Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Christina L. Sancken Date

Determining the Long Term Outcomes Due to Chikungunya Virus Infection:
A Descriptive Systematic Review of the Literature

By

Christina L. Sancken
Degree to be awarded: MPH

Global Health

_____

Sophia Hussen, MD MPH
Committee Chair

Determining the Long Term Outcomes Due to Chikungunya Virus Infection: A Descriptive Systematic Review of the Literature

By

Christina L. Sancken

B.S., Truman State University, 2010

Thesis Committee Chair: Sophia Hussen, MD MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Health
2016

Abstract

Determining the Long Term Outcomes Due to Chikungunya Virus Infection:
A Descriptive Systematic Review of the Literature

By Christina L. Sancken

Background. Chikungunya virus affects people of all ages in tropical areas around the world, and can cause potentially severe long-term outcomes (≥3 months) due to viral infection. A systematic review of the literature was conducted to describe the variability of long-term outcomes associated with chikungunya virus infection and to characterize potential risk factors for these outcomes.

Methods. The Cochrane Review method for systematic reviews of the literature was used as a framework to search for appropriate literature in the PubMed, Embase, and Medline databases meeting predefined inclusion and exclusion criteria. Full text was obtained for all studies meeting inclusion criteria, organized in an EndNote X7 file, and references of each included article were reviewed for other related articles. Pertinent information was abstracted from final included articles into a Summary of Findings table.

Results. The literature search identified 294 articles relating to chikungunya virus sequelae. Upon review, 24 articles were selected for inclusion in this review. All 24 studies described long-term outcomes attributed to chikungunya virus infection, but not all studies addressed the same outcomes. Symmetrical arthritis and arthralgia of the hands, fingers, wrists, and knees were most commonly reported, especially in females and people over age 40. Pre-existing conditions, comorbid conditions, and family history are thought to play a role in determining long-term outcomes related to chikungunya virus infection. Only two studies exclusively addressed pediatric patient outcomes. Neurodevelopmental delays and dermatologic outcomes were noted.

Conclusions. Long-term outcomes vary widely and affect people of all ages. Research is required to establish the causal effects of long-term outcomes related to chikungunya virus infection, with the focus on pediatric outcomes and risk factors for long-term outcomes in adults. Directing research in these areas could help researchers, clinicians, and other public health professionals better understand the potential of future outbreaks and better respond to the health needs of affected individuals.

Determining the Long Term Outcomes Due to Chikungunya Virus Infection: A Descriptive Systematic Review of the Literature

By

Christina L. Sancken

B.S., Truman State University, 2010

Thesis Committee Chair: Sophia Hussen, MD MPH

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Health
2016

Acknowledgements

First, I would like to thank my thesis advisor, Dr. Sophia Hussen, for the continuous support, patience, and motivation to help me throughout the writing process. She consistently encouraged me to do more and do better, and I thank her immensely for those thoughtful insights.

I would also like to acknowledge Leora Feldstein for being my sounding board during the initial project formation and for her helpful advice.

Finally, I would like to thank my family for their encouragement and kind understanding this past year. This accomplishment would not have been possible without all of them.

Christina L. Sancken

Table of Contents

Chapter 1 – Introduction

Introduction and Rationale

Chikungunya virus (CHIKV) is an alphavirus that belongs to the Togaviridae family and is transmitted to humans by infected mosquitos[1]. In the Americas and Asia, CHIKV is predominately spread by the *Aedes aegypti* and *Aedes albopictus* mosquitoes, but the species *Aedes furcifer*, *Aedes taylori*, *Aedes luteocephalus*, *Aedes africanus*, and *Aedes neoafricanus* transmit infection in West and Central Africa[2, 3]. CHIKV is the cause of Chikungunya fever and was first documented in Tanganyika territory, now Tanzania, in the early 1950s after a dengue-like illness with severe joint pain occurred[2, 4]. It was quickly named Chikungunya, a Makonde word meaning "that which bends up"[4, 5]. Cases were then identified in Asia, Australia and Oceania, South America, Europe, and the Caribbean over the next several decades, making Chikungunya a global issue[5].

Those infected with CHIKV may be asymptomatic, but most individuals (~75%) experience acute onset of symptoms three to seven days after being bitten by an infected mosquito[2]. Common acute symptoms include high fever (>39 degrees Celsius), symmetric polyarthralgia, and headache, but other less common symptoms such as rash, arthralgia/myalgia, nausea, vomiting, and conjunctivitis may occur[2, 5, 6]. Severity of these symptoms usually correlates with the viral load present in the blood of infected indviduals[5]. Symptoms may vary by age of individual and typically last 3-10 days[2, 5, 6]. Some CHIKV-infected individuals also experience chronic symptoms, especially joint pain, for longer than one year[2]. It is important to note that, regardless of symptom presentation, any infected individual may still contribute to the spread of CHIKV to susceptible mosquito vectors during the viremic phase (first week) of illness, and consequently, to other human hosts[2].

CHIKV affects men, women, and children, but there are certain populations at greater risk of developing severe disease[2]. Neonates who were exposed to CHIKV intrapartum, born to an infected mother, are at a particularly high risk (~50% infection rate) for severe complications such as encephalopathy and long-term neurologic disorders[2, 5, 8]. Older people (> age 65), those with underlying health issues, and the immunocompromised are also at a higher risk for potentially severe disease outcomes such as neurological, ocular, cardiovascular, dermatological, or renal complications[2, 5]. A 2009 study of an outbreak of Chikungunya fever on Reunion Island reported that as many as 89% of patients with atypical or severe cases of Chikungunya fever were those with underlying health conditions, and that hypertension, diabetes mellitus, and cardiovascular diseases were the top three comorbidities for severe outcomes due to CHIKV infection[9].

Because many of these symptoms are clinically similar to other arboviruses, such as dengue, diagnosis of CHIKV infection generally needs to be done in a laboratory to detect the virus in blood or serum samples obtained from suspected cases and to confirm infection[5]. Reverse-transcriptase-polymerase chain reaction (RT-PCR), serology, and virus isolation are the three methods typically used to diagnose CHIKV infection[2]. RT-PCR and virus isolation are used to diagnose infection only during the acute phase of the illness, while serology should be utilized in the acute phase *and* the convalescent phase (10-14 days after symptoms appear) if the acute phase serum initially tested negative for CHIKV[2, 5]. Serology tests for both immunoglobulin M (IgM) antibodies, which develop to fight new infections in the acute phase, and immunoglobulin G (IgG) antibodies that control infection in the convalescent phase[2].

Because there is no antiviral medication to treat symptoms of CHIKV, supportive care is recommended after ruling out other arboviruses and serious illnesses[2]. During the acute phase,

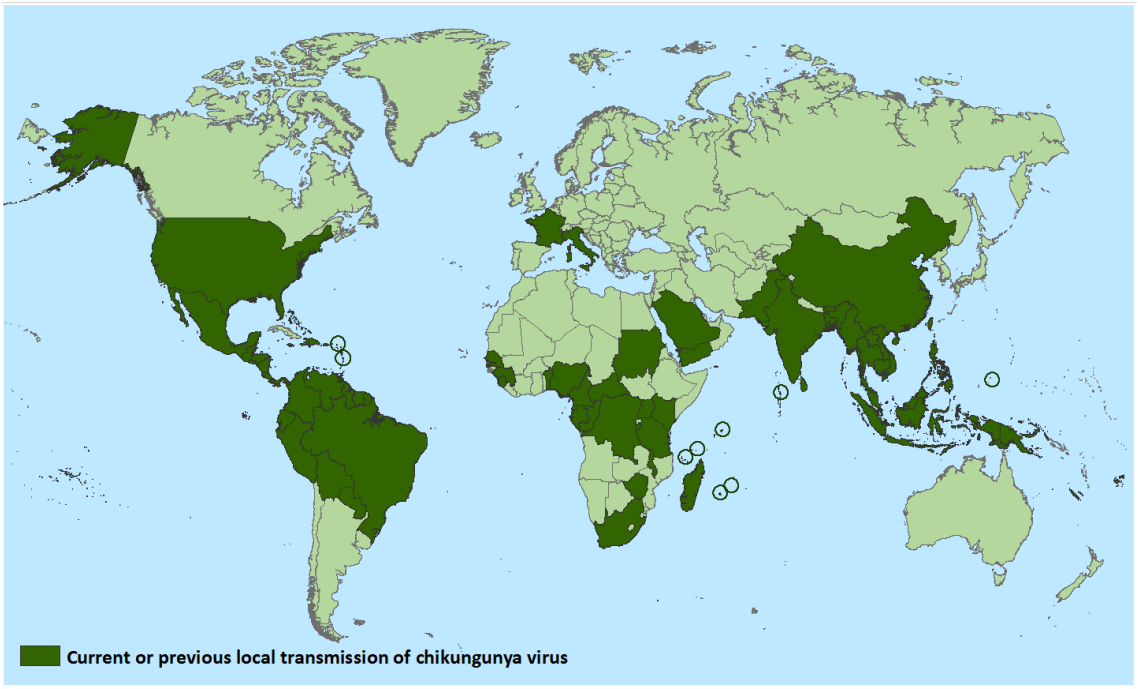
patients are advised to rest, drink plenty of fluids, use acetaminophen to reduce fever, and ibuprofen or another non-steroidal anti-inflammatory drug (NSAID) to reduce swelling that occurs with joint symptoms[2]. For individuals with prolonged symptoms, long-term anti-inflammatory therapy may be the best option for pain management[2]. Upon recovery from infection, life-long immunity is expected[10, 11].

Currently, there is no vaccine to prevent CHIKV infection[2, 5]. Environmental and personal behavioral precautions to prevent mosquito bites are the basis of recommendations by various organizations working to prevent arbovirus infection around the globe[2, 12]. Risk of infection is highest during the rainy season due to mosquito breeding habits. Subsequently, environmental precautions should be taken to ensure stagnant water is removed or covered whenever possible to inhibit larval growth. Using insecticides responsibly, trash management, and installing screens on windows and doors are also appropriate environmental strategies to prevent mosquito breeding[2, 5, 12]. Individuals may modify personal behavior to protect themselves from infection by wearing DEET-containing repellent, wearing long sleeves and long pants where appropriate, and by using insecticide-treated bed nets when resting during the day since *Aedes* mosquitos bite only during this time[2, 12].

The Centers for Disease Control and Prevention (CDC) reports that there were an estimated 28 travel-related (imported) CHIKV cases to the United States per year between 2006-2013 from travelers returning from affected areas, and almost 500 imported and confirmed CHIKV cases were reported in an August 2014 update[13]. The CDC also reports that none of the cases between 2006-2013 resulted in autochthonous (local) transmission, but the 2014 update identified four locally transmitted cases in Florida[13]. The United States is only one example of a nation where imported cases have affected the population, but local outbreaks seem to have been

avoided to date[14]. Other countries with travel-related infection have not been so fortunate – imported cases from India resulted in local outbreaks in Italy in 2007 and France in 2010[15-17]. Latin America and the Caribbean are the most recently affected regions, with the outbreak starting in December 2013[18]. To date, autochthonous transmission has occurred in more than 45 countries and territories, as shown in Figure 1[19].

Figure 1. Reported distribution of autochthonous chikungunya cases



Few studies have estimated the economic impacts placed on communities due to CHIKV infection, but should be considered an important aspect of disease burden. Direct costs to the individual, such as doctor visits, diagnostic testing, supportive care treatment, and hospitalization in severe cases, place a large economic burden on under- or uninsured patients. The outbreak on Reunion Island in 2005-2006 affected an estimated 244,000 people and incurred an estimated $29.98 million (converted to 2016 US dollars from 2006 Euros) in direct medical costs[20-22].

During the same outbreak, an estimated $19.68 million (converted to 2016 US dollars from 2006 Euros) in indirect costs, such as sick leave, were incurred[21, 22]. Costs may become unmanageable for those with severe cases that miss work due to illness. Other studies have estimated burden of CHIKV infection by using disability-adjusted life years (DALYs). One such study was conducted using data from the 2006 outbreak in India, in which an estimated 25,588 DALYs were lost due to CHIKV infection[23]. It is important to note that these estimates may not represent the true direct and indirect costs or burden of disease associated with CHIKV infection on Reunion Island or India, as long-term costs were not assessed and only those who sought medical care were included in these studies. This information should not be assumed true for other countries and territories affected by Chikungunya.

