

The Identification of Risk Factors for Chronic Chikungunya Arthralgia in Grenada, West Indies: A Cross-Sectional Cohort Study

Claire J. Heath,^{1,2} Jason Lowther,^{2,3} Trevor P. Noël,^{2,3} Idis Mark-George,² Derek B. Boothroyd,¹ George Mitchell,⁴ Calum MacPherson,^{2,3} and A. Desiree LaBeaud¹

¹Stanford University, School of Medicine, California; ²WINDREF, St. George's, Grenada; ³St. George's University, School of Medicine, Grenada; ⁴Ministry of Health, St. George's, Grenada

Background. Chikungunya virus (CHIKV) is a re-emerging arboviral pathogen. In 2014, an explosive CHIKV outbreak occurred in Grenada, West Indies, infecting approximately 60% of the population. In approximately 50% of cases, CHIKV infection transitions to painful arthralgia that can persist for years. Elucidation of the risk factors for chronic disease is imperative to the development of effective risk management strategies and specific therapeutics.

Methods. We conducted a cross-sectional study of 240 people who were tested for CHIKV during the outbreak. We administered questionnaires to examine demographic, behavioral, psychological, social, and environmental factors to identify associations with chronic disease. Physical examinations were performed and persistent symptoms were recorded.

Results. Ethnicity and socioeconomic status were not associated with risk of chronic joint pain. Female sex increased risk, and age was demonstrated to be predictive of chronic CHIKV sequelae. Mosquito avoidance behaviors did not reduce risk. Patients suffering joint pains, generalized body ache, and weakness in the extremities during acute infection were more likely to develop chronic arthralgia, and an increased duration of acute disease also increased risk.

Conclusions. These data demonstrate that chronic CHIKV affects people across the ethnic and socioeconomic spectrum, and it is not reduced by vector avoidance activity. Increased duration of acute symptoms, in particular acute joint pain, was strongly correlated with the risk of persistent arthralgia, thus effective clinical management of acute CHIKV disease could reduce burden of chronic CHIKV.

Keywords. arthralgia; arthritis; Caribbean; Chikungunya; Grenada.

Chikungunya virus (CHIKV) is an arthropod-borne virus (arbovirus), transmitted by *Aedes albopictus* and *Aedes aegyptiae* species mosquitoes [1]. Arthropod-borne viruses (arboviruses) comprise many of the most important “emerging” pathogens due to their geographic expansion and their increasing global health impact on naive populations. Chikungunya virus is a rapidly re-emerging pathogen that, over the last decade, has expanded its range across Africa and Asia and then emerged in Europe, the Pacific Region, and the Americas [2–5].

In 2013, CHIKV re-emerged in the Americas on the Caribbean Island of St. Martin, and it was first identified in Southeast Asia by the Asian genotype [6]. The rapid spread of the virus throughout the Caribbean was facilitated by an immunologically naive population and large numbers of travelers to

the region from neighboring mainland countries and also travel between islands in the region.

Chikungunya virus causes both acute and chronic disabling illness. Initial week-long prostrating fevers are often followed by severe skeletal and joint pain, frank arthritis, and, more rarely, eye inflammation, vision loss, Guillain-Barre Syndrome, paralysis, vasculitis, encephalitis, hepatitis, and/or myopericarditis [7–9]. The term “chikungunya” means “that which bends up” in reference to the severe arthralgia associated with the acute phase of infection and the resulting posture of those afflicted.

To date, the precise mechanisms for CHIKV’s disabling sequelae remain to be fully elucidated unknown. Underlying comorbidities such as cardiovascular disease, hypertension, concomitant osteoarthritis, obesity, and diabetes have been identified as potentially increasing the severity of CHIKV disease [7, 8, 10–17]. In addition, age at the time of acute infection has been reported by several investigators to be predictive of persistent arthralgia after CHIKV infection [15, 17–23].

As the threat of CHIKV expansion looms, there is a specific need to study the determinants of severe human disease. The lessons learned will be valuable to assess risk and suitable therapies for severe disease.

Currently, there are no specific therapies or approved CHIKV vaccines. Ninety percent of those infected with CHIKV suffer

Received 18 August 2017; editorial decision 16 October 2017; accepted 8 November 2017.

Correspondence: C. J. Heath, PhD, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto, CA (cjheath@stanford.edu).

Open Forum Infectious Diseases®

© The Author(s) 2018. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com.

DOI: 10.1093/ofid/ofx234

joint pain, which can persist for years in up to 50% of patients [12]. Characterization of the risk factors and mechanisms underlying chronic disease is imperative to identify the determinants of severe human disease, assess risk, and ultimately develop risk control measures and specific therapies for this debilitating disease. In addition, syndromic surveillance may prove diagnostically valuable, in regions where CHIKV is endemic and laboratory confirmation of the disease is limited.

Our study site, Grenada, is the main island of a tri-island state of Grenada, Carriacou, and Petit Martinique in the southern Antilles. Between July and November of 2014, an explosive outbreak of CHIKV occurred in Grenada with even the most conservative estimates of attack rate at approximately 60% of the population affected [24–26]. In this study, we investigate the epidemiological, demographical, physical, and behavioral risk factors associated with development of CHIKV-related chronic arthralgia in Grenada.

METHODS

Participant Recruitment

Between November 2015 and January 2016, study participants were recruited from a health service database of patients who had had their blood tested for CHIKV during the outbreak between July and November of 2014 [24, 25]. Chikungunya virus infection had been confirmed by polymerase chain reaction and/or immunoglobulin M enzyme-linked immunosorbent assay as we have previously described [25]. The database included people who had presented at primary care facilities, hospitals, and also to St. George's University Health Centre. All persons on this database were eligible for recruitment to our study. Healthcare in Grenada is provided free of charge to its citizens, and facilities include a General Hospital, larger local health centers in each Parish, and smaller health stations throughout the island, which are organized so that no household is more than 3 miles from a healthcare provider.

