

## **CHIKUNGUNYA FEVER: ORAL HEALTH CARE IMPLICATIONS**

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## **Abstract**

Chikungunya virus (CHIKV) was first isolated in humans in 1952, following an epidemic in Tanzania. The origin of the name means “to bend forward or become contorted,” in reference to the posture adopted by patients due to the joint pain that occurs during the infection. Epidemiology data suggest that by the end of 2015, about 1.6 million people had been infected with CHIKV. The acute period of the disease is characterized by high fever, myalgia, joint pain, and severe and disabling polyarthritis, sometimes accompanied by headache, backache, and maculopapular rash, predominantly on the thorax. Around half of the patients will progress to the subacute and chronic phases, that is manifested by persistent polyarthritis/polyarthralgia, accompanied by morning stiffness and fatigue, which could remain for years. Oral features may include gingivitis possibly as a consequence of arthralgia of the hands leading to limited oral health measures as well as burning sensation and oral mucosal ulceration. Treatment in the acute phase includes acetaminophen, and weak opioids (tramadol or codeine) should be used in cases of severe or refractory pain. For patients who have progressed to the subacute stage and who have not had notable benefit from common analgesics or opioids, NSAIDs, or adjunctive pain medications (anticonvulsants or antidepressants) may be of benefit. In patients with moderate-to-severe musculoskeletal pain or in those who cannot be given or tolerate NSAIDs or opiates, prednisolone should be prescribed.

**Keywords:** Arboviruses, Chikungunya fever, Epidemiology, Oral, Dental.

## Introduction

The Chikungunya virus (CHIKV), which belongs to the family *Togaviridae*, genus *Alphavirus*, was first isolated in humans in 1952, following an epidemic in Tanzania, Africa. The origin of the name comes from the makonde dialect and means "to bend forward or become contorted", in reference to the posture adopted by patients due to the joint pain that occurs during the infection (Lumsden, 1955). The main vectors of CHIKV are the yellow fever mosquitos *Aedes aegypti* and *Aedes albopictus*, whose females have the capacity to infect humans through bites (Carvalho, Lourenco-de-Oliveira, Braga, 2014).

Since the first Chikungunya fever epidemic described in Tanzania until 2013, the Americas had recorded only imported cases, most of them in the United States, when, in October of that year, the first cases were reported on Saint Martin Island in the Caribbean. However by the end of 2015, about 1.6 million people had been infected with CHIKV (Leparc-Goffart, Nougairède, Cassadou, Prat, de Lamballerie, 2014; Pan American Health Organization, 2016; Weaver, Lecuit, 2015). According to the World Health Organization (WHO), 349,936 suspected cases of Chikungunya fever were reported world wide in 2016, of which 146,914 were laboratory confirmed, most of them in Brazil (265,000 suspected cases) (Brazilian Health Ministry, 2017; Pan American Health Organization, 2017).

CHIKV, as well as Zika and Dengue viruses, are transmitted by the same mosquito – *Aedes aegypti*. CHIKV is inoculated into the human skin through mosquito bites along with saliva and a series of immunomodulatory and anti-hemostatic molecules, which induce early cell infiltration and the production of pro-inflammatory cytokines. There is then a phase of intense viral replication in cutaneous fibroblasts and macrophages, dissemination to the lymph nodes and release of the virus into the circulation and consequent infection and impairment of target organs, such as joints and muscles (Agarwal, Joshi, Nagar, Sharma, Sukumaran et al., 2016; Lum, Ng, 2015; Rougeron, Sam, Caron, Nkoghe, Leroy et al., 2015).

The mechanism by which disease chronicity occurs is not fully known. It appears to be the result of a combination of direct and indirect damages. Direct cell and tissue damage seems to be caused by viral replication, leading to activation of (the indirect) immune response in target tissues (Assuncao-Miranda, Cruz-Oliveira, Da Poian, 2010) or deregulation of the mechanisms of inflammatory process control, caused by the presence of viral RNA (Chirathaworn, Rianthavorn, Wuttirattanakowit, Poovorawan, 2010).

Synovial joint involvement is common (see below) and the synovial histopathological changes observed after CHIKV infection are similar to those found in patients with rheumatoid arthritis (RA) or other chronic inflammatory arthropathies and include synovial hyperplasia, vascular proliferation and perivascular macrophages infiltration (Hoarau, Jaffar Bandjee, Krejbich Trotot, Das, Li-Pat-Yuen et al., 2010).