In addition to economic costs, personal costs due to CHIKV infection are also an important consideration. Poor mental health outcomes, such as depression, may be present in some patients with prolonged symptoms[24]. Other personal costs associated with CHIKV infection that affect quality of life may include fatigue, hair loss, and skin, sleep and digestive disorders[24]. Due to the severity of symptoms and other potentially detrimental outcomes mentioned in this section, CHIKV infection is an epidemic of global public health importance.

Problem Statement

The Pan American Health Organization (PAHO) and the World Health Organization (WHO) reported that there have been almost 1.7 million cumulative cases of CHIKV infection since 2013 in the Americas alone[7]. As of the March 4, 2016 update, there have been 991,134 individuals affected by CHIKV throughout the Latin and non-Latin Caribbean islands, Central America, and coastal South America[7]. Of the total affected by CHIKV, there are 693,489

suspected cases and 37,480 confirmed cases[7]. Seventy-one deaths have been either directly or indirectly attributed to CHIKV infection[7].

CHIKV infection is a quickly emerging public health issue in tropical and sub-tropical climate areas due to its potential for large outbreaks in vulnerable populations[2]. Previously mentioned studies have shown that these symptoms can be debilitating and potentially have long-lasting consequences, but not much is known about these long-term effects of CHIKV infection. Learning more about who is particularly susceptible to long-term outcomes due to CHIKV infection may help public health practitioners close the economic and personal cost gaps on this issue. Determining who is currently at high risk for long-term outcomes could potentially identify how best to protect from infection, either through environmental, behavioral, or other precautions, to reduce transmission. By doing this, uncomplicated recovery from infection and positive health outcomes may be within reach. This may also determine where research is lacking and provoke future studies on long-term health outcomes.

Purpose Statement

The purpose of this study was to describe long-term health outcomes in CHIKV infected individuals. Specifically, this thesis aimed to describe the variability of long-term sequelae, including who is most affected, duration of illness, and variety of symptoms, related to CHIKV infection by critically examining the available literature across a wide range of publication dates and geographic regions.

Research Questions

Two research questions will serve as a guide for this thesis:

1. What is the variability of long-term outcomes of CHIKV infection?

2. Are there conditions that make an individual more prone to developing long-term complications due to CHIKV infection?

Significance Statement

The findings from this thesis endeavor to assess the risks, demographics, and long-term health outcomes identified in studies completed around the globe that will then be used to provide valuable information for the improvement of prevention strategies dealing with severe long-term health outcomes at an individual level.

Definition of Terms

Acute Illness – A sudden onset of symptoms.

Arbovirus – Arthropod-borne virus

Arthralgia – Joint pain and/or stiffness

Arthritis – Joint swelling and pain and/or stiffness

Autochthonous cases – Locally acquired and laboratory confirmed cases of CHIKV infection.

Confirmed cases – Individuals with laboratory-confirmed blood samples containing CHIKV antigens or antibodies.

Long-Term – For the purpose of this thesis, 'long-term' represents continuous or intermittent illness lasting three or more months after infection.

Sequela – Outcome resulting from a previous infection.

Suspected cases – Individuals with symptoms representing CHIKV infection, but not laboratory-confirmed.

Travel-related cases – Infection that was acquired abroad, but not diagnosed until return to home country.

Chapter 2 – Methodology

Introduction

The Cochrane Review method for systematic reviews of the literature is normally used for evaluating health interventions, but may also be used to assess the probable course of disease or health outcomes for persons with a health issue[25]. The Cochrane Review general methods include 1) defining a review question and developing criteria for including studies, 2) searching for studies using bibliographical databases, 3) selecting included studies, 4) assessing the risk of bias, 5) analyzing the data, 6) presenting the results in a 'Summary of Findings' table, and 7) interpreting the results and making conclusions[25].

Therefore, a systematic review of the literature was completed using the Cochrane Review method in order to describe the variation in long-term outcomes due to CHIKV infection, including who is most affected and duration of illness. A predefined search strategy was used based on this method. Inclusion and exclusion criteria were developed prior to the literature search, and articles were subsequently organized for review.

Search Strategy

Using the Cochrane Review recommendations, PubMed, Embase, and Medline databases for peer-reviewed literature were systematically searched for articles relating to long-term outcomes due to CHIKV infection. All searches included ("Chikungunya" AND "sequela"). All articles from the databases were exported to EndNote X7. Titles and abstracts were reviewed for relevant information using the inclusion and exclusion criteria listed below.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Article must address only Chikungunya;

- Article must address long-term outcomes due to CHIKV infection; and
- Full text available through database or an Emory library.

Exclusion criteria:

- Studies addressing only acute symptoms of CHIKV infection;
- Studies addressing CHIKV infection in animal models;
- Studies addressing only investigative treatment options or illness management;
- Systematic reviews and meta-analyses;
- Comments and letters to the editor;
- Articles addressing co-infection with CHIKV; and
- Articles in languages other than English or Spanish.

Full text was obtained for all studies meeting the inclusion criteria, and duplicate articles were removed. Articles not meeting inclusion criteria during full text review were excluded. References cited in the included articles were examined to identify other relevant articles not originally found in the initial search. Other potentially appropriate articles from the references were searched in PubMed; however, no additional articles were added to the literature review after screening for inclusion/exclusion criteria.

Data Extraction and Synthesis

Pertinent information from included articles was organized in a Summary of Findings (SOF) table, including first author, date of publication, country of study, population characteristics, sample size (CHIKV+ patients only), study design, method of CHIKV infection confirmation, time since acute infection (months), long-term outcomes of CHIKV infection (≥3 months or 90 days after acute illness) and duration of long-term effects (if reported), and other notes important to the study (e.g. recommendations for further study, potential risk factors for

long-term outcomes, etc.). Included articles are organized alphabetically in the SOF table and by length of follow-up time in the "Results" section of this thesis.

Ethical Considerations

As this review consisted of summarizing existing published data, Institutional Review Board approval was not required.

Chapter 3 – Results of the Literature Review

Introduction

The literature search identified 294 articles relating to CHIKV sequelae, which were imported into EndNote X7. Duplicates were removed, leaving 258 articles for title and abstract review. Using the inclusion and exclusion criteria, 122 articles were excluded upon title review and 71 were excluded during abstract review. Forty-one articles were excluded at full text review. Twenty-four articles remained and were included in this review.

Key information was abstracted from each article and organized in the SOF table (Appendix B). Studies were conducted in several countries, including Reunion Island (n=11), India (n=5), France (n=2), South Africa (n=2), Germany (n=1), Mauritius (n=1), Sri Lanka (n=1), and the United States (n=1). CHIKV infection was laboratory confirmed either by detection of IgM or IgG antibodies, RT-PCR, qRT-PCR, or cell culture unless otherwise noted. This review is organized below by follow-up time after acute symptom onset. Several studies included more than one follow-up time and appear in multiple sections below.

3-8 Months Follow-Up Time

In the 3-8 months after symptom onset, commonly reported CHIKV sequelae for adult patients were persistent joint pain, especially in the knees and smaller joints. Patients in several studies reported more than one joint being affected. Neurocognitive delays and dermatologic symptoms were noted in pediatric patients.

A case description of a 47-year old patient who had returned to the United States after traveling to the Dominican Republic reported persistent burning pain in the right lower extremity and extreme weakness (myelopathy) at 3.5 months after onset of acute symptoms[26]. Bank et al. suggest that the time between infection and myelopathy is due to an immune-mediated response

rather than continuous viral activity. The patient was reported to have regained full strength at six months follow-up, but sustained residual neuropathic pain for an unknown period of time.

A longitudinal population-based survey identified 509 CHIKV case-patients living in a rural area in India for a prospective cohort study[27]. Sixty-nine children <16 years of age, 303 adults between 16-54 years of age, and 137 elderly >54 years of age were initially included in the study. At the time of survey, 315 participants reported pain in a variety of areas, including shoulder (51%), elbow (46%), upper arm (21%), forearm (8%), wrist (46%), hand (43%), hip (10%), thigh (14%), knee (81%), calf (30%), ankle (51%), feet (20%), neck (19%), upper back (20%), and lower back (31%). At four months of follow-up, 202 participants were assessed. Location of pain included shoulder (46%), elbow (38%), upper arm (14%), forearm (7%), wrist (46%), hand (42%), hip (9%), thigh (14%), knee (66%), calf (24%), ankle (50%), feet (17%), neck (16%), upper back (16%), and lower back (26%). Follow-up was continued at 12 months and again at 21-24 months. Chopra et al. note that smaller joints seem to be the more affected, but the knee was affected most.

A cohort study of 30 patients living in an endemic area in India reported CHIKV-associated musculoskeletal disorders 3-6 months after acute infection[28]. All patients were categorized into one of five musculoskeletal disorder types: rheumatoid arthritis (RA)-like illness (20%), undifferentiated inflammatory arthritis (20%), seronegative spondylarthritis (23%), soft tissue rheumatism (13%) and nonspecific arthralgias (24%). Patients reported low backache (27%), knee pain (67%), ankle and/or heel pain (67%), shoulder pain (50%), and hand and/or wrist pain (77%), with 96% of patients experiencing polyarthralgia. At 3-6 months, 63% (compared to 91% at 1-3 months) were IgM positive, 13% (compared to 8% at 1-3 months) were rheumatoid factor positive, and 80% (compared to 66% at 1-3 months) were C-reactive protein

positive. Patients were also known to complain of painful, puffy feet, ankles, and sometimes hands and wrists that were associated with chronic illness. Ultrasound revealed tenosynovitis and enthesopathy in knee, ankle/heel, and hand/wrist joints. Chopra et al. note that two of the 30 patients were previously diagnosed with psoriatic arthritis, and that CHIKV may be a factor in reactive arthritis and psoriatic arthritis.

A cohort study in southern India included 403 participants with a mean age of 37.7 years to assess duration of clinical symptoms due to CHIKV infection[29]. CHIKV infection was clinically diagnosed as having fever and joint pain between May-June 2006. Only a subset of patients in this study had laboratory confirmed CHIKV infection. The mean duration of joint pain was 3.8 months, with a variation of 5.3 months. At the 3-6 month follow-up, 16% of the 403 participants reported joint pain. From 6-12 months follow-up, 12.7% reported joint pain, 7% reported joint pain at 12+ months follow-up, and 0.74% reported joint pain at 30 months follow-up. Ninety-six percent of participants reported joint pain in the knee, 80% in the wrist, 77% in the ankle, 77% in the phalanges, 72% in the tarsals, 48% in the metatarsals, 4% in the shoulder, 3.2% in the hip, and 2% in the elbow. Swelling of joints was reported in 46% of participants. The number of joints affected was also noted – 36% of participants reported six affected joints, 23% had five, 14% had three, and 6% had one joint involved. It is unclear, however, at which point during the study that the types and number of joints were assessed. This analysis also involved a nested case-control study to identify risk factors for chronic joint pain. Associated risk factors included age >35 years (OR=2.0), >4 joints affected (OR=3.4), swelling in joints (OR=8.6), fever lasting ≥4 days (OR=3.6), and high-grade fever (OR=4.6). Rash was also associated (OR=4.0), but was not statistically significant.

A prospective longitudinal study was conducted on Reunion Island with 180 patients who had enrolled at an emergency department of a hospital for febrile arthralgia[30]. Telephone interviews were conducted to assess clinical symptoms at 4, 6, 14 and 36 months. At the four-month and six-month follow-up, 129 patients and 122 patients, respectively, were interviewed. The majority of patients had polyarthritis (4 or more joints affected), followed by oligoarthritis (2-3 joints affected) and monoarthritis (one joint affected) at both follow-up times. Affected joints included the spine, shoulder, elbow, wrist, hand, hip, knee, ankles, and feet. Participants reported that fingers, wrists, knees, and ankles were most affected, and 90% of the joint pain was symmetrical. Five of 180 (2.8%) participants reported a history of arthralgias.