Participants were contacted via telephone and invited to attend a one-time appointment at one of the various healthcare facilities throughout the island. Home visit appointments were also offered to ensure maximum accessibility to the study.

Interview

In an in-person interview, informed consent (or parental consent for those aged <18 years) was obtained, and participants were administered questionnaires (Supplementary Figure 1) on the demographical, physical, environmental, behavioral, and social factors of their daily lives, and medical history, including any comorbidities, was also recorded. In particular, the symptoms suffered during their acute CHIKV illness, and any symptoms suffered since, were recorded. Subjects who reported persistent arthralgia, defined as suffering joint pains within the last month, were asked to complete the Arthritis Impact Measurement Scale (AIMS) questionnaire [27, 28], in order that the severity of their disease could be assessed. All interviews

were conducted by 1 of 2 members of our field research team, to ensure consistency in technique and reporting.

Physical Exam

Study subjects then undertook a comprehensive physical examination administered by a single Grenadian registered nurse, again to ensure consistency and standardization of assessment. Height, weight, blood pressure, visual acuity, and reflex measurements were recorded. Current arthritis/arthralgia symptoms were documented, and extensive joint examinations were conducted to measure swelling, stiffness or restricted motion, and to verify reported symptoms.

Arthritis Severity Scoring

The severity of disease sequelae in “chronic” participants was quantified using the internationally validated AIMS score [27, 28]. The scale assesses the impact of arthritis/arthralgia on the participant's functionality in various domains of life. The physical and symptom domains measure the impact of disease on the patient's ability to move joints normally and their reported degree of pain, respectively. The affect and social domains of the scale assess the impact of arthralgia on the subject's mood, sense of well being, social interactions, the pursuit of hobbies/leisure, and care of others.

Statistical Analysis

Demographic, ethnicity, physical, environmental, behavioral, and social factors were analyzed as they pertained to risk of suffering from persistent, chronic CHIKV-associated arthralgia. Subjects suffering from “chronic” arthralgia were defined as those that answered positively to the question “Have you suffered from joint pain since your initial CHIKV illness?” AND also answered “yes” to one of the questions; “Have you suffered joint pain in the last day/week/month?” Because our study was conducted 1 year after the end of the Grenadian outbreak, people answering positively to these questions have suffered symptoms within the chronic phase of the disease as classified by international consensus [29–31].

Initially, unadjusted univariate analyses were performed using Fisher's exact test, to give crude associations of each variable or prognostic factor with the risk of chronic CHIKV arthralgia. The category boundaries for age group were as follows: <25 years, 25–44 years, 45–64 years, and ≥65 years. These were chosen to allow for comparison of data with other similar studies [15, 17, 23]. Subsequently, multivariate logistic regression models adjusting for both sex and age group were fitted to each of the other variables in turn for estimating adjusted odds ratios and associated 95% confidence intervals (CIs) for developing chronic CHIKV arthralgia status. For evaluating sex and age group, only those 2 variables were included in 1 logistic regression model. Wald χ^2 tests were used to calculate *P* values for binary variables, and likelihood ratio χ^2 tests were used for nominal variables, to give χ^2 likelihood ratios and precision estimates.

For the variables of length of initial symptoms and length of initial joint pain, a Cochran-Armitage trend test was performed initially to test for associations of these with the risk of chronic joint pain. Subsequently, a multcategory logistic regression model was used to determine the odds ratio per category increase in duration.

RESULTS

A total of 240 participants were recruited to the study. Of these, 85 of the participants (35.4%) satisfied our criteria for suffering from chronic arthralgia and were administered the AIMS questionnaire to determine severity. The average time to follow up from initial presentation was 448 days (range, 391–556 days).

Of 240 participants, 64 (26.6%) were male and 176 (73.4%) were female. The age range of participants was 4–89 years, with both the mean and the median age being 40 years.

In our cohort, unadjusted estimates found that female sex did increase the risk of chronic CHIKV joint pain, although narrowly missing the threshold for significance ($P = .058$). However, when adjusted for age, this affect was reduced ($P = .123$; odds ratio [OR], 1.68; 95% CI, 0.87–3.26), suggesting that age was a more important predictor of chronic CHIKV arthralgia (Table 1).

Indeed, unadjusted analysis of participant age demonstrated an association with the risk of chronic arthralgia. This association varied by age group (43% chronic for age <25 years, 48% for 25–44 years, 63% for 45–64 years, and 21% for ≥65 years; $P = .021$). After adjustment for sex, and using the <25 years as

the reference group, the highest relative risk was in the 45- to 64-year-olds category (OR, 2.20; 95% CI, 0.93–5.18), followed by the 25–44 years group (OR, 1.17; 95% CI, 0.53–2.58), then the ≥65 years group (OR, 0.42; 95% CI 0.04–11.19) ($P = .043$).

The ethnic distribution of participants in this study was representative of the demography of Grenada with 193 of 240 participants (80.8%) being of African descent. Of the other participants, 12 were white (5%), 5 were East Indian (2.1%), 2 were Asian (0.8%), and 27 subjects (11.3%) identified as “Other”. When adjusted for age and sex, no association was observed between ethnicity and chronic disease risk ($P = .5130$), and, in particular, African descent was not indicative of increased risk when compared with all other ethnic groups ($P = .5761$; OR, 0.81; 95% CI, 0.39–1.70) (Table 1).

St. George’s parish is the most urbanized, affluent, and densely populated parish in Grenada, and residents of this parish represented 138 of 240 (57%) of our study subjects (Table 1). No differences in the risk of developing chronic CHIKV arthralgia were detected in participants from St. George’s compared with any of the other less affluent, more rural, parishes (OR, 1.15; 95% CI, 0.65–2.05; $P = .6273$).

