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EDITORIAL

# Lessons Learned From Chikungunya in the Americas

Jonathan J. Miner and Deborah J. Lenschow

In 2013, chikungunya virus arrived in the Western Hemisphere, spreading like wildfire across the islands of the Caribbean, Mexico, Central America, and South America, resulting in ~3 million infections (1). Similar to historical outbreaks in the Eastern Hemisphere, chikungunya virus spread quickly in a population without preexisting immunity. The chikungunya virus outbreak also created new challenges for rheumatologists, who were suddenly encountering a disease entity with which there was little familiarity. Included among these challenges was identifying the factors that predispose patients to the development of chronic arthritis, understanding the pathogenesis driving persistent arthritis, and determining treatments that would be efficacious and safe in patients with chikungunya arthritis. In this issue of *Arthritis & Rheumatology*, two new studies and a review address some new discoveries from the chikungunya virus epidemic in the Americas and discuss lessons learned from prior outbreaks of chikungunya arthritis in the Eastern Hemisphere (2–4).

Upon infection with chikungunya virus, ~90% of patients develop acute symptoms, which can include fever, inflammatory arthritis with morning stiffness, and severe pain throughout the first week after infection (5). Some patients also develop a rash and conjunctivitis during the acute phase of the illness. Severe cases can even cause viral encephalitis and occasionally death in neonates (6). Also of concern, especially to the rheumatologist, is the fact that many patients infected with chikungunya virus develop arthralgias and arthritis, which can persist for up to 3 years (7). The mechanisms underlying persistent chikungunya arthritis remain a mystery and are an area of active scientific investigation.

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Alphaviruses are enveloped, single-stranded positive sense RNA viruses belonging to the *Togaviridae* family (5). Alphaviruses can be divided into New World alphaviruses that typically cause encephalitis (e.g., Western equine encephalitis virus) and Old World alphaviruses that cause viral arthritis (e.g., chikungunya virus and Ross River virus). Like some other arthritogenic alphaviruses, chikungunya virus is spread by *Aedes* mosquitos, and in particular *A aegypti*, which is found primarily in tropical and subtropical climates.

Numerous epidemiologic studies were published in the wake of the 2006 chikungunya virus epidemic on Réunion Island, where approximately one-third of the island's population was infected (6,8–11). Those studies defined the frequency of acute and chronic manifestations of disease in the Eastern Hemisphere. However, less was known about epidemiologic outcomes of the chikungunya virus outbreak in the Americas. In one of their studies published in this issue of *Arthritis & Rheumatology*, Chang et al (2) set out to determine the frequency of chronic joint pain after chikungunya virus infection in a Colombian cohort. The authors enrolled 485 serologically confirmed cases and clinically reevaluated the patients 20 months after infection. As noted in our study of a small cohort of chikungunya virus–infected American travelers to Haiti (12), the most commonly affected joints in the patients included the small joints of the distal extremities. At the 20-month follow-up the authors found that arthralgias were persistent in ~25% of the patients. They also identified some interesting correlates of persistent joint pain, including college graduate status, headache at onset of infection, and ≥4 weeks of initial pain, among others.

There are several major implications of this study by Chang et al (2). First, the presence of persistent joint inflammation strongly suggests that the chikungunya virus strain that spread to the Americas caused a chronic arthritis disease phenotype similar to what was described in prior outbreaks in the Eastern Hemisphere. The authors also raised important limitations of the study. For example, Mayaro virus is an arthritogenic Old World

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alphavirus that is found in the Amazon and causes inflammatory arthritis with morning stiffness, similar to chikungunya arthritis. Anti–Mayaro virus and anti–chikungunya virus antibodies may cross-react (13), thereby confounding diagnostic testing. Thus, although Mayaro virus was not known to be spreading in this region of Colombia at the time of the study, the presence of confounding Mayaro virus infections could not be completely excluded. Another intriguing question, which was not addressed in this epidemiologic study, is why chikungunya virus tends to preferentially infect distal joints. Notably, a recent study by Prow et al showed that mice infected with chikungunya virus have more severe disease, more robust viral replication, and impaired antiviral type I interferon (IFN) response when the mice are housed at lower temperatures (14). Since distal joints are slightly cooler than proximal joints, temperature-dependent antiviral immunity could be a possible explanation of why chikungunya virus preferentially affects small joints in the distal extremities (3).