A retrospective descriptive study on Reunion Island included 30 patients (23 boys and 7 girls) <18 years of age who requested medical attention at the emergency department of a hospital with neurologic illness related to CHIKV infection[31]. The mean age was 5.5 years (range 3 days-17 years). Twenty-one children were seen for follow-up six months after presentation to the emergency department. Of the 21 children, one had language development regression and autistic tendencies with echolalia, one had persistent neurodevelopmental delay with microcephaly and strabismus, and one had recurrent seizures after stopping anticonvulsant medication. Six of 12 children who had severe acute infection and one with mild acute infection developed neurologic sequelae or died. MRIs for two neonates showed atrophy in the frontal lobes and parietal cavitations in the white matter.

A retrospective cohort study was conducted with 20 patients who had traveled to endemic countries from Germany[32]. Nine had traveled to Mauritius, three to India, two each to Reunion Island, Malaysia, and the Seychelles, one to Madagascar, and one to Indonesia. The study included 14 women and six men with a mean age of 44.6 years (range 12-64 years). All

participants reported severe joint pain during the acute phase of infection. Seven of the 16 participants available for follow-up at six months reported persistent arthralgia, but the study ended before their recovery. Two of 16 patients experienced joint pain for more than six months after acute infection.

A longitudinal cohort study of 513 patients (237 men and 276 women) with a mean age of 35 years (range 1-90 years) was conducted in rural Sri Lanka to assess CHIKV-associated outcomes seven months after an outbreak of CHIK[33]. CHIKV infection was diagnosed clinically by assessing patients who reported fever, rash and joint pain. One participant died before follow-up, leaving 512 for Chronic Arthritic Disability (CAD) assessment. Weight-bearing joints were most affected (ankle, knees, feet), but pain in the wrists and back was also reported. CAD occurred in all age groups defined by Kularatne et al., but affected the 63-72 year-old age group the most, with 31/41 (75.6%) symptomatic participants. The 0-12 year-old group was least affected, with 9/91 (9.9%) reporting CAD. Appendix B provides further details on CAD by age group. Thirty-four (7%) participants gave a past history of arthritis, and of the 34, 21 (62%) experienced exacerbation of arthritis with CHIKV infection. Kularatne et al. observed that females were more likely to be affected by CAD than males. Other non-arthritic complications, including carpal tunnel syndrome (22%), post-viral fatigue syndrome (2%), thrombophlebitis (0.4%), respiratory tract infection (0.8%), calf swelling (0.2%), and facial swelling (0.6%) were also noted.

A retrospective descriptive study was conducted on Reunion Island with 13 infants (mean age 3.4 months) who presented with skin blistering or lesions on ≥10% of the body[34]. Eight boys and five girls were included. Twelve infants were seen during a 6-9 month (mean 7.4 months) follow-up period. All 12 infants with severe bullous lesions had improved pigmentation with

few central spots. Two infants had developed hypertrophic keloid scarring, one infant had developed photosensitivity, and one infant had developed xerotic eczema. Another follow-up was done at 36 months.

9-14 Months Follow-Up Time

In the 9-14 month follow-up time period, patients reported persistent arthritis in more than one joint, with the knee, wrist and hands being most affected. Morning joint stiffness was characterized during this follow-up time. Risk factors for long-term outcomes were also hypothesized during this time period, including older age and being female, among others.

A prospective cohort study on Reunion Island followed 21 CHIKV patients who experienced chronic arthritis[35]. Thirteen females and eight males were included, with a mean age of 57.3 years ± 12.2 years. All 21 patients were diagnosed with RA at a mean of 10 months (range 4-18 months) after the CHIK fever outbreak on the island. At the time of RA diagnosis, 18/21 patients had symmetric polyarthritis, 3/21 patients had oligoarthritis (≤5 joints affected), 5/21 had joint erosion, 12/21 had joint space narrowing, and 9/21 patients had normal x-rays. Patients were followed up at a mean of 27.6 months after the outbreak. Bouquillard & Combe note that immunologic profiles may be helpful in diagnosing RA as a result of CHIKV infection.

A longitudinal follow-up study was conducted in India 10 months after CHIKV diagnosis[36]. Two hundred three patients (96 males, 107 females) with a mean age of 35 years were recruited from five different health facilities. At the 10-month follow-up, 100/203 patients continued to have CHIKV-associated symptoms, including joint pain (94/203), fatigue (27/203), tingling/numbness in extremities (12/203), rash (1/203), myalgia (1/203), bone pain (1/203), and neuritis without joint pain (1/203). Five patients had limited mobility of at least one joint and one patient had fixed flexion deformity of the fingers on both hands. At least one joint was

affected in 55/94 patients with joint pain and 74/94 patients reported having morning stiffness in at least one joint lasting more than one hour. Of the 94 patients who had joint pain, the knee was the most common joint affected (59.5%), followed by the ankle (54.2%), small joints in the lower limbs (52.1%), small joints in the upper limbs (40.4%), wrist (30.8%), elbow (29.7%), shoulder (14.8%), lumbo-sacral vertebrae (13.8%), hip (10.6%), sacroiliac joint (10.6%), and the cervical neck vertebrae (8.5%). Polyarthritis was observed in 65.9% of the 94 patients with joint pain, while 23.4% of patients had oligoarthritis and 9.4% had monoarthritis. Manimunda et al. note that 36% of all patients met RA criteria set by the American College of Rheumatology.

A descriptive prospective cohort study was conducted on Reunion Island with 54 adult patients with a mean age of 40 years (range 18-65 years) with typical CHIKV infection symptoms[37]. Follow-up was done by telephone at 3.33 months and 10 months, although no information was reported for the 3.33-month follow-up. Patients with several arthralgic joints were more likely to have persistent joint pain at 10 months and were significantly older than patients reporting one or few joints affected. Five patients (9.3%) had pre-existing orthopedic illness. Thiberville et al. note that age is an independent risk factor for symptomatic CHIKV infection at 10 months, and being female is independently associated with having a higher number of joints involved at acute infection and at 10 months. Females were also more likely to report persistent symptoms.

A longitudinal population-based survey identified 509 CHIKV case-patients living in a rural area in India for a prospective cohort study[27]. Population characteristics and results at baseline and four months are described previously. At 12 months of follow-up, 59 participants were assessed. Location of pain included shoulder (53%), elbow (46%), upper arm (12%), forearm (3%), wrist (59%), hand (56%), hip (7%), thigh (7%), knee (57%), calf (19%), ankle

(15%), feet (19%), neck (15%), upper back (19%), and lower back (22%). Follow-up was continued at 21-24 months. Here, the wrist was affected most, followed by the knee and hand.

A prospective longitudinal study was conducted on Reunion Island with 180 patients who had enrolled at an emergency department of a hospital for febrile arthralgia[30]. Telephone interviews were conducted to assess clinical symptoms at 4, 6, 14 and 36 months. At the 14-month follow-up, 148 patients were interviewed. The majority of patients had oligoarthritis (2-3 joints affected), with the number of patients experiencing polyarthritis (4 or more joints affected) and monoarthritis (one joint affected) being about equal. Affected joints included the spine, shoulder, elbow, wrist, hand, hip, knee, ankles, and feet. Schilte et al. noted risk factors for arthralgia at the 14-month follow-up included C-reactive protein>10 at inclusion (OR=3.12), diabetes at inclusion (OR=2.83), permanent arthralgia at month 4 (OR=6.28), memory disorder at month 4 (OR=7.4), and concentration disorder at month 4 (OR=15.79).

15-20 Months Follow-Up Time

During the 15-20 month follow-up time period, patients most commonly reported persistent joint pain. Postulated risk factors were having a comorbid condition, older age, and severity of joint pain during the acute phase of CHIKV infection. Arthritis and arthralgia were not uncommon among patients during this follow-up time period.

A retrospective cohort study on Reunion Island involved 147 CHIK+ patients with a mean age of 52 years (± 12 years, range 16-86 years)[38]. All patients reported joint pain during the acute phase of infection. Follow-up was done by telephone 15 months (range 12-17 months) after infection. Of the 147 CHIK+ patients interviewed at 15 months, 43% reported no symptoms, 21% reported intermittent symptoms, and 36% reported persistent symptoms. Fifty-seven percent of patients at 15 months reported pain, 41% reported morning stiffness lasting 45

or more minutes, and 15% reported swelling. Patients were categorized as having mild (70 patients), moderate (13 patients), or severe (1 patient) pain using a joint pain intensity (NRS) score. Sissoko et al. note that 76/147 patients presented with a comorbidity, including hypertension (48 patients), osteoarthritis (38 patients), diabetes mellitus (32 patients), and chronic cardiac disease (14 patients). Risk factors for persistent arthralgia were age 45+ (OR=4.2), NRS≥7 (OR=3.6), osteoarthritis (OR=3.2), one or more comorbid conditions (OR=3.0), and hypertension (OR=2.4).

A retrospective cohort study based on the cross-sectional population-based survey included 512 CHIK+ participants with a mean age of 36 years (range 1 month-93 years) on Reunion Island[39]. Population breakdown by age group is found in Appendix B. CHIK+ participants reported a variety of symptoms at the 16-month (range 13-20 months) follow-up. The most common symptom was light cerebral disorder (75%), followed by fatigue (54%), sensorineural disorders (49%), musculoskeletal pain (43%), memory troubles (42%), and blurred vision (42%). Symptoms reported less commonly are mood disturbance (38%), attention deficit (37%), skin problems (36%), sleep disorders (31%), headaches (26%), alopecia (22%), skin lesions (20%), digestive disorders (18%), hearing difficulties (18%), and depression (15%). CHIK+ patients are significantly more likely to self-report certain symptoms than CHIK- individuals, including musculoskeletal pain, fatigue, light cerebral disorders, sleep disorders, memory troubles, attention deficit, mood disturbances, depression, sensorineural disorders, and blurred vision. Gerardin et al. note that being over age 40 is a risk factor rheumatic symptoms at follow-up (40-49 years OR=2.7; 50-59 years OR=3.3; 60-69 years OR=3.9; 70+ years OR=3.5). Risk factors for sensorineural disorders at follow-up may also be age related, especially for those over 40 years (40-49 OR=2.6; 50-59 years OR=2.7; 60-69 years OR=2.7; 70+ years OR=2.6).

Gerardin et al. also state that 43-75% of CHIK+ patients reported persistent or late-onset symptoms that are thought to be attributable to CHIKV infection.

A cross-sectional study on Reunion Island was conducted in order to assess quality of life of 106 known CHIKV patients seeking health care in 13 different facilities at then end of the outbreak lasting 17 months[40]. Seventy-nine women and 27 men with a mean age of 47.3 years (± 11.9 years) were included. Fifty-six patients (53%) had long-term pain lasting three or more months. The mean duration of long-term pain was 128 days ± 41 days with a range of 95-318 days. The Brief Pain Inventory (BPI) scale (0=no pain, 10=maximal pain) was used to measure intensity of joint pain. De Andrade et al. note that BPI scores were higher in those with long-term pain (BPI = 6.8 ± 1.9) that for those without (BPI = 5.9 ± 1.9).

A descriptive cohort study of 103 high school-aged children and adults (average age excluding middle-aged adults was 16 years) who had visited the northern Transvaal bushveld was performed in South Africa[41]. CHIKV was diagnosed in eight subjects, of which five (four middle-aged adults and one 16 year old) had arthritis and fever episodes up to 20 months after infection. Older patients were more likely to be affected by long-term outcomes than the high school-aged children.

A cohort study of 88 patients was conducted on Reunion Island with a mean age of 58.3 years (± 18 years) in order to characterize persistent arthralgia due to CHIKV infection[42]. Fifty-eight had been previously hospitalized for acute CHIKV infection, 56 reported persistent arthralgia (35 were CHIK+), and 32 reported full recovery. Thirty-nine of the 88 patients disclosed a history of arthralgia before CHIKV infection. Follow-up with the 56 patients who had reported persistent arthralgia was completed at 18.7 months (± 2.1 months). Of the 56 patients with persistent arthralgia, 32 reported pain of the metacarpo-phalangeal joints (15 upon

physical examination), 32 with knee pain (12), 28 with wrist pain (9), 27 with metatarsal pain (15), 26 with ankle pain (16), 25 with shoulder pain (17), 13 each with elbow pain (8) and rachis pain (7), 10 with hip pain (3), and one with sternoclavicular joint pain (1). The mean number of self-reported joints involved when was 6.2 (± 4.2 joints), while upon physical examination the mean number of joints involved was 3 (± 3.8 joints). Borgherini et al. report other population characteristics, including that 40/56 patients had a comorbid condition, 23/56 had hypertension, 21/56 had ischemic heart disease, 18/56 had diabetes mellitus, and 29/56 had pre-existing arthralgia.

