Occurrence of Chronic Stage Chikungunya in the General Population of Martinique during the First 2014 Epidemic: A Prospective Epidemiological Study

Brieg Couzigou,¹ Anne Criquet-Hayot,¹ Emilie Javelle,² Sandrine Tignac,¹ Edith Mota,¹ François Rigaud,¹ Alizé Alain,³ Odile Troisgros,⁴ Sandrine Pierre-Francois,⁵ Sylvie Abel,⁵ Rishika Banydeen,⁶ and André Cabié^{5,7*}

¹Department of General Medicine, University Hospital of Martinique, Fort de France, France; ²Department of Tropical and Infectious Diseases, Laveran Military Teaching Hospital, Marseille, France; ³Department of Critical Care and Emergency, University Hospital of Pointe-à-Pitre, Pointe-à-Pitre, France; ⁴Rehabilitation Unit, University Hospital of Martinique, Le Lamentin, France;

⁵Department of Tropical and Infectious Diseases, University Hospital of Martinique, Fort-de-France, France;

⁶Clinical Research Department, University Hospital of Martinique, Fort-de-France, France; ⁷University of the French West Indies, EA4537; INSERM CIC1424, Fort-de-France, France

Abstract. Chronic stage chikungunya (CHIK), defined by persisting symptoms more than 3 months after initial diagnosis of acute infection, is frequent. However, its burden and impact have rarely been described prospectively in a general population during an ongoing epidemic in the Caribbean. From January 2014 to January 2015, a severe CHIK outbreak occurred in Martinique. Our objective was to describe epidemiological characteristics and outcomes of chronic stage CHIK in its local population. Participants, clinically diagnosed with probable CHIK infection, were included prospectively by general practitioners during the epidemic's peak from April to October 2014. All identified cases benefited from a follow-up phone call 3 months or more after initial diagnosis during which they were interrogated about persisting clinical signs, past and ongoing treatment, and quality of life. Five hundred and nine subjects participated in the study. Mean age at initial diagnosis was 43.2 ± 23.6 years with a female–male ratio of 1.98. Two hundred participants (39.3%) had probable chronic stage CHIK: 98.5% still experienced pain at least 3 months after acute infection, with 84.3% of reported joint pains; 21.2% were woken up by the pain; 47.2% felt depressed/anxious; and 31.3% experienced memory/concentration disorders. Resumption of daily activity and work was complicated for 55.8% and 36.2% of cases. Persistent impact on morbidity, health outcomes, psychological, and economic aspects further underline the crucial role of community-based medicine and the necessity of an evidence-based multidisciplinary approach toward chronic stage CHIK identification, management, and follow-up in this particular world region.

INTRODUCTION

Chikungunya (CHIK) fever is a viral disease caused by the CHIK virus, an arbovirus from the *Togaviridae* family. It is transmitted to humans via infected female *Aedes* mosquito bites. CHIK infection was first described in 1952–1953 on the Makonde plateau in the southern province of Tanzania (formerly Tanganyika).¹ Since then, sporadic and major epidemics have been reported in more than 60 countries located in the African, Indian, Southeast Asian, and eastern Pacific regions. More recently, CHIK has emerged in the Americas, first reaching the Caribbean and then extending to Central, South, and North America. Overall, local transmission was documented in 44 countries and territories of the Americas.^{2,3} As such, CHIK is considered as an emerging or reemerging major public health and economic threat worldwide.

The onset of CHIK illness usually occurs between 4 and 8 days but can range from 2 to 12 days. Symptoms appear in 80% of patients with the commonest presenting features being acute fever (92% of cases), usually associated with polyarthralgia (87%), backache (67%), and headache (62%), and in some cases, with a cutaneous rash.⁴ Articular pains usually cause sufferers to adopt a stooped appearance, hence giving the name “chikungunya,” which means “to become contorted” or “that which bends up” in the Makonde language. These joint pains are often very debilitating and can last either for a few days or be prolonged to several weeks or years.^{3–5} French experts have defined three stages of the CHIK

disease; an acute stage (Day [D] 1 to D21), a post-acute stage (D21 to 3 months), and a chronic stage (beyond 3 months).⁶

Although studies from recent outbreaks in epidemic countries have described extensively the features of the acute stage, including atypical, severe, and lethal complications, they have also particularly highlighted the burden of chronic stage CHIK, which is a frequent complication of acute CHIK disease.^{7–11} Chronic stage CHIK is defined by the absence of return to the preexisting condition more than 3 months after CHIK onset. The chronic stage can last a few months to several years. Schematically, the disease progresses either to cure without sequelae spontaneously or after treatment, or else to a prolonged persistence of CHIK disease symptoms. Indeed, chronic rheumatic and musculoskeletal disorders, fatigue, depression, sleep perturbation, and quality-of-life impairment have often been described during the follow-up of patients in epidemic areas.^{3,5,6,12–14} Although the overall proportion of patients with symptoms decreases over time after CHIK disease onset (from 100% to 88% during the first 6 weeks to less than 50% after 3–5 years, with variable findings depending on the studies), the time required for a complete healing of all symptoms is still uncertain, as some infected individuals remain symptomatic for years after initial infection.^{5,15–17}

During the 2005–2006 epidemic in the French overseas island of Reunion, a third of the population (244,000 estimated cases) was affected, with 203 infection-associated deaths and an overall attack rate of 35%.^{18,19} At the time, most of the exploratory research on chronicity and related health outcomes in chronic stage CHIK patients was conducted either prospectively on hospitalized and circumscribed patient samples or retrospectively amidst the local population.^{12,13,17,19,20} These Reunionese studies report a highly variable relative frequency of chronic stage CHIK ranging from 43% to 75%,

* Address correspondence to André Cabié, Department of Tropical and Infectious Diseases, University Hospital of Martinique (Pierre-Zobda Quitman Hospital), CS 90632, Fort-de-France 97261, Martinique (FWI), France. E-mail: andre.cabie@chu-martinique.fr

which might be because of varying numbers of included study participants and differing study designs, participant selection processes, mode of CHIK diagnosis, and follow-up times.^{12–14,16,21–25} However, no prospective community-based study was carried out even though public health recommendation guidelines placed community-based general medicine at the forefront of the fight against CHIK disease.^{6,26} Moreover, most of the studies conducted on Reunion Island and in other epidemic world areas focused mainly on CHIK-induced rheumatism and rarely considered the whole panel of health outcomes associated with persisting CHIK infection.^{5,12–14}

The first known CHIK cases were observed in the French Caribbean overseas territories of Martinique, Guadeloupe, Saint Martin, and French Guyana in December 2013. Despite anticipatory and precautionary measures inspired by the Reunionese experience, local French Caribbean populations were seriously affected.²⁷ In Martinique, about 36% of the population was estimated to have been infected during the acute phase of the epidemic which lasted from January 2014 till January 2015 (approximately 145,000 estimated cases).²⁷ During the epidemic, as per the recommendations of public health authorities, half of symptomatic patients were solely managed by community-based general practitioners (GPs). The remaining proportion of patients did not seek medical advice.²⁷

Considering the notable CHIK attack rate observed during the Martinique epidemic and the high proportions of chronic stage CHIK cases observed during the epidemics on Reunion Island, in neighboring territories of the Indian Ocean and in other world areas, a similar scenario seemed very plausible in Martinique amidst its local population, as well as in other populations of the Caribbean and Americas, with major consequences in terms of chronic pain and handicap.

