Osteoarticular manifestations of Mayaro virus infection

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Purpose of review
To carry out an update on the state of the art of the Mayaro virus (MAYV) infection and its osteoarticular implications.

Recent findings
There is a wide distribution of MAYV in Latin America and documented exported cases to the United States and Europe. Although osteoarticular involvement is not the most frequent, it is one the most associated with disability. The main mechanisms related to arthropathy involves cellular infiltrates (i.e. macrophages, natural killer cells, lymphocytes) together with production of cytokines, such as IL-6, IL-7, IL8, IL-12p70.

Summary
MAYV infection is an emerging disease, which has been reported in many and increasing number of countries of Latin America. There is a high risk of epidemic outbreaks, given the inadequate vector control (*Aedes* mosquitoes). Its main symptoms, like other arbovirus infections, involve the presence of headache, rash, conjunctivitis, and arthralgias. MAYV arthropathy is usually severe, can last in time, and is associated with severe disability. There is currently no treatment for MAYV. Prevention of MAYV as a public health burden will be achieved by integrating vector control with vaccines (still under development).

Keywords
arthropathy, Latin America, Mayaro virus, outbreaks

INTRODUCTION

Viral vector-borne diseases have become very relevant because of different socioeconomic and environmental factors that have allowed its geographic distribution to expand. This has generated a crisis in public health, especially in developing countries [1▪,2,3▪]. Additionally, the impact of these diseases has been associated with high rates of physical and even mental disability and quality of life impairment [2,3▪]. These infections are mainly transmitted by species of mosquitoes in the genus *Aedes* (*Aedes aegypti* and *Aedes albopictus*), which are widely distributed in Asia