21-26 Months Follow-Up Time

Wrist, hand, ankle, and knee pain among adult patients were common during the 21-26 month follow-up time period. Synovitis in the fingers, as well as joint and bone erosions were also reported. In CHIKV-infected pediatric patients, there was a moderate language and coordination developmental delay, compared to normal development in non-CHIKV pediatric patients. Reported risk factors for developmental delay were CHIKV infection and small head circumference.

A longitudinal population-based survey identified 509 CHIKV case-patients living in a rural area in India for a prospective cohort study[27]. Population characteristics and results at baseline, four months and 12 months are described previously. At 21-24 months of follow-up, 24 participants were assessed. Location of pain included shoulder (50%), elbow (46%), upper arm (13%), forearm (0%), wrist (67%), hand (63%), hip (13%), thigh (4%), knee (54%), calf (8%), ankle (58%), feet (33%), neck (21%), upper back (25%), and lower back (33%). Here, the wrist was affected most, followed by the hand, ankle, and knee.

A prospective cohort study was conducted on Reunion Island to assess the neurocognitive outcomes of 33 CHIKV-infected neonates compared to 135 uninfected neonates[43]. Infants were evaluated every six months until around age 24 months (range 15.8-26.7 months). Results are given for the 24-month follow-up time only. The mean gestational age for the 33 CHIKV-infected neonates was 38.06 weeks (± 1.29 weeks), with four preterm births and 29 full-term births. Seven neonates were small for their gestational age. The five-minute Apgar score of CHIKV-infected neonates did not differ from uninfected neonates, although head growth z-scores and the percentage of neonates breastfeeding at discharge did. The study used the Revised Brunet-Lezine (RBL) scale to determine neurocognitive development at age 24 months and calculated the Developmental Quotient (DQ) using RBL subscores. DQ scores of 70-85 signify moderate developmental delay and scores less than 70 signify severe developmental delay. The mean DQ scores were significantly lower in CHIKV-infected neonates. The mean global DQ score was 86.3 (81.2-93.5), the movement and posture DQ score was 98.5 (91.0-105.3), the coordination DQ score was 83.5 (76.0-90.9), the language DQ score was 80.0 (74.8-87.5), and the sociability DQ score was 90.5 (84.2-97.5). All mean DQ scores for uninfected neonates were above 93 (90.3-128.5). Gerardin et al. note that statistically significant risk factors for global developmental delay include CHIKV infection (adjusted IRR=2.79) and a head circumference of <-2 standard deviations (adjusted IRR=2.38).

A case description of one 60-year old French man presented to a clinic on Reunion Island with acute flu-like symptoms and arthralgia affecting the fingers and toes with hand tenosynovitis[44]. One year after acute infection, he had developed refractory tenosynovitis in both wrists. At 24 months after acute infection, the patient presented to a clinic in France with symmetrical inflammatory arthritis in his wrists and edema in both hands. The patient also

experienced synovitis in the extensors and flexors of the wrists and fingers. Radiography showed subchondral problems in the hands, wrists, and fingers. An MRI showed bilateral periostal inflammation with edema and synovitis in the fingers. The left ankle was also inflamed. Joint and bone erosions were noted nearly two years after acute infection.

27-32 Months Follow-Up Time

During the 27-32 month follow-up time period, persistent joint pain and swelling, joint erosion, and joint space narrowing were reported. Risk factors associated with long-term joint pain during this time period were symmetrical joint pain, older age, being female, severity of symptoms during acute infection, and having a pre-existing condition.

A retrospective cohort study involving 173 patients (30 men, 143 women) with a mean age of 52.1 years was conducted in Mauritius to assess the long-term rheumatic symptoms of CHIKV infection[45]. A patient was considered CHIK+ if they reported having fever, arthralgia, and/or rash during the outbreak in 2006. Patients were interviewed at approximately 27.5 months after the outbreak. One hundred thirty-six patients with a mean age of 54.7 years (± 12.7 years) reported musculoskeletal symptoms at follow-up. Of the 136 that reported symptoms at follow-up, 133 had persistent joint pain and was most common in the 51-60 year-old age group (41 patients). Joint swelling occurred in 96/136, 101/136 had symmetrical joint pain, 32/136 had joint pain, swelling and stiffness, and 32/136 had arthralgia without any swelling or stiffness. Arthralgia without swelling or stiffness was associated with a better recovery rate than those with swelling and stiffness. Persistent symptoms were associated with older age (50+ years), being female, and symmetrical pain at baseline. Pre-existing musculoskeletal problems were also associated with long-term symptoms, but were not statistically significant compared to those with any pre-existing condition. Essackjee et al. also report that treatment or any combination of

treatments of symptoms at baseline did not have an effect on long-term outcomes (paracetamol OR=2.4; NSAIDs OR=2.1; glucocorticoids OR=5.8; injection OR=0.5; antibiotics OR=0.1; paracetamol and NSAIDs OR=2.5).

A prospective cohort study on Reunion Island followed 21 CHIKV patients who experienced chronic arthritis[35]. Population characteristics and results at 10 months are described previously. At the 27.6-month (± 6.4 months) follow-up, 17/21 patients had joint erosion, 17/21 patients had joint space narrowing, 4/21 patients had normal hand and feet x-rays, and 7/21 patients were taking long-term steroid treatment. Bouquillard & Combe note that immunologic profiles may be helpful in diagnosing RA as a result of CHIKV infection.

A prospective cohort study was conducted on Reunion Island and included 403 French military (median age 40 years, range 21-54 years) that had participated in a previous study[46]. A baseline survey was completed six months after the outbreak on Reunion Island to assess acute infection and early chronic stage information (not reported). Follow-up was completed 30 months after acute infection. Arthralgia was reported in 124/403 patients and arthritis was reported in 57/403 patients. Symptoms during acute infection were associated with persistent rheumatic disorders (RDs) at follow-up. Arthralgia at six months was 14 times more frequent in those reporting arthralgia/arthritis at 30 months compared to those with no RDs. Pre-existing rheumatic conditions were reported 1.3 times more frequently in those with RDs at 30 months. Yaseen et al. also note that the severity of acute symptoms negatively affected long-term recovery and increased the risk of long-term arthritis.

33-38 Months Follow-Up Time

Joint pain in the feet, ankles, knees, hands, and wrists were commonly reported among patients during the 33-38 month follow-up time period, with almost always more than one joint

affected. Joint erosions and tendonitis were reported. Neurologic sequelae in adult and pediatric patients were also described. In adult patients, these included epilepsy and post-infection dementia. In pediatric patients, these included cerebral palsy, blindness, and poor neurocognitive development. Dermatologic sequelae in pediatric patients were resolved, but some scarring was observed during this follow-up time period.

A cohort study of 14 patients selected from a larger study in India was conducted to describe chronic inflammatory arthritis at 36 months after acute infection[47]. The mean age of patients reporting persistent symptoms was 58.4 years, while the mean age of patients reporting improvement of symptoms was 49.4 years. IgM antibodies were detectable at 36 months after acute infection in five of 14 patients. Seven of 14 patients were IgG+ at 36 months. One patient had a normal MRI; four patients regressed and had tendonitis with or without tears, bursal effusion, and/or subchondral erosion; two patients progressed and had erosions or effusions in metacarpophalangeal joints, joint deformities, osteoarthritis, and/or synovial thickening; and seven patients had persisting symptoms with joint effusions, bony erosions, marrow edema, joint degeneration, subchondral erosions, and/or ACL and meniscus tears. Chaaithanya et al. note that although the sample size was small, the study suggests that there is an association between persistence of IgM antibodies and long-term joint symptoms.

An ambispective cohort study on Reunion Island included 57 patients (21 adults, 36 infants) with a mean age of 63.9 years (range 33-88 years) for the adults and a mean age of 1.6 months (range 4 days-5.4 months) for the infants[48]. All patients were identified as having CHIKV-associated neurologic symptoms. Patients with pre-existing conditions or known causes of encephalitis were excluded. At baseline, 24/57 patients had altered mental status (probable or possible encephalitis), and 33/57 were classified as having nonencephalitic CHIKV-associated

CNS disease (NECACD). Outcomes due to altered mental status and NECACD were reported at 36 months after acute infection. Outcomes included intensive support care (10 patients with altered mental status, 3 patients with NECACD), length of hospital stay greater than four days (14, 13), died (3, 4), vegetative state (0, 0), lower severe disability (1, 2), upper severe disability (0, 2), lower moderate disability (1, 1), upper moderate disability (3, 2), lower good recovery (1, 1), upper good recovery (7, 7), and not assessed (8, 14). Three adult patients were identified with neurologic sequelae, including epilepsy, post-infection dementia, and cognitive disorder. One infant developed cerebral palsy and blindness, and four infants had poor neurocognitive performance.

A retrospective descriptive study was conducted on Reunion Island with 13 infants (mean age 3.4 months) who presented with skin blistering or lesions on ≥10% of the body[34]. Population characteristics and results at 6-9 months are described previously. Nine children were seen during a 36-month follow-up. The mean age was 3.2 years. Two children regained full pigmentation of the skin with no other sequelae, five children experienced discrete peripheral hyperpigmentation, and two children persisted with scarring. Robin et al. note that CHIKV should be considered in infants presenting to health care facilities with bullous skin lesions in epidemic areas.

A prospective longitudinal study was conducted on Reunion Island with 180 patients who had enrolled at an emergency department of a hospital for febrile arthralgia[30]. Telephone interviews were conducted to assess clinical symptoms at 4, 6, 14 and 36 months. At the 36-month follow-up, 102 patients were interviewed. The great majority of patients experienced polyarthritis (4 or more joints affected), followed by oligoarthritis (2-3 joints affected) and monoarthritis (one joint affected). The most affected joints were foot, ankles, knee, hand, and

wrist. Schilte et al. noted clinical signs of 62 patients with arthralgia at 36 months. They include local swelling in 39/62 arthralgic patients, osteo-ligamentous pain in 22/62, myalgia in 24/62, cutaneous lesions in 31/62, asthenia in 48/62, sleeping disorder in 35/62, dysgeusia in 11/62, depression in 31/62, memory disorder in 27/62, and concentration disorder in 24/62 arthralgic patients.

39 or More Months Follow-Up Time

During this follow-up time period, some patients reported full recovery of symptoms, while others reported persistent symptoms. Some patients reported mild joint discomfort in the hands and wrists made worse with excess use at follow-up. Others reported persistent joint stiffness with no pain in the mornings. The most commonly reported affected joints were the wrists, ankles, knees, hands, and fingers.

A retrospective cohort study of 107 patients in South Africa was conducted. Patients were contacted and questioned a mean of 48 months (range 36-60 months) after acute infection[49]. Patients were divided into four groups. Group 1 (94 patients) had a mean age of 37 years with 42/96 being less than 17 years of age. Patients in this group had fully recovered by follow-up time, but were able to estimate how long symptoms lasted. Thirty-eight reported recovery within a few weeks, 41 reported recovery over one year, and 15 reported recovery within two to three years. Group 2 (four patients) had a mean age of 54 years (range 45-60 years), and all four patients reported mild discomfort or occasional stiffness of proximal interphalangeal joints at follow-up time. Three patients each reported metacarpophalangeal joint pain and wrist pain. Three patients reported worsening of joint pain when exercising. Group 3 (three patients) had a mean age of 60 years (range 55-65 years) and reported persistent joint stiffness, but no pain at follow-up. Group 4 (six patients) had a mean age of 50 years (range 16-

64 years) with all reporting persistent joint pain and stiffness with or without swelling at time of follow-up. Patients in Groups 3 and 4 commonly reported morning stiffness for a mean of 35 minutes for those with no joint pain and mean of 24 minutes for those with joint pain. No patients had evidence of joint erosion. Most commonly reported joints affected were wrist, ankle, knees, metacarpophalangeal joints, and proximal interphalangeal joints. Three patients reported distal interphalangeal joint pain.