We have previously reported the characteristics of the patients seeking care at the time of the outbreak [25]. Among the participants in the current study, during acute illness, the most commonly recorded symptom was joint pain (Table 2), which was experienced by 91% of study participants and is a signature symptom of acute CHIKV disease. This was followed by fever (81%), generalized body ache (75%), headache (72%),

Table 1. Demographic Characteristics of Study Participants

Variable	Subcategory	Number of Participants (%)	Odds Ratio	95% CI	Adjusted P Value
Sex					.058
	Male	64 (26.6)	Reference	Reference	
	Female	176 (73.4)	1.68	0.87–3.26	
Age Group (years)					.0430
	<25	40 (16.7)	Reference	Reference	
	25–44	109 (45.4)	1.17	0.53–2.58	
	45–64	71 (29.6)	2.20	0.93–5.18	
	≥65	20 (8.3)	0.42	0.10–1.81	
Ethnicity					.5130
	African Descent	84 (80.8)	Reference	Reference	
	White	12 (5)	1.27	0.30–5.46	
	East Indian	5 (2.1)	0.58	0.07–4.50	
	Asian	2 (0.8)	0.00	0.00–∞	
	Other	27 (11.3)	1.61	0.64–4.03	
Parish of Residence					.6744
	St. George’s	136 (57.1)	Reference	Reference	
	St. Andrew	42 (17.5)	1.19	0.54–2.60	
	St. David	35 (14.5)	0.49	0.20–1.24	
	St. John	13 (5.42)	1.22	0.32–4.71	
	St. Patrick	11 (4.6)	0.84	0.25–2.86	
	St. Mark	2 (0.83)	0.65	0.04–11.19	

Abbreviations: CI, confidence interval.

Table 2. The Association of Acute Chikungunya-Disease Symptoms With Chronic CHIKV Arthralgia*

Acute Symptom	Number of Participants With Symptom (%)	Adjusted P Value	Adjusted Odds Ratio	95% CI Lower	95% CI Upper
Fever	194 (80.8)	.0442	2.26	1.02	4.99
Chills	159 (66.25)	.1165	1.64	0.88	3.04
Generalized body ache	180 (75)	.0244	2.24	1.11	4.53
Joint pains	219 (91.3)	.0183	6.50	1.37	30.75
Muscle pains	149 (62.1)	.0992	1.67	0.91	3.05
Bone pains	104 (43.3)	.2315	1.42	0.80	2.52
Itchiness	117 (48.7)	.4102	1.28	0.72	2.27
Headache	172 (71.6)	.1096	1.71	0.89	3.30
Retro-orbital pain	88 (36.6)	.0259	1.96	1.08	3.55
Dizziness	94 (39.1)	.0563	1.77	0.98	3.18
Photosensitivity	79 (32.9)	.0067	2.36	1.27	4.39
Stiff neck	72 (30.0)	.0074	2.41	1.27	4.58
Red eyes	27 (11.25)	.1349	2.04	0.80	5.17
Runny nose	31 (12.9)	.1461	1.88	0.80	4.39
Earache	16 (6.6)	.3039	1.88	0.56	6.24
Sore throat	60 (25.0)	.0188	2.28	1.15	4.55
Cough	54 (22.5)	.2007	1.60	0.78	3.28
Shortness of breath	40 (16.6)	.4507	1.34	0.63	2.84
Loss of appetite	148 (61.6)	.1309	1.58	0.87	2.87
Strange taste in mouth	87 (36.25)	.0211	2.02	1.11	3.66
Nausea	83 (34.6)	.0360	1.92	1.04	3.55
Vomiting	43 (17.9)	.9542	0.98	0.46	2.06
Diarrhea	60 (25.0)	.5868	1.20	0.63	2.29
Abdominal pain	56 (23.3)	.1936	1.59	0.79	3.19
Rash	123 (51.3)	.8208	1.07	0.59	1.93
Bloody nose	3 (1.2)	.7240	0.64	0.05	7.87
Bleeding gums	9 (3.7)	.7620	0.80	0.19	3.33
Bruising	5 (2.1)	.2486	0.26	0.03	2.59
Impaired mental status	29 (12.1)	.0004	7.85	2.51	24.55
Seizures	3 (1.25)	.9882	0.00	0.00	∞
Weakness in the extremities	146 (60.8)	.0116	2.18	1.19	3.99

Abbreviations: CHIKV, Chikungunya virus; CI, confidence interval.

*Acute symptoms associated with risk of chronic CHIKV arthralgia are highlighted.

chills (66%), muscle pain (62%), and other general symptoms of febrile illness. It is interesting to note that, of these most common symptoms, joint pain ($P = .0183$; OR, 6.5; 95% CI, 1.37–30.75), generalized body ache ($P = .0244$; OR, 2.24; 95% CI, 1.11–4.53), and weakness in the extremities (reported by 60.8% of patients) ($P = .0116$; OR, 2.18; 95% CI, 1.19–3.99) were associated with risk of subsequently developing chronic sequelae. Other symptoms, such as fever, retro-orbital pain, photosensitivity, stiff neck, sore throat, and impaired mental state, were also associated with increased chronic disease risk (Table 2), although this is likely due to these being indicative of increased acute disease severity.

The impact of social economic status (SES) on the risk of developing chronic CHIKV disease was assessed via a variety of proxy measures of SES, pertaining to the participants' occupation, educational status, living environment, and income (Table 3). Using these measures, SES was not significantly implicated in a patient's likelihood of developing chronic disease sequelae. However, it

should be noted that indicators of dwelling conditions, ie, having an outdoor pit latrine (OR, 1.99; 95% CI, 0.83–4.80; $P = .1249$) and/or a household floor of described as "other" in the questionnaire (suggesting a dirt floor) (OR, 2.63; 95% CI, 0.46–15.02; $P = .2762$), were more associated with chronic disease than educational and occupational measures (Table 3), suggesting that a poorer immediate environment increased the risk of persistent CHIKV disease sequelae.