With the objective of providing a more comprehensive description of the burden of chronic stage CHIK, the present prospective study describes the epidemiological characteristics and health outcomes of chronic stage CHIK cases in the general population of Martinique during one of the first epidemics (January 2014–January 2015) to involve the Caribbean region and the Americas.

PARTICIPANTS AND METHODS

Area of investigation. Martinique is a French overseas island located in the south of the Caribbean basin (latitude 14°30' N, longitude 61° W). Its surface area is 1,128 km² and its climate is tropical, with an annual average temperature ranging from 22°C to 30°C. In 2008, Martinique was classified as a territory with a high human development index of 0.904. As such, it is currently considered one of the most developed islands of the Caribbean region. The island is also densely populated (356 persons/km²) with a total of 395,027 inhabitants in 2012. The latter are mostly of French African Caribbean origin, descendants of black Africans, French Caucasians, and immigrants from the Indian subcontinent. The population is served by 16 public health structures, including the University Hospital of Martinique, 14 private health institutions, 485 GPs, and two on-call physician systems.^{28,29}

No other arboviruses, apart from dengue, CHIK, and Zika viruses, actually circulate in the French West Indies islands, including Martinique. Mandatory reporting of dengue fever,

CHIK fever (since the CHIK epidemic on Reunion Island in late 2005–early 2006), and Zika infections (since May 2015) is in place in Martinique.³⁰

Study design. This is a prospective epidemiological study targeting CHIK cases seen solely by community-based GPs amidst the general population of a Caribbean population, namely, that of Martinique Island. It was conducted in two phases: 1) the first stage consisted in the recruitment of CHIK cases during the peak of the CHIK epidemic in Martinique from April to October 2014 and 2) the second stage took place from November 2014 to February 2015 and consisted in participant follow-up in the form of phone interviews conducted 3 months or more after diagnosis of acute CHIK infection.

Ethical considerations. The survey design and data collection process were approved by national independent ethics committees consisting of the French data protection authority (*Commission Nationale Informatique et Liberté*) and the National Council for Statistical Information (*Conseil National de l'Information Statistique*). Both ethics committees recommended, as per French law, that the sole collection of oral informed consent from study participants was sufficient. This recommendation is based on the fact that the present study has a purely observational design and, as such, does not modify conventional medical practice and procedures.

Study participants and case ascertainment. To recruit a representative participant sample for the first study phase, GPs were enrolled from seven private practices and four medical care homes located in different areas of the island, as well as via the unique emergency call center of Martinique.

Participating GPs included all participants diagnosed with clinical CHIK infection according to standardized case definitions recommended by the World Health Organization. Participants were thus categorized as probable CHIK cases when they met the following: 1) clinical criteria (acute onset of fever > 38.5°C, severe arthralgia/arthritis, and/or cutaneous rashes not explained by other medical conditions) and 2) epidemiological criteria (residing or having visited epidemic areas, having reported CHIK transmission within 15 days before symptom onset).⁴ A further study inclusion criteria was that the participant had to be seen by a GP in the first 48 hours following disease onset.

It is to be noted that at the time of the study, there was no other circulating arbovirus such as dengue or Zika viruses on the island.^{31,32}

Data collection. Oral informed consent for study participation was obtained from all identified individuals or from their parents/legal guardians if they were less than 18 years of age. Once participant consent was obtained during the phase of acute infection, it was documented both in the participant's medical file and on the study questionnaire administered by participating GPs. The latter questionnaire was a standardized structured one in French which collected the following information: date of examination, age, gender, area of residence and contact details, presence of risk factors of atypical or severe form of acute CHIK infection (advanced pregnancy (third trimester), extreme ages (children and elderly people aged 65 years and older), chronic illnesses, and immunodepression), and prescribed ongoing treatment. All filled questionnaires were recovered by three physicians between April and October 2014.

During the follow-up phase from November 2014 to February 2015, the presence of chronic stage CHIK was

evaluated via phone interviews scheduled at least 3 months after initial symptom onset. Data were recovered by a trained physician using a standardized structured questionnaire which was specifically developed for study purposes. Participants were firstly interrogated about whether they perceived having made a complete recovery from CHIK infection. The presence and intensity of persisting articular and/or muscular pain were noted on the basis of a Numerical Rating Scale (NRS) ranging from 0 to 10 denoting increasing pain severity with increasing NRS value.³³ Pain scores were then categorized into three classes: light (1–3), moderate (4–6), and severe (7–10).

Information on the occurrence and localization of articular edema, presence and duration of morning stiffness, perturbed sleep cycle due to pain, anatomical localization of where pain is the most debilitating, frequency of medical visits due to CHIK pain, memory or concentration trouble since CHIK, feelings of depression or anxiety, past medication intake for pain in the acute phase, ongoing pain treatment, and type of medication taken (conventional drugs, phytotherapy, homeotherapy, and physiotherapy) were collected. The French version of the standardized EQ-5D questionnaire, measuring health outcome in terms of impact on quality of life (QoL), was also filled out (Supplemental Material).^{34,35} Inquiries were also made on any perceived hardships and limitations in resuming daily activities, social activities, school, work, and sports.

Outcomes. The primary outcome measure was self-perceived recovery from symptomatic manifestations of CHIK. Based on this outcome, the participant sample was divided into two groups: 1) the “symptomatic group” made up of participants with probable chronic stage CHIK infection and 2) the “remission” group consisting of totally asymptomatic participants.

Statistical analysis. A complete descriptive analysis was performed using Stata software version 12 (StataCorp LP; College Station, TX).