### **Clinical features**

The incubation period usually lasts 2–4 days and after this, the acute period of the disease occurs abruptly, coinciding with maximum viremia. It is characterized by high fever, myalgia, joint pain and severe and disabling polyarthritides, sometimes accompanied by headache, backache and maculopapular rash, predominantly on the thorax (Pialoux, Gauzere, Jaureguiberry, Strobel, 2007). Other less frequent manifestations may include asthenia, myalgia (60-93%), headache (40-81%), nausea/vomiting, diarrhea, photophobia, retro-orbital pain, conjunctivitis, axial pain, macular/maculopapular exanthema (34-50%), with or without cutaneous pruritus, edema of the face and extremities, and cervical or generalized lymphadenopathy (Chopra, Anuradha, Ghorpade, Saluja, 2012; Chopra, Anuradha, Lagoo-Joshi, Kunjir, Salvi et al., 2008; Dupuis-Maguiraga, Noret, Brun, Le Grand, Gras et al., 2012; Madariaga, Ticona, Resurrecion, 2016; Manimunda, Vijayachari, Uppoor, Sugunan, Singh, et al., 2010; Simon, Javelle, Cabie, Bouquillard, Troisgros et al., 2015). After the end of the acute

phase (7–14 days), about 40-50% of patients will progress to the subacute and chronic phases, that is manifested by persistent polyarthritis/polyarthralgia, accompanied by morning stiffness and fatigue, which could remain even after years (Rodriguez-Morales, Cardona-Ospina, Fernanda Urbano-Garzon, Sebastian Hurtado-Zapata, 2016).

The subacute phase (15 days to 3 months) is characterized by the persistence of arthralgia/arthritis, bursitis, tenosynovitis, associated with morning stiffness and asthenia, with continuous or intermittent progression (Dupuis-Maguiraga et al., 2012; Simon et al., 2015; Waymouth, Zoutman, Towheed, 2013). The prevalence of chronic joint manifestations after CHIKV infection varies from 14.4 to 87.2%.<sup>23</sup> In a recent meta-analysis the prevalence of post-Chikungunya (post-Chik) chronic inflammatory joint disease (CIJD) ranged from 25.3 to 40.2% (Rodriguez-Morales et al., 2016).

The joint involvement beyond 3 months characterizes the chronic phase. The symptoms could be persistent (20-40%) or recurrent (60-80%) (Essackjee, Goorah, Ramchurn, Cheeneebash, Walker-Bone, 2013; Schilte, Staikowsky, Couderc, Madec, Carpentier, et al., 2013) and includes the presence of oligo or polyarthralgia of variable intensity, usually symmetrical, predominating in wrists, hands, ankles and knees, in association with morning stiffness and joint edema.<sup>25</sup> Among the factors associated with chronicity and poor prognosis are female gender, age over 60 years, prominent joint involvement in the acute phase, previous joint disease and/or the presence of comorbidities, elevated levels of C-reactive protein (CRP) and rise in CHIKV specific IgG titre through the recovery phase are considered as predictors for the chronic phase of the disease (Gérardin, Fianu, Michault, Mussard, Boussaïd et al., 2013). The persistence of positive CHIKV IgM beyond the acute phase is associated with erosive arthritis and chronic articular symptoms (Malvy, Ezzedine, Mamani-Matsuda, Autran, Tolou et al., 2009; Marques, Luna, Toche, Andrade, Dantas et al., 2016). Disease may evolve atypically in patients over 65 years of age and/or with co-morbidities (Economopoulou, Dominguez, Helynck, Sissoko, Wichmann et al., 2009).

## **Oral features**

The mouth is frequently affected in CHIKV fever. Gingivitis is common, possibly as a consequence of arthralgia of the hands leading to limited oral health measures. Indeed, gingivitis seems to be worse in chronic phase rather than acute phase (Katti, Shahapur, Udapudi, 2011). Nevertheless, gingival pain has also been reported as a common finding, together with burning sensation and oral mucosal ulceration. The prevalence of aphthous-like ulceration seems to vary from 2 to 12% among individuals with CHIKV fever (Katti et al., 2011; Borgherini, Poubeau, Staikowsky, Lory, Le Moullec et al., 2009; Suryawanshi, Dube, Khadse, Jalgaonkar, Sathe et al., 2009; Bhat, Rai, Ramesh, Nandakishore, Sukumar et al., 2011) usually during acute phase. Although synovial joint involvement is a hallmark of the disease, temporomandibular joints are involved in less than 6% of the cases (Katti et al., 2011). Children may present with fever, facial rash and intra-oral lesions described as “Koplik spots” (Mac Donald-Ottevanger, Gravenberch-Ramnandanlall, Zijlmans, 2015). Hypopigmented macules on lips, crusted lesions on the lips and angle of mouth, oral mucosal pigmentation as well as oral candidiasis have also been reported (Bandyopadhyay, Ghosh, 2010).