We hypothesized that mosquito avoidance behaviors were likely to determine the frequency and intensity of CHIKV exposure (ie, mosquito bites), and therefore may contribute to the severity of acute infection, and thus have an influence on the subsequent course of disease. However, we found that none of the various mosquito avoidance and repelling behaviors practiced by the participants reduced their risk of chronic disease (Figure 1). However, mosquito avoidance behaviors were not routinely nor consistently practiced (Figure 1), with most participants responding "never" to questions regarding the use of

Table 3. Association of Proxy Measures of SES the Risk of Chronic CHIKV Arthralgia

Variable	Subcategory	Odds Ratio	95% CI	Adjusted P Value
Highest level of education				.874
	Primary School	Reference	Reference	
	Secondary School	0.69	0.29–1.65	
	Tertiary College	0.91	0.38–2.20	
	University Undergraduate	0.73	0.30–1.78	
	Professional Degree	2.89	0.36–22.99	
	Other Postgraduate	0.86	0.20–3.63	
	Other	0.81	0.04–15.50	
No. of rooms in House		1.00	0.90–1.11	.961
No. of people in house		0.95	0.82–1.11	.534
No. of children (<18) in house		1.06	0.85–1.32	.617
House construction material				.519
	Concrete (Wall)	Reference	Reference	
	Wood (Board)	1.38	0.59–3.20	
	Concrete and Wood	1.44	0.71–2.92	
Floor Type				
	Wood	0.93	0.51–1.70	.817
	Cement	0.98	0.54–1.79	.946
	Tile	0.97	0.55–1.72	.916
	Other	2.63	0.46–15.02	.2762
Bathroom Type				.1249
	Indoor Toilet	Reference	Reference	
	Pit Latrine	1.99	0.83–4.8	
Have air conditioning (Y/N)		0.61	0.27–1.38	.233
Have a refrigerator (Y/N)		1.28	0.41–3.95	.671

Abbreviations: CHIKV, Chikungunya virus; CI, confidence interval; N, no; SES, social economic status; Y, yes.

repellents (60.4% responding “never”), mosquito coils (65.8%), and sleeping under mosquito nets (75%). In contrast, however, the controlling of mosquito breeding sites around the home was practiced “always” by 45% of subjects.

Increased frequency of mosquito bites missed the cutoff for significance in this study, but it was correlated with increased risk of chronic CHIKV disease ($P = .063$). Chikungunya virus infection is rarely asymptomatic, and being bitten by a virus-carrying mosquito usually manifests in observable illness [8]. Thus, an increase in the frequency of bites, particularly in an epidemic situation, will increase the likelihood of CHIKV disease.

The majority of participants (57.8%) reported that their acute illness had resolved within 1 week (Table 4), and a further 25.7% of participants had recovered within 1–2 weeks. Smaller proportions of participants reported that their acute illness lasted for 3 (6.3%) and 4 weeks (5.1%).

Using an unadjusted Cochran-Armitage trend test, the duration of symptoms during the initial acute illness was linearly

associated with increased risk of suffering from chronic CHIKV disease sequelae ($P = .001$). In particular, increased duration of joint pain specifically, during the acute syndrome, increased the likelihood of suffering from persistent arthritis and arthralgia ($P \geq .0001$) in unadjusted analyses. Adjustment for sex and age group yielded adjusted P values of .0061 and .0089, respectively (Table 4). Moreover, the adjusted OR for chronic disease per one category increase in duration of symptoms was 1.45 (95% CI, 1.14–1.84; $P = .0025$), and per 1 category increase in length of joint pain specifically was 1.33 (95% CI, 1.14–1.56; $P = .0004$).

Other studies have reported associations of body mass index (BMI) with chronic CHIKV arthralgia. Thus, we calculated BMI from the height and weight measurements of our study participants, to allow for analysis of this factor and comparison of our data. Although initial unadjusted univariate analyses of participants’ BMI associated obesity with the risk of chronic arthralgia ($P = .036$), after multivariate adjustment for age and sex, we found that obesity was not associated with chronic CHIKV arthralgia in Grenada ($P = .1045$; OR, 1.68; 95% CI, 0.90–3.16). Of note, however, high cholesterol did increase the risk of chronic arthralgia (OR, 0.39; 95% CI, 0.16–0.91; $P = .0304$). No association was found between chronic arthralgia and any of the other comorbidities assessed in our cohort. Of all the domains of life assessed by the AIMS score, the physical impact of chronic CHIKV disease (ie, the impact on mobility, ability to walk and bend, and limb function) had the highest average score of all the domains, indicating that all participants with persistent CHIKV disease experienced reduced physical ability after infection (Figure 2). Scores for the symptomatic (pain) domain of the scale were the widest ranging but, with the exception of the work domain, had the lowest average impact score. The affect and social domains both scored, on average, higher than physical pain on the impact scale, indicating that participants were debilitated psychologically and socially by their chronic CHIKV disease. The aspect of work was the lowest impacting in our participants. However, this domain was mainly assessed by loss of work days and income, which, due to paid sick leave in Grenada, did not affect most people.

In addition, each domain of the arthritis impact scale was, to varying degrees, positively associated with the duration of initial illness, and in particular duration of joint pain during acute disease (Figure 3), suggesting that prolonged acute illness not only increases likelihood of developing chronic arthralgia but also increases the impact of chronic disease.

DISCUSSION

This study describes the widespread morbidity that the CHIKV epidemic had on the population of Grenada, and our data demonstrate that chronic CHIKV disease affects people across the ethnic and socioeconomic spectrum.

