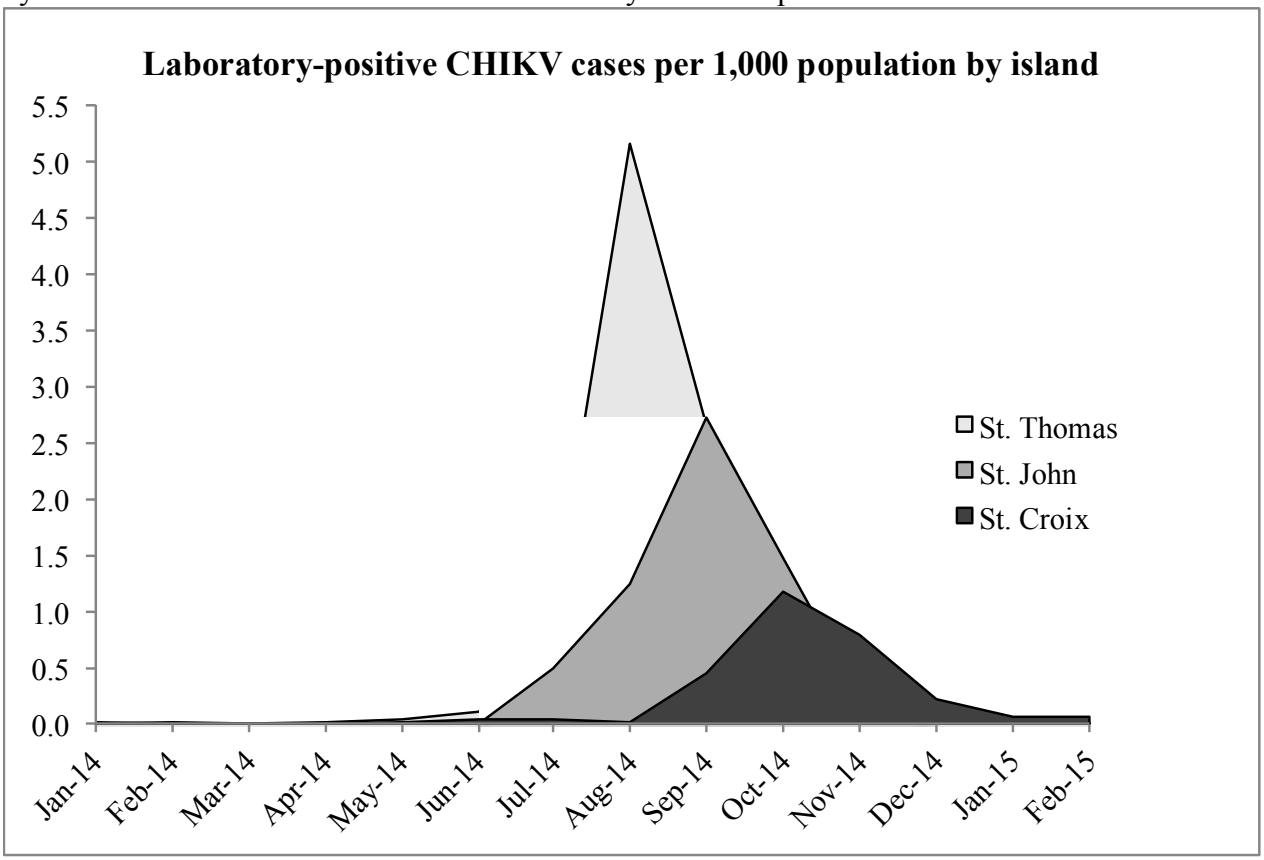
*Individuals suspected of CHIKV infection but without confirmed laboratory-test results

**Fever over 38 °C was marked “yes” only if the individual was febrile at the time of medical visit

Table 2.2: CHIKV cases per 1,000 population by age category and gender from January 2014 to April 2015 [37].

	Cases/1,000 Population		
Age Category	Males	Females	Total
0-14	1.75	1.67	1.77
15-24	8.62	5.20	7.55
25-54	1.33	3.18	2.39
55-64	10.01	14.58	13.06
≥65	9.77	12.31	11.71
Total	5.00	6.57	6.15

Figure 2.1: Epidemic curve of reported laboratory-positive CHIKV cases per 1,000 population by month of illness onset and island from January 2014 to April 2015.



Chapter 3: Assessment of persistent arthralgia associated with the 2014-2015 chikungunya virus outbreak on the U.S. Virgin Islands

3.1 Introduction

Chikungunya virus (CHIKV), an emerging alphavirus transmitted by the *Aedes (Stegomyia) aegypti* and *Aedes (Stegomyia) albopictus* mosquitoes, was newly introduced into the Americas in December of 2013 [36]. As of April 2016, almost 2 million suspected or confirmed cases have been reported in 45 different countries in the Caribbean, Central, South, and North America [18,19]. Acute symptoms of the virus, which include fever, severe polyarthralgia, headache and myalgia, often resolve within 7-10 days [1–3]. However, up to 79% of cases from previous outbreaks in the Indian Ocean Basin, have reported persistent arthralgia, resulting in decreased quality of life for months following initial infection [2–13]. Currently, there is no antiviral treatment or vaccine for CHIKV infection, there are no effective therapeutics for chronic symptoms, and public health prevention measures, such as mosquito reduction, have proven to be ineffective [1,21].

Between 1952 and 2000, CHIKV outbreaks had been reported in many Asian and African countries, typically with inter-epidemic periods of approximately ten years [16]. However, beginning in 2001, outbreaks began to occur yearly in Asia, Africa, Oceania and Europe [16,21]. In December of 2013, the first case of CHIKV in the Americas was confirmed on the Caribbean island of Saint Martin [17]. The U.S. Virgin Islands (USVI), one of the many regions in the Caribbean affected by the epidemic, identified its first locally acquired case of CHIKV on the island of Saint Thomas on June 6, 2014. Subsequently, almost 2,000 suspected cases of CHIKV were reported on the USVI, with the last laboratory-confirmed case reported on February 23, 2015.

Of particular concern is the prevalence of persistent arthralgia associated with CHIKV infection and the long-term-public health impact of the disease. The true prevalence of persistent arthralgia associated with CHIKV illness in the Americas and health outcomes linked to persistent arthralgia remain unknown [55]. To date, the burden of persistent arthralgia associated with CHIKV illness has been assessed from outbreaks in only six countries (La Réunion, Italy, India, Malaysia, Mauritius and Singapore) [3,4,7–12]. Studies conducted in these countries followed CHIKV cases up to 36 months post-acute infection. One year after illness onset, prevalence of persistent arthralgia ranged from 7-78.6%, however some of these studies had small sample sizes and lacked a comparison group [3,4,7–11]. Furthermore, these study populations differ vastly from the USVI in demographics, geographical location and size.

In this study, we aimed to determine the prevalence of persistent arthralgia in the USVI due to CHIKV disease by following laboratory-positive cases of CHIKV in the USVI for one year. Additionally, we compared the prevalence of persistent arthralgia in this group to that of a separate group of individuals without CHIKV disease but with similar healthcare seeking behaviors as CHIKV cases.

3.2 Methods

3.2.1 Study Setting and Subjects

Residents of the USVI, who visited a hospital or healthcare clinic on Saint John, Saint Thomas or Saint Croix and met the definition of a suspected CHIKV case, were reported to the USVI Department of Health (DOH). The USVI DOH defined a suspected case of CHIKV as a resident of any age with acute onset of fever (>38°C) and severe arthralgia or arthritis not explained by another medical condition. Suspected cases who were laboratory-positive were eligible for

inclusion in the study and were asked to be interviewed at 1-2, 6 and 12 months after illness onset to assess prevalence of persistent arthralgia. In a prior CHIKV study, persistent arthralgia was defined as joint pain that occurred more than 15 days beyond the acute phase of illness [22]. Here, we further defined it as frequency of joint pain at least once per week that occurred more than 15 days after the acute phase of illness.

At 12 months, we interviewed individuals (i.e. comparison group) visiting the same hospital or healthcare clinic as laboratory-positive cases to determine the prevalence of persistent arthralgia among them. This strategy was employed due to the rapid onset of the outbreak. The comparison group consisted of residents of any age, sitting in the waiting room of the emergency room of a hospital or at a health clinic in the USVI between June 24 and June 29, 2015. These individuals were either waiting to be seen by a clinician or were accompanying a relative or friend who was waiting to be seen by a clinician. Individuals were excluded from this comparison group if they had symptoms or positive laboratory test results for CHIKV, i.e. if they reported any of the following: febrile illness defined as self-reported fever in the last seven days, concurrent fever and acute joint pain in the last 12 months, or responded "yes" to being tested for CHIKV and test results were positive. Residents who reported fever and acute joint pain concurrently in the last 12 months were excluded in an attempt to exclude those who may have had CHIKV illness but did not seek healthcare for it.

After screening, 179 eligible individuals were interviewed on all three islands and asked whether they would like to be tested for CHIKV to confirm that they were non-diseased. If they consented, phlebotomists drew 4-5 milliliters of blood for IgG antibody testing. Forty-five (25%) consented to testing, and 12 were excluded from the comparison group because they tested

positive for CHIKV IgG antibodies (Table 3.1). The study was designed to frequency match laboratory-positive cases to similar healthcare seekers based on island of residence.

3.2.2 Laboratory Testing

A laboratory-positive case was defined as a suspected case with either of the following: 1) isolation of CHIKV from or demonstration of CHIKV nucleic acid in blood using reverse-transcriptase polymerase chain reaction (RT-PCR) or 2) CHIKV-specific IgM antibodies in serum using enzyme-linked immunosorbent assay (ELISA) with either confirmatory CHIKV-specific neutralizing antibodies using plaque reduction neutralization test (PRNT) and a 90% plaque reduction cutoff or CHIKV-specific IgG antibodies using ELISA [40].

Individuals were confirmed negative if RT-PCR did not detect CHIKV nucleic acid in blood within the first five days of illness onset, if individuals had no evidence of CHIKV virus-specific IgM antibodies in serum after the first five days of illness onset or if there was no evidence of CHIKV-specific neutralizing antibodies using PRNT [42]. All blood samples were spun to separate the serum from the clot and stored at 4°C and transported on ice to the Division of Vector-Borne Diseases of the CDC in Fort Collins, Colorado for viral and antibody testing. Once the RNA was extracted from the samples, the CHIKV RNA was stored at -80°C.