Normal distribution of the data was first verified by the Shapiro–Wilk test. Mean and standard deviation were reported for continuous normally distributed data, whereas median, interquartile, and min–max ranges were described for nonnormally distributed data. Categorical variables were presented as frequencies or percentages.

The following tests were used for group comparisons when appropriate: Student’s *t*-test or Wilcoxon–Mann–Whitney tests for continuous variables and χ^2 or Fisher’s exact tests for categorical variables. All inferential analyses were performed by means of a 2-sided test, with a level of significance of 5%.

RESULTS

A total of 1,214 participants with clinically diagnosed CHIK infection were recruited by participating GPs from April to October 2014. At the study baseline, phone numbers were available for 987 participants only, among whom 71 provided incorrect contact details, four participants were duplicate entries, seven participants refused to participate, and three participants died. During the follow-up phase (November 2014 to February 2015), 393 cases were not reachable by phone. Between the initial recruitment and the follow-up phases, 705 participants (58.1%) were lost to follow-up. Overall, after follow-up, 509 participants were considered for statistical analysis corresponding to a total participation rate (in both study phases) of 41.9% (509/1,214) (Figure 1).

FIGURE 1. Participant selection process during prospective study on chronic stage chikungunya infection in the general population of Martinique from April 2014 to February 2015.

Statistical comparison according to characteristics such as age, gender, and presence of risk factors yielded no significant difference between lost to follow-up participants and final study recruits (Supplemental Table 1, with *P* values as follows: age, *P* = 0.8; female gender, *P* = 0.2; and presence of risk factors, *P* = 0.2).

Baseline participant characteristics. The 509 study participants were recruited by GPs from three distinct sources as follows: 29.5% from private practices, 33.4% from medical care homes, and 37.1% from the emergency call center database. Three hundred and thirty-eight of the study participants (66.4%) were women. The mean age at acute CHIK infection onset was 43.2 ± 23.6 years (median 44 years; range 1–95 years) and did not differ significantly between men and women (40.3 years versus 44.7 years, respectively; *P* = 0.05). Participants originated from all parts of the island with 36.7% of cases living in the North of the island, 44.8% in the Center, and 15.1% in the South. Risk factors of atypical or severe form of acute CHIK infection, such as advanced pregnancy (third trimester), extreme ages (children and elderly people aged 65 years and older), chronic illnesses, and immunodepression, were present in 23% of participants.

Characteristics at follow-up. Symptoms. The median time between the onset of acute stage and participant follow-up was of 27.6 weeks, interquartile range (IQR) [25.4–30.3 weeks], and range [13.1–37.7 weeks]. Overall, 200 participants (39.3%) declared still feeling symptoms, associated with probable chronic stage CHIK infection, 3 months or more after initial acute phase (Table 1). Participants in the

TABLE 1
Characteristics of participants with probable chronic CHIK infection diagnosed at least 3 months after initial acute infection

Characteristics	Chronic stage CHIK status*		Total (N = 509)
	Remission (N = 309)	Symptomatic (N = 200)	
Age at clinical diagnosis of acute CHIK (years), median (Q1–Q3)	31.0 (16–51)	55.0 (42–72)	44.0 (24–61)
Women, n (%)	186 (60.2)	152 (76.0)	338 (66.4)
Presence of risk factors†	59 (19.1)	58 (29.0)	117 (23.0)
Persisting pain, n (%)	6 (1.9)	197 (98.5)	203 (39.9)
Articular pain, n (%)	5 (83.3)	166 (84.3)	171 (84.2)
Muscular pain, n (%)	1 (16.7)	6 (3.0)	7 (3.4)
Articular + muscular pain, n (%)	–	25 (12.7)	25 (12.3)
Pain severity level‡ (%)			
Light	4 (1.3)	118 (59.0)	122 (24.0)
Moderate	1 (0.3)	63 (31.5)	64 (12.6)
Severe	1 (0.3)	15 (7.5)	16 (3.1)
Edema, n (%)	3 (1.0)	70 (35.0)	73 (14.4)
Persisting pain and edema, n (%)	2 (0.6)	69 (34.5)	71 (14.0)
Morning stiffness, n (%)	5 (1.6)	128 (64.0)	133 (26.1)
Perturbed sleep due to pain, n (%)	–	42 (21.2)	42 (8.3)
Memory or concentration trouble, n (%)	2 (0.7)	62 (31.3)	64 (12.6)
Anxiety or depression, n (%)	2 (0.7)	94 (47.2)	96 (18.9)

* April 2014 to February 2015, Martinique (N = 509). CHIK = chikungunya; Q1 = first quartile; Q3 = third quartile.

† Presence of different signs was evaluated 3 months or more after clinical diagnosis of probable CHIK infection by phone interviews. Persistence of signs allowed the categorization of participants into two groups: 1) remission group and 2) symptomatic group. Differences between the two groups were all statistically significant ($P < 0.05$).

‡ Risk factors of atypical or severe form of acute CHIK infection (advanced pregnancy (third trimester), extreme ages (elderly and young people), chronic illnesses (diabetes, asthma, cardiac problems, chronic rheumatism, sickle cell anemia, thalassemia, renal failure, and hepatic problems), and immunodepression).

§ Pain was noted on the basis of a Numerical Rating Scale (NRS) ranging from 0 to 10 denoting increasing pain severity with increasing NRS value [28]. Pain severity was then categorized into three classes: light (1–3), moderate (4–6), and severe (7–10).

remission group were significantly younger in comparison with participants in the symptomatic group (median ages at diagnosis of 31 and 55 years, respectively; $P < 0.0001$). A significantly greater proportion of women was also observed in the symptomatic group (76.0% versus 60.2%, $P < 0.0001$). Risk factors of atypical or severe form of acute CHIK were also more frequent in the symptomatic group (29% of cases versus 19.1% in the remission group; $P = 0.0129$).

In the symptomatic group, 197 participants (98.5%) still experienced persistent pain, among whom 84.3% declared feeling articular pain, 3.0% reported muscular pain, and 12.7% reported both articular and muscular pain (Table 1). Overall, according to the NRS, pain severity was estimated as light in 59% of cases, moderate in 31.5%, and severe in 7.5%. Edema was reported in 70 participants (35%) among whom 98.6% reported articular edema, 44.9% reported hand edema, 84.1% declared feet edema, and 31.9% reported with articular, hand, and feet edema. Sixty-nine participants (34.5%) experienced both persisting pain and edema.