Increasing age was found to be a significant risk factor for chronic CHIKV arthralgia in our cohort, with those in the

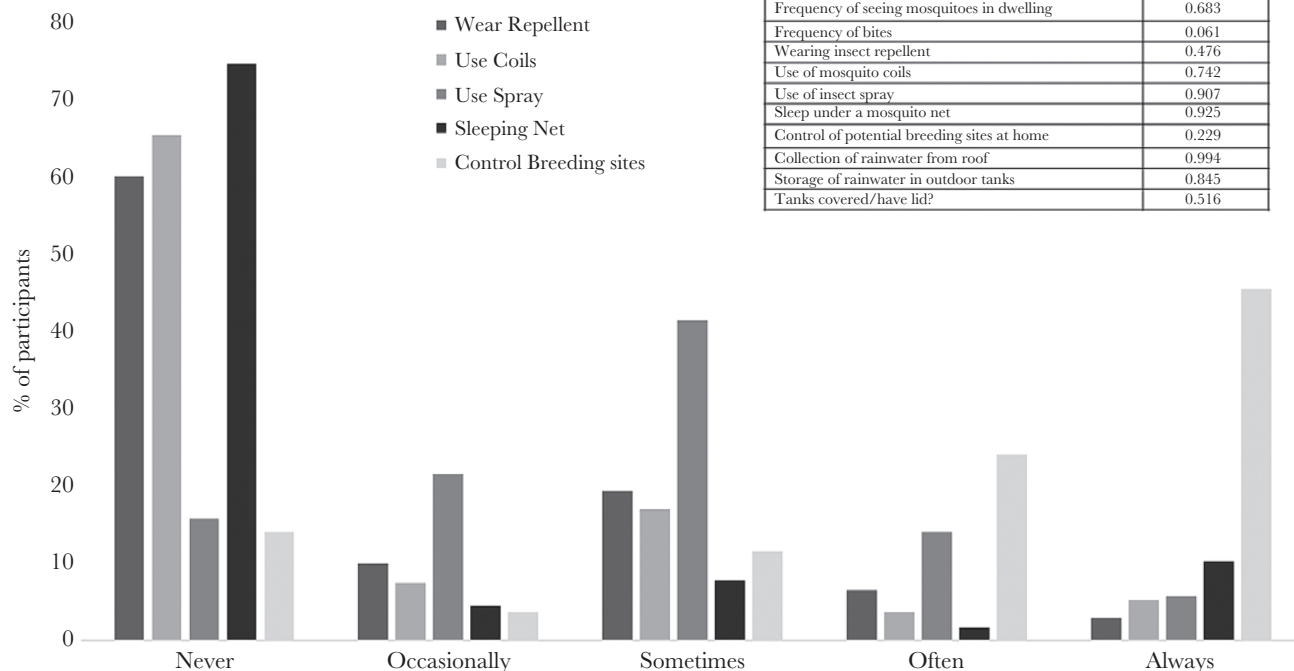


Figure 1. Analysis of the association of mosquito vector avoidance behaviors and the risk of chronic Chikungunya virus arthralgia.

Measure of Vector Avoidance Behavior	P-value
Mosquito screens on windows at dwelling	0.169
Frequency of seeing mosquitoes in dwelling	0.683
Frequency of bites	0.061
Wearing insect repellent	0.476
Use of mosquito coils	0.742
Use of insect spray	0.907
Sleep under a mosquito net	0.925
Control of potential breeding sites at home	0.229
Collection of rainwater from roof	0.994
Storage of rainwater in outdoor tanks	0.845
Tanks covered/have lid?	0.516

25- to 44-year-old age group at the highest risk. This is in concordance with several other studies conducted in similar settings who have found age to be predictive of rheumatic sequelae after CHIKV infection [15, 17, 19, 20, 22, 23, 32–34]. We found that female gender increased the risk of chronic arthralgia, although narrowly missing the cutoff for significance, which is in concordance with several studies that have shown females to be at higher risk for persistent arthritis/

arthralgia than men [19, 33, 35–37]. A total of 35.4% of our study participants met our definition of persistent arthralgia, which strongly concurs with a recent meta-analysis on the incidence of chronic arthralgia performed by Rodríguez-Morales et al. [35]. Their analyses showed that in studies with >200 participants, 34% of CHIKV-infected patients would go on to develop chronic arthritis. This proportion is also similar to that recently reported by Feldstein et al. [38], in the US Virgin Islands.

The parish of participant’s residency was not found to be a risk factor for CHIKV disease in Grenada. However, it should be noted that parish of residency is often not where participants worked, with many traveling into the capital of St. George’s each day. This is of relevance to CHIKV infection because *Aedes* spp are daytime feeders. Nonetheless, the amount of time spent outdoors, either as part of their occupation or outside of work, was not found to be correlated with risk of chronic disease in this study.

Similarly, no proxy measure of SES was found to be significantly implicated in increased risk of chronic arthralgia, although indicators of participants’ immediate living environment was more associated than educational and occupational indicators. Previous studies that have examined environmental and social factors that impacted upon the manifestations of CHIKV disease in small island settings have also described primary associations with housing conditions [39, 40]. The socialized healthcare system in Grenada may have minimized the impact of economic status on CHIKV disease outcome during

Abbreviations: CHIKV, Chikungunya virus; CI, confidence interval.