3.2.3 Recruitment

Name, phone number, age, sex, acute clinical symptoms and CHIKV test result were recorded for each suspected case by doctors and nurses at local healthcare facilities using a standardized report form. Laboratory-positive cases were contacted by telephone and invited to participate in a follow-up investigation at 1-2, 6 and 12 months post-acute illness. Interviewing of these individuals 1-2 months after illness onset took place between August 22 and September 10, 2014

and between December 28, 2014 and January 5, 2015. Due to the two and half month interruption of interviews, 371 laboratory-positive cases were ineligible for the 1-2 month follow-up (Table 3.2), however, these individuals were contacted for both the 6 month (1/26/15-8/18/2015) and 12 month (7/2/15-2/14/2016) follow-up interviews. Only individuals with working phone numbers were contacted (Table 3.2). Verbal informed consent was obtained for the 1-2, 6 and 12-month follow-up telephone interviews. Those who refused to participate, those who did not answer the phone after three attempts, or those who had died, were excluded from the study.

3.2.4 Data Collection

At every interview, laboratory-positive cases were asked about presence, frequency and duration of joint pain, as well as history of arthritis. Self-reported history of arthritis was defined as being diagnosed by a doctor prior to experiencing CHIKV illness. The 6 and 12 month questionnaires also asked about the timing and anatomical location of persistent arthralgia. The 12-month questionnaire asked additional questions about difficulty walking, climbing stairs, lifting heavy objects, getting in and out of cars and opening jars. The same 12-month questionnaire administered to laboratory-positive cases was administered to the comparison group.

3.2.5 Statistical Analysis

Descriptive statistics were used to summarize and compare frequencies of demographic information, arthralgia characteristics, and difficulty with daily activities among laboratory-positive cases and the comparison group. Three separate regression models were fitted for each time point. Generalized linear models using the binomial family with robust variance estimators were constructed to estimate prevalence differences using the identity link and prevalence ratios

using the log link. Age grouping (≤35, >35-≤55, and >55 years), sex and self-reported history of arthritis were included in all models. All data were analyzed using STATA14.0™ (StataCorp 2015, Texas, USA).

A multidimensional bias analysis was conducted to determine the magnitude of nonresponse bias introduced due to differential loss to follow-up among laboratory-positive cases, 6 and 12 months after illness onset [56]. We assumed 100% follow-up for the comparison group because they were only interviewed at one point in time. We also assumed that prevalence differences for CHIKV cases lost to follow-up ranged from the same prevalence differences of individuals who were not lost to follow-up to the "worst-case scenario", where the prevalence difference for the missing CHIKV cases was set equal to the observed prevalence difference for the comparison group (Supplementary Table 3.1).

3.3 Results

3.3.1 Descriptive Analysis

One to two months after disease onset, 86 laboratory-positive CHIKV cases were interviewed (median age: 45 years, and 58% female, Table 3.3). Cases reported having on average, 12.6 days of acute joint pain during illness (median: 7 days, range: 0-62 days). At 1-2 months, 55% (95% CI: 44-65%) of cases reported having joint pain within the last week of being interviewed. Of these cases (n=47), 66% reported daily joint pain and 17% reported having joint pain 2-3 days per week, Table 3.3.

Six months after disease onset, follow-up was attempted for the 86 cases interviewed at 1-2 months, of which 62 were interviewed. An additional 103 CHIKV-positive cases were interviewed (median age: 52 years, and 65% female, Table 3.3). At 6 months, 53% (95% CI: 45-

60%) of cases reported having joint pain within one month of the interview. Of these cases (n=87), 48% reported daily joint pain, 20% reported having joint pain 2-3 days per week and 74% reported having pain in more than one joint (Figure 1). Knee, ankle, foot and finger were the most prevalent pain sites among cases reporting joint pain, (44%, 40%, 39% and 36%, respectively).

Twelve months after acute illness, follow-up was obtained for 128 of the 165 cases interviewed at six months (median age: 52 years, and 64% female, Table 3.3). At 12 months, 40% (95% CI: 31-48%) of cases reported having joint pain within one month of the interview. Of these cases (n=51), 55% reported daily joint pain, 16% reported having joint pain 2-3 days per week and 73% reported having pain in more than one joint (Figure 3.2). Knee, finger, shoulder and foot were the most prevalent pain sites among cases reporting joint pain, (49%, 39%, 33% and 29%, respectively).

The comparison group consisted of 167 individuals from all three islands (median age: 35 years and 65% female, Table 3.3). Of these individuals, 16% (95% CI: 10-21%) reported joint pain within one month of being interviewed. Of these individuals (n=26), 50% reported daily joint pain, 19% reported having joint pain 2-3 days per week and 62% reported having pain in more than one joint (Figure 3.1 & 3.2). Knee, finger, ankle and shoulder were the most prevalent pain sites among the comparison group reporting joint pain, (73%, 38%, 27% and 23%, respectively).

3.3.2 Statistical Analysis

One to two months after disease onset, the difference in prevalence of persistent arthralgia between cases and the comparison group was 42% (95% CI: 32-52%), after adjusting for age, sex and self-reported history of arthritis (Table 3.4). Six months after disease onset, the

difference in prevalence of persistent arthralgia between cases and the comparison group was 32% (95% CI: 23-40%) and 12 months after onset the difference in prevalence was 19% (95% CI: 11-28%). One to two months after illness onset, cases were 4.60 (95% CI: 3.10-6.93) times more likely to experience persistent arthralgia compared to similar healthcare seekers. Six months after illness onset, cases were 3.25 (95% CI: 2.16-4.88) times more likely to experience persistent arthralgia compared to similar healthcare seekers and 2.33 (95% CI: 1.49-3.63) times more likely to experience persistent arthralgia 12 months after illness onset (Table 3.4).

A seroprevalence study conducted in the USVI by the CDC in June 2015 found that of the 509 individuals who were tested, 171 (34%) had evidence of CHIKV antibodies. Of the 171 individuals, 121 (71%) reported having symptomatic infection [57]. Based on this information, we estimated the fraction of the population with symptomatic infection is 24% (0.34 * 0.71) and an estimated 24,622 USVI residents experienced symptomatic CHIKV infection during the 2014 outbreak. Therefore, it is likely that approximately 7,879 CHIKV cases experienced persistent arthralgia due to CHIKV six months after illness onset and 4,678 CHIKV cases experienced persistent arthralgia due to CHIKV twelve months after illness onset.

3.3.3 12-Month Activity Assessment

During the 12-month interview, 28% of cases and 12% of the comparison group reported difficulty walking (Table 3.3). Thirty-three percent of cases also reported difficulty climbing stairs, whereas only 12% of the comparison group reported difficulty climbing stairs. A higher proportion of cases also reported difficulty lifting a heavy object, getting in and out of a car and opening a jar (22%, 21% and 26%, respectively) compared to similar healthcare seekers with joint pain, (10%, 6% and 8% respectively). Furthermore, 22% (95% CI: 15-29) of cases reported

that their health was either somewhat or much worse compared to one year prior, before experiencing CHIKV illness. In contrast, 10% (95% CI: 5-14) of the comparison group reported that their health was either somewhat or much worse compared to one year prior (Table 3.3).

After adjusting for age, sex and self-reported history of arthritis, cases were 1.81 (95% CI: 1.08-3.02) times more likely to have difficulty walking and 1.96 (95% CI: 1.23-3.12) times more likely to have difficulty climbing stairs compared to similar healthcare seekers (Table 3.5). Cases were also 2.63 (95% CI: 1.31-5.29) times more likely to have difficulty getting in and out of a car and 2.43 (95% CI: 1.40-4.32) times more likely to have difficulty opening a jar compared to similar healthcare seekers.

3.3.4 Analysis Restricted to CHIKV Cases with Complete Follow-up

Forty-eight CHIKV cases were interviewed at all three time points. Among these cases, daily joint pain decreased from 33% one to two months after acute illness, to 17% six months after acute illness and remained at 16% twelve months after illness (Figure 3.3). One to two months after acute illness, 42% of the cases reported no joint pain. Six months after acute illness, this percentage was 58% and was even greater (71%) at 12 months after illness.

3.3.5 Multidimensional Bias Analysis

Using the "worst-case scenario", the multidimensional bias analysis yielded decreased but still statistically significant prevalence differences at both 6 and 12 months after acute onset, (0.32 to 0.28 and 0.21 to 0.15, respectively, Supplementary Table 3.1).

3.4 Discussion

Although acute symptoms of CHIKV virus are well-documented [58], the burden of long-term sequelae due to CHIKV remains unknown [55]. Our year-long prospective cohort study of 86-

165 laboratory-positive CHIKV cases and 167 similar healthcare seekers assessed the prevalence of persistent arthralgia due to CHIKV disease at 1-2, 6 and 12 months after acute illness. One to two months after disease onset, 51% of cases reported persistent arthralgia at least once per week. Six months after disease onset, 44% of cases reported persistent arthralgia at least once per week, and after 12 months, 33% of CHIKV cases still reported persistent arthralgia. In contrast, only 12% of the comparison group reported joint pain at least once per week when they were interviewed at the same time as the 12-month case interviews.

CHIKV cases and the comparison group had similar average annual household incomes, healthcare seeking behaviors and equal gender proportions. A larger proportion of the comparison group was employed or students and had a lower prevalence of self-reported history of arthritis compared to CHIKV cases, likely because they were younger. CHIKV cases enrolled in the study tended to be older because they were more likely to be at home and available for phone interviews compared to younger residents. After adjustment for age, sex and self-reported history of arthritis, however, CHIKV cases still had a significantly higher prevalence of persistent arthralgia compared to similar healthcare seekers at all three time points (Table 3.4). Six months after illness onset, increased age was associated with an increase in prevalence of persistent arthralgia among cases. This is consistent with findings from the La Réunion outbreak that found increased age (≥45), was a risk factor for persistent arthralgia among cases [9,12]. Also after adjustment for age, sex and self-reported history of arthritis, cases had significantly more difficulty performing daily activities such as walking, climbing stairs, getting in and out of cars, and opening jars compared to similar healthcare seekers, indicating a decreased quality of life associated with CHIKV illness (Table 3.5). Overall, characteristics of persistent arthralgia,

including symmetry of pain, joints affected, and time of day of pain were similar between CHIKV cases and the comparison group. Of note, however, is that a higher proportion of CHIKV cases reported presence of persistent arthralgia in the morning and also more severe pain in the morning, compared to similar healthcare seekers (Table 3.3).