Chapter 4 – Discussion, Recommendations, and Conclusion

Synthesis of Results

All 24 studies described long-term outcomes attributed to CHIKV-infection. Symmetrical arthritis and arthralgia of the hands, fingers, wrists, and the knees are common among CHIKV patients across all follow-up times, and especially in those age 40 years and older. Patients across studies also reported having more than one affected joint. Several studies reported patients having comorbid conditions or pre-existing arthralgia, arthritis or psoriatic arthritis. Three studies reported specifically on morning joint stiffness lasting 24 minutes up to over an hour as a result of CHIKV infection[36,38,49]. Four studies found that some patients presented with joint erosions and joint space narrowing in as little as 10 months after acute infection[35,44,47,49].

Two studies included pediatric outcomes only[34,43]. The first study assessed developmental delays using DQ scores in two-year old children who were diagnosed with CHIK as neonates[43]. The DQ scores for language and coordination fell in the moderate developmental delay category, suggesting that neonates infected with CHIKV may have long-term neurologic problems two years after acute infection. The second study focused on severe bullous skin lesions, reporting that lesions were healing and skin repigmentation occurring at six to nine months follow-up time, although photosensitivity and eczema also occurred during this time[34]. Two children in this study recovered fully by 36 months with no other outcomes, five children exhibited hyperpigmentation, and two children exhibited keloid scarring. Another study included children <18 years of age, but MRIs for two neonates showed atrophy in the frontal lobes and parietal cavitations in the white matter, and one showed persistent neurodevelopmental delay with microcephaly[31].

Seven studies recorded comorbidities or pre-existing conditions of CHIK+ patients[30,33,37,38,42,45,46]. These include hypertension, ischemic heart disease or chronic cardiac disease, diabetes mellitus, pre-existing arthritis, osteoarthritis, orthopedic, or musculoskeletal symptoms. However, it is unclear whether having any of these conditions is a precursor to long-term outcomes of CHIKV-infection.

Thirteen studies identified possible risk factors for long-term outcomes related to CHIKV-infection in addition to long-term outcomes[27,29,30,33,35,37-39,41,43,45-47]. Severe joint pain and high grade fever during acute infection, history of smoking, persistence of IgM antibodies, being a woman, being older than 40 years, having more than four joints affected, C-Reactive Protein levels greater than ten at baseline, memory or concentration disorders, and a high self-reported joint pain intensity score may be related to long-term joint symptoms. Possible risk factors for developmental delay in children were CHIKV infection and small head circumference.

Limitations and Delimitations

Several limitations of the studies included in this review should be noted. Randomized control trials (RCTs) are considered the gold standard for providing evidence towards a cause and effect relationship, but this study design was not used in any of the included articles. Although RCTs provide the best evidence, this approach would not be appropriate to address the questions this thesis aims to answer, since efficacy of medications or other interventions are not being tested. Because no RCTs were included, the strength of evidence that CHIKV infection may cause long-term outcomes is considered moderate to low. Many of the studies were observational in nature and relied on self-reported data. Self-reported data, especially in long-term retrospective and prospective study designs, introduces recall bias, which affects the

validity of the study. Follow-up time varied in each study, ranging from 3.5 months to 60 months, making conclusions across included studies somewhat difficult. Not all studies followed-up until the end of long-term symptoms, therefore, it is unknown how long symptoms may actually last. It should also be noted that these studies were mainly focused on outbreaks in Africa, India, and Southeast Asia. The generalizability and representativeness of the course of acute CHIKV infection to long-term outcomes in other regions is therefore unknown, although this is not expected to vary by region, as the vector and human biology are essentially the same. The sample size for each study also varied greatly, from one to as many as 513 patients.

Potential delimitations of this review should also be mentioned. Because of the vast literature describing clinical manifestations of CHIKV infection, a more narrow approach was taken to describe long-term sequelae and possible risk factors for long-term outcomes while excluding literature focused on acute symptoms only. The narrow scope of the inclusion and exclusion criteria and the applied MeSH terms may have unintentionally missed articles that should have been included. References of included studies were reviewed to find other potentially fitting articles to ensure all possible studies were included, as well as abstract and full text reviewing before deciding that an article did not fit criteria. Finally, several French-language articles were excluded because of the language limitations of the reviewer. These articles may have provided more information confirming results of other studies or may have provided novel or differing conclusions.

Gaps in Knowledge

Long-term pediatric outcomes due to CHIKV infection *in utero* or shortly after birth in outbreak situations have rarely been documented. Although the main outcomes associated with this population seem to be neurologic in nature, it is unclear how long neurologic symptoms may

last and whether joint symptoms arise and persist as in older patients. It is essential to identify how these outcomes affect pediatric patients so that public health professionals are able to allocate resources and plan effective studies that demonstrate the health impact and economic burden of these effects on CHIK+ children and their families. The currently available data may not be sufficient in providing the information necessary to describe all possible long-term outcomes in CHIK+ children. This information is required in order to implement improved health care and chronic symptom management efforts for CHIK+ children.

One study found that IgM antibodies were detectable 36 months after acute infection in several patients and suggested that persistence of these antibodies may contribute to long-term joint pain. However, the study did not discern if these patients experienced longer or more severe joint pain than patients who were IgG positive at the same follow-up time. In addition to CHIK+ serology, several studies also identified pre-existing conditions, comorbid conditions, and family history of rheumatic disorders that may exacerbate long-term outcomes, although the strength of these relationships vary by study. The combination of IgM presence and risk factors for long-term outcomes suggest that serology and immunologic profile studies with a complete patient history could play an integral role in determining how long symptoms may last and how severe symptoms could be. Determining whether a distinct correlation exists between serology, immunologic profiles, patient history, and long-term outcomes such as RA or neurologic problems, is needed to identify those at greatest risk for long-term outcomes and better prepare public health professionals to communicate these risks to clinicians, other health professionals, and people living in or traveling to outbreak-prone areas.

Several of the studies recruited case-patients who were seeking medical care for CHIKV symptoms, but did not take into account asymptomatic case-patients. Therefore, studies are only

able to identify a subsection of those who are infected, indicating that the true infection rate after an outbreak is not known. By not capturing asymptomatic case-patients, under-reporting of laboratory-confirmed cases becomes an issue and means that the current global burden of CHIKV infection could be vastly under-estimated. This is an especially significant issue to be addressed for further vaccine development to prevent CHIKV infection. The feasibility of vaccine advancement is dependent on confirmed symptomatic and asymptomatic case reporting, which could identify persons most vulnerable to CHIKV infection and if a vaccine would truly benefit susceptible populations.

Recommendations

Clinicians should consider CHIKV in the differential diagnosis of patients experiencing long-term joint symptoms in endemic areas. Including serology for detection of IgM antibodies and immunologic profiles of symptomatic individuals who present to a healthcare facility could better describe how antibodies and personal risk factors contribute to long-term outcomes due to CHIKV infection. Others living in the same household as a symptomatic individual should also be tested to identify asymptomatic cases, since environmental and genetic risk factors may be shared. This would more closely estimate the true infection rate.

As almost all studies concluded before patient symptoms resolved, ongoing large prospective cohort or case control studies in endemic areas until patient symptom resolution should be considered. Long-term studies would also identify asymptomatic cases, give researchers a better insight on the numerous outcomes associated with CHIKV infection, and help determine underlying causes of long-term outcomes. These studies may also provide information for vaccine trials and identify populations who would benefit most from the vaccine.

Neurocognitive and other outcomes in infants should be a long-term research priority. It is imperative to understand how these outcomes affect quality of life beyond the time frame of the current studies so that progression or regression of disease is well defined and so that appropriate action may be taken to prevent and treat outcomes.

Conclusion

Long-term outcomes due to CHIKV infection vary widely and affect people of all ages. Symptom intensity ranges from very mild to very severe joint pain, and in some cases can last five years or perhaps longer. Other outcomes include neurologic symptoms, dermatologic symptoms, and abnormal MRIs of affected joints. It is thought that pre-existing conditions, comorbid conditions, and having a family history of rheumatic disorders are risk factors associated with long-term outcomes of CHIKV infection.

Future studies should focus on establishing a stronger cause-and-effect relationship between possible risk factors and long-term outcomes of CHIKV infection so that clinicians are better prepared to identify those at risk of long-term outcomes and treat appropriately. These studies should also prioritize describing the neurocognitive outcomes in infants beyond what is currently available. By directing research in these areas, researchers, clinicians, and other public health professionals will gain a better understanding of what potential future outbreaks could bring and better know how to respond to the health needs of those affected.

References

1. Brighton, S.W., Prozesky, O.W., & de la Harpe, A.L. (1983). Chikungunya virus infection: A retrospective study of 107 cases. *S Afr Med J, 63*, 313-315.
2. Centers for Disease Control and Prevention and Pan American Health Organization. (2011). Preparedness and response for chikungunya virus: Introduction in the Americas. Retrieved January 20, 2016 from http://www.paho.org/hq/index.php?Itemid=40931
3. Powers, A.M. & Logue, C.H. (2007). Changing patterns of chikungunya virus: Re-emergence of a zoonotic arbovirus. *Journal of General Virology, 88*, 2363-2377. DOI: 10.1099/vir.0.82858-0
4. Robinson, M.C. (1955). An epidemic of virus disease in southern province, Tanganyika territory, in 1952-53. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 49*, 28-32.
5. Weaver, S.C. & Lecuit, M. (2015). Chikungunya virus and the global spread of a mosquito-borne disease. *NEJM, 372*, 1231-1239. DOI: 10.1056/NEJMra1406035
6. Calabrese, L.H. (2008). Emerging viral infections and arthritis: the role of the rheumatologist. *Nature Clinical Practice Rheumatology, 4*, 2-3. DOI: 10.1038/ncprheum0679
7. Pan American Health Organization and World Health Organization. (2015). Number of reported cases of chikungunya fever in the Americas by country or territory: 2013-2015. Retrieved January 18, 2016 from http://www.paho.org/hq/?Itemid=40931
8. Ramful, D., Carbonnier, M., Pasquet, M., Bouhmani, B., Ghazouani, J., Noormahomed, T,…Alessandri, J.L. (2007). Mother-to-child transmission of chikungunya virus infection. *Pediatr Infect Dis J., 26*, 811-815. DOI: 10.1097/INF.0b013e3180616d4f
9. Economopoulou, A., Dominguez, M., Helynck, B., Sissoko, D., Wichman, O., Quenel, P.,…Quatresous, L. (2009). Atypical chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005-2006 outbreak on Reunion. *Epidemiol Infec., 137*, 534-541. DIO: 10.1017/S0950268808001167
10. World Health Organization. (2016). Dengue control: chikungunya. Retrieved January 22, 2016 from http://www.who.int/denguecontrol/arbo-viral/other_arboviral_chikungunya/en/
11. Gasque, P., Couderc, T., Lecuit, M., Roques, P. & Ng, L.F.P. (2015). Chikungunya virus pathogenesis and immunity. *Vector-Borne and Zoonotic Diseases, 15*, 241-249. DOI: 10.1089/vbz.2014.1710
12. World Health Organization. (2016). Dengue control: control strategies. Retrieved January 22, 2016 from http://www.who.int/denguecontrol/control_strategies/en/
13. Staples, J.E. & Fischer, M. (2014). Chikungunya virus in the Americas – what a vectorborne pathogen can do. *NEJM, 371*, 887-889. DOI: 10.1056/NEJMp1407698
14. Lanciotti, R.S., Kosoy, O.L., Laven, J.J., Panella, A.J., Velez, J.O., Lambert, A.J., & Campbell, G.L. (2007). Chikungunya virus in US travelers returning from India, 2006. *Emerging Infectious Diseases, 13*, 764-767. Retrieved January 23, 2016 from www.thelancet.com
15. Weaver, S.C. (2014). Arrival of chikungunya virus in the New World: prospects for spread and impact on public health. *PLoS Negl Trop Dis, 8*, e2921. DIO: 10.1371/journal.pntd.0002921