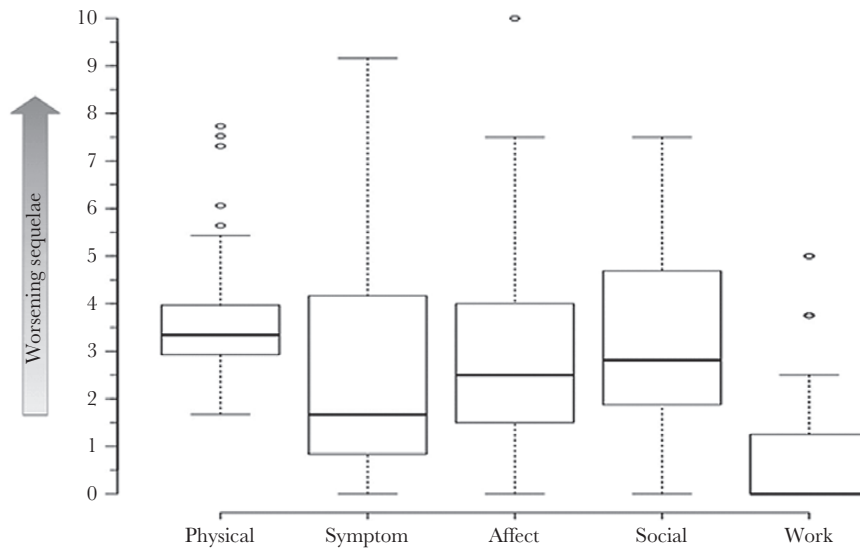


Figure 2. Arthritis impact scores in subjects with Chikungunya virus-related persistent arthritis and arthralgia in each distinct life domain.



* Positive association is shown in blue, negative in red. Increasing size of a circle denotes increasing association.

Domain	Adjusted p-value	
	Duration of symptoms	Duration of joint pain
Physical	0.0185	0.6799
Symptom	0.4611	0.2745
Affect	0.4097	0.43480
Social	0.7724	0.1325
Work	0.0011	0.2495

Figure 3. Correlation of duration of acute symptoms and initial joint pain with each life domain in arthritis impact quality-of-life assessment.

Table 5. Association of Comorbidities With the Risk of Chronic CHIKV Arthralgia

Comorbidity	Odds Ratio	95% CI	P Value
Previous dengue infection	1.98	0.75–5.13	.1718
Asthma	0.95	0.45–2.00	.8945
Respiratory illness	1.59	0.69–3.64	.2735
Cardiovascular illness	1.33	0.44–4.04	.6095
Stroke	0.00	0.00–∞	.9886
Hypertension	1.14	0.55–2.36	.7281
High cholesterol	0.39	0.16–0.91	.0304
Diabetes	1.65	0.53–5.17	.3894
Seizure disorders	1.79	0.10–30.94	.6878
Cancer	0.00	0.00–∞	.9849

Abbreviations: CHIKV, Chikungunya virus; CI, confidence interval.

the outbreak, which may not be the case in countries with different systems [17]. This universal system also lends confidence to estimates of the number of people infected with CHIKV in Grenada during the epidemic, because people are more likely to seek medical advice and report their symptoms. Likewise, it is perhaps unsurprising that educational level, as measured here by years of schooling, was not implicated in risk of chronic arthralgia in our study, because school in Grenada is free and compulsory until age 16, mitigating gaps in education that may be a risk factor in other countries where CHIKV is endemic.

No mosquito avoidance behavior was found to be associated with decreased risk of disease (Table 2). However, we found that preventative measures, such as the wearing of repellent, were not commonly practiced by the majority of participants (Figure 3). In addition, traditionally used efforts targeted at combatting night time bites, eg, sleeping under a bed net and using mosquito coils in the home during the evening, are ineffective against daytime feeding *Aedes* vectors. This lack of engagement in avoidance practices in high-risk populations, seemingly due to perceived ineffectiveness, has been reported elsewhere [41], and it poses a challenge to public health authorities in strengthening communication, education, and outreach to increase the adoption of protective behaviors in these populations to control the spread of CHIKV and similar arboviruses in future outbreaks.

The frequency of being bitten by mosquitoes narrowly missed the threshold for significance. However, it is a limitation of our study that, in an environment where mosquitoes abound, and suffering bites is an everyday occurrence, self-reported frequency of bites is largely subjective. In addition, because CHIKV is rarely asymptomatic, even a single bite by an infected vector is likely to manifest as febrile disease. In the context of an epidemic, however, the frequency of being bitten also raises questions regarding the implications of viral load on disease severity.

The severity of acute CHIKV disease has previously been reported to be predictive of recovery and long-term arthritis and arthralgia symptoms [18, 21, 34, 42]. Similarly in our study,

several acute symptoms—including dizziness, retro-orbital pain, photosensitivity, stiff neck, sore throat, and altered mental state, which are suggestive of more severe illness—were found to be associated with increased chronic disease risk. Disease severity and the subsequent risk of arthritis/arthralgia has been correlated with viral load during the acute phase [20]. These observations are informative for early recognition and management of patients at risk for developing persistent rheumatic symptoms. Weakness in the hands during acute illness was highly associated with the risk of persistent arthralgia in our study participants. Previous studies of chronic CHIKV disease patients have demonstrated joint space narrowing in the distal joints upon radiographic imaging [43–45] and remarkable persistent arthritis of these joints [46], suggesting that disseminated infection and inflammation during acute illness increases the likelihood of persistent arthralgia symptoms. Clinical management of acute symptoms, particularly inflammation, and the minimization of acute disease duration could reduce the incidence, morbidity, and economic impact of chronic CHIKV disease.

In addition to the physical restrictions persistent arthralgia had on “chronic” participants in this study, the AIMS assessment found that chronic CHIKV disease impacted psychologically and socially on sufferers, even more so than did physical pain. These data are in support of several other studies that have reported depression and/or depressed mood or a reduction in overall quality of life as a long-term consequence of CHIKV infection [22, 47–50]. Thus, medical follow up with chronic CHIKV sufferers should include awareness of and support for potential depression and anxiety. In addition, this psychological and sociological morbidity has implications for the development of intervention programs in regions of high CHIKV incidence.

This study is limited in that we were only able to follow up with patients from the outbreak database who were contactable. This may have affected the data in terms of the demography of the study, because some patients on the database were foreign students of St. George’s University, who were no longer on the island. In addition, being contactable by telephone is an indicator of relative SES. Notwithstanding, as previously stated, the ethnic and SES distribution of our study participants is reflective of the permanent population of Grenada. Moreover, in a cross-sectional cohort study such as presented here, particularly when the long term-effects of a disease are being investigated, it is likely that those people experiencing chronic sequelae are more inclined to participate, and thus the incidence of chronic CHIKV disease in the general population may be overestimated. However, as discussed above, we found that the proportion of our cohort meeting our criteria for chronic disease was concordant with several studies of similar size [15, 17, 23, 35, 38].