Certain limitations should be considered when interpreting the results of this study. Persistent arthralgia was assessed via self-reporting and not by a physical examination, which may affect the accuracy of reporting. Therefore, further clinical investigation may be required to examine more closely the differences in physical characteristics of persistent arthralgia in CHIKV cases and non-cases. Only 25% of the comparison group agreed to be blood-tested for this study. Therefore, it is possible that some individuals from the comparison group may have indeed been infected with CHIKV. This limitation would, however, tend to underestimate the association between CHIKV and persistent joint pain. Given the time constraint of the outbreak and the exclusion criteria, however, these individuals were the most likely group to be disease-free from CHIKV for the 12-month period during which the cases were followed. Individuals in the comparison group were only interviewed at one point in time rather than at three points in time, and it is possible that persistent arthralgia prevalence may have varied over time or varied with season. However, the Behavioral Risk Factor Surveillance System survey from 2009 indicates that 15.2% (95% CI: 13.6-16.8%) of USVI adult residents reported having been told by a clinician that they have arthritis [60]. This is consistent with our estimate of persistent arthralgia prevalence (12%) among the comparison group. Finally, the study sample only represents 35-45% of eligible individuals who tested positive for CHIKV. We sought to minimize attrition by minimizing the respondent burden with a brief questionnaire and protocol for follow-up calls, but

acknowledge that more resources would be necessary to collect a more representative sample in the future.

This is the first study in the Americas designed to prospectively follow confirmed cases of CHIKV. Our results emphasize that following the 2014-2015 CHIKV outbreak in the USVI, a significant proportion of persistent arthralgia and difficulty with daily activities was associated with CHIKV illness up to one year after disease onset. These findings highlight the need for CHIKV therapeutic and vaccine research to manage and prevent acute illness and long-term morbidity. The results also underscore the need for additional epidemiologic studies to estimate the burden of persistent arthralgia, the impact on quality of life and other long-term sequelae that may be associated with CHIKV disease.

3.5 Tables and Figures

Table 3.1: Number of similar healthcare seekers interviewed and tested by island.

	Comparison group*		
Island	Saint John	Saint Croix	Saint Thomas
Interview period	6/27/15	6/24/15 – 6/25/2015	6/26/15-6/29/15
No IgG testing	2	35	97
Tested IgG (-)	4	19	10
Tested IgG (+)*	0	7	5
Total Eligible	**6**	**54**	**107**

*Individuals who tested positive for CHIKV IgG antibodies were excluded from the analysis.

Table 3.2: Eligibility and enrollment numbers of laboratory-positive cases at 1-2, 6 and 12 months after illness onset.

	Date of laboratory positive test result		
	6/22/14-8/13/14, & 10/30/14- 2/23/15	8/14/14-10/29/14	Total interviewed
1-2 month Interview			
Eligible Individuals	191	371	562
Missing phone number	40	Individuals were ineligible for 1-2 month follow-up due to 2 month interruption in study start date	40
Phone # not-in-service or incorrect	24		24
Did not pick up after 3 calls	29		29
Refused	11		11
Died	1		1
Total interviewed	**86**	**0**	**86**
6 month interview			
Eligible Individuals	86	371	457
Missing Phone number	-	116	116
Phone # not-in-service or incorrect	7	86	93
Did not pick up after 3 calls	15	55	70
Refused	2	9	11
Died	0	2	2
Total interviewed	**62**	**103**	**165**
12-month interview			
Eligible Individuals	62	103	165
Missing Phone number	0	0	0
Phone # not-in-service or incorrect	2	7	9
Did not pick up after 3 calls	9	15	24
Refused	3	1	4
Died	0	0	0
Total interviewed	**48**	**80**	**128**

Table 3.3: Percentage of laboratory-positive cases and similar healthcare seekers by demographics and joint pain characteristics at 1-2, 6 and 12 months after disease onset.

Time Period	**1-2 month follow-up**	**6 month follow-up**	**12 month follow-up**	
	CHIKV (+) (n=86)	CHIKV (+) (n=165)	CHIKV (+) (n=128)	Comparison group (n=167)
Median age in years (range)	45 (1-89)	52 (1-96)	52 (1-92)	35 (2-78)
	% (n)	**% (n)**	**% (n)**	**% (n)**
Female	58 (50)	65 (108)	64 (82)	65 (108)
Employed or a student	57 (49)	58 (96)	57 (73)	75 (125)
History of self-reported arthritis	15 (13)	22 (37)	23 (30)	17 (28)
Annual household income < $50,000	-	-	64 (82)	72 (121)
Joint pain day of interview	44 (38)	36 (59)	27 (34)	8 (14)
Joint pain within month of interview	55 (47)*	53 (87)	40 (51)	16 (26)
Difficulty walking	-	-	28 (36)	12 (20)
Difficulty climbing stairs	-	-	31 (40)	12 (20)
Difficulty lifting a heavy object	-	-	21 (27)	10 (16)
Difficulty getting in and out of a car	-	-	21 (27)	6 (10)
Difficulty opening a jar	-	-	26 (33)	8 (13)
Health was somewhat/much worse after 1 year			22 (28)	10 (16)
Subsample of individuals reporting joint pain within month of interview:	**(n=47)**	**(n=87)**	**(n=51)**	**(n=26)**
Joint pain frequency:				
Daily	66 (31)	48 (42)	55 (28)	50 (13)
2-3 times per week	17 (8)	20 (17)	16 (8)	19 (5)
Once per week	9 (4)	15 (13)	12 (6)	8 (2)
Less than once per week	9 (4)	14 (12)	18 (9)	23 (6)
Don't know		3 (3)	0 (0)	0 (0)
Symmetrical joint pain	-	31 (27)	27 (14)	27 (7)
Joint pain interrupts sleep	-	31 (27)	37 (19)	29 (8)
Joint pain time of day:				
Morning	-	18 (16)	24 (12)	8 (2)
Day	-	11 (10)	10 (5)	4 (1)
Night	-	13 (11)	12 (6)	19 (5)
Morning & Night	-	6 (5)	4 (2)	4 (1)
Present at all times or activity dependent	-	49 (43)	45 (23)	58 (15)
Don't know		2 (2)	6 (3)	6 (2)
Worst time of day for joint pain:				
Morning	-	33 (29)	41 (21)	12 (3)
Day	-	10 (9)	14 (7)	4 (1)
Night	-	23 (20)	16 (8)	31 (8)
Morning & Night		3 (3)	6 (3)	0 (0)
Present at all times or activity dependent	-	26 (23)	16 (8)	46 (12)
Don't know		3 (3)	8 (4)	6 (2)

*Joint pain within one week of the interview

Table 3.4: Prevalence differences (PR) and prevalence ratios (PR) of persistent arthralgia in laboratory-positive cases compared to similar healthcare seekers, unadjusted and adjusted for age group, sex and self-reported history of arthritis at 1-2, 6 and 12 months after disease onset.

	1-2 Month Analysis (n=249)			6 Month Analysis (n=331)			12 Month Analysis (n=295)		
	PD	**95% CI**	**p-value**	**PD**	**95% CI**	**p-value**	**PD**	**95% CI**	**p-value**
Unadjusted	0.42	0.30-0.54	<0.001	0.33	0.24-0.42	<0.001	0.21	0.11-0.30	<0.001
Adjusted	0.42	0.32-0.52	<0.001	0.32	0.23-0.40	<0.001	0.19	0.11-0.28	<0.001
	PR	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**
Unadjusted	4.48	2.83-7.09	<0.001	3.77	2.41-5.88	<0.001	2.74	1.69-4.43	<0.001
Adjusted	4.60	3.10-6.93	<0.001	3.25	2.16-4.88	<0.001	2.33	1.49-3.63	<0.001

Table 3.5: Prevalence differences and prevalence ratios of difficulty carrying out daily activities in laboratory-positive cases compared to similar healthcare seekers, adjusting for age group, sex and self-reported history of arthritis at 12 months after disease onset.

	12 Month Analysis					
Daily Activity	**PD**	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**
Difficulty walking	0.11	0.03-0.18	0.007	1.81	1.08-3.02	0.023
Difficulty climbing stairs	0.12	0.05-0.19	0.001	1.96	1.24-3.12	0.004
Difficulty getting in and out of a car	0.09	0.03-0.14	0.001	2.63	1.31-5.29	0.007
Difficulty opening a jar	0.15	0.07-0.23	<0.001	2.43	1.40-4.32	0.002
Difficulty lifting a heavy object	0.04	-0.02-0.11	0.209	1.65	0.94-2.93	0.084

Figure 3.1: Affected joints among CHIKV cases and the comparison group, 6 months after illness onset.

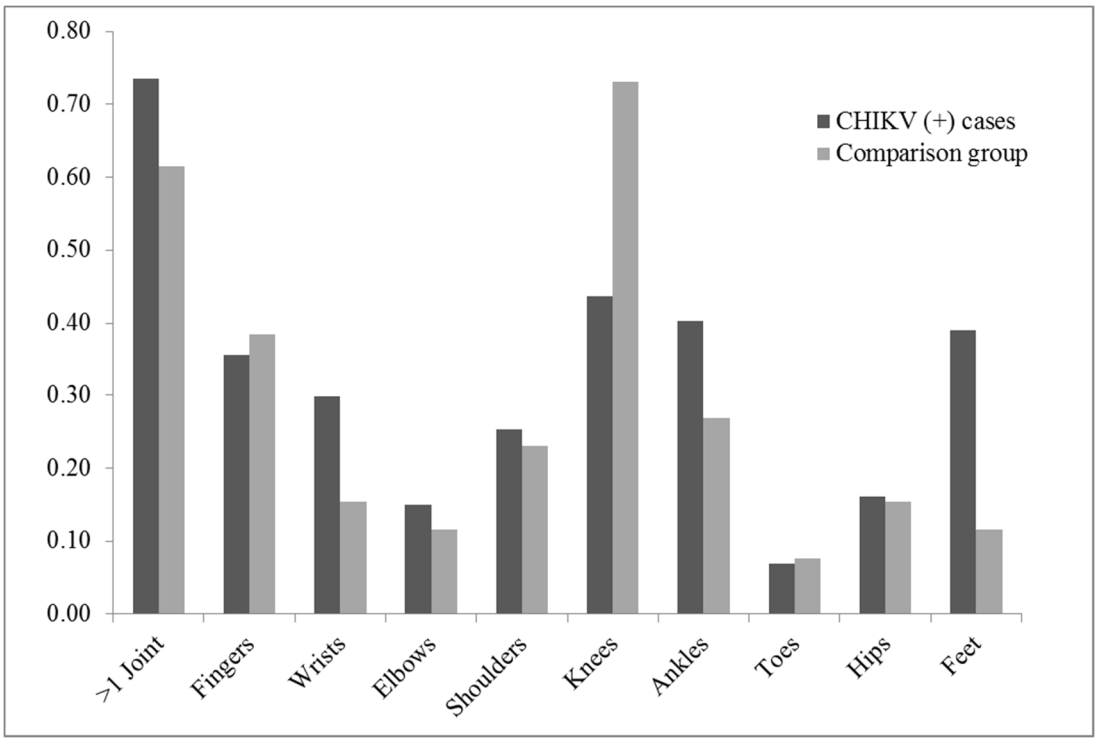


Figure 3.2: Affected joints among CHIKV cases and the comparison group, 12 months after illness onset.