16. Rezza, F., Nicoletti, L., Angelini, R., Romi, R., Finarelli, A.C., Panning, M.,…Cassone, A. (2007). Infection with chikungunya virus in Italy: an outbreak in a temperate region. *Lancet, 370*, 1840-1846. Retrieved January 23, 2016 from www.thelancet.com
17. Grandadam, M., Caro, V., Plumet, S., Thiberge, J.M., Souares, Y., Failloux, A.B.,…Despres, P. (2011). Chikungunya virus, southeastern France. *Emerging Infectious Diseases, 17*, 910-913. DOI: 10.3201/eid1705.101873
18. Leparc-Goffart, I., Nougairede, A., Cassadou, S., Prat, C., & de Lamballerie, X. (2014). Chikungunya in the Americas. *Lancet, 383*, 514. Retrieved January 24, 2016 from www.thelancet.com
19. Centers for Disease Control and Prevention. (2015). Chikungunya virus: geographic distribution. Retrieved January 24, 2016 from http://www.cdc.gov/chikungunya/geo/
20. Renault, P., Solet, J.L., Sissoko, D., Balleydier, E., Larrieu, S., Filleul, L.,…Pierre, V. (2007). A major epidemic of chikungunya virus infection on Reunion Island, France, 2005-2006. *Am J Trop Med Hyg, 77*, 727-731. Retrieved February 12, 2016 from http://www.ajtmh.org/content/77/4/727.full.pdf+html
21. Soumahoro, M.K., Boelle, P.Y., Gauzere, B.A., Atsou, K., Pelat, C., Lambert, B.,…Hanslik, T. (2011). The chikungunya epidemic on La Reunion Island in 2005-2006: A cost-of-illness study. *PLoS Negl Trop Dis, 5*, e1197. DOI: 10.1371/journal.pntd.0001197
22. Oanda. Currency converter. (2016). Retrieved February 12, 2016 from http://www.oanda.com/currency/converter/
23. Krishnamoorthy, K., Harichandrakumar, K.T., Kumari, A.K., & Das, L.K. (2009). Burden of chikungunya in India: estimates of disability adjusted life years (DALY) lost in 2006 epidemic. *J Vector Borne Dis, 46*, 26-35. Retrieved February 12, 2016 from http://www.mrcindia.org/journal/issues/461026.pdf
24. Soumahoro, M.K., Gerardin, P., Boelle, P.Y., Perrau, J., Fianu, A., Pouchot, J.,…Hanslik, T. (2009). Impact of chikungunya virus infection on health status and quality of life: a retrospective cohort study. *PLoS ONE, 4*, e7800. DOI: 10.1371/journal.pone.00078
25. Cochrane Collaboration, The. (2011). Cochrane handbook for systematic reviews of interventions: Version 5.1.0. Retrieved from http://handbook.cochrane.org
26. Bank, A., Batra, A., Colorado, R.A., & Lyons, J.L. (2016). Myeloradiculopathy associated with chikungunya virus infection. *J Neurovirol, 22*, 125-128. DOI: 10.1007/s13365-015-0372-9
27. Chopra, A., Anuradha, V., Ghorpade, R., & Saluja, M. (2012). Acute chikungunya and persistent musculoskeletal pain following the 2006 Indian epidemic: a 2-year prospective rural community study. *Epidemiol Infect, 140*, 842-850. DOI: 10.1017/S0950268811001300
28. Chopra, A., Anuradha, V., Lagoo-Joshi, V., Kunjir, V., Salvi, S., & Saluja, M. (2008). Chikungunya virus aches and pains: An emerging challenge. *Arthritis & Rheumatism, 58*, 2921-2922. DOI: 10.1002/art.23753
29. Ramachandran, V., Kaur, P., Kanagasabi, K., Vadivoo, S., & Murhekar, M.V. (2014). Persistent arthralgia among chikungunya patients and associated risk factors in Chennai, South India. *Journal of Postgraduate Medicine, 60*, 3-6. DOI: 10.4103/0022-3859.128795
30. Schilte, C., Staikovsky, F., Couderc, T., Madec, Y., Carpentier, F., Kassab, S.,…& Michault, A. (2013). Chikungunya virus-associated long-term arthralgia: A 36-month prospective longitudinal study. *PLoS Negl Trop Dis, 7*, e2137. DOI: 10.1371/journal.pntd.0002137

31. Robin, S., Ramful, D., Le Seach, F., Jaffar-Bandjee, M.C., Rigou, G., & Alessandri, J.L. (2008). Neurologic manifestations of pediatric chikungunya infection. *Journal of Child Neurology, 23*, 1028-1035. DOI: 10.1177/0883073808314151
32. Taubitz, W., Cramer, J.P., Kapaun, A., Pfeffer, M., Drosten, C., Dobler, G.,…& Loscher, T. (2007). Chikungunya fever in travelers: Clinical presentation and course. *Clinical Infectious Diseases, 45*, e1-e4. DOI: 10.1086/518701
33. Kularatne, S.A.M., Weerasinghe, S.C., Gihan, C., Wickramasinghe, S., Dharmarathne, S., Abeyrathna, A., & Jayalath, T. (2012). Epidemiology, clinical manifestations, and long-term outcomes of a major outbreak of chikungunya in a hamlet in Sri Lanka: A longitudinal cohort study. *Journal of Tropical Medicine, 2012*, Article ID 639178. DOI: 10.1155/2012/639178
34. Robin, S., Ramful, D., Zettor, J., Benhamou, L., Jaffar-Bandjee, M.C., Riviere, J.P.,…& Alessandri, J.L. (2010). Severe bullous skin lesions associated with chikungunya virus infection in small infants. *Eur J Pediatr, 169*, 67-72. DOI: 10.1007/s00431-009-0986-0
35. 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. DOI: 10.1016/j.jbspin.2009.08.005
36. Manimunda, S.P., Vijayachari, P., Uppoor, R., Sugunan, A.P., Singh, S.S., Rai, S.K.,…& Guruprasad, D.R. (2010). Clinical progression of chikungunya fever during acute and chronic arthritic stages and the changes in joint morphology as revealed by imaging. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 104*, 392-399. DOI: 10.1016/j.trstmh.2010.01.011
37. 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. DOI: 10.1371/journal.pntd.0002004
38. Sissoko, D., Malvy, D., Ezzedine, K., Renault, P., Moscetti, 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. DOI: 10.1371/journal.pntd.0000389
39. Gerardin, P., Fianu, A., Malvy, D., Mussard, C., Boussaid, K., Rollot, O., Michault, A.,…& Favier, F. (2011). Perceived morbidity and community burden after a chikungunya outbreak: the TELECHIK survey, a population-based cohort study. *BMC Medicine, 9*. DOI: 10.1186/1741-7015-9-5
40. de Andrade, D.C., Jean, S., Clavelou, P., Dallel, R., & Bouhassira, D. (2010). Chronic pain associated with the chikungunya fever: long lasting burden of an acute illness. *BMC Infectious Diseases, 10*. DOI: 10.1186/1471-2334-10-31
41. Fourie, E.D. & Morrison, J.G.L. (1979). Rheumatoid arthritic syndrome after chikungunya fever. *S Afr Med J, 56*, 130-132.
42. Borgherini, G., Poubeau, P., Jossaume, A., Gouix, A., Cotte, L., Michault, A.,…& Paganin, F. (2008). Persistent arthralgia associated with chikungunya virus: A study of 88 adult patients on Reunion Island. *Clinical Infectious Diseases, 47*, 469-475. DOI: 10.1086/590003
43. Gerardin, P., Samperiz, S., Ramful, D., Boumahni, B., Bintner, M., Alessandri, J.L.,…& Fritel, X. (2014). Neurocognitive outcome of children exposed to perinatal mother-to-child

chikungunya virus infection: The CHIMERE cohort study on Reunion Island. *PLoS Negl Trop Dis, 8*, e2996. DOI: 10.1371/journal.pntd.0002996

44. Malvy, D., Ezzedine, K., Mamani-Matsuda, M., Autran, B., Tolou, H., Receveur, M.C.,…& Mossalayi, D. (2009). Destructive arthritis in a patient with chikungunya virus infection with persistent specific IgM antibodies. *BMC Infectious Diseases, 9*. DOI: 10.1186/1471-2334-9-200
45. Essackjee, K., Goorah, S., Ramchurn, S.K., 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. DOI: 10.1136/postgradmedj-2012-131477
46. Yaseen, H.M., 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 Musculoskeletal Disorders, 15*. DOI: 10.1186/1471-2474-15-249
47. Chaaithanya, I.K., Muruganandam, N., Raghuraj, U., Sugunan, A.P., Rajesh, R., Anwesh, M.,…& Vijayachari, P. (2014). Chronic inflammatory arthritis with persisting bony erosions in patients following chikungunya infection. *Indian J Med Res, 140*, 142-145.
48. Gerardin, P., Couderc, T., Bintner, M., Tournebize, P., Renouil, M., Lemant, J.,…& Michault, A. (2016). Chikungunya virus-associated encephalitis: A cohort study on La Reunion Island, 2005-2009. *Neurology, 86*, 94-102.
49. Brighton, S.W., Prozesky, O.W., & de la Harpe, A.L. (1983). Chikungunya virus infection: A retrospective study of 107 cases. *S Afr Med J, 63*, 313-315.

Appendix A. Flow Chart of Included Studies

Appendix B. Summary of Findings Table

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Bank, 2016	USA	47 year-old woman who had travelled to the Dominican Republic	1	Case description	IgM IgG	3.5 months	Persistent burning pain in right lower extremity; Lower extremity weakness; Full strength after 6 months; Continued neuropathy for an unknown period of time	The time interval between acute infection and myelopathy suggests that this is an immune-mediated occurrence rather than viral activity
Borgherini, 2008	Reunion Island	Mean Age: 58.3 ± 18 years; Male:Female 1.1:1; 58 hospitalized for acute CHIKV infection; 56 reported persistent arthralgia and 32 reported full recovery; History of arthralgia was reported in 39 patients	88	Cohort	IgM (35 patients were positive)	18.7 ± 2.1 months	Self-reported pain of affected joints in 56 patients with persistent arthralgia: Metacarpo-phalangeal – 32 Metatarsals – 27 Wrists – 28 Ankles – 26 Elbows – 13 Shoulders – 25 Knees – 32 Rachis – 13 Sternoclavicular joints – 1 Hips – 10 Mean number of joints involved (self-reported): 6.2 ± 4.2 Pain upon physical examination in same 56 patients: Metacarpo-phalangeal – 15 Metatarsals – 15 Wrists – 9 Ankles – 16 Elbows – 8 Shoulders – 17 Knees – 12 Rachis – 7 Sternoclavicular joints – 1 Hips – 3 Mean number of joints involved (self-reported): 3 ± 3.8	Comorbidity 40/56 patients; Hypertension 23/52 patients; Ischemic heart disease 21/56 patients; Diabetes mellitus18/56 patients; Pre-existing arthralgia 29/56 patients High discordance between self-reported joint pain and pain during physical examination (could be due to intermittent pain or patient exaggeration) It is unknown if/when the 56 patients recovered Author recommends a large, prospective case-control study

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Bouquillard, 2009	Reunion Island	13 females, 8 males; Mean age: 57.3 ± 12.2 years; All patients diagnosed with RA and no other definite diagnosis of arthritis	21	Prospective cohort	IgM IgG	Diagnosis of RA at 10 months (baseline); Follow-up at 27.6 ± 6.4 months	At Baseline: 18 patients had symmetric polyarthritis; 3 patients had oligoarthritis (≤5 swollen joints); 5 patients with joint erosion; 12 patients with joint space narrowing; 9 patients with normal x-rays At Follow-Up: 17 patients with joint erosion; 17 patients with joint space narrowing; 4 patients with normal x-rays	Three patients had a history of smoking None of the patients had a family history of inflammatory arthritis Immunologic profiles may help in diagnosing RA Cannot know if RA is caused by CHIKV infection
Brighton, 1983	South Africa	Group 1 (94 patients) Mean age: 37, with 42 patients age <17 years; Group 2 (4 patients) Mean age: 54 years Group 3 (3 patients) Mean age: 60 years Group 4 (6 patients) Mean age: 50 years	107	Retrospective cohort	Serology	36-60 months	Group 1: 94 patients (87.9%) had fully recovered at follow-up; Group 2: 4 patients (3.7%) reported mild discomfort or occasional stiffness; Group 3: 3 patients (2.8%) reported residual persistent stiffness, but no pain; Group 4: 6 patients (5.6%) reported persistent joint pain and stiffness with or without swelling; Patients in groups 3 and 4 commonly reported morning stiffness for a mean of 35 minutes (for those with no joint pain) and 24 minutes (for those with joint pain); Group 4 patients had high titers against CHIKV; No patients had evidence of joint erosion (x-ray);	Group 4 patient ages: 16, 52, 52, 54, 60, 64 years Of particular interest is the 16-year old, since studies today focus on long-term outcomes in older individuals.