CONCLUSIONS

This study demonstrates that the significant morbidity of chronic CHIKV disease affects people across all demographic and social

strata and presents a significant physical, social, and economic burden to affected populations. Identification of risk factors for chronic disease after acute outbreaks, as presented herein, is imperative for prevention, early intervention, and minimization of the impact of this potentially devastating disease.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We would foremost like to express our gratitude to the people of Grenada who participated in this study. Thanks also to the nursing staff at each of the Parish health centers and the Grenadian Ministry of Health for facilitating this research.

Disclaimer. The funders had no role in the design, conduct or reporting of this work.

Financial support. This work was funded by the American Society of Tropical Medicine and Hygiene and the American Committee on Arthropod-borne Viruses via the Robert E. Shope International Fellowship in Infectious Diseases (to C. J. H.).

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Robinson MC. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-53. I. Clinical features. *Trans R Soc Trop Med Hyg* **1955**; 49:28-32.
2. Weaver SC. Arrival of Chikungunya virus in the new world: prospects for spread and impact on public health. *PLoS Negl Trop Dis* **2014**; 8:e2921.
3. Zeller H, Van Bortel W, Sudre B. Chikungunya: its history in Africa and Asia and its spread to new regions in 2013-2014. *J Infect Dis* **2016**; 214:436-40.
4. Yactayo S, Staples JE, Millot V, et al. Epidemiology of Chikungunya in the Americas. *J Infect Dis* **2016**; 214:441-5.
5. Wahid B, Ali A, Rafique S, Idrees M. Global expansion of Chikungunya virus: mapping the 64-year history. *Int J Infect Dis* **2017**; 58:69-76.
6. Gay N, Rousset D, Huc P, et al. Seroprevalence of Asian lineage Chikungunya virus infection on Saint Martin Island, 7 months after the 2013 emergence. *Am J Trop Med Hyg* **2016**; 94:393-6.
7. Leparc-Goffart I, Nougairess A, Cassadou S, et al. Chikungunya in the Americas. *Lancet* **2014**; 383:514.
8. Staples JE, Breiman RF, Powers AM. Chikungunya fever: an epidemiological review of a re-emerging infectious disease. *Clin Infect Dis* **2009**; 49:942-8.
9. Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. *N Engl J Med* **2015**; 372:1231-9.
10. Economopoulou A, Dominguez M, Helyncx B, et al. Atypical Chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005-2006 outbreak on Réunion. *Epidemiol Infect* **2009**; 137:534-41.
11. Htun NS, Odermatt P, Eze IC, et al. Is diabetes a risk factor for a severe clinical presentation of dengue?—review and meta-analysis. *PLoS Negl Trop Dis* **2015**; 9:e0003741.
12. Erin Staples J, Ann M. Powers, *Chikungunya*. Centers for Disease Control and Prevention Yellow Book, Chapter 3 Diseases Related to Travel, **2015**. Available at: <https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/chikungunya> (Accessed 2nd August 2017).
13. Rajapakse S, Rodrigo C, Rajapakse A. Atypical manifestations of Chikungunya infection. *Trans R Soc Trop Med Hyg* **2010**; 104:89-96.
14. Toledo J, George L, Martinez E, et al. Relevance of non-communicable comorbidities for the development of the severe forms of dengue: a systematic literature review. *PLoS Negl Trop Dis* **2016**; 10:e0004284.
15. Gérardin P, Fianu A, Michault A, et al. Predictors of Chikungunya rheumatism: a prognostic survey ancillary to the TELECHIK cohort study. *Arthritis Res Ther* **2013**; 15:R9.
16. Murillo-Zamora E, Mendoza-Cano O, Trujillo-Hernández B, et al. Persistent arthralgia and related risks factors in laboratory-confirmed cases of Chikungunya virus infection in Mexico. *Rev Panam Salud Publica* **2017**; 41:e72.
17. Sissoko D, Malvy D, Ezzedine K, et al. Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. *PLoS Negl Trop Dis* **2009**; 3:e389.
18. Borgherini G, Poubeau P, Jossaume A, et al. Persistent arthralgia associated with Chikungunya virus: a study of 88 adult patients on Reunion Island. *Clin Infect Dis* **2008**; 47:469-75.
19. Essackjee K, Goorah S, Ramchurn SK, et al. Prevalence of and risk factors for chronic arthralgia and rheumatoid-like polyarthritides more than 2 years after infection with Chikungunya virus. *Postgrad Med J* **2013**; 89:440-7.
20. Hoarau JJ, Jaffar Bandjee MC, Krejbich Trotot P, et al. Persistent chronic inflammation and infection by Chikungunya arthritogenic alphavirus in spite of a robust host immune response. *J Immunol* **2010**; 184:5914-27.
21. Larrieu S, Poudroux N, Pistone T, et al. Factors associated with persistence of arthralgia among Chikungunya virus-infected travellers: report of 42 French cases. *J Clin Virol* **2010**; 47:85-8.
22. Schilte C, Staikowsky F, Staikowsky F, et al. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. *PLoS Negl Trop Dis* **2013**; 7:e2137.
23. Elsinga J, Gerstenbluth I, van der Ploeg S, et al. Long-term Chikungunya sequelae in Curaçao: burden, determinants and a novel classification tool. *J Infect Dis* **2017**; 216:573-81.
24. LaBeaud AD, Noël TP, et al. Chikungunya in the Western Hemisphere: A review of the 2014 epidemic, the potential long-term impact, and research opportunities. In 60th Annual Caribbean Public Health Agency (CARPHA) Health Research Conference; **2015**; St. George's University, St. George's, Grenada.
25. Macpherson C, Noel T, Jungkind D, et al. Clinical, molecular and serological outcomes of the Chikungunya outbreak in Grenada. In 60th Annual Caribbean Public Health Agency (CARPHA) Health Research Conference; **2015**; St. George's University, St. George's, Grenada.
26. Forde MS, Martin F, Mitchell G, Bidaisee S. Public health response and lessons learned from the 2014 chikungunya epidemic in Grenada. *Rev Panam Salud Publica* **2017**; 41:e57.
27. Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis. The arthritis impact measurement scales. *Arthritis Rheum* **1980**; 23:146-52.
28. Guillemin F, Coste J, Pouchot J, et al. The AIMS2-SF: a short form of the arthritis impact measurement scales 2. French quality of life in rheumatology group. *Arthritis Rheum* **1997**; 40:1267-74.
29. Sissoko D, Malvy D, Ezzedine K, et al. Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. *PLoS Negl Trop Dis* **2009**; 3:e389.
30. National Institutes of Allergy and Infectious Diseases of the National Institutes of Health, U.S. Department of Health and Human Services. Gaps and Opportunities in Chikungunya Research: Expert Consultation on Chikungunya Disease in the Americas; **2015**; Rockville, Maryland.
31. Javelle E, Ribera A, Degasne I, et al. Specific management of post-Chikungunya rheumatic disorders: a retrospective study of 159 cases in Reunion Island from 2006-2012. *PLoS Negl Trop Dis* **2015**; 9:e0003603.
32. Mohd Zim MA, Sam IC, Omar SF, et al. Chikungunya infection in Malaysia: comparison with dengue infection in adults and predictors of persistent arthralgia. *J Clin Virol* **2013**; 56:141-5.
33. Moro ML, Grilli E, Corvetta A, et al. Long-term Chikungunya infection clinical manifestations after an outbreak in Italy: a prognostic cohort study. *J Infect* **2012**; 65:165-72.
34. Yaseen HM, Simon F, Deparis X, Marimoutou C. Identification of initial severity determinants to predict arthritis after Chikungunya infection in a cohort of French gendarmes. *BMC Musculoskelet Disord* **2014**; 15:249.
35. Rodríguez-Morales AJ, Cardona-Ospina JA, Fernanda Urbano-Garzón S, Sebastian Hurtado-Zapata J. Prevalence of post-Chikungunya infection chronic inflammatory arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* **2016**; 68:1849-58.
36. van Aalst M, Nelen CM, Goorhuis A, et al. Long-term sequelae of chikungunya virus disease: a systematic review. *Travel Med Infect Dis* **2017**; 15:8-22.
37. Win MK, Chow A, Dimatatac F, et al. Chikungunya fever in Singapore: acute clinical and laboratory features, and factors associated with persistent arthralgia. *J Clin Virol* **2010**; 49:111-4.
38. Feldstein LR, Rowhani-Rahbar A, Staples JE, et al. Persistent arthralgia associated with Chikungunya virus outbreak, US Virgin Islands, December 2014-February 2016. *Emerg Infect Dis* **2017**; 23:673-6.