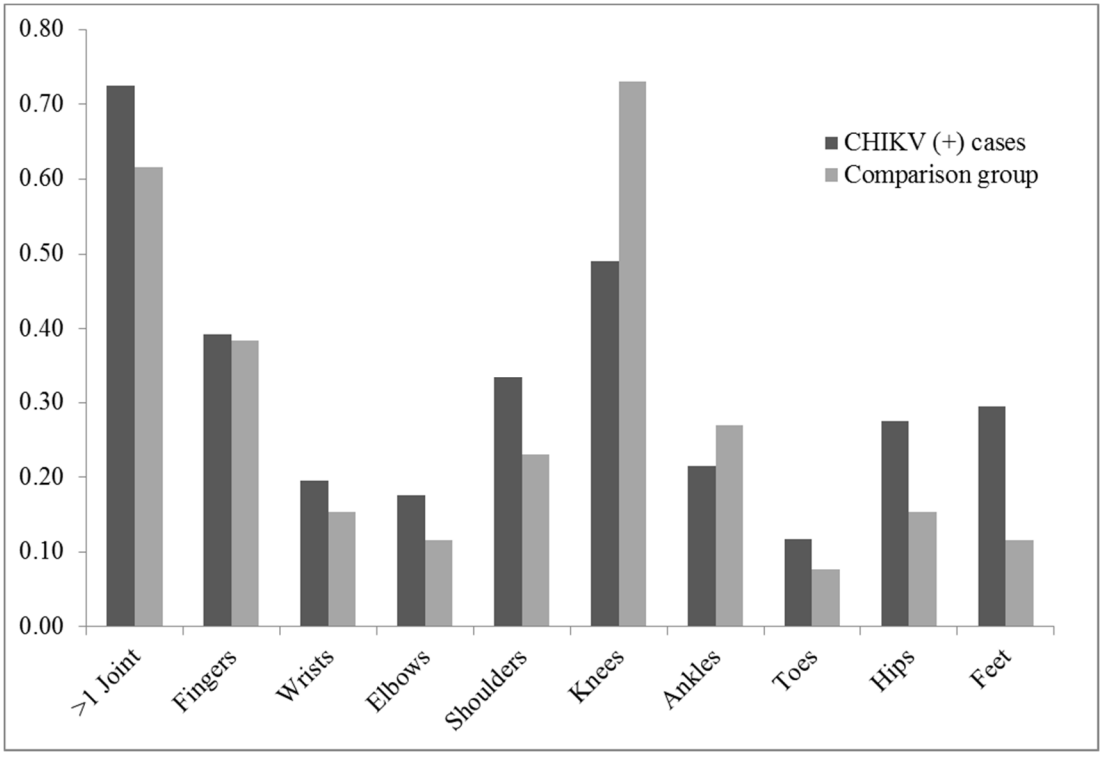
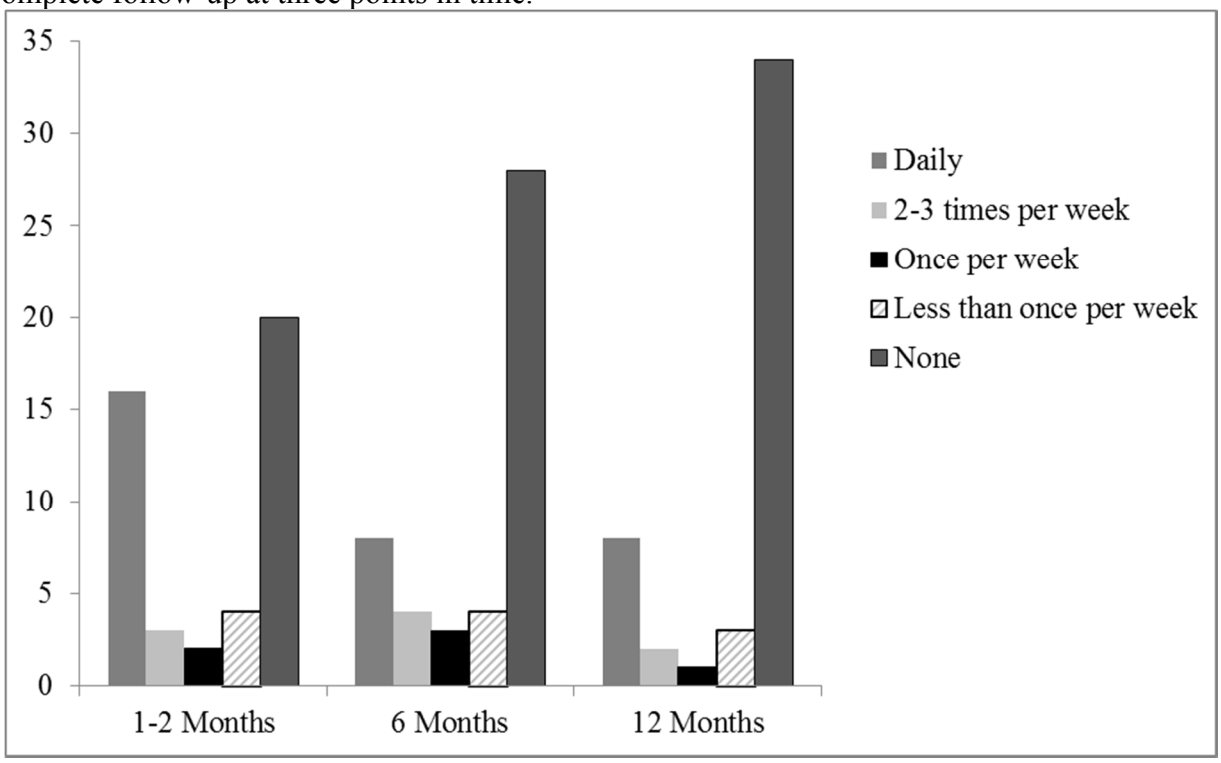


Figure 3.3: Frequency of persistent arthralgia among the 48 laboratory-positive cases with complete follow-up at three points in time.



3.6 Supplementary Table

Supplementary Table 3.1: Multidimensional bias analysis: range of persistent arthralgia (PA) prevalence difference estimates of CHIKV cases compared to similar healthcare seekers, imputed for CHIKV cases lost to follow-up at 6 and 12 months.

6 Month Analysis							
CHIKV (+) PA prevalence	**Comparison group PA prevalence**	**Range of PA prevalence of missing cases**	**Cases lost to follow-up**	**# of imputed cases with PA**	**Total number of cases with PA**	**Adjusted CHIKV (+) PA prevalence**	**Adjusted prevalence difference**
72 ÷ 162* = 0.44	20 ÷ 167 = 0.12	0.44	24	0.44 * 24 = 10.56	72+10.56= 82.65	82.65 ÷ 186	0.44 - 0.12 = **0.32**
0.44	0.12	0.34	24	0.34 * 24 = 8.16	72+8.16= 80.16	80.16 ÷ 186	0.42 - 0.12 = **0.30**
0.44	0.12	0.24	24	0.24 * 24 = 5.76	72+5.76= 77.76	77.76 ÷ 186	0.41 - 0.12 = **0.29**
0.44	0.12	0.12	24	0.12 * 24 = 2.88	72+2.88= 74.88	74.88 ÷ 186	0.40 - 0.12 = **0.28**
12 Month Analysis							
CHIKV (+) PA prevalence	**Comparison group PA prevalence**	**Range of PA prevalence of missing cases**	**Cases lost to follow-up**	**# of imputed cases with PA**	**Total number of cases with PA**	**Adjusted CHIKV (+) PA prevalence**	**Adjusted prevalence difference**
42 ÷ 129 = 0.33	20 ÷ 167 = 0.12	0.33	36	0.33 * 36 = 11.88	42 + 11.88 = 53.88	53.88 ÷ 165	0.33 - 0.12 = **0.21**
0.33	0.12	0.23	36	0.23 * 36 = 8.28	42 + 8.28 = 50.29	50.29 ÷ 165	0.30 - 0.12 = **0.18**
0.33	0.12	0.17	36	0.17 * 36 = 6.12	42 + 6.12 = 48.12	48.12 ÷ 165	0.29 - 0.12 = **0.17**
0.33	0.12	0.12	36	0.12 * 36 = 4.32	42 + 4.32 = 44.32	44.32 ÷ 165	0.27 - 0.12 = **0.15**

*3 of the 165 cases responded “don’t know” to frequency of joint pain

Chapter 4: Estimating the cost of illness and burden of disease associated with the 2014-2015 chikungunya outbreak in the U.S. Virgin Islands

4.1 Introduction

Chikungunya virus (CHIKV), an emerging alphavirus transmitted by the *Aedes (Stegomyia) aegypti* and *Aedes (Stegomyia) albopictus* mosquito species, was introduced into the Americas in December of 2013 [36]. As of April 2016, almost 2 million suspected or confirmed cases have been reported in 45 different countries in the Caribbean, Central, South, and North America [18,19]. Acute symptoms of the virus, which include high fever, severe polyarthralgia, headache and myalgia, often resolve within 7-10 days [1–3]. However up to 79% of cases from previous outbreaks in the Indian Ocean Basin have reported persistent arthralgia and chronic inflammatory rheumatism, resulting in decreased quality of life for months to years following initial infection [2–13]. Currently, there is no antiviral treatment or vaccine for the infection, there are no effective therapeutics for chronic symptoms, and public health prevention measures, such as mosquito reduction, have thus far proven to be insufficient [1,21].

The U.S. Virgin Islands (USVI) experienced its first CHIKV outbreak from June 2014 to February 2015, with almost 2,000 suspected reported cases in a population of 103,574 people [37,40]. Previous studies from CHIKV outbreaks in La Réunion, Colombia, and India identified high healthcare costs incurred by ill individuals, lost wages due to absenteeism, decreased quality of life for months following infection, and a large resource burden on unprepared healthcare systems [26–31]. To our knowledge, the economic impact of the first CHIKV epidemic in the Caribbean and years lived with disability (YLDs) associated with long-term sequelae of CHIKV illness have not been measured. This information would inform decisions about prevention and control measures for inevitable future CHIKV outbreaks.

In this study, we estimate the direct medical costs and cost of lost wages due to absenteeism associated with the 2014-2015 CHIKV outbreak in the USVI and estimate the YLDs associated with long-term sequelae of the outbreak. This analysis was conducted by using surveillance data from the USVI Department of Health (DOH), medical cost data from the three public hospitals in the USVI, and interviews from a study that followed a subset of laboratory-positive CHIKV cases for 12 months.