## **Diagnostic evaluation**

In geographic areas where the virus is commonly present the diagnosis of Chikungunya fever is typically clinical, since the association of acute fever with acute arthralgia and/or severe acute arthritis is highly suggestive (Brazilian Medical Council, 2016; Sissoko, Ezzedine, Moendandze, Giry, Renault, Malvy, 2015). Hence during epidemic situations, in the presence of acute fever, arthralgia/severe arthritis, with or without rash, the possibility of Chikungunya fever should be strongly considered. However, other acute febrile diseases should be included in the differential diagnosis, especially in instances of severe and/or atypical clinical disease (Marques et al., 2017).

In epidemic situations, patients in the acute phase may have the diagnosis established based on clinical-epidemiological criteria, without confirmatory

serology or associated haematology. For patients at risk (elderly, pregnant, children aged under 2 years or persons with comorbidities), the recommendation is that only the full blood cell count (FBC) should be requested (Marques et al., 2017). A more detailed laboratory evaluation may be necessary according to the patient's general conditions, comorbidities and drug use, especially in elderly patients (Simon et al., 2015; Brazilian Medical Council, 2016).

The most frequent laboratory finding in Chikungunya fever is lymphopenia, being more intense in the viraemic phase of the disease (Leparc-Goffart et al., 2014). Thrombocytopenia is less frequent than that observed in dengue. Patients who require hospitalization may have leukopenia, neutropenia, abnormal liver and/or renal biochemistry, hypocalcemia and elevation of creatine phosphokinase (CPK) and/or lactate dehydrogenase (LDH). Levels of CRP may be elevated (Waymouth et al., 2015; Borgherini, Poubeau, Jossaume, Gouix, Cotte et al., 2008; Staikowsky, Talarmin, Grivard, Souab, Schuffenecker et al., 2009; Staples, Fischer, 2014; Taubitz, Cramer, Kapaun, Pfeffer, Drosten et al., 2007).

In the chronic phase, in addition to the routine exams (FBC, erythrocyte sedimentation rate (ESR) and CRP), the need for autoantibody request should be evaluated if the clinical presentation is suggestive of autoimmune disease as well as evaluation of possible comorbidities. Analysis of synovial fluid may be necessary to confirm the inflammatory nature of joint involvement and to aid in differential diagnosis including gout and septic arthritis (Simon et al., 2015; Marques et al., 2017).

Since the clinical epidemiological criteria used for the diagnosis of chikungunya fever (Chikungunya: case definitions..., 2015) in epidemic situations show high agreement with the result of the specific serology for CHIKV (Marques et al., 2017), it is not recommended to perform this test for the diagnosis of uncomplicated cases. Because of the high attack rate of CHIKV (20 to 50% of the exposed population) (Cunha, Trinta, Montalbano, Sucupira, de Lima et al., 2017), performing specific serology for all cases is

practically unfeasible from an economic point of view. For acute cases, the serology (ELISA) for CHIKV (IgM and IgG) should only be performed in atypical forms or in view of the need for differential diagnosis, and should be requested from the 10th day of onset of symptoms. In chronic forms, the request for serology is recommended for diagnostic confirmation, but not for the start of treatment.<sup>20,23</sup>

## **Treatment**

According to the recommendations of the Brazilian Society of Rheumatology for the treatment of Chikungunya fever,<sup>45</sup> in the acute phase, the main objective of the treatment is the relief of musculoskeletal pain. Acetaminophen is the first choice in these cases, at usual doses; weak opioids (tramadol or codeine) should be used in cases of severe or refractory pain. Non-steroidal anti-inflammatory drugs (NSAIDs), salicylates and corticosteroids should be avoided at this stage.