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Brighton, 1983 (cont'd from pg. iii)							Wrists and ankles were most affected, followed by knees, then MP/PIP joints of the hands; Three patients reported DIP joint pain of the hand	
Chaaithanya, 2014	India	Patients were selected from a larger study of 203 individuals; Mean age of patients reporting persistent symptoms: 58.4 years; Mean age of patients reporting improvement of symptoms: 49.4 years	14	Cohort	IgM IgG	36 months	IgM+ at 36 months: 5/14 patients IgG+ at 36 months: 7/14 patients (3 patients seroconverted) 1 patient went from IgM+ to IgG- X-ray findings: 1 patient recovered and had a normal MRI; 4 patients regressed and had tendonitis with or without tears, bursal effusion, and/or subcondral erosion; 2 patients progressed and had erosions/effusions in MP joints, joint deformities, osteoarthritis and/or synovial thickening; 7 patients had persisting symptoms with joint effusions, bony erosions, marrow edema, joint degeneration, subchondral erosions, and/or ACL and meniscus tears	IgM was still detectable 36 months after acute infection Small sample size, but study suggests that there is an association between persistence of IgM antibodies and long-term joint pain
Chopra, 2008	India	Patients with post-CHIKV musculoskeletal disorders in an epidemic region	30	Cohort	IgM	3-6 months	% of patients presenting with symptoms at 3-6 months: RA-like illness – 20 Undifferentiated inflammatory illness – 20 Seroneg. spondylitis – 23	Two patients were identified with a previous history of psoriatic arthritis (controlled in both cases) CHIKV may be a factor in reactive arthritis and psoriatic

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Chopra, 2008 (cont'd from pg. iv)							Soft tissue rheumatism – 13 Nonspecific arthralgia – 24 Low back pain – 27 Knee pain – 67 Ankle/heel pain – 67 Shoulder pain – 50 Hand/wrist pain – 77 IgM+ 63 Rheumatoid Factor+ 13 CRP+ 80	arthritis A long-term prospective study arose from this (see Chopra, 2012)
Chopra, 2012	India	Rural participants; 69 children (<16 years); 303 adults (16-54 years) 137 elderly (>54 years)	509	Longitudinal population survey identified participants for a prospective cohort study	IgM IgG	Time since survey: 4 months (n=202) 12 months (n=59) 21-24 months (n=24)	Location of Pain – percent of patients with pain at survey, 4, 12, and 21-24 months: Shoulder – 51.4, 46, 52.5, 50; Elbow – 45.4, 38.1, 45.8, 45.8; Upper arm – 21.3, 13.9, 11.9, 12.5; Forearm – 8.3, 7.4, 3.4, 0; Wrist – 45.7, 45.5, 59.3, 66.7; Hand – 43.2, 42.1, 55.9, 62.5; Hip – 10.2, 8.9, 6.8, 12.5; Thigh – 14.3, 14.4, 6.8, 4.2; Knee – 81.3, 66.3, 57.2, 54.2; Calf – 30.2, 23.8, 18.6, 8.3; Ankle – 50.8, 50, 15.3, 58.3; Feet – 19.7, 16.8, 18.6, 33.3; Neck – 19.4, 15.8, 15.3, 20.8; Upper back – 20.3, 15.8, 18.6, 25; Lower back – 30.8, 26.2, 22, 33.3	Smaller joints seemed to be more affected, but the knee was affected most Not all cases were lab confirmed and 13 cases were RF+ only Estimated 43% of the rural population had symptomatic CHIKV infection during the outbreak Women were more affected than men Severe initial joint pain and pre-existing osteoarthritis could be risk factors for long-term outcomes of CHIKV infection
de Andrade, 2010	Reunion Island	Patients seeking health care in 13 different facilities;	106	Cross-sectional	IgM IgG	17 months	56 (53%) patients had long-term pain (≥3 months, or 90 days);	Pain was assessed using the Brief Pain Inventory scale (0=no pain, 10=maximal pain),

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
de Andrade, 2010 (cont'd from pg. v)		Mean age: 47.3 ± 11.9 years; Female:Male 3:1					Mean duration for chronic pain: 128 ± 41; Range of chronic pain: 95-318 days; Brief Pain Inventory for chronic pain is higher than for those without: 6.8 ± 1.9 and 5.9 ± 1.9, respectively *Results on other pain scales/characteristics were not given for this group alone	the short-form McGill Pain Questionnaire (0=none, 3=severe), and the DN4-interview questionnaire (yes/no) that differentiates between neuropathic pain and other types of pain
Essackjee, 2013	Mauritius	Mean age: 52.1 years; 154 (89%) were of Indo-Mauritian origin; 170 (98%) complained of CHIKV infection symptoms; 82.6% of the participants were women	173	Retrospective cohort	Not lab-confirmed. A patient was considered CHIK+ if they had fever, arthralgia and rash.	27.5 months	At follow-up with 136 patients: Reported persistent musculoskeletal symptoms, most commonly in the 51-60 year age range (41 patients); Mean age for persistent symptoms: 54.7 ± 12.7 years; Pain in joints – 133; Joint swelling – 96; Symmetrical – 101; Pain, swelling, stiffness – 32; Arthralgia w/o swelling or stiffness – 32 (associated with better recovery rate); Age 50+ and symmetrical joint pain was associated with RA at follow-up	Older age at time of infection, being female, and baseline symmetrical joint pain are thought to be related to persisting symptoms Subject to patient recall At follow-up with 136 patients: Pre-existing MSK pathology/symptoms – 25 (OR=3.9) Any pre-existing condition – 16 Treatment at baseline of 136 patients: Took at least 1 drug – 135 Paracetamol – 120 (OR=2.4) NSAIDs – 116 (OR=2.1) Glucocorticoids – 19 (OR=5.8) Injection – 15 (OR=0.5) Antibiotics – 2 (OR=0.1) Paracetamol and NSAIDs – 109 (OR=2.5)
Fourie, 1979	South Africa	High school-aged children and adults who were visiting	130	Cohort/Case descriptions	Serology	18 months	CHIKV was isolated in only 8 subjects; 5 patients (4 middle-aged	Older patients were more affected by long-term outcomes

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Fourie, 1979 (cont'd from pg. vi)		the northern Transvaal bushveld; Average age (excluding middle-aged adults): 16 years					and one 16-year old) had arthritis and fever episodes up to 20 months after infection	
Gerardin, 2011	Reunion Island	Women: 645 Men: 449 Mean age: 36 years (Range 1 month-93 years)	512	Retrospective cohort based on a cross-sectional population-based SEROCHIK survey	IgG	16 months (Range 13-20 months)	512 people were found to be CHIKV+ <20 – 214 20-29 – 124 30-39 – 159 40-49 – 180 50-59 – 187 60-69 – 133 ≥70 – 97 Symptoms – % CHIKV+: Musculoskeletal pain – 42.8; Fatigue – 53.6; Light cerebral disorders – 75.3; Headache – 25.9; Sleep disorders – 31.2; Memory troubles – 42.2; Attention difficulties – 37.1; Mood disturbance – 38.4; Depression – 14.7; Sensorineural disorders – 48.8; Blurred vision – 42; Hearing difficulties – 17.8; Digestive disorders – 18.3; Dermatological disorders – 36.1; Skin lesions – 19.9; Alopecia – 21.9	Compared to CHIKV- individuals, CHIKV+ individuals were statistically significantly more likely (p-val<0.05) to self-report musculoskeletal pain, fatigue, light cerebral disorders, sleep disorders, memory troubles, attention difficulties, mood disturbance, depression, sensorineural disorders, and blurred vision Determinants for rheumatic symptoms at follow-up include being CHIKV+ (OR=2.1) and being over age 40 (40-49 OR=2.7; 50-59 OR=3.3; 60-69 OR=3.9; 70+ =3.5) Determinants for sensorineural disorders at follow-up include being over age 40 (40-49 OR=2.6; 50-59 OR=2.7; 60-69 OR=2.7; 70+ =2.6) Gender, BMI, nor comorbidities seemed to have an impact on rheumatic symptoms at follow-up Gender, age, BMI, nor comorbidities seemed to have

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Gerardin, 2011 (cont'd from pg. vii)								an impact on fatigue and light cerebral disorders at follow-up (ORs<1.8 for all variables) Overall, 43-75% of CHIKV+ patients reported persistent or late-onset symptoms that are thought to be attributable to CHIKV infection
Gerardin, 2014	Reunion Island	Neonates and previously CHIKV-infected neonates	33	Prospective cohort	IgM IgG	24 months	RBL scale data for maternal characteristics: Avg. maternal age: 28.1 ± 7.1 years Born in Indian Ocean – 32 Born in France – 1 Primary school education – 19 High school education – 10 University education – 4 Live alone – 15 Lives with partner – 18 Parity 0 – 11 Parity 1 – 13 Parity 2 – 2 Parity ≥3 – 6 Pre-pregnancy BMI<25 – 17 " " BMI 25-29.9 – 8 " " BMI≥30 – 8 30 mothers smoked during pregnancy, 1 did not Low 5-itemsocial deprivation score – 3 Moderate 5-IDS – 12 High 5-IDS – 17 RBL scale data for neonatal characteristics: Mean gestational age: 38.06 ± 1.29 weeks 4 preterm, 29 full-term births	Study's focus is on vertical transmission of CHIKV The Revised Brunet-Lezine (RBL) scale was used at 24 months to assess neurocognitive function Subscores from the RBL were used to find the Developmental Quotient between infected and non-infected neonates DQ score 70-85 signifies moderate developmental delay, and less than 70 signifies severe developmental delay Statistically significant risk factors (p-val<0.05) for global developmental delay were CHIKV infection (Adjusted IRR=2.79) and head circumference < -2 SD (Adjusted IRR=2.38)

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Gerardin, 2014 (cont'd from pg. viii)							7 small, 26 normal size for gestational age Mean 5-minute apgar score – 9.75 15 breastfeeding, 17 not breastfeeding at discharge Mean head growth z-score - -0.37 Head circumference at 24 months: -1 SD≤z-score< +2 SD – 26 -2 SD≤z-score< -1.5 SD – 1 z-score< -2 SD – 4 DQ scores measured between 15.8-27 months for exposed and infected neonates: Global – 86.3 Movement/Posture – 98.5 Coordination – 83.5 Language – 80.0 Sociability – 90.5	
Gerardin, 2016	Reunion Island	Adult patient mean age: 63.9 ± 15.6 years (Range 33-88 years) Infant patient mean age: 1.6 ± 1.15 months (Range 4 days-5.4 months)	57 (21 adults, 36 infants)	Ambispective cohort (CHIKV+ patients with neurologic symptoms were chosen retrospectively and were followed over a period of time)	IgM or RT-PCR	36 months	At baseline, among the 57 patients with CHIKV-associated CNS, 24 (42.1%) had altered mental status (probable/possible encephalitis) and 33 (57.9%) were classified as having nonencephalitic CHIKV-associated CNS disease (NECACD); Outcomes for altered mental status, NECACD: Intensive care support – 10, 3 Length of stay >4 days – 14, 13 Dead – 3, 4	Patients were included only if they had no pre-existing conditions or if there was no other known cause of encephalitis The burden of neurologic sequelae thought to be caused by CHIKV infection could not be calculated precisely (17.6%-43.1%)