Morning stiffness was also felt by 64% of participants of the symptomatic group, whereas 21.2% of cases declared to have a perturbed sleep cycle because of experienced pain. Overall, the anatomical sites, described as being the most problematic by symptomatic participants in terms of pain, edema, and stiffness, were the ankles (24.1%) and hands (23.6%) (Figure 2). Moreover, 31.3% of the 200 probable chronic stage CHIK cases reported memory or concentration trouble, whereas 47.2% declared suffering from anxiety or depression.

Treatment patterns. The treatment patterns followed by the study participants according to their probable chronic stage CHIK infection status are presented in Table 2. All participants were administered treatment in the acute stage of CHIK infection. During the follow-up phase, treatment patterns differed significantly between the remission and symptomatic groups.

During the follow-up phase, twice the median number of medical consultations due to pain was registered in the symptomatic group (median of two consultations; range, 0–8). Seventy-six of the 200 probable chronic stage CHIK cases (38%) declared having taken painkillers such as acetaminophen (97.4%), codeine, or tramadol (3.9%); nonsteroidal anti-inflammatory drugs (15.8%); corticoids via injections or per os (6.5%); methotrexate (2.6%); and adalimumab (1.3%). Symptomatic participants also reported the use of homeopathy, phytotherapy, and physiotherapy in 19.6%, 61.3%, and 18.6% of cases, respectively.

Frequency (%)

FIGURE 2. Distribution of most problematic anatomical sites in terms of pain, edema, and stiffness among participants with probable chikungunya infection in the general population of Martinique from April 2014 to February 2015 (N = 200). This figure appears in color at www.ajtmh.org.

Impact on QoL. The impact of probable chronic stage CHIK on daily life is reported in Table 3. More than half of the 200 symptomatic participants (55.8%) found it hard or impossible to go back to normal daily activities. Work/school or sports resumption proved to be difficult in 36.2% and 38.7% of cases, respectively. Social activity was also impeded by CHIK in 53.8% of chronic stage participants. Based on the EQ-5D QoL scale, mobility, self-care, and daily activities were described as being problematic for 30.6%, 19.5%, and 33.1% of participants of the symptomatic group, respectively. The standardized QoL scale also reported moderate or extreme pain/discomfort and anxiety/depression in 91.4% and 50.2% of chronic stage participants.

Overall, the impact on QoL was significantly worse in the symptomatic group (median QoL score: 71; range: 0–100) as compared with the remission group (median QoL score: 90; range: 40–100) ($P < 0.0001$).

DISCUSSION

To the best of our knowledge, the present study is one of the few exploratory prospective epidemiological investigations on chronic stage CHIK in the Caribbean region, targeting a CHIK-naïve insular population recruited in a primary care setting. Only rare community-based prospective studies were found to be reported in the scientific literature concerning insular Caribbean populations.^{36–41} In other world regions, past exploratory research on chronicity was conducted either prospectively on hospitalized and circumscribed patient samples or retrospectively amidst the general population.^{5,12–14}

In light of the emerging public health burden of CHIK disease for the Caribbean region and the Americas, the present study aims mainly to provide a more comprehensive description of the epidemiological characteristics and health outcomes of chronic stage CHIK cases in the general population of Martinique. Study results first demonstrate that at more than 3 months after acute infection (median time of 27.6 weeks from disease onset), 39.3% of participants considered themselves as not having recovered from CHIK infection due to persisting disease symptoms, namely, pain, edema, and stiffness. The frequency of probable chronic CHIK stage in the Martinican population (39.3%) was found to be

lower than proportions reported during epidemics on Reunion Island (43–75%). This disparity can be explained by the fact that the Martinique study targeted the general population, consisting most probably of cases of lesser severity as compared with the ones identified on Reunion Island, where most studies concerned hospitalized or circumscribed populations, comprising mostly of more severe acute cases, among whom higher proportions of chronic stage CHIK patients were observed.^{12–14,16,21–25} Chronic stage CHIK rate in Martinique was, however, slightly higher than rates documented in India (10–24%) or Singapore (35.9%).^{42–44} These discrepancies in chronic stage CHIK rates between Martinique and other world regions may further result from particular features of the CHIKV virus strain involved during an epidemic, differences in genetic backgrounds of populations, differences in health practices as well as variable numbers of included participants between studies, and different study designs and varying participant follow-up times, spanning periods of a few months to 6 years in some cases.^{5,12–14,16,45,46}

Second, the distribution of cases, according to age, gender, and presence of risk factors of atypical or severe form of acute CHIK infection (advanced pregnancy (third trimester), extreme ages (children and elderly people aged 65 years and older), chronic illnesses, and immunodepression), was found to be significantly different between the group of chronic stage CHIK symptomatic participants versus asymptomatic ones in Martinique. Indeed, participants in the symptomatic group tended to be older (median age 55 years), were more frequently women (76%), and presented more often the afore-mentioned risk factors (29%) (Table 1). Similar results were reported on Reunion Island and during other investigations.^{12,14,20,36–38,43,47–50} These trends could be explained by the fact that a higher humoral immune response during acute CHIK infection phase could be associated with evolution toward chronic stage CHIK and persistent arthralgia.⁵¹ Indeed, women, as compared with men, are known to have a stronger humoral immune system linked to female hormones.⁵² Increasing age also tends to generate a higher humoral immune response.⁵³ However, although a female predisposition toward chronic joint disease and pain presentation after CHIK infection cannot be ruled out, the latter could also be related to differences in access or adhesion to primary care between men and women.¹⁴ Other independent predictors of non-recovery from CHIK infection, described by medical teams, are severe initial joint pain, severe rheumatic involvement (at least six affected joints) at presentation, and presence of arthralgia 4 months after disease onset.^{12,16,21}

Third, regardless of age, gender, and length of disease duration, participants with chronic manifestations of CHIK infection have a deteriorated QoL as assessed by the EQ-5D generic tool (Supplemental Material).^{34,35} The present study brings out the negative impact of chronic stage CHIK on daily life activities, work, school, sports, and other social activities. The same effects on health outcome were also described in studies conducted on Reunion Island and in Italy and India.^{24,43,46,54} These different observations underline the notion that, unlike other viral infections, CHIK infections tend to have a significant mid- and long-term impact on the QoL of individuals, with serious sanitary, economic, and cultural repercussions. Indeed, chronic stage CHIK leads to bigger public health expenses resulting from a rise in the number of medical and paramedical visits due to disease management, increased

TABLE 2

Chikungunya treatment patterns of participants according to probable chronic CHIK infection status. November 2014 to February 2015, Martinique (N = 509)

Characteristics	Chronic stage CHIK status*		
	Remission (N = 309)	Symptomatic (N = 200)	Total (N = 509)
No. of medical visits due to CHIK-related pain, median (Q1–Q3)	1 (1–1)	2 (1–3)	1 (1–2)
Drug intake during chronic stage CHIK, n (%)	5 (1.6)	76 (38.0)	81 (15.9)
Use of homeopathy, n (%)	29 (9.4)	39 (19.6)	68 (13.4)
Use of phytotherapy, n (%)†	83 (26.9)	122 (61.3)	205 (40.4)
Physiotherapy practice, n (%)	1 (0.3)	37 (18.6)	38 (7.5)

CHIK = chikungunya; Q1 = first quartile; Q3 = third quartile.