For patients who have progressed to the subacute stage and who have not had notable benefit from common analgesics or opioids, NSAIDs, or adjunctive pain medications (anticonvulsants or antidepressants) may be of benefit. In patients with moderate to severe musculoskeletal pain or in those who cannot be given or tolerate NSAIDs or opiates, prednisolone at a dose of up to 20 mg/day is recommended, this being gradually reduced over a 6 to 8 week period (depending upon the clinical response).<sup>45</sup>

For treatment of chronic joint symptoms, in addition to the aforementioned drugs, antimalarials, preferably hydroxychloroquine (400 mg/day), methotrexate (10 to 25 mg/week) or sulfasalazine (2 to 3 g/day) may be used.<sup>45</sup> Tumor necrosis factor inhibitors (anti-TNF) may be prescribed after rheumatologic evaluation for patients with chronic inflammatory joint disease that has been refractory to the use of aforementioned treatments.<sup>45</sup>



Physical therapy is important at all stages of the disease to maintain patient mobility. Patients also require advice concerning posture control, exercises and graded return to normal motor function. This may include heat, active free, resisted, proprioceptive and aerobic exercises, stretching, manual therapy and aquatic physiotherapy (Marques, Duarte, Ranzolin, Dantas, Cavalcanti et al., 2017).

## References

1. Agarwal, A., Joshi, G., Nagar, D. P., Sharma, A. K., Sukumaran, D., Pant, S. C., ... Dash, P. K. (2016). Mosquito saliva induced cutaneous events augment Chikungunya virus replication and disease progression. *Infection, Genetics and Evolution*, 40, 126-135. doi: 10.1016/j.meegid.2016.02.033.
2. Assuncao-Miranda, I., Cruz-Oliveira, C., Da Poian, A.T. (2010). Molecular mechanisms involved in the pathogenesis of alphavirus-induced arthritis. *Biomedical Research International*, 2013, 973516. doi: 10.1155/2013/973516.
3. Bandyopadhyay, D., Ghosh, S.K. (2010). Mucocutaneous manifestations of Chikungunya fever. *Indian Journal of Dermatology*, 55, 64-67. doi: 10.4103/0019-5154.60356.
4. Bhat, R. M., Rai, Y., Ramesh, A., Nandakishore, B., Sukumar, D., Martis, J., Kamath, G. H. (2011). Mucocutaneous manifestations of chikungunya Fever: a study from an epidemic in coastal karnataka. *Indian Journal of Dermatology*, 56, 290-294. doi: 10.4103/0019-5154.82483.
5. Brazilian Medical Council. Febre de Chikungunya - Manejo Clínico. 2015. (Accessed August, 9, 2017, at [http://portal.cfm.org.br/index.php?option=com\\_content&view=article&id=25398:2015-03-16-17-58-53&catid=3](http://portal.cfm.org.br/index.php?option=com_content&view=article&id=25398:2015-03-16-17-58-53&catid=3).)
6. Brazil. Monitoramento dos casos de dengue, febre de chikungunya e febre pelo vírus Zika até a Semana Epidemiológica 19 (2017). *Brazilian Health Ministry*, 48.
7. 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.

8. Borgherini, G., Poubeau, P., Staikowsky, F., Lory, M., Le Moullec, N., Becquart, J. P., ... Paganin F. (2007). Outbreak of chikungunya on Reunion Island: early clinical and laboratory features in 157 adult patients. *Clinical Infectious Diseases*, 44, 1401-1407.
9. Carvalho, R. G., Lourenco-de-Oliveira, R., Braga, I.A. (2014). Updating the geographical distribution and frequency of *Aedes albopictus* in Brazil with remarks regarding its range in the Americas. *Memórias do Instituto Oswaldo Cruz*, 109, 787-96.
10. Chikungunya: case definitions for acute, atypical and chronic cases. Conclusions of an expert consultation, Managua, Nicaragua, 20-21 May 2015 (2015). *Releve epidemiologique hebdomadaire* 90, 410-414.
11. Chirathaworn, C., Rianthavorn, P., Wuttirattanakowit, N., Poovorawan, Y. (2010). Serum IL-18 and IL-18BP levels in patients with Chikungunya virus infection. *Viral Immunology*, 23, 113-117. doi: 10.1089/vim.2009.0077.
12. Lumsden, W. H. (1955). An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-53. II. General description and epidemiology. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 49, :33-57.
13. 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. *Epidemiology & Infection*, 140, 842-850. doi: 10.1017/S0950268811001300.
14. 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.
15. Cunha, R. V., Trinta, K. S., Montalbano, C. A., Sucupira, M. V., de Lima, M. M., Marques, E., ... Croda, J. (2017). Seroprevalence of Chikungunya Virus in a Rural Community in Brazil. *PLOS Neglected Tropical Diseases*, 11, e0005319. doi: 10.1371/journal.pntd.0005319.
16. Dupuis-Maguiraga, L., Noret, M., Brun, S., Le Grand, R., Gras, G., Roques, P. (2012). Chikungunya disease: infection-associated markers from the acute to the chronic phase of arbovirus-induced arthralgia. *PLOS Neglected Tropical Diseases*, 6, e1446. doi: 10.1371/journal.pntd.0001446.
17. Economopoulou, A., Dominguez, M., Helynck, B., Sissoko, D., Wichmann, O., Quenel, P., ... Quatresous, I. (2009). Atypical Chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005-2006 outbreak on Reunion. *Epidemiology & Infection*, 137, 534-541. doi: 10.1017/S0950268808001167.