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Gerardin, 2016 (cont'd from pg. ix)							Vegetative state – 0, 0 Lower severe disability – 1, 2 Upper severe disability – 0, 2 Lower moderate disability – 1, 1 Upper moderate disability – 3, 2 Lower good recovery – 1, 1 Upper good recovery – 7, 7 Not assessed – 8, 14 3 adult patients were diagnosed with neurologic sequelae, including epilepsy, post-infectious dementia, and cognitive disorder; 1 infant developed cerebral palsy and blindness; 4 infants had poor neuro-developmental performance	
Kularatne, 2012	Sri Lanka	237 men and 276 women in a rural village with the triad of CHIKV symptoms; 120 were school-aged children; Mean age: 35 years (Range 1-90 years)	513	Longitudinal cohort	Triad of clinical features (fever, rash, joint pain)	7 months	1 patient died, leaving 512 for analysis Chronic Arthritic Disability (CAD) by age group: 0-12: 9/91 (9.9%) 13-22: 20/74 (27%) 23-32: 35/81 (43.2%) 33-42: 44/79 (55.7%) 43-52: 46/76 (60.5%) 53-62: 36/53 (67.9%) 63-72: 31/41 (75.6%) 73-82: 8/12 (66.7%) 83-92: 1/2 (50%) Non-arthritic complications: Carpal tunnel syndrome: 110/512 (21.5%)	Females were more likely to suffer from CAD than males 34/512 (7%) gave past history of arthritis 21 of the 34 (62%) with arthritis history experienced exacerbation of arthritis with CHIKV infection CAD is still being followed-up

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Kularatne, 2012 (cont'd from pg. x)							Postviral fatigue syndrome: 8/512 (1.6%) Thrombophlebitis: 2/512 (0.4%) Respiratory tract infection: 4/512 (0.8%) Calf swelling: 1/512 (0.2%) Facial swelling: 3/512 (0.6%)	
Malvy, 2009	France	60-year old French man living on Reunion Island presenting with acute flu-like symptoms and arthralgia	1	Case description	IgM IgG	24 months	At 1-year follow-up (2006): Patient had developed refractory tenosynovitis in wrists At 2-year follow-up (2007): Patient had symmetrical inflammatory arthritis in wrists with fixed edema in both hands (worse on the right hand); Synovitis in extensors and flexors of wrists and fingers; Radiography showed subchondral defects in hands, wrists, and fingers; MRI showed bilateral periostal inflammation and edematous carpitis with synovitis in the fingers; The left ankle showed inflammation	Joint and bone erosion occurred nearly two years after acute infection
Manimunda, 2010	India	Patients >10 years of age recruited from five different health facilities; Male:Female 1:1.15; Median age: 35 years (IQR 25-44 years)	203	Longitudinal follow-up	IgM	10 months	100/203 patients had symptoms at follow-up: Join pain – 94/203 (46.3%); Fatigue – 27/203 (13.3%); Tingling/Numbness in extremities – 12/203 (5.9%); One patient each had rash, myalgia, bone pain, and neuritis without joint pain; Two patients had fatigue	36% of patients met RA criteria set by the ACR Underlying causes should be studied

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Manimunda, 2010 (cont'd from pg. xi)		22 patients 10-13 years old; 13 patients 14-19 years old; 39 patients 20-29 years old; 62 patients 30-44 years old; 67 patients ≥45 years old					alone; At least one joint was affected in 55/94 patients (58.5%); Five patients had limited mobility of at least one joint; One patient had fixed flexion deformity of the fingers on both hands; Morning joint stiffness in at least one joint lasting >1 hr in 74/94 patients (78.7%); Joint Type – % affected of 94 patients: Knee – 59.5% Ankle – 54.2% Small joints in lower limbs – 52.1% Small joints in upper limbs – 40.4% Wrist – 30.8% Elbow – 29.7% Shoulder – 14.8% LS – 13.8% Hip – 10.6% SI – 10.6% Cervical neck – 8.5% Number of joints involved in 94 patients with pain: Polyarthritis – 65.9% Oligoarthritis – 23.4% Monoarthritis – 9.4%	
Ramachandran, 2014	India	Mean age: 37.7 ± 14.3 years; 40% males; Median monthly income: $66.50 (Range $19-$950);	403	Retrospective cumulative Prospective cohort Nested Case-control	Fever and joint pain between May-June 2006;	Up to 30 months	Joint pain duration out of 403 patients: 3-6 months – 16% 6-12 months – 12.7% 12+ months – 7% Up to 30 months – 0.74%	Due to infrequent water supply, water was stored at homes (possible risk factor for mosquito breeding)

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Ramachandran, 2014 (cont'd from pg. xii)		148 had no education or little primary education; 154 middle school education; 101 had either high school or college education			Lab confirmed in subset		Mean duration of joint pain: 114.4 days ± 157.9; Knee – 96% Wrist – 80% Ankle – 77% Phalanges – 77% Tarsals – 72% Metatarsals – 48% Shoulder – 4% Elbow – 2% Hip – 3.2% Number of joints involved: 6 – 36% 5 – 23% 3 – 14% 1 – 6% Swelling was reported in 46% of patients	Risk factors for persistent arthritis: 35+ years old (OR=2.0) >4 joints affected (OR=3.4) Swelling in joints (OR=8.6) Rash (OR=4.0) High-grade fever (OR=4.6) Rash was not statistically significant.
Robin, 2008	Reunion Island	Children <18 years old who presented at a hospital with neurologic illness related to CHIKV infection; Mean age: 5.5 years (Range 3 days – 17 years); 23 boys, 7 girls	30	Retrospective descriptive	RT-PCR IgM	6 months	21 children for follow-up; One had language development issues with autistic tendencies and echolalia; One had persistent neurodevelopmental delay with microcephaly and strabismus; One had recurrent seizures after stopping medication; Neurologic sequelae or fatal issues concerned 6 of 12 patients who had severe acute infection and one patient with mild acute infection; MRIs for two neonates showed atrophy in the frontal lobes, bilateral frontal, and parietal cavitations in the white matter	Timeline is not clearly defined

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Robin, 2010	Reunion Island	Mean age: 3.4 months; 8 boys, 5 girls; Presented with skin blistering/ lesions on ≥10% of the body	13	Retrospective descritpive	RT-PCR IgM	6-9 months (Mean 7.4 months) 36 months (Mean 3.2 years)	At 6-9 month follow-up on 12 infants: Severe bullous lesions had healed to a state of repigmentation with some central spots; Two patients developed hypertrophic keloid scarring; Photosensitivity was reported in one patient; Xerotic eczema was reported in one patient At 36 month follow-up on 9 children: Full repigmentation of the skin with no other sequelae in two patients; Discrete peripheral hyperpigmentation was observed in five patients; Persisting disgracious keloid scarring in two patients	Focus is on severe bullous skin lesion recovery – all 13 infants with this complication were included in the follow-up study
Schilte, 2013	Reunion Island	Patients enrolled for febrile arthralgia	180	Prospective longitudinal	qRT-PCR IgM IgG	4, 6, 14, and 36 months	M4 – 129 patients: The majority of patients had polyarthritis, followed by oligoarthritis and monoarthritis; M6 – 122 patients: The majority of patients had polyarthritis, followed by oligoarthritis and monoarthritis; M14 – 148 patients: The majority of patients had oligoarthritis, with polyarthritis and monoarthritis being about equal M36 – 102 patients: The great majority had	Telephone interviews were conducted at 4, 6, 14, and 36 months 76 of 180 patients were able to be followed at all time points All patients had arthralgia at time of acute infection 5 of 180 had previous history of arthralgias Monoarthralgia – 1 joint affected Oligoarthralgia – 2-3 joints affected Polyarthralgia – 4+ joints

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Schilte, 2013 (cont'd from pg. xiv)							polyarthritis, followed by oligoarthritis and monoarthritis; Of 62 patients with arthralgia at M36: Local swelling – 39/62 Osteo-ligamentous pain – 22/62 Myalgia – 24/62 Cutaneous lesion – 31/62 Asthenia – 48/62 Sleeping disorder – 35/62 Dysgeusia – 11/62 Depression – 31/62 Memory disorder – 27/62 Concentration disorder – 24/62	affected Statistically significant (CI does not include 1) risk factors for arthralgia at M14: CRP at inclusion >10 (OR=3.12) Diabetes at inclusion (OR=2.83) Permanent arthralgia at M4 (OR=6.28) Memory disorder at M4 (OR=7.4) Concentration disorder at M4 (OR=15.79)
Sissoko, 2009	Reunion Island	Patients >16 years; Seropositive for CHIKV infection between March 1-June 30, 2005; 69% women, 31% men; Mean age: 52 ± 12 years (Range 16-86)	147	Retrospective cohort	IgM	15 months (median time between onset and interview): 439 days (Range 370-508 days)	Symptoms at 15-month follow-up: None – 63 (43%) Intermittent – 31 (21%) Persistent – 53 (36%) Symptom presentation at 15-month follow-up: Pain – 84 (57%) Morning stiffness ≥45 minutes – 61 (41%) Swelling – 22 (15%) Joint pain intensity (NRS score) at 15-month follow-up: Mild – 70 (83.3%) Moderate – 13 (15.5%) Severe – 1 (1.2%) 63 (43%) patients reported full recovery at 15 months, 31 (21%) reported at least 1 relapse in symptoms, and 53 (36%) reported permanent symptoms	All patients reported joint pain during acute phase infection Comorbidities: Total – 76/147 (52%) Hypertension – 48 (33%) Osteoarthritis – 38 (26%) Diabetes mellitus – 32 (22%) Chronic cardiac disease – 14 (10%) Statistically significant (CI does not include 1) risk factors for persistent arthritis at 15 months: Age ≥45 years (OR=4.2) ≥1 Comorbidity (OR=3.0) Hypertension (OR=2.4) Osteoarthritis (OR=3.2) NRS ≥7 (OR=3.6) Data were self-reported by telephone interviews

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Taubitz, 2007	Germany	Patients who traveled to epidemic countries (western Indian Ocean, India, Southeast Asia); 14 women, 6 men; Mean age: 44.6 years (Range 12-64 years); 9 traveled to Mauritius; 3 to India; 2 each to Reunion Island, Malaysia, Seychelles; 1 to Madagascar; 1 to Indonesia	20	Retrospective cohort	IgM IgG RT-PCR Cell culture	6 months	2 (13%) patients experienced joint pain >6 months after acute infection Persistent arthralgia occurred in 7 patients, but study ended before their recovery	Unclear timeframe for the 7 patients experiencing persistent arthralgia Unclear if acute symptoms were same/similar to symptoms at time of interview
Thiberville, 2013	Reunion Island	Adult patients (18-65 years old) with typical CHIKV infection symptoms; Mean age: 40 years; Male:Female 1.7:1	54	Prospective cohort (descriptive only)	RT-PCR	3.33 months (100 days) 10 months (300 days)	Patients with several arthralgic joints were more likely to have persistent joint pain at 10 months Patients reporting persistent joint pain at 10 months were significantly older Five (9.3%) patients had pre-existing orthopedic illness	Patients were chosen from a larger clinical trial Follow-up data at 3.33 months and 10 months were collected by telephone interviews No data at 3.33-month follow-up were reported Age was considered an independent risk factor for symptomatic illness at 10 months Being female was independently associated with having a higher number of joints involved at acute infection and at 10 months Females were more likely to report persistent symptoms

First Author, Year of Study	Country of Study	Population Characteristics	Sample Size	Study Design (if applicable)	Method CHIKV Infection Confirmed	Time Since Acute Infection	Long-term Outcomes (≥3 months after acute illness)	Notes and Observations
Yaseen, 2014	France	French military who participated in surveys in 2006 and 2008; Median age: 40 years	403	Prospective cohort	Serology	Baseline at 6 months after acute infection (2006 data) 30 months (2008 data)	124 (31.3%) patients of 403 reported arthralgia at 30 months; 57 (14.1%) patients of 403 reported arthritis; CHIKV+ was associated with arthralgia/arthritis at 30 months; Symptoms in acute infection were associated with persistent RDs at 30 months and especially at 6 months; Arthralgia at 6 months was 14 times more frequent in those reporting arthralgia/arthritis at 30 months compared to those with no RDs; Rheumatic comorbidities were reported 1.3 times more frequently in those with RDs at 30 months	Limited analysis was performed for the CHIKV+ group (101 patients) Arthritis – joint swelling and pain and/or stiffness Arthralgia – joint pain and/or stiffness Severity of acute CHIKV infection phase negatively affects long-term recovery and increases risk of long-term arthritis