



## Editorial

# Chikungunya again and again: lessons learned from bedside to bench



## Chikungunya una y otra vez: lecciones aprendidas del paciente al laboratorio

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The chikungunya virus (CHIKV) is an alphavirus belonging to the *Togaviridae* family, member of the Semliki Forest antigenic complex, which along with other alphaviruses (*O'nyong-nyong*, *Mayaro* and *Ross River*) causes acute arthropathy in human beings.<sup>1</sup> It is initially transmitted by the *Aedes (Ae) aegypti* mosquito and after the epidemic of 2006 in La Reunión by *Ae albopictus*, thanks to an adaptive mutation of alanine to valine at position 226 of the genome of its membrane glycoprotein E1 (A226V).<sup>2,3</sup> Phylogenetic studies have found that the CHIKV originated in Africa, more than 500 years ago, determining that a common lineage diverged into two branches called Western Africa (WA) and Eastern/Central/Southern Africa (ECSA).<sup>1</sup> While the ECSA lineage spread outside Africa causing multiple urban epidemics in Asia almost 150 years ago, the WA lineage maintained local outbreaks in Africa through enzootic transmission.<sup>4</sup> It was in Asia where the ECSA lineage continued to circulate and evolved into a separate genotype called the Asian lineage. In early 2000, the ECSA lineage arrived in Kenya and from there it expanded to the islands of the Indian Ocean, India and Southeast Asia, creating an unprecedented epidemic and evolving again towards a new lineage with the A226V mutation (Indian Ocean lineage) mentioned above.<sup>5</sup> During the last decade, CHIKV continued to cause epidemics in the Pacific Islands, the Indian

subcontinent, Oceania and South East Asia.<sup>6–8</sup> Finally, in 2013 the Asian lineage reached the Western Hemisphere with the first autochthonous cases reported in the Island of Saint Martin.<sup>9</sup> From there, the virus rapidly spread throughout the Caribbean, Central and South America, affecting 42 countries in 2015.<sup>10</sup>

The mosquito bite of an infected patient with viremia is where transmission initially begins.<sup>11</sup> The virus replicates during a few days, before it can be transmitted to another person.<sup>12</sup> After the mosquito bite, the virus, due to cell tropism infects the macrophages and the fibroblasts in the dermis, after an incubation period of 3–7 days, from where it spreads through the lymphatic vessels and the bloodstream to the joint capsule, muscular, epithelial and endothelial cells.<sup>11</sup> The virus replicates causing viremia, fever, rash, myalgia, arthralgia and arthritis.<sup>13</sup> At this point is established the acute phase, which lasts approximately 2 weeks and is characterized by the appearance of immunoglobulin M (which persists for weeks up to 3 months) followed by the production of immunoglobulin G, which will provide antiviral immunity for years.<sup>2,11,13</sup> After the acute phase, the infection with CHIKV may progress to a chronic stage where the rheumatic symptoms can last for several months or even years.<sup>13</sup> Multiple studies have demonstrated the fundamental role of cytokines

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in the immunopathogenesis of the infection and the interaction of the virus with the host. A meta-analysis revealed the significant elevation of multiple immune mediators in patients with CHIKV during the acute phase of the disease, when compared with healthy controls, in multiple independent cohorts from different geographic locations, among which interleukin 6 (IL-6) stands out.<sup>14</sup> This interleukin has already been evaluated in chronic patients and has been postulated as the driving force of arthropathy due to CHIKV.<sup>15</sup>

In August 2014, CHIKV first arrived in Northern Colombia, causing 106,763 cases reported in the first year and covering the entire territory (32 state departments) with *Ae aegypti* as the only vector, since the Asian lineage is the only one genotype described updated in our country.<sup>16-23</sup> Specifically, the first autochthonous cases of CHIKV infection notified to the Colombian Ministry of Health were from the Municipality of Mahates, a city located in the Department of Bolívar; a territory in the Caribbean region, bordering the Northwest of the Caribbean Sea (Atlantic Ocean) of Colombia.<sup>16</sup> According to the statistics of the Pan American Health Organization (PAHO), Colombia occupies the third place of accumulated cases in the Americas, with 294,831 cases, after the Dominican Republic with 539,362 cases and Brazil with 773,010 cases.<sup>24</sup> At the end of 2015, the Colombian Ministry of Health declared the end of the epidemic, however, the cases have continued to be reported so far, with reports of 346 cases notified in the epidemiological week 44 of 2019 in Colombia (381 clinically confirmed, 46 confirmed by laboratory and 52 suspected cases), even above the cases of infection with Zika confirmed clinically and by laboratory (272 and 11, respectively).<sup>25-28</sup>

It is for these reasons that the article published in this issue of the Colombian Journal of Rheumatology becomes so relevant. The results of the authors allow us to know the characteristics of the disease in our population, both in its acute phase and 9 months after the infection, demonstrating the commitment both functional and of the quality of life. The authors also demonstrate the importance of IL-6 in the immunopathogenesis in the chronicity of the disease, raising the possibility of using it as a biomarker of chronicity. In addition, they evidence low percentages of positivity of rheumatoid factor and anti-CCP, confirming the hypothesis that suggests that the Asian lineage (so far the only one isolated in our country) is associated with less aggressive presentations of the disease with less chronicity.<sup>29</sup>

With the questions raised as a result of the present investigation, the way is opened for future research in the Colombian population with chronic manifestations of the disease, and thus fill the gaps in the interaction of this pathogen with the host.

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