18. 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. *Postgraduate Medical Journal*, 89, 440-447. doi: 10.1136/postgradmedj-2012-131477.
19. Gérardin, P., Fianu, A., Michault, A., Mussard, C., Boussaïd, K., Rollot, O., ... Favier F (2013). Predictors of Chikungunya rheumatism: a prognostic survey ancillary to the TELECHIK cohort study. *Arthritis Research & Therapy*, 15, R9. doi: 10.1186/ar4137.
20. Hoarau, J. J., Jaffar Bandjee, M. C., Krejbich Trotot, P., Das, T., Li-Pat-Yuen, G., Dassa, B., ... Gasque P (2010). Persistent chronic inflammation and infection by Chikungunya arthritogenic alphavirus in spite of a robust host immune response. *Journal of Immunology*, 184, 5914-5927. doi: 10.4049/jimmunol.0900255.
21. Katti, R., Shahapur, P., Udapudi, K. (2011). Impact of chikungunya virus infection on oral health status: An observational study. *Indian Journal of Dental Research*, 22 (4), 613. doi: 10.4103/0970-9290.90325.
22. Leperc-Goffart, I., Nougairède, A., Cassadou, S., Prat, C., de Lamballerie, X. (2014). Chikungunya in the Americas. *Lancet* ;383, 514. doi: 10.1016/S0140-6736(14)60185-9.
23. Lum, F. M., Ng, L. F. (2015). Cellular and molecular mechanisms of chikungunya pathogenesis. *Antiviral Research*, 120, 165-174. doi: 10.1016/j.antiviral.2015.06.009.
24. Mac Donald-Ottevanger, M. S., Gravenberch-Ramnandanlall, C. I., Zijlmans, C. W. (2015). Chikungunya in children. *Nederlands Tijdschrift voor Geneeskunde*, 159, A8403.
25. Madariaga, M., Ticona, E., Resurrecion, C. (2016). Chikungunya: bending over the Americas and the rest of the world. *Brazilian Journal of Infectious Diseases*, 20, 91-98. doi: 10.1016/j.bjid.2015.10.004.
26. 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, 200. doi: 10.1186/1471-2334-9-200.
27. 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.