39. Raude J, Setbon M. The role of environmental and individual factors in the social epidemiology of Chikungunya disease on Mayotte Island. *Health Place* **2009**; 15:659–69.
40. Setbon M, Raude J. Population response to the risk of vector-borne diseases: lessons learned from socio-behavioural research during large-scale outbreaks. *Emerg Health Threats J* **2009**; 2:e6.
41. Fritzell C, Raude J, Adde A, et al. Knowledge, attitude and practices of vector-borne disease prevention during the emergence of a new arbovirus: implications for the control of Chikungunya virus in French Guiana. *PLoS Negl Trop Dis* **2016**; 10:e0005081.
42. Sepúlveda-Delgado J, Vera-Lastra OL, Trujillo-Murillo K, et al. Inflammatory biomarkers, disease activity index, and self-reported disability may be predictors of chronic arthritis after Chikungunya infection: brief report. *Clin Rheumatol* **2017**; 36:695–9.
43. Bouquillard E, Combe B. Rheumatoid arthritis after Chikungunya fever: a prospective follow-up study of 21 cases. *Ann Rheum Dis* **2009**; 68:1505–6.
44. Bouquillard E, Combe B. A report of 21 cases of rheumatoid arthritis following Chikungunya fever. A mean follow-up of two years. *Joint Bone Spine* **2009**; 76:654–7.
45. Bouquillard E, Fianu A, Bangil M, et al. Rheumatic manifestations associated with Chikungunya virus infection: A study of 307 patients with 32-month follow-up (RHUMATOCHIK study). *Joint Bone Spine* **2017**. doi: 10.1016/j.jbspin.2017.01.014.
46. Eyer-Silva WA, Pinto HB Neto, Silva GA, Ferry FR. A case of Chikungunya virus disease presenting with remarkable acute arthritis of a previously damaged finger joint. *Rev Soc Bras Med Trop* **2016**; 49:790–2.
47. Bhatia MS, Gautam P, Jhanjee A. Psychiatric morbidity in patients with Chikungunya fever: first report from India. *J Clin Diagn Res* **2015**; 9:VC01–3.
48. Couturier E, Guillemin F, Mura M, et al. Impaired quality of life after Chikungunya virus infection: a 2-year follow-up study. *Rheumatology (Oxford)* **2012**; 51:1315–22.
49. Soumahoro MK, Gérardin P, Boëlle PY, et al. Impact of Chikungunya virus infection on health status and quality of life: a retrospective cohort study. *PLoS One* **2009**; 4:e7800.
50. Ramachandran V, Malaisamy M, Ponnaiah M, et al. Impact of Chikungunya on health related quality of life Chennai, South India. *PLoS One* **2012**; 7:e51519.