* Presence of different signs was evaluated 3 months or more after clinical diagnosis of probable CHIK infection by phone interviews. Persistence of signs allowed the categorization of participants into two groups: 1) remission group and 2) symptomatic group. Differences between the two groups were all statistically significant ($P < 0.05$).

† Use of local medicinal herbs.

TABLE 3
Impact on daily life of participants according to probable chronic stage CHIK infection status

Characteristics	Chronic stage CHIK status*		Total (N = 509)
	Remission (N = 309)	Symptomatic (N = 200)	
Resumption of daily activities n (%)			
Impossible	–	3 (1.5)	3 (0.6)
Hard	14 (4.5)	108 (54.3)	122 (24.0)
Without difficulty	294 (95.1)	88 (44.2)	382 (75.2)
Not applicable	1 (0.3)	–	1 (0.2)
Resumption of school/work n (%)			
Impossible	–	2 (1.0)	2 (0.4)
Hard	23 (7.4)	70 (35.2)	93 (18.3)
Without difficulty	223 (72.2)	36 (18.1)	259 (51.0)
Not applicable	63 (20.4)	91 (45.7)	154 (30.3)
Resumption of sports activities, n (%)			
Impossible	–	7 (3.5)	7 (1.4)
Hard	21 (6.8)	70 (35.2)	92 (18.0)
Without difficulty	228 (74.0)	25 (12.6)	253 (49.9)
Not applicable	59 (19.2)	97 (48.7)	156 (30.8)
Restricted social activity due to CHIK (%)	5 (1.6)	107 (53.8)	112 (22.1)
QoL mobility, n (%)†			
No problem in walking	300 (97.1)	138 (69.4)	439 (86.2)
Some problem in walking	6 (1.9)	54 (27.1)	60 (11.8)
Confined to bed	3 (1.0)	7 (3.5)	10 (2.0)
QoL self-care, n (%)†			
No problem	304 (98.4)	161 (80.4)	465 (91.3)
Some problem	2 (0.6)	26 (13.1)	28 (5.5)
Inability	3 (1.0)	13 (6.5)	16 (3.2)
QoL daily activities, n (%)†			
No problem	302 (98.1)	133 (66.8)	435 (85.8)
Some problem	3 (1.0)	56 (28.1)	59 (11.6)
Inability	3 (1.0)	10 (5.0)	13 (2.6)
QoL pain/discomfort, n (%)†			
None	299 (96.8)	17 (8.5)	316 (62.2)
Moderate	10 (3.2)	176 (88.4)	186 (36.6)
Extreme	–	6 (3.0)	6 (1.2)
QoL anxiety/depression, n (%)†			
None	300 (97.1)	99 (49.8)	399 (78.5)
Moderate	9 (2.9)	96 (48.2)	105 (20.7)
Extreme	–	4 (2.0)	4 (0.8)
QoL score, median (Q1–Q3)†	90 (90–100)	71 (60–80)	83 (75–95)

November 2014 to February 2015, Martinique (N = 509). CHIK = chikungunya; QoL = quality of life; Q1 = first quartile; Q3 = third quartile.

* Presence of different signs was evaluated 3 months or more after clinical diagnosis of probable CHIK infection by phone interviews. Persistence of signs allowed the categorization of participants into two groups: 1) remission group and 2) symptomatic group. Differences between the two groups were all statistically significant ($P < 0.05$).

† Items from the French version of the standardized EQ-5D questionnaire, measuring health outcome in terms of impact on QoL. The QoL score ranges from 0 to 100, with a score of 0 denoting the worst state in terms of health outcome and a score of 100 denoting the best state [34–35].

medical expenses due to therapeutics, a surge in sick leaves, and a loss of efficiency at work due to pain, asthenia, and other symptoms.⁵⁵ When estimated in terms of disability adjusted life years (DALYs), overall burden of CHIK disease (acute and chronic stages) has been estimated at 0.01–265.62 DALYs per million in several Indian states and 40.44–45.14 DALYs lost/100,000 in Colombia.^{56,57} Labeaud et al.⁵⁵ further report 2.12–1.41 DALYs per million for CHIK globally in 2005, with 0.22–9.79 years lost due to disability per chronic case. CHIK chronicity and related health outcomes also significantly weigh down on psychological aspects. In the present study, 47% of chronic stage CHIK participants reported anxiety or depression, whereas 31% reported memory or concentration disorders. A further 21% of cases experienced a perturbed sleep cycle due to pain. It is, therefore, important for community-based GPs, at the forefront of CHIK management and treatment, to recognize the symptoms of chronic CHIK stage and to offer adequate psychological and physical care as precociously as possible to ensure a better acceptance of the illness by the patient and his/her entourage.⁶

Concerning therapeutic aspects, phytotherapy use was reported as being more frequent among chronic stage CHIK

participants as compared with homeopathy use: 61% against 19.5%, respectively. This contrast perfectly reflects traditions and customs amidst Martinique's local population where local medicinal herbs are often preferred to or used concomitantly with conventional drugs, especially among older age groups. On the other hand, physiotherapy was underused by chronic stage symptomatic CHIK participants. Only 18.6% of the latter resorted to physiotherapy for pain management mostly because of the fact that GPs were often not aware of physiotherapy techniques for pain relief and, as such, failed to prescribe those techniques. Moreover, many participants were not willing to resort to physiotherapy because they were scared of being hurt. The lack of physiotherapists in Martinique further limits the scope of expanding the use of physiotherapy for efficient timely management of chronic stage CHIK, which is often further complicated by polyarthralgia.^{5,6,11}