4.2 Methods

4.2.1 Study Setting and Subjects

Residents of the USVI who visited a hospital or healthcare clinic on Saint John, Saint Thomas, or Saint Croix and met the definition of a suspected CHIKV case were reported to the USVI DOH. The USVI DOH defined a suspected case of CHIKV as a resident of any age with acute onset of fever (>38°C) and severe arthralgia or arthritis not explained by another medical condition. All suspected cases were included in estimating the direct and indirect cost of the outbreak. Suspected cases who were laboratory-positive were eligible for inclusion in the follow-up study, in which we interviewed laboratory-positive CHIKV cases at 1-2, 6 and 12 months after illness onset. During the same time period as the 12 month follow-up interviews, individuals with similar healthcare seeking behaviors were interviewed as a comparison group, regarding presence of persistent arthralgia. A similar healthcare seeker was defined as a USVI resident who did not report experiencing sudden onset of fever and joint pain in June 2014-June 2015.

4.2.2 Laboratory Testing

A laboratory-positive case was defined as a suspected case with either of the following: 1) isolation of CHIKV from or demonstration of CHIKV nucleic acid in blood using reverse-transcriptase polymerase chain reaction (RT-PCR) or 2) CHIKV-specific IgM antibodies in

serum using enzyme-linked immunosorbent assay (ELISA) with either confirmatory CHIKV-specific neutralizing antibodies using plaque reduction neutralization test (PRNT) and a 90% plaque reduction cutoff or CHIKV-specific IgG antibodies using ELISA [40]. All blood samples were spun to separate the serum from the clot, stored at 4°C, and transported on ice to the Division of Vector-Borne Diseases of the Centers for Disease Control and Prevention (CDC) in Fort Collins, Colorado for viral and antibody testing.

4.2.3 Recruitment

Demographic information, clinical symptoms, and CHIKV test results were recorded for each suspected case by doctors and nurses at local healthcare facilities using a standardized report form. Laboratory-positive cases were contacted by telephone and invited to participate in a follow-up investigation at 1-2, 6 and 12 months after the acute phase of illness. Interviewing of these individuals 1-2 months after illness onset took place between August 22 and September 10, 2014 and between December 28, 2014 and January 5, 2015. Due to a two and half month interruption of interviews, 371 laboratory-positive cases were ineligible for the 1-2 month follow-up. However, these individuals were contacted for both the 6 month (1/26/15 to 8/18/2015) and 12 month (7/2/15 to 2/14/2016) follow-up interviews. Only individuals with working phone numbers were contacted (406 of 562 cases). Verbal informed consent was obtained for the 1-2, 6 and 12 month follow-up telephone interviews. Those who refused to participate, those who did not answer the phone after three attempts, or those who had died, were excluded from the study (Supplementary Table 4.1).

4.2.4 Data Collection

At every interview, laboratory-positive cases were asked about presence and frequency of persistent arthralgia, employment status, and the number of work days and days of daily

activities/chores missed due to illness. In a prior CHIKV study, persistent arthralgia was defined as joint pain that occurred more than 15 days beyond the acute phase of illness [21]. Here, we further define it as frequency of joint pain at least once per week that occurred more than 15 days after the acute phase of illness. The 1-2 month questionnaire asked questions about hospitalization and healthcare utilization after initial infection (Table 4.1). The 12 month questionnaire asked additional questions about use of prescription medication and healthcare utilization after initial infection (Table 4.1).

4.2.5 Estimating Indirect Costs

Wages lost per CHIKV cases were estimated assuming a standard 40-hour work week, and by using the average hourly wage for each island (Table 4.2) [61]. Average hourly wages from the USVI were not available by gender or age. Of all suspected reported CHIKV cases who were tested, 30% tested negative for CHIKV. Therefore we used 0.70 as the proportion of non-tested suspected reported CHIKV cases who would have been positive had they been tested.
The following formula was used to estimate value of time lost due to CHIKV disease:

*Time lost= Mean # of work days missed at each time point * 40 hour work week * average hourly wage * (total # of reported laboratory-positive CHIKV cases + 0.70 * # of suspected but not tested reported CHIKV cases)*

To obtain an estimate of the total wages lost for cases who were not captured by surveillance, we used data from a seroprevalence study conducted by the CDC in June 2015. Of the 509 individuals who were tested, 171 (34%) had evidence of CHIKV antibodies [57]. Of the 171 individuals, 121 (71%) reported having symptomatic infection [57]. Based on this information, we estimated the fraction of the population with symptomatic infection to be 24% (0.34 * 0.71).

The estimated number of symptomatic CHIKV infections in the USVI population was multiplied by wages lost per person to obtain an overall cost estimate of absenteeism due to the outbreak. In reviewing both CHIKV and dengue cost-of illness methodologies, some studies included all individuals with the disease or condition regardless of employment status (to capture overall loss of productivity), while others included only those who were officially employed [27,28,30,62–70]. As a sensitivity analysis, we calculated absenteeism associated with CHIKV illness for only those who were employed (52.2% of the USVI population as of 2010) [71].

4.2.6 Estimating Direct Medical Costs

The medical costs for two phases of the illness were estimated with two different sources of data. For the acute phase of illness, inpatient and outpatient charges of all suspected CHIKV cases from Governor Juan F. Luis Hospital and Medical Center (JFLHMC), the public hospital in Saint Croix were obtained from the finance department of the hospital. Mean costs of inpatient and outpatient visits were calculated separately and multiplied by the total number of inpatient and outpatient visits captured by the USVI DOH surveillance system (Table 4.3). These costs were applied to patients on all three islands, because cost data for suspected CHIKV cases were unavailable from Schneider Regional Medical Center (SRMC) in Saint Thomas and Myra Keating Community Health Center (MKCHC) in Saint John, the other two public healthcare facilities in the USVI. A sensitivity analysis was conducted for the missing cost data from SRMC and MKCHC based on the mean cost of standard outpatient and inpatient visits from those two healthcare facilities (Table 4.4).

For the cost of subsequent outpatient visits up to 12 months after illness onset, the mean cost of standard outpatient visit was obtained from the finance departments of JFLHMC, SRMC and

MKCHC (Table 4.5). The mean number of additional healthcare visits reported by cases for treatment of CHIKV after acute illness from the interview sample was calculated from the 1-2 and 12 month questionnaires. The mean numbers of visits was multiplied by the total number of reported laboratory-positive cases and 70% of suspected but not tested cases by island, to obtain an overall estimate of additional healthcare costs up to 12 months after acute illness. Note that these calculations are limited to reported cases, because unreported, symptomatic cases did not utilize healthcare.

Current literature indicates that a recall period of 1-2 months provides reliable estimates for healthcare utilization [72–75]; however, previous studies have shown that 5% - 47% of visits were not reported when individuals were interviewed about healthcare utilization of physician visits during a 12 month recall period [76,77], while other studies have shown no underreporting [78]. Due to potential underreporting of healthcare utilization 12 months after illness onset, a sensitivity analysis was performed using a range of underreporting from 5-47% (Table 4.6).

4.2.7 Estimating YLDs

We calculated YLDs to estimate the amount of time, ability, and activity lost due to persistent arthralgia from CHIKV illness [79]. YLDs due to long-term sequelae of CHIKV were calculated by the following equation [80]:

$$YLD = \text{Disability weight} * \text{Number of symptomatic CHIKV infections in the USVI} * \text{Prevalence of persistent arthralgia 12 months after acute illness onset}$$

Prior studies estimating YLDs for CHIKV have used disability weights for osteoarthritis and rheumatoid arthritis since a disability weight has not been assigned to CHIKV disease

[27,29,31,81]. However, these weights are from the 1990 Global Burden of Disease [82]. Here, we use the disability weight for post-acute effects from infectious diseases from the 2013 Global Burden of Disease Study [83], and use the weights for osteoarthritis and rheumatoid arthritis as a sensitivity analysis to maintain consistency with previous studies. The proportion of symptomatic CHIKV infections in the USVI population from the seroprevalence study used to calculate indirect costs was also used to calculate YLDs.

To ensure that reported persistent arthralgia among cases was due to CHIKV and not from other causes, we used the following prevalence estimate: prevalence of persistent arthralgia among CHIKV cases interviewed at 12 months (33%, 95% confidence interval (CI): 25-41%) net of the prevalence of persistent arthralgia in the comparison group of USVI residents with similar healthcare seeking behavior as CHIKV cases (n=167, 12%, 95% CI: 7-17%). This latter estimate is consistent with the prevalence of reported arthritis in the USVI population from the Behavioral Risk Factor Surveillance System Report (15%) [71]. Years of Life Lost (YLLs) were not calculated because cause of death could not be determined for the three suspected CHIKV cases who died.

4.3 Results

4.3.1 Study Population

One to two months after acute disease onset, 86 laboratory-positive CHIKV cases were interviewed. Of the cases who were employed (33%), 89% reported missing work due to CHIKV illness (Table 4.1). On average, employed cases reported missing 6 days of work 1-2 months after onset of CHIKV symptoms. One to two months after their initial visit to the hospital or healthcare clinic, 33% of cases reported seeking additional healthcare after initial infection and 9% reported being hospitalized due to CHIKV illness.

Six months after disease onset, 165 laboratory-positive CHIKV cases were interviewed. Of the cases who were employed (41%), 88% reported missing work due to CHIKV illness (Table 4.1). On average, employed cases reported missing two additional days of work 4-5 months after the 1-2 month interview.

Twelve months after disease onset, 128 of the 165 laboratory-positive CHIKV cases were interviewed. Of the cases who were employed (34%), 9% reported missing work due to CHIKV illness (Table 4.1). On average, employed cases reported missing one additional day of work six months after their 6-month interview. Twenty-five percent of cases reported seeking additional healthcare 10-11 months after the 1-2 month interview. Of the cases interviewed, 24% reported taking prescription medication in the last 12 months for CHIKV-related symptoms. Forty percent (n=12) of those who reported taking prescription medication indicated that they were prescribed prednisone for joint pain and 47% (n=14) reported taking prescribed opioids for joint pain.

4.3.2 Indirect Cost Estimate

The average cost of absenteeism related to CHIKV disease 1-2 months after illness onset, ranged from $713 - $825 per person, depending on the island (Table 4.2). Six months after illness onset the average cost of absenteeism ranged from $275–$318 per person and 12 months after illness onset the average cost per person ranged from $148-$172. The total estimated cost of absenteeism associated with acute and long-term CHIKV illness up to 12 months after CHIKV disease onset was $1,760,975 for all reported laboratory-positive cases and 70% of all suspected but not tested CHIKV cases. However, when using the estimated proportion of symptomatic CHIKV infection in the USVI (0.24), almost 13 times the number of individuals were infected with CHIKV than were captured by surveillance data. When including these additional cases, the

total estimated cost of absenteeism associated with acute and long-term CHIKV illness up to 12 months after CHIKV disease onset was $32,137,766. The total estimated cost of absenteeism associated with acute and long-term CHIKV illness up to 12 months after CHIKV disease onset for only the USVI population that is employed (52%) was $16,775,914, but this figure does not account for absenteeism from school and other non-market activities.