Mechanisms of persistent chikungunya arthritis are not well understood, although it is known that there are some intriguing similarities in the immunologic phenotypes of peripheral blood mononuclear cells from patients with rheumatoid arthritis and those with chikungunya arthritis (12). Several hypotheses have been proposed, including the persistence of a low level of replicating virus in the joints, the induction of autoimmunity, and the persistence of viral RNA in the synovium that can act as a pathogen-associated molecular pattern (PAMP) to activate pattern-recognition receptors and trigger chronic inflammation. In a second study by Chang et al (3), the authors looked for evidence of viral persistence in patient synovial fluid 22 months after infection. The results were negative; the authors were unable to culture replicating virus from the synovial fluid and found no evidence of chikungunya viral RNA or proteins in the synovial fluid by several different techniques, including quantitative reverse transcriptase–polymerase chain reaction and mass spectrometry.

A major implication of that study by Chang et al (3) was that persistent chikungunya arthritis may result from induction of autoimmunity rather than low-level viral persistence. Similar to prior studies (5,12), the authors found no association between the presence of anti–cyclic citrullinated peptide autoantibodies or rheumatoid factor antibodies and persistent disease. However, one prior study had identified chikungunya virus RNA and protein in perivascular synovial macrophages in a patient 18 months after infection (15). Viral antigen also persisted in macrophages of nonhuman primates several months after infection (16). Thus, although chikungunya virus RNA was not detected in synovial fluid from patients, the persistence of viral RNA and/or viral antigen in affected joints cannot be excluded without synovial biopsies. Indeed, the absence of viral antigen in synovial fluid does not exclude the possibility that viral RNA in synovial macrophages or other cell types within the joint may be contributing to chronic disease. As a hypothetical example, defective viral genomes, which may have the capacity to replicate and produce PAMPs without generating viral antigen, may be able to activate the type I IFN response locally and cause chronic joint pain. Chang et al did not evaluate IFN-stimulated genes, which would be expected to be up-regulated in the presence of PAMPs. Finally, it is important to underscore that viral RNA testing, as with any testing, has a limit of detection, making very low levels of PAMP difficult to detect.

Nevertheless, the negative findings in this second study by Chang et al (3) are consistent with the authors' hypothesis that persistent immunologic activation, rather than persistent virus, may explain the persistence of chronic joint pain in patients with chikungunya arthritis. The absence of infectious virus is likely to minimize the risk associated with immunomodulatory therapies (e.g., abatacept, tofacitinib, and fingolimod), which remain to be tested in humans but have shown some efficacy in mouse models of chikungunya arthritis (12,17).

Despite promising therapeutic studies in mouse models of chikungunya virus pathogenesis, it is important to underscore that the efficacy and risks of immunosuppressive therapies during the acute phase of infection remain unknown. Since some patients have died of encephalitis during chikungunya virus outbreaks (10), and immunosuppression might confer added risk of severe infection, the use of immunosuppressive therapies for chikungunya arthritis should be considered with caution. This point is also underscored in the third article on chikungunya arthritis, by Zaid et al (4), published in this issue of *Arthritis & Rheumatology*. The authors review the clinical manifestations and epidemiology of chikungunya arthritis as well as the current body of evidence for therapies for chikungunya arthritis (4). Whereas nonsteroidal antiinflammatory drugs have shown some efficacy in treating pain associated with acute and chronic chikungunya arthritis, the authors correctly emphasize the fact that efficacy of disease-modifying antirheumatic drug (DMARD) therapies in chikungunya arthritis has not been clearly established. Small studies have suggested that there may be a role for certain DMARDs in the treatment of chronic chikungunya arthritis (18); however, carefully blinded, randomized controlled trials are necessary to draw firm conclusions about therapeutic interventions. Since chronic joint pain eventually resolves spontaneously,

therapeutic interventions should be stopped periodically to assess for resolution of symptoms.

Patients infected with chikungunya virus develop long-lived immunity. Therefore, many of the people affected by the recent chikungunya virus epidemic in the Americas have developed protective immunity against chikungunya virus. Nevertheless, other chikungunya virus strains that are spread by *Aedes albopictus* might still have the potential to cause outbreaks in previously unaffected parts of the continental US. For example, a very large outbreak on Réunion Island in the Indian Ocean in 2006 was associated with a mutation in the chikungunya virus genome, which led to enhanced replication and transmission in *A albopictus* mosquitos (19), a species that is found in more temperate climates, including parts of Europe and the continental US. Understanding the relationship between viral genetics and the capacity of chikungunya virus to spread in specific mosquito vectors is important, since this has implications for the potential of specific chikungunya virus strains to spread to particular geographic locations. Indeed, the distribution of these specific mosquito vectors correlates with prior chikungunya virus epidemics and has also predicted future outbreaks. The particular strain of chikungunya virus that spread to the Americas in 2013 lacked the *A albopictus*–adapted mutation, which may have limited the spread of chikungunya virus to regions where *A aegypti* mosquitoes are prevalent, including the islands of the Caribbean, the US Gulf Coast, Mexico, Central America, and South America.