It is to be noted that the present research work has certain strengths and limitations that are to be considered when interpreting the results. The Martinique study forms part of the few studies in the Caribbean region to have conducted an exploratory assessment of participants clinically diagnosed with probable CHIK infection in a primary care setting. To our

best knowledge, the Martinique study is the only one to examine longitudinally such a large cohort of participants ($N = 509$), with a broad geographical assessment of the study population all over the island (recruiting GPs were located in different areas of the territory).^{36–41} The approach to gathering late illness symptoms and QoL attributes (diverse range of physical and psychological health outcomes) has also been rarely conducted by other research teams. However, less than half of the eligible subjects identified by GPs finally participated in the follow-up phase, with 705 participants (58.1%) lost to follow-up between the initial recruitment and the follow-up phases. Nonetheless, statistical comparison according to characteristics such as age, gender, and presence of risk factors yielded no significant difference between lost to follow-up participants and study recruits (Supplemental Table 1). This allows us to hypothesize that attrition bias, in terms of illness intensity and duration, is minimized and that the present study results are fairly reliable. With a participant sample representative of the general population and acceptable result reliability, the study findings provide a fair estimate of the probable burden of chronic stage CHIK infection among Martinique's inhabitants from April 2014 to February 2015.

Moreover, because of data collection via a phone-administered questionnaire during follow-up phase, participants did not benefit from a second medical examination by a GP. As such, recovery from or persistence of CHIK symptoms were solely based on the individual's self-perception and self-assessment. However, the same methodology has been used by different teams in the Indian Ocean area for the evaluation of CHIK burden in population-based studies.^{37,43} Moreover, during the Martinique study, phone interviews were structured, standardized, and conducted by the same trained physician for all 509 study participants. A validated generic quality of health assessment tool (EQ-5D) was also used (Supplemental Material).^{34,35} It can also be hypothesized that recall bias leading to potential underestimation of either current or past symptoms is minimal in this present case as median time between onset of acute stage and participant follow-up was of 27.6 weeks, IQR [25.4–30.3 weeks], and range [13.1–37.7 weeks].

It is to be further noted that the present study design did not allow laboratory confirmation of CHIK infection either at initial participant enrollment or retrospectively. Confirmation by blood serology or polymerase chain reaction tests is only recommended for subjects considered to be at risk for atypical or severe forms of acute CHIK infection such as advanced pregnancy (third trimester), extreme ages (children and elderly people aged 65 years and older), chronic illnesses, and immunodepression.^{4,6} But even then, tests are not systematic. In the study sample, the proportion of at-risk participants, having benefited from laboratory confirmation of their CHIKV status, could not be evaluated. Nonetheless, risk of infection by other circulating arboviruses, notably dengue or Zika viruses, was minimal at the time of the CHIK epidemic in Martinique (end 2013–year 2014).²⁷ The most recent dengue epidemic in Martinique had already ended by March 2014 and the island's first Zika cases were only reported from December 2015.^{31,32}

The current study design did not integrate a control group either, which would have allowed to more accurately assess the attributable burden of persistent symptoms associated with CHIK infection. However, significant differences in terms

of pain, stiffness, and edema frequencies between remission and symptomatic groups, the use of standardized case definitions for clinical diagnosis of CHIK infection, differential diagnosis conducted by GPs during initial enrollment, and the absence of any other co-circulating arboviruses strongly underline the fact that observed symptoms are most probably due to CHIK infection and that potential misclassification bias is thus limited.

CONCLUSIONS

Chronic stage CHIK is a frequent complication of acute CHIK disease. This study allows a better and more precise insight into the epidemiological characteristics and the diverse physical and psychological outcomes linked to chronic stage CHIK disease in a general insular population of the Caribbean region. The evaluation of individuals, shortly after initial acute infection, may be useful in the early recognition of subjects with the highest risk of presenting prolonged CHIK illness and in the development of future prevention and care strategies for this emerging virus infection in the region of the Americas. In light of the persistent impact on morbidity, health outcomes, and psychological, economic, and sociocultural aspects and in the absence of specific treatment or vaccine, the necessity of an evidence-based multidisciplinary approach toward chronic stage CHIK identification, management, and follow-up in the general population is even further underlined by the present study as is the crucial role of community-based medicine. Further research is required to accurately assess the long-term clinical and economic impact as well as the QoL impairment directly attributable to CHIK in affected populations.

Received July 8, 2017. Accepted for publication March 15, 2018.

Published online May 29, 2018.

Note: Supplemental information and table appear at www.ajtmh.org.

Authors' addresses: Brieg Couzigou, Anne Criquet-Hayot, Sandrine Tignac, Edith Mota, and François Rigaud, Department of General Medicine, University Hospital of Martinique, Fort de France, France, E-mails: brieg.couzigou10@gmail.com, anne.criquet-hayot@urml-m.org, sandrine.tignac@urml-m.org, edithmota@live.fr, and fr.rigaud@gmail.com. Emilie Javelle, Department of Tropical and Infectious Diseases, Laveran Military Teaching Hospital, Marseille, France, E-mail: emilie.javelle@gmail.com. Alizé Alain, Department of Critical Care and Emergency, University Hospital of Pointe-à-Pitre, Pointe-à-Pitre, France, E-mail: alain.alizee@outlook.com. Odile Troisgros, Rehabilitation Unit, University Hospital of Martinique, Le Lamentin, France, E-mail: odile.troisgros@gmail.com. Sandrine Pierre-Francois, Sylvie Abel, and André Cabié, Department of Tropical and Infectious Diseases, University Hospital of Martinique, Fort-de-France, France, E-mails: sandrine.pierre-francois@chu-martinique.fr, sylvie.abel@chu-martinique.fr, and andre.cabie@chu-martinique.fr. Rishika Banydeen, Department of Clinical Research, University Hospital of Martinique, Fort-de-France, France, E-mail: rishika.banydeen@chu-martinique.fr.

REFERENCES

1. Robinson MC, 1955. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952–53. I. Clinical features. *Trans R Soc Trop Med Hyg* 49: 28–32.
2. Ramon-Pardo P, Cibrelus L, Yactayo S; Chikungunya Expert Group, 2015. Chikungunya: case definitions for acute, atypical and chronic cases. Conclusions of an expert consultation, Managua, Nicaragua, 20–21 May 2015. *Wkly Epidemiol Rec* 90: 410–414.