4.3.3 Direct Cost Estimate: Acute Phase of Illness

The average cost of an outpatient visit for a suspected CHIKV case during the acute phase of illness was $1,526 and the average cost of an inpatient visit was $16,982 (Table 4.3). These costs include laboratory testing and prescription medication. Of the 1,929 suspected reported cases, 1,850 had outpatient visits and 79 suspected cases were hospitalized. Therefore, the total estimated cost of outpatient and inpatient healthcare visits associated with suspected CHIKV cases during the acute phase of the outbreak was $4,168,177, with the 79 hospitalized cases comprising 32% of the total cost. As shown from the sensitivity analysis in Table 4.4, adjusting the direct costs by the relative average outpatient cost reduces the total estimated direct cost by 27% because the majority of inpatient stays were on Saint Croix.

4.3.4 Direct Cost Estimate: Up to 12 months After Acute Phase of Illness

The 86 CHIKV cases interviewed 1-2 months after acute illness reported, on average, having 0.5 additional healthcare visits related to CHIKV disease (Table 4.5). The average cost of a standard outpatient visit varies by healthcare facility and island but ranges from $234-$600. The 128 CHIKV cases interviewed 12 months after acute illness reported having on average 0.62 additional healthcare visits related to CHIKV disease 10-11 months after their 1-2 month interview. Therefore, the total estimated cost of additional outpatient healthcare visits related to CHIKV disease up to one year after illness onset was $620,431 (Table 4.5). The sensitivity

analysis for the potential underreporting of healthcare utilization 12 months after illness onset provided the following range of total estimated costs of additional outpatient healthcare visits related to CHIKV disease up to one year after illness onset: $620,431 for zero underreporting to $781,078 for 47% underreporting (Table 4.6). As a result, the total estimated direct cost associated with the CHIKV outbreak on the USVI ranges from $4,788,608-$4,949,255.

4.3.5 Total Cost Estimate of the 2014-2015 CHIKV Outbreak

The total direct and indirect estimated cost associated with the 2014-2015 CHIKV outbreak in the USVI ranges from $36,926,374-$37,087,021, depending on the degree of underreporting of healthcare utilization.

4.3.6 Years Lived with Disability

As an alternative to the indirect cost calculation, the estimated number of YLDs associated with long-term sequelae from the 2014-2015 CHIKV outbreak in the USVI was 1,131.77 when using the disability weight for post-acute effects of infectious diseases and ranges from 806.19 – 1,204.12 when using disability weights consistent with prior studies (Table 4.7).

4.4 Discussion

This study estimated the total direct and indirect cost and burden of disease associated with the 2014-2015 CHIKV outbreak in the USVI. The total estimated cost associated with the outbreak ranged from $36.9-$37.1 million, of which 13% was direct costs and 87% was indirect costs. An estimated 1% of gross domestic product (GDP) in the USVI was lost due to the CHIKV outbreak (GDP in 2014= $3.67 billion [84]).

Notably, 10% of cases reported prednisone use during the 12-month interview, raising concerns about prescribing practices for symptoms of CHIKV. While prednisone constitutes a small

percentage of the direct costs ($0.01-$2.83 per tablet depending on the dosage [85]), prednisone use may actually enhance viral replication and worsen CHIKV symptoms [86,87]. Although public media campaigns during the outbreak informed residents that no treatment for CHIKV was available, these results suggest that providers may require additional information on appropriate treatment plans.

Our direct cost estimate of the outbreak in the USVI was comparable to the cost estimate of the 2005-2006 outbreak in La Réunion, ($4.8-$4.9 million for 24,609 cases in the USVI ($195-$201 per case) compared to $50.4 million for 266,000 cases in La Réunion ($189 per case), after adjusting for inflation) [28,88]. Our indirect cost estimates, however, were substantially higher because we accounted for absenteeism among all cases, not just those who were employed. We also used self-report data for up to 12 months after acute illness whereas absenteeism during the outbreak in La Réunion was calculated by estimating the excess number of work days missed during the epidemic period only [28]. The seroprevalence estimate of symptomatic CHIKV cases suggests that almost one quarter of the USVI population had symptomatic infection. The surveillance data may not have captured many of these cases because during the height of the outbreak, hospitals and healthcare clinics reached capacity and had to turn residents away who were seeking care. Additionally, due to public health announcements in the media during the outbreak, many residents were aware of symptoms associated with infection and knew treatment for CHIKV did not exist, so they may have opted to stay home instead of seeking healthcare.

We estimated that the number of years lived with disability associated with chronic symptoms of CHIKV ranges from 806.19-1204.12. Our YLD estimates are much more conservative than the disability-adjusted life year estimates from Latin America, due to the fact that we provided a

lower estimate of persistent arthralgia attributable to CHIKV illness (21% compared to ~50% in Latin America) [29,89]. This difference is present because we subtracted the prevalence of persistent arthralgia in a comparison group of USVI residents with similar healthcare seeking behavior (12%) from the prevalence of persistent arthralgia among cases 12 months after acute illness (33%), whereas the study in Latin America did not [89]. It should also be noted that calculating indirect costs and YLDs would be "double-counting" the cost of burden and policy-makers should focus on one of the two measures. Of the five published CHIKV cost-of-illness studies, two presented both indirect costs and YLDs, while the other three studies only presented YLDs [27–29,31,81].

Certain limitations should be considered when interpreting the results of this study. The total direct and indirect estimated costs of the 2014-2015 CHIKV outbreak in the USVI may have been underestimated. Ambulatory service charges, absenteeism of caretakers for those who were ill due to CHIKV and additional hospitalization costs after the acute phase of illness could not be measured and were therefore not included in analysis. The mean cost of outpatient and inpatient visits was solely based on data from JFLMC, and does not account for varying costs from SMRC, MKCHC and private healthcare clinics. We addressed this issue by conducting a sensitivity analysis of direct costs based on the standard cost of healthcare visits at SMRC and MKCHC. Although another sensitivity analysis was conducted to account for underreporting of healthcare utilization, the true magnitude of underreporting up to 12 months after illness onset remains unknown. Additionally, there are two potential sources of bias in the estimates of disability: 1) if cases with persistent arthralgia were more likely to participate in the follow-up study, disability would be over-estimated, and 2) if the cause of death among the three cases who died was primarily CHIKV, disability would be underestimated by excluding their years of life

lost. Our YLD estimates are however, either consistent or more conservative than previous CHIKV studies [55,81,89,90].

Despite these limitations, this is the first cost-of-illness study of the CHIKV outbreak in the Caribbean and the first attempt to quantify the number of years lived with disability due to long-term sequelae of CHIKV illness in the Caribbean. The results from this study highlight the significant economic and long-term health burden of a CHIKV outbreak and provide evidence to inform policy decisions about prevention and control measures for inevitable future CHIKV outbreaks.

4.5 Tables and Figures

Table 4.1: Percentage of laboratory-positive cases 1-2, 6, and 12 months after disease onset who missed work, daily activities/chores, sought additional healthcare, were hospitalized due to CHIKV illness and prescribed medication for CHIKV.

Interview date	**1-2 Month (n=86)**			**2-6 Month (n=165)**			**7-12 Month (n=128)**		
Employment Status	**% (n)**	**Median (range)**	**Mean**	**% (n)**	**Median (range)**	**Mean**	**% (n)**	**Median (range)**	**Mean**
Working	32.6 (28)	-	-	40.6 (67)	-	-	33.6 (43)	-	-
Child/Student	24.4 (21)	-	-	15.8 (26)	-	-	23.4 (30)	-	-
Missed work/school									
Working (days)	89.3 (25)	4.5 (0-21)	5.57	88.1 (58)	0.5 (0-60)	2.2	9.3 (4)	0 (0-40)	1.2
Child/Student (days)	52.6 (10)*	1.0 (0-7)	1.63	61.5 (16)	2.3 (0-20)	3.4	6.7 (2)	0 (0-60)	2.1
Missed daily activities/chores (days)	85.9 (61)	5 (0-62)	11.67	86.0 (135)	5.0 (0-140)	13.0	15.1 (19)	0 (0-168)	6.4
Additional healthcare (visits)	32.6 (28)	0 (0-6)	0.5	-	-	-	24.6 (34)	0 (0-17)	0.6
Hospitalization (stays)	9.3 (8)	0 (0-14)	0.36	-	-	-	-	-	-
Prescribed medication	-	-	-	-	-	-	24.19 (30)	-	-

*Many of the students interviewed at the 1-2 month follow-up were on summer vacation when they became ill with CHIKV and therefore the number of school days missed may be lower than expected.

Table 4.2: Indirect cost estimates due to absenteeism from the CHIKV outbreak in the USVI up to 12 months after disease onset.

Time period after acute illness	**1-2 Months**			**2-6 Months**			**7-12 Months**		
Median number of work days missed	4.5			0.5			0		
Mean number of work days missed	5.57			2.15			1.16		
Mean number of work hours missed	44.56			17.2			9.28		
Island	St. Thomas	St. Croix	St. John	St. Thomas	St. Croix	St. John	St. Thomas	St. Croix	St. John
Average Hourly Wage ($) [61]	18.51	18.43	16.00	18.51	18.43	16.00	18.51	18.43	16.00
Wages lost per case by island ($)	824.81	821.24	712.96	318.37	317.00	275.20	171.77	171.03	148.48
Number of reported laboratory-positive cases + 70% of suspected not-tested cases	804	508	34	804	508	34	804	508	34
Number of estimated cases by island when proportion of population with symptomatic infection=0.24	11,948	11,709	965	11,948	11,709	965	11,948	11,709	965
Total value of time lost by island for reported suspected cases ($)	663,147	417,190	24,241	255,969	161,036	9,357	138,103	86,883	5,048
Total value of time lost by island when proportion of population with symptomatic infection=0.24	9,854,759	9,615,802	687,951	3,803,857	3,711,715	265,547	2,052,293	2,002,570	143,272
Total wages lost by island for employed, reported suspected cases ($)	346,163	217,773	12,654	133,616	84,061	4,884	72,090	45,353	2,635
Total wages lost by island for among all employed when proportion of population with symptomatic infection=0.24	5,144,184	5,019,449	359,110	1,985,613	1,937,515	138,616	1,071,297	1,045,342	74,788
Indirect cost of the CHIKV outbreak of all individuals ($)	**32,137,766**								
Indirect cost of the CHIKV outbreak of employed individuals* ($)	**16,775,914**								

*52.2% of the USVI population is employed as of 2010 [71]

Table 4.3: Direct cost estimate of the acute phase of the CHIKV outbreak in the USVI based on costs estimates from St. Croix.