This implies that potential remains for other chikungunya virus strains to eventually spread in the continental US in a population without preexisting immunity against arthritogenic alphaviruses. Furthermore, chikungunya virus–related alphaviruses, including Mayaro virus, which is endemic in South America, also have the potential to emerge and cause outbreaks. A combined effort of basic, translational, and clinical research will prepare future generations for new epidemics, whether it be a re-emergence of chikungunya virus, or the emergence of other arthritogenic alphaviruses.

## AUTHOR CONTRIBUTIONS

Dr. Miner drafted the initial version of the article. Drs. Miner and Lenschow revised the editorial critically for important intellectual content and approved the final version to be published.

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## QUESTÕES

(As questões poderão ser respondidas em português, inglês ou espanhol)

The present editorial addresses three articles published in the same issue of *Arthritis* and *Rheumatology*. Read the editorial thoroughly and answer the following questions:

1. What is the main topic addressed by all three articles? (2,5 pts)
2. What is the main scientific question addressed by each of the articles? (2,5 pts)
3. The editorial highlights negative aspects and limitations of the second article. Please list them (2,5 pts)
4. When discussing the second article (by Chan et al.), Drs. Miner and Lenschow discuss how the findings of the study may impact on use of immunomodulatory therapies as treatment for the disease. Please comment on this (2,5 pts)

Answers/Gabarito:

1. The articles mainly address the rheumatologic manifestations of Chikungunya virus infections, especially on long term follow up.
   Os artigos abordam principalmente as manifestações reumatológicas das infecções por virus chikungunya, especialmente em seguimento crônico.

2. Article 1 – the authors evaluated patients infected with chikungunya during an outbreak in Colombia, aiming to determine the frequency of chronic joint pain.
   Article 2 – the authors investigated whether the virus (or its particles) persisted in the synovial fluid at 22 months after primary infection.
   Article 3 – the authors review clinical manifestations and epidemiology of chikungunya arthritis, as well as current therapeutic approaches and their efficacy.
   Artigo 1: os autores avaliaram pacientes que haviam sido infectados pelo vírus chikungunya na epidemia da Colômbia, a fim de determinar a frequência de envolvimento articular crônico.
   Artigo 2: os autores investigaram se o vírus (ou suas partículas) persistiam no líquido sinovial dos pacientes, avaliados aos 22 meses pós-infecção.
   Artigo 3: os autores revisaram as manifestações clínicas e epidemiológicas da artrite por chikungunya, assim como as abordagens terapêuticas disponíveis e sua eficácia.

3. The findings in article 2 disagree with those from previous studies that suggest persistence of viral antigens in the tissue of infected patients. Although no evidence of viral presence was detected in the synovial fluid, the methods used may be considered limited:
   1) Synovial biopsies were not evaluated.
   2) It is possible that the virus or viral particles are confined to cells from the immune system, such as macrophages.
   3) Viral RNA testing has limited detection efficacy when the virus is present at low levels.

Os achados do artigo 2 contradizem aqueles de outros estudos publicados, que demonstram persistência de partículas virais nos tecidos dos pacientes previamente infectados. Embora o artigo de Chan et al. (artigo 2) não tenha evidenciado presença do vírus no líquido sinovial dos pacientes avaliados, apontam-se limitações nos métodos empregados:

1) Biópsias sinoviais não foram avaliadas,

2) É possível que partículas virais estivessem confinadas ao interior de células do sistema imunológico, como macrófagos, não testadas no estudo,

3) os métodos de detecção viral têm baixa sensibilidade para detectar o vírus em baixas concentrações.

4. Although the second study supports persistent immunological activation as the most probable mechanism of chronic arthritis after chikungunya infection, immunomodulatory treatment must be handled with caution. Immunosuppression may confer risk of severe viral dissemination, such as encephalitis.
Embora o segundo estudo sugira ativação imunológica persistente, ao invés de presença do vírus, como principal mecanismo de artrite crônica pelo chikungunya, tratamentos imunomoduladores devem ser usados com cuidado. A imunossupressão pode aumentar o risco de disseminação viral, especialmente encefalite.

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**Folha de Resposta 1**

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**Folha de Resposta 2**

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**Folha de Resposta 3**

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**Folha de Resposta 4**