3. Burt FJ, Rolph MS, Rulli NE, Mahalingam S, Heise MT, 2012. Chikungunya: a re-emerging virus. *Lancet* 379: 662–671.
4. World Health Organization (Regional Office for South-East Asia), 2008. *Guidelines on Clinical Management of Chikungunya Fever*. WHO Publications SEA-CD-180: 1–17. Available at: http://www.wpro.who.int/mvp/topics/ntd/Clinical_Mgmt_chikungunya_WHO_SEARO.pdf. Accessed March 30, 2016.
5. Couderc T, Lecuit M, 2015. Chikungunya virus pathogenesis: from bedside to bench. *Antiviral Res* 121: 120–131.
6. Simon F et al., 2015. French guidelines for the management of chikungunya (acute and persistent presentations). November 2014. *Med Mal Infect* 45: 243–263.
7. Jossieran L, Paquet C, Zehgnoun A, Caillere N, Le Tertre A, Solet JL, Ledrans M, 2006. Chikungunya disease outbreak, Reunion Island. *Emerg Infect Dis* 12: 1994–1995.
8. Simon F et al., 2007. Chikungunya infection: an emerging rheumatism among travelers returned from Indian Ocean islands. Report of 47 cases. *Medicine (Baltimore)* 86: 123–137.
9. Queyriaux B, Simon F, Grandadam M, Michel R, Tolou H, Boutin J-P, 2008. Clinical burden of chikungunya virus infection. *Lancet Infect Dis* 8: 2–3.
10. Borgherini G, Poubeau P, Staikowsky F, Lory M, Le Moullec N, Becquart JP, Wengling C, Michault A, Paganin F, 2007. Outbreak of chikungunya on Reunion Island: early clinical and laboratory features in 157 adult patients. *Clin Infect Dis* 44: 1401–1407.
11. Simon F, Javelle E, Oliver M, Leparac-Goffart I, Marimoutou C, 2011. Chikungunya virus infection. *Curr Infect Dis Rep* 13: 218–228.
12. Sissoko D, Malvy D, Ezzedine K, Renault P, Moschetti F, Ledrans M, Pierre V, 2009. Post-epidemic chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. *PLoS Negl Trop Dis* 3: e389.
13. Soumahoro M-K, Gérardin P, Boelle P-Y, Perrau J, Fianu A, Pouchot J, Malvy D, Flahault A, Favier F, Hanslik T, 2009. Impact of chikungunya virus infection on health status and quality of life: a retrospective cohort study. *PLoS One* 4: e7800.
14. de Andrade DC, Jean S, Clavelou P, Dalle R, Bouhassira D, 2010. Chronic pain associated with the chikungunya fever: long lasting burden of an acute illness. *BMC Infect Dis* 10: 31.
15. Ganu MA, Ganu AS, 2011. Post-chikungunya chronic arthritis—our experience with DMARDs over two year follow up. *J Assoc Physicians India* 59: 83–86.
16. Schilte C, Staikowsky F, Staikovsky F, Couderc T, Madec Y, Carpentier F, Kassab S, Albert ML, Lecuit M, Michault A, 2013. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. *PLoS Negl Trop Dis* 7: e2137.
17. Javelle E, Ribera A, Degasne I, Gauzere BA, Marimoutou C, Simon F, 2015. Specific management of post-chikungunya rheumatic disorders: a retrospective study of 159 cases in Reunion Island from 2006–2012. *PLoS Negl Trop Dis* 9: e0003603.
18. Renault P et al., 2007. A major epidemic of chikungunya virus infection on Reunion Island, France, 2005–2006. *Am J Trop Med Hyg* 77: 727–731.
19. Bouquillard E, Combe B, 2009. A report of 21 cases of rheumatoid arthritis following chikungunya fever. A mean follow-up of two years. *Joint Bone Spine* 76: 654–657.
20. Hoarau JJ et al., 2010. Persistent chronic inflammation and infection by chikungunya arthritogenic alphavirus in spite of a robust host immune response. *J Immunol* 184: 5914–5927.
21. Gérardin P et al., 2013. Predictors of chikungunya rheumatism: a prognostic survey ancillary to the TELECHIK cohort study. *Arthritis Res Ther* 15: R9.
22. Borgherini G, Poubeau P, Staikowsky F, Lory M, Le Moullec N, Becquart JP, Wengling C, Michault A, Paganin F, 2007. Outbreak of chikungunya on Reunion Island: early clinical and laboratory features in 157 adult patients. *Clin Infect Dis* 44: 1401–1407.
23. Staikowsky F, Le Roux K, Schuffenecker I, Laurent P, Grivard P, Develay A, Michault A, 2008. Retrospective survey of chikungunya disease in Reunion Island hospital staff. *Epidemiol Infect* 136: 196–206.
24. Marimoutou C, Vivier E, Oliver M, Boutin JP, Simon F, 2012. Morbidity and impaired quality of life 30 months after chikungunya infection: comparative cohort of infected and uninfected French military policemen in Reunion Island. *Medicine (Baltimore)* 91: 212–219.
25. Gérardin P, Fianu A, Malvy D, Mussard C, Boussaïd K, Rollet O, Michault A, Gaüzere B-A, Bréart G, Favier F, 2011. Perceived morbidity and community burden after a chikungunya outbreak: the TELECHIK survey, a population-based cohort study. *BMC Med* 9: 5.
26. Fenétrier E, Sissoko D, Vernazza-Licht N, Bley D, Gaüzère BA, Malvy D, 2013. Feedback from primary care practitioners two years after the chikungunya epidemic on Reunion Island, 2005–2006. *Bull Soc Pathol Exot* 106: 193–200.
27. Antilles-Guyane CIRE, 2015. Le chikungunya aux Antilles Point épidémiologique du 12 janvier au 1er mars 2015 (S2015-03 à S2015-09). *Le Point Épidémiologique* 2: 1–3.
28. Pan American Health Organization, 2012. French Guiana, Guadeloupe and Martinique. *Health in the Americas 2012 Edition: Country Volume*. Washington DC: PAHO, 322–341.
29. Agence Régionale de Santé Martinique, 2015. *Statiss Antilles-Guyane 2014*. Available at: http://www.ars.martinique.sante.fr/fileadmin/MARTINIQUE/Actualites/Autres_actu/2016/STATISS/ars-statiss-ag_2014_2_.pdf. Accessed March 30, 2016.
30. French National Public Health Agency, 2015. *Maladies Infectieuses: Maladies à Transmission Vectorielle*. Available at: <http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-transmission-vectorielle/Zika>. Accessed March 30, 2016.
31. Antilles-Guyane CIRE, 2014. Surveillance de la dengue Bulletin du 24 mars au 20 avril 2014 (S2014-13 à S2014-16). *Le Point Épidémiologique* 4: 1–4.
32. Antilles-Guyane CIRE, 2016. *Emergence du Virus Zika aux Antilles-Guyane: Situation Épidémiologique*. Le Point Épidémiologique 12: 1–8. Available at: http://www.ars.martinique.sante.fr/fileadmin/MARTINIQUE/Actualites/Autres_actu/2016/ZIKA/PE/PE_Zika_2016-12.pdf. Accessed March 30, 2016.
33. Jones KR, Vojir CP, Hutt E, Fink R, 2007. Determining mild, moderate, and severe pain equivalency across pain-intensity tools in nursing home residents. *J Rehabil Res Dev* 44: 305–314.
34. The EuroQol Group, 1990. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 16: 199–208.
35. Brooks R, 1996. EuroQol: the current state of play. *Health Policy* 37: 53–72.
36. Heath CJ, Lowther J, Noël TP, Mark-George I, Boothroyd DB, Mitchell G, MacPherson C, Desiree LaBeaud A, 2018. The identification of risk factors for chronic chikungunya arthralgia in Grenada, West Indies: a cross-sectional cohort study. *Open Forum Infect Dis* 5: ofx234.
37. Elsinga J, Gerstenbluth I, van der Ploeg S, Halabi Y, Lourens NT, Burgerhof JG, van der Veen HT, Bailey A, Grobusch MP, Tami A, 2017. Long-term chikungunya sequelae in Curaçao: burden, determinants, and a novel classification tool. *J Infect Dis* 216: 573–581.
38. Duncan J, Gordon-Johnson KA, Tulloch-Reid MK, Cunningham-Myrie C, Ernst K, McMorris N, Grant A, Graham M, Chin D, Webster-Kerr K, 2017. Chikungunya: important lessons from the Jamaican experience. *Rev Panam Salud Publica* 41: e60.
39. Feldstein LR, Rowhani-Rahbar A, Staples JE, Weaver MR, Halloran ME, Ellis EM, 2017. Persistent arthralgia associated with chikungunya virus outbreak, US Virgin Islands, December 2014–February 2016. *Emerg Infect Dis* 23: 673–676.
40. Anfasa F, Provacia L, GeurtsvanKessel C, Wever R, Gerstenbluth I, Osterhaus AD, Martina BE, 2017. Hyperferritinemia is a potential marker of chronic chikungunya: a retrospective study on the Island of Curaçao during the 2014–2015 outbreak. *J Clin Virol* 86: 31–38.
41. Kumar A, Best C, Benskin G, 2017. Epidemiology, clinical and laboratory features and course of chikungunya among a cohort of children during the first Caribbean epidemic. *J Trop Pediatr* 63: 43–49.
42. Wina MK, Chowa A, Dimatatacc F, Goc CJ, Leoc YS, 2010. Chikungunya fever in Singapore: acute clinical and laboratory