Outpatient		**Inpatient**	
Median cost of a healthcare visit ($)	1,364.73	Median cost of a healthcare visit ($)	14,551.10
Mean cost of an outpatient healthcare visit ($)	1,526.21	Mean cost of an inpatient visit ($)	16,982.73
Total number of outpatient suspected reported cases	1850	Total number of inpatient suspected reported cases	79
Total cost of outpatient visits related to CHIKV ($)	2,823,488.50	Total cost of inpatient visits related to CHIKV	1,341,635.67
Total cost of outpatient and inpatient visits related to CHIKV ($)	**4,168,177**		

Table 4.4: Sensitivity analysis of direct cost estimate of the acute phase of the CHIKV outbreak in the USVI where acute phase costs on St. Croix are adjusted by the relative costs of an average outpatient visits on St. Thomas and St. John.

	Outpatient			**Inpatient**		
	St. Croix	St. Thomas	St. John	St. Croix	St. Thomas	St. John*
Mean cost of an outpatient healthcare visit ($)	1,526.21	763.11	595.22	16,982.73	8,491.37	-
Total number of outpatient suspected reported cases	712	1,081	57	49	30	0
Total cost of outpatient visits related to CHIKV ($)	1,086,662	824,917	33,928	832,154	254,741	0
Total cost of outpatient and inpatient visits related to CHIKV ($)	**3,032,400**					

*MKCHC does not have inpatient facilities. All individuals needing inpatient services were transported to SMRC on St. Thomas.

Table 4.5: Direct cost estimate of the CHIKV outbreak in the USVI up to 12 months after illness onset.

Outpatient			
Island	**St. Croix**	**St. Thomas**	**St. John**
Mean cost of a healthcare visit* ($)	600	300	234
Number of reported laboratory-positive cases + 70% of suspected not-tested cases	508	804	34
Mean number of additional healthcare visits at 1-2 months	0.5	0.5	0.5
Total cost of healthcare visits up to 1-2 months ($)	152,400	120,600	3,978
Mean number of additional healthcare visits at 12 months	0.62	0.62	0.62
Total cost of healthcare visits up to 12 months ($)	188,976	149,544	4,933
Cost of outpatient visits related to CHIKV up to 12 months ($)	620,431		
Cost of acute outpatient and inpatient visits related to CHIKV ($)	**4,168,177**		
Total direct cost estimate of the CHIKV outbreak up to 12 months ($)	**4,788,608**		

*The mean cost of an outpatient visit associated with a suspected CHIKV cases is higher than the mean cost of a standard outpatient visit due to additional serological testing for both chikungunya and dengue fever virus.

Table 4.6: Sensitivity analysis of reporting of healthcare utilization 12 months after acute onset of CHIKV illness.

Outpatient						
Island	**St. Croix**	**Total Cost**	**St. Thomas**	**Total Cost**	**St. John**	**Total Cost**
Mean cost of a healthcare visit ($)	600		300		234	
Mean number of additional healthcare visits at 12 months	0.62	188,976	0.62	149,544	0.62	4,933
5% underreporting	0.65	198,120	0.65	156,780	0.65	5,171
15% underreporting	0.70	213,360	0.70	168,840	0.70	5,569
25% underreporting	0.78	237,744	0.78	188,136	0.78	6,206
35% underreporting	0.84	256,032	0.84	202,608	0.84	6,683
45% underreporting	0.90	274,320	0.90	217,080	0.90	7,160
47% underreporting	0.91	277,368	0.91	219,492	0.91	7,240
Cost of outpatient visits at 1-2 months ($)	276,978					
Range of cost of outpatient visits at 12 months ($)	343,453 – 504,100					
Total cost range of outpatient visits related to CHIKV illness up to 12 months after acute illness	**620,431 – 781,078**					

Table 4.7: Years lived with disability due to persistent arthralgia attributable to the CHIKV outbreak.

	Osteoarthritis	**Post-acute effects**	**Rheumatoid arthritis**
Disability weight	0.156	0.219	0.233
Proportion of population with symptomatic infection=0.24	24,609		
Prevalence of persistent arthralgia attributable to CHIKV 12 months after illness onset	0.21 (95% CI: 0.11-0.31)		
Years lived with Disability	**806.19**	**1,131.77**	**1204.12**

4.6 Supplementary Table

Supplementary Table 4.1: Eligibility and enrollment numbers of laboratory-positive cases at 1-2, 6 and 12 months after illness onset.

	Date of laboratory positive test result		
	6/22/14-8/13/14, & 10/30/14- 2/23/15	8/14/14-10/29/14	Total interviewed
1-2 month Interview			
Eligible Individuals	191	371	562
Missing phone number	40	Individuals were ineligible for 1-2 month follow-up due to 2 month interruption in study start date	40
Phone # not-in-service or incorrect	24		24
Did not pick up after 3 calls	29		29
Refused	11		11
Died	1		1
Total interviewed	**86**	**0**	**86**
6 month interview			
Eligible Individuals	86	371	457
Missing Phone number	-	116	116
Phone # not-in-service or incorrect	7	86	93
Did not pick up after 3 calls	15	55	70
Refused	2	9	11
Died	0	2	2
Total interviewed	**62**	**103**	**165**
12-month interview			
Eligible Individuals	62	103	165
Missing Phone number	0	0	0
Phone # not-in-service or incorrect	2	7	9
Did not pick up after 3 calls	9	15	24
Refused	3	1	4
Died	0	0	0
Total interviewed	**48**	**80**	**128**

Source: LR Feldstein et al., Assessment of persistent arthralgia associated with the 2014-2015 chikungunya virus outbreak on the U.S. Virgin Islands, 2016, manuscript in progress.

Chapter 5: An assessment of household characteristics and individual-level practices of vector-control: Results from the 2014-2015 chikungunya virus outbreak in the U.S Virgin Islands

5.1 Introduction

Mosquitoes and the infectious diseases they transmit continue to be a significant public health challenge globally. Recent large-scale chikungunya (CHIKV) and Zika virus epidemics in the Americas and their associated severe and life-threatening outcomes illustrate this growing threat [19,91]. Furthermore, no antiviral or therapeutic treatment or vaccine for CHIKV or Zika virus currently exists [25,91]. Vector-control is the only prevention method presently available to reduce transmission of CHIKV, Zika and dengue (DENV) viruses [59].

The U.S. Virgin Islands (USVI) was one of the many regions in the Caribbean affected by the CHIKV epidemic in 2014 [40]. In response to the initial cases of CHIKV, the USVI Department of Health (DOH) worked in collaboration with the Centers for Disease Control and Prevention (CDC) to educate healthcare providers and the public regarding CHIKV disease, and to provide recommendations for vector-control at the household level in the form of media campaigns and educational materials.

As part of a larger study assessing long-term sequelae of CHIKV illness, we interviewed laboratory-positive CHIK cases and a comparison group at 6 and 12 months after acute illness to assess differences in household characteristics and individual-level practices of vector-control.

5.2 Methods

5.2.1 Study Setting and Subjects

Residents of the USVI who visited a hospital or healthcare clinic on Saint John, Saint Thomas, or Saint Croix and met the definition of a suspected CHIKV case were reported to the USVI DOH.

The USVI DOH defined a suspected case of CHIKV as a resident of any age with acute onset of fever (>38°C) and severe arthralgia or arthritis not explained by another medical condition. Suspected cases who tested laboratory-positive for CHIKV were eligible for inclusion in the study and were asked to be interviewed at 6 and 12 months after illness onset. At 12 months, we interviewed individuals who visited the same hospital or healthcare clinic as laboratory-positive cases (i.e. comparison group). Inclusion and exclusion criteria for laboratory-positive cases and the comparison group are defined in Table 5.1.

5.2.2 Data Collection

Laboratory-positive cases were contacted by telephone and invited to participate in a follow-up investigation 6 and 12 months after illness onset. Individuals were contacted for the 6-month interview between 1/26/15-8/18/2015 and for the 12-month interview between 7/2/15-2/14/2016. Verbal informed consent was obtained from all individuals. Those who refused to participate, those who did not answer the phone after three attempts, or those who had died, were excluded from the study. The 6-month questionnaire asked about use of mosquito repellent and air conditioners, emptying of water containers, and household characteristics. The 12-month questionnaire asked about the amount of time spent outdoors per day and annual household income. The same questions from the 6 and 12-month questionnaire were posed to the comparison group.

5.2.3 Statistical Analysis

Descriptive statistics were used to summarize and compare frequencies of demographic information, household characteristics, and individual-level practices of vector-control among laboratory-positive cases and the comparison group. Generalized linear models using the

binomial family with robust variance estimators were constructed to estimate prevalence differences using the identity link.

5.3 Results

At 6 months after illness onset, 165 CHIKV cases were interviewed (Table 5.2). Twelve months after onset, 128 of the 165 cases and 167 similar healthcare seekers (comparison group) were interviewed. Although the majority of CHIKV cases and similar healthcare seekers reported having screens on all of their windows (84% and 82%, respectively), 88% of cases and 80% of similar healthcare seekers reported seeing mosquitoes in their homes. A significantly greater proportion of cases reported having an air-conditioner in their homes than similar healthcare seekers (36%, 95% Confidence Interval [CI]: 28-44%, and 21%, 95% CI: 15-28%, respectively). However, when taking into account the proportion of cases and similar healthcare seekers who reported never using their air conditioner, the difference in owning an air conditioner between cases and the comparison group was no longer significant.

There were no statistically significant differences between cases and similar healthcare seekers of all other household characteristics, individual behavior practices of vector-control, and hours spent outdoors. Less than half of cases and the comparison group reported ever using mosquito repellent. Of those who did report using mosquito repellent, 42% of cases and 59% of similar healthcare seekers reported using it once a month or less. Anecdotally, many of these individuals shared that they only used repellent when spending time at the beach.

5.4 Discussion

These results question current vector-control efforts and indicate that individual-level behavior practices of vector-control may be unrealistic or insufficient. Twenty-three percent of USVI

residents live below the poverty line as of 2012 [92]. For much of the USVI population, owning an air conditioner and actually using it is not affordable. Home improvements such as screening in porches and altering landscapes to avoid standing water, the most common breeding site for *Aedes* spp. mosquitoes, may also be unaffordable. Moreover, due to the humid climate and considerable rainfall in the USVI (1,023 millimeters per year on average), the presence of standing water is inevitable [93]. Even if residents are dutiful about emptying their own containers of water, the *Aedes* spp. mosquito can travel up to 230 meters [51,52]. This situation is not unique to the USVI. The percent of people living below the poverty line in Latin American and Caribbean countries with ongoing Zika virus transmission ranges from 21-70%, and many of these countries have even more rainfall than the USVI [94,95].