28. Marques, C. D. L., Albuquerque, C. A., Luna, M. S., Santos, P. R., Dantas, A. T., Ranzolin, A., ... Duarte AL (2017). Concordance between clinical-epidemiological criteria and chikungunya fever serology. *Annals of Rheumatic Diseases*, 76, 988.
29. Marques, C. D. L., Duarte, A. L. B. P., Ranzolin, A., Dantas, A. T., Cavalcanti, N. G., Gonçalves, R. S. G., ... Christopoulos, G. (2017). Recommendations of the Brazilian Society of Rheumatology for diagnosis and treatment of Chikungunya fever. Part 1 - Diagnosis and special situations. *Revista Brasileira de Reumatologia English Edition*, S2255-5021,17, 30046-30049. doi: 10.1016/j.rbre.2017.05.006.
30. Marques, C. D. L., Duarte, A. L. B. P., Ranzolin, A., Dantas, A. T., Cavalcanti, N. G., Gonçalves, R. S. G., ... Christopoulos, G.(2017). Recommendations of the Brazilian Society of Rheumatology for the diagnosis and treatment of chikungunya fever. Part 2 - Treatment. *Revista Brasileira de Reumatologia English Edition*, in press. doi: 10.1016/j.rbre.2017.06.004.
31. Marques, C. D. L., Luna, M., Toche, P., Andrade, C., Dantas, A., Ranzolin, A., ... Duarte, A. (2016). Chikungunya Fever Outbreak in Brazil: Preliminary Assessment in a Cohort of Patients with Rheumatological Manifestations. *Arthritis & Rheumatism*, 68.
32. Pan American Health Organization (2016). Chikungunya Autochthonous Transmission in the Americas. (Accessed August, 9, 2017, at <http://www.paho.org/hq/index.php?Itemid=40931>.)
33. Pan American Health Organization (2017). Chikungunya: New cases of Chikungunya in the Americas 2013-2017 (2017)., Accessed August, 09, 2017, at [http://ais.paho.org/phis/viz/ed\\_chikungunya\\_amro.asp](http://ais.paho.org/phis/viz/ed_chikungunya_amro.asp).)
34. Pialoux, G., Gauzere, B. A., Jaureguiberry, S., Strobel, M. (2007). Chikungunya, an epidemic arbovirosis. *Lancet Infectious Diseases*, 7, 319-327.
35. Rodriguez-Morales, A. J., Cardona-Ospina, J. A., Fernanda Urbano-Garzon, S., Sebastian Hurtado-Zapata, J. (2016). Prevalence of Post-Chikungunya Infection Chronic Inflammatory Arthritis: A Systematic Review and Meta-Analysis. *Arthritis Care & Research*, 68, 1849-1858. doi: 10.1002/acr.22900.
36. Rougeron, V., Sam, I. C., Caron, M., Nkoghe, D., Leroy, E., Roques, P. (2015). Chikungunya, a paradigm of neglected tropical disease that emerged to be a new health global risk. *Journal of Clinical Virology*, 64, 144-152. doi: 10.1016/j.jcv.2014.08.032.
37. Schilte, C., Staikowsky, 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*

*Neglected Tropical Diseases*, 7, e2137. doi: 10.1371/journal.pntd.0002137.

38. Simon, F., Javelle, E., Cabie, A., Bouquillard, E., Troisgros, O., Gentile, G., ... Wendling, D. (2015). French guidelines for the management of chikungunya (acute and persistent presentations). November 2014. *Médecine et Maladies Infectieuses*, 45, 243-263. doi: 10.1016/j.medmal.2015.05.007
39. Sissoko, D., Ezzedine, K., Moendandze, A., Giry, C., Renault, P., Malvy, D. (2010). Field evaluation of clinical features during chikungunya outbreak in Mayotte, 2005-2006. *Tropical Medicine & International Health*, 15, 600-607. doi: 10.1111/j.1365-3156.2010.02485.x.
40. Suryawanshi, S. D., Dube, A. H., Khadse, R. K., Jalgaonkar, S.V., Sathe, P. S., Zawar, S. D., Holay, M. P. (2009). Clinical profile of chikungunya fever in patients in a tertiary care centre in Maharashtra, India. *Indian Journal of Medical Research*, 129, 438-441.
41. Staikowsky, F., Talarmin, F., Grivard, P., Souab, A., Schuffenecker, I., Le Roux, K., ... Michault, A. (2009). Prospective study of Chikungunya virus acute infection in the Island of La Reunion during the 2005-2006 outbreak. *PLoS One*, 4, e7603. doi: 10.1371/journal.pone.0007603.
42. Staples, J. E., Fischer, M. (2014). Chikungunya virus in the Americas--what a vectorborne pathogen can do. *New England Journal of Medicine*, 371, 887-889. doi: 10.1056/NEJMp1407698.
43. Taubitz, W., Cramer, J. P., Kapaun, A., Pfeffer, M., Drosten, C., Dobler, G., ... Löscher, T. (2007). Chikungunya fever in travelers: clinical presentation and course. *Clinical Infectious Disease*, 45, e1-4.
44. Waymouth, H. E., Zoutman, D. E., Towheed, T. E. (2013). Chikungunya-related arthritis: case report and review of the literature. *Seminars in Arthritis and Rheumatism*, 43, 273-278. doi: 10.1016/j.semarthrit.2013.03.003.
45. Weaver, S.C., Lecuit, M. (2015). Chikungunya virus and the global spread of a mosquito-borne disease. *New England Journal of Medicine*, 372, 1231-1239. doi: 10.1056/NEJMra1406035.