- features, and factors associated with persistent arthralgia. *J Clin Virol* 49: 111–114.
43. Ramachandran V, Malaisamy M, Ponnaiah M, Kaliaperuam I, Vadivoo S, Gupte MD, 2012. Impact of chikungunya on health related quality of life Chennai, south India. *PLoS One* 7: e51519.
 44. Mathew AJ, Goyal V, George E, Thekkemuriyil DV, Jayakumar B, Chopra A; Trivandrum COPCORD Study Group, 2011. Rheumatic-musculoskeletal pain and disorders in a naive group of individuals 15 months following a chikungunya viral epidemic in south India: a population based observational study. *Int J Clin Pract* 65: 1306–1312.
 45. Marimoutou C, Ferraro J, Javelle E, Deparis X, Simon F, 2015. Chikungunya infection: self-reported rheumatic morbidity and impaired quality of life persist 6 years later. *Clin Microbiol Infect* 21: 688–693.
 46. Thiberville S-D, Boisson V, Gaudart J, Simon F, Flahault A, de Lamballerie X, 2013. Chikungunya fever: a clinical and virological investigation of outpatients on Reunion Island, south-west Indian Ocean. *PLoS Negl Trop Dis* 7: e2004.
 47. Yaseen HM, Simon F, Deparis X, Marimoutou C, 2014. Identification of initial severity determinants to predict arthritis after chikungunya infection in a cohort of French gendarmes. *BMC Musculoskelet Disord* 15: 249.
 48. Essackjee K, Goorah S, Ramchurn SK, Cheeneebash J, Walker-Bone K, 2013. Prevalence of and risk factors for chronic arthralgia and rheumatoid-like polyarthritis more than 2 years after infection with chikungunya virus. *Postgrad Med J* 89: 440–447.
 49. Brighton SW, Prozesky OW, de la Harpe AL, 1983. Chikungunya virus infection. A retrospective study of 107 cases. *S Afr Med J* 63: 313–315.
 50. Chow A et al., 2011. Persistent arthralgia induced by chikungunya virus infection is associated with interleukin-6 and granulocyte macrophage colony-stimulating factor. *J Infect Dis* 203: 149–157.
 51. McClelland EE, Smith JM, 2011. Gender specific differences in the immune response to infection. *Arch Immunol Ther Exp (Warsz)* 59: 203–213.
 52. Singh T, Newman AB, 2011. Inflammatory markers in population studies of aging. *Ageing Res Rev* 10: 319–329.
 53. Moro ML et al. Study Group “Infezioni da Chikungunya in Emilia-Romagna”, 2012. Long-term chikungunya infection clinical manifestations after an outbreak in Italy: a prognostic cohort study. *J Infect* 65: 165–172.
 54. Flahault A et al., 2007. Chikungunya, La Réunion and Mayotte, 2005–2006: an uneventful epidemic? *Sante Publique* 19: S165–S195.
 55. Labeaud AD, Bashir F, King CH, 2011. Measuring the burden of arboviral diseases: the spectrum of morbidity and mortality from four prevalent infections. *Popul Health Metr* 9: 1.
 56. Krishnamoorthy K, Harichandrakumar KT, Krishna Kumari A, Das LK, 2009. Burden of chikungunya in India: estimates of disability adjusted life years (DALY) lost in 2006 epidemic. *J Vector Borne Dis* 46: 26–35.
 57. Cardona-Ospina JA, Villamil-Gómez WE, Jimenez-Canizales CE, Castañeda-Hernández DM, Rodríguez-Morales AJ, 2015. Estimating the burden of disease and the economic cost attributable to chikungunya, Colombia, 2014. *Trans R Soc Trop Med Hyg* 109: 793–802.