Several studies show that CHIKV and DENV cases in Thailand, Malaysia, and the Philippines were more likely to dispose of garbage haphazardly or have garbage piles near the house than non-diseased individuals [32–35]. One of the Thailand studies also found that being a CHIKV case was associated with spending eight or more hours per day outside of the house and the Malaysian study found that the use of mosquito coils was protective against CHIKV illness [32,33]. However, other personal protective measures and mosquito risk factors assessed by these studies, such as mosquito repellent use, screens on windows, and uncovered water containers in or near homes were not associated with CHIKV or DENV disease [32,33,35].
In this study, cases may have over-reported emptying containers at least once per week and using mosquito repellent. They may have also underreported the presence of used car tires, buckets and clogged gutters in their yards or near their homes because they knew that all of these factors could increase their risk of becoming infected with CHIKV. However, cases were asked many other questions before the mosquito risk factor questions. As a result, a friendly and comfortable

rapport was developed between the interviewer and the case, so that cases would feel at ease responding honestly to potentially sensitive questions.

The results from this study and from prior studies highlight the need for large-scale prospective intervention studies to more accurately assess the effectiveness of individual-level vector-control measures. Vector-control behavior by an individual or a family may not reduce the mosquito population enough to halt disease transmission. Instead, vector-control may only be sufficient at the community or population-level. Given the ongoing Zika epidemic in the Americas and the high incidence of birth defects among infants of previously infected pregnant women, these findings suggest that individual-level vector-control cannot be the sole method for reducing disease transmission in the USVI. Lastly, this study emphasizes the urgent need for investment in therapeutic and vaccine research to mitigate the ongoing Zika virus epidemic and prevent future CHIKV and DENV outbreaks.

5.5 Tables

Table 5.1: Inclusion and exclusion criteria for cases and similar healthcare seeking individuals.

<table>
<tr><th></th><th>Laboratory-positive cases</th><th>Comparison Group</th></tr>
<tr><td rowspan="2">Inclusion Criteria</td><td>A suspected case with either of the following laboratory results:
1) Isolation of CHIKV from or demonstration of CHIKV nucleic acid in blood using reverse-transcriptase polymerase chain reaction (RT-PCR)</td><td rowspan="2">Residents of any age, sitting in the waiting room of the emergency room of a hospital or at a health clinic in the USVI between June 24 and June 29, 2015 and either waiting to be seen by a clinician or were accompanying a relative or friend who was waiting to be seen by a clinician.</td></tr>
<tr><td>2) CHIKV-specific IgM antibodies in serum using an enzyme-linked immunosorbent assay (ELISA) with either CHIKV-specific neutralizing antibodies using plaque reduction neutralization test (PRNT) and a 90% plaque reduction cutoff or CHIKV-specific IgG antibodies using ELISA</td></tr>
<tr><td rowspan="3">Exclusion Criteria</td><td>A suspected case with laboratory testing and either of the following results:
1) No evidence of CHIKV nucleic acid in blood within the first 5 days of illness onset by RT-PCR</td><td>Symptoms or positive laboratory results for CHIKV:
1) Febrile illness defined as self-reported fever in the last 7 days,</td></tr>
<tr><td rowspan="2">2) No evidence of CHIKV-specific IgM antibodies in serum using ELISA after the first 5 days of illness onset</td><td>2) Concurrent fever and acute joint pain in the last 12 months or</td></tr>
<tr><td>3) Responded “yes” to being tested for CHIKV and results were positive</td></tr>
</table>

Note: All blood samples were spun to separate the serum from the clot and stored at 4°C and transported on ice to the Division of Vector-Borne Diseases of the CDC in Fort Collins, Colorado for viral and antibody testing.

Table 5.2: Percentage of laboratory-positive cases and similar healthcare seekers by individual-level vector-control behavior and household characteristics.

6 month interview questions	**CHIKV cases (n=165)**		**Comparison group (n=167)***	
Median age in years (range)	52	(1-96)	35	(2-78)
	%	**95% CI**	**%**	**95% CI**
Female	65.5	58.2 - 72.7	64.7	56.4 – 73.0
Screens on all windows	83.9	78.1 - 89.7	81.6	75.7 - 87.5
Screened in porch/patio	7.8	2.0 - 7.8	7.3	3.3 - 11.3
Has an air-conditioner unit	36.0	28.4 - 43.6	21.3	15.1 - 27.6
Air-conditioner use				
All of the time	18.2	8.0 - 28.4	8.8	0.0 - 17.4
Only at night	25.5	13.9 – 37.0	50.0	33.2 - 66.8
Only in the summer	30.7	18.7 - 43.1	29.4	14.1 - 44.7
Never	25.5	13.9 – 37.0	11.8	0.9 - 22.6
Uses mosquito repellent	49.0	41.1 - 56.9	41.9	34.4 - 49.0
Mosquito repellent use				
Everyday	24.3	14.6 - 34.1	11.6	4.0 - 19.1
2-3 times per week	20.3	11.1 - 29.4	15.9	7.3 - 24.6
Once per week	13.5	5.7 - 21.3	13.0	5.1 – 21.0
Once per month	18.9	10.0 - 27.8	26.1	15.7 - 36.5
Less than once per month	23.0	13.4 - 32.6	33.3	22.2 - 44.5
Empties uncovered containers at least once per week	34.2	26.7 - 41.8	39.9	32.4 - 47.4
Sees mosquitoes in house	87.5	82.2 - 92.8	79.6	73.4 - 85.8
Has any of the following in yard or near house:				
Potted plants	56.6	48.7 - 64.5	44.3	36.8 - 51.8
Vegetation	82.9	76.9 - 88.9	77.3	70.9 - 83.6
Buckets	31.6	24.2 – 39.0	36.5	29.2 - 43.8
Clogged gutter	5.9	2.2 - 9.7	6.0	2.2 - 9.6
Pool	6.6	2.6 - 10.5	6.0	2.2 - 9.6
Boat	1.3	0.0 - 3.1	0.6	0.0 - 1.8
Used car tires	4.6	1.3 - 7.9	8.4	4.2 - 12.6
Cistern	80.9	74.7 - 87.2	75.5	68.9 – 82.0
12 month interview questions	**CHIKV cases (n=128)**		**Comparison group (n=167)**	
Average number of hours spent outdoors per day				
<1 hour	24.8	17.2 - 32.4	22.8	16.4 - 29.1
1-4 hours	53.0	44.9 - 62.3	43.7	36.2 - 51.2
5-8 hours	11.2	5.7 - 16.7	18.0	12.1 - 23.8
>8 hours	10.4	5.1 - 15.8	15.6	10.1 - 21.1
Annual household income ≤ $50,000	67.8	59.5 - 76.1	75.2	68.5 - 81.8

*All interview questions were administered to the comparison group during the same time period as the 12-month case interviews.

Chapter 6: Conclusion

Findings from this dissertation are consistent with previous studies that have identified risk factors for CHIKV disease, estimated the prevalence of persistent arthralgia, and estimated cost of illness associated with an outbreak. As shown in Chapter 2, incidence of reported CHIKV infection was highest among residents aged 55-64. No symptoms apart from fever >38 ºC and arthralgia or arthritis were significantly associated with CHIKV infection. Because this analysis used only data from passive surveillance, a seroprevalence study was conducted to determine the true incidence of CHIKV in the USVI, the proportion of asymptomatic cases, and demographic risk factors for disease. Data from this seroprevalence study are still being analyzed and will be compared to the analysis in Chapter 2 to assess any differences as a result of using a convenience sample rather than a random one. Ideally, at the start of the next outbreak, active surveillance should be conducted by going from house to house to determine household attack rates, proportion of asymptomatic infection, clinical manifestations of disease and risk factors for severe disease.

Chapter 3 demonstrated that following the 2014-2015 CHIKV outbreak in the USVI, a significant proportion of persistent arthralgia and difficulty with daily activities was associated with CHIKV illness up to one year after disease onset. These results underscore the need for additional epidemiologic studies in other Caribbean and Latin American countries to estimate the burden of persistent arthralgia, the impact on quality of life and other long-term sequelae that may be associated with CHIKV disease. These findings also provide a basis for conducting long-term (>1 year) prospective cohort studies to follow CHIKV cases and a comparison group to assess prevalence, clinical characteristics and biological mechanisms of persistent arthralgia.

Studies of this nature will be useful in determining risk factors for persistent arthralgia attributable to CHIKV, such as history of arthritis, other preexisting conditions and prior injuries.

Chapter 4 is the first cost-of-illness study of the CHIKV outbreak in the Caribbean and the first attempt at quantifying the number of years lived with disability due to long-term sequelae of CHIKV illness in the Caribbean. The total estimated cost associated with the 2014-2015 CHIKV outbreak in the USVI ranged from $37.2 to $37.4 million, of which 14% was direct medical costs and 86% was indirect costs due to absenteeism from work. The results from this study highlight the significant economic and long-term health burden of a CHIKV outbreak and provide valuable information for policy-makers to generate informed decisions about prevention and control measures for inevitable future CHIKV outbreaks. The findings also provide a basis for estimating the cost-effectiveness of a CHIKV vaccine when it becomes available. Although it is not standard practice to include a comparison group for cost-of-illness studies, this study would have benefited from interviewing a non-infected group of individuals during the same 12-month period as the cases to estimate healthcare utilization and work days missed directly attributable to CHIKV illness. Chapter 4 underscores the necessity of developing standard methodology to calculate disability-adjusted life years and cost of illness for CHIKV, and other arboviruses so that results can be directly comparable across studies, countries and diseases.

In Chapter 5, although household characteristics and individual-level behavior practices of vector-control did not differ between laboratory-positive CHIKV cases and similar healthcare seekers in the USVI, several studies have identified potential individual-level risk factors for acquiring CHIKV infection. The broad range of results across studies highlights the need for large-scale prospective intervention studies to assess the effectiveness of personal protective

measures, such as mosquito repellent use, presence of screens on windows and doors, and removal of vector-breeding sites during an outbreak. Vector-control practices are of particular importance due to lack of other prevention and control measures available, long-term persistent arthralgia associated with CHIKV disease and severe outcomes of other arboviral diseases, such as microcephaly from Zika virus [96].

This study provides valuable information on the first CHIKV outbreak in the USVI. These findings have already been shared with the USVI Department of Health and have aided in surveillance and targeted control efforts for the Zika virus outbreak that began in January of 2016. The results from this study emphasize the urgent need for investment in therapeutic, vaccine, and individual and community-level vector-control research to prevent acute illness and long-term morbidity attributable to CHIKV outbreaks in susceptible populations.

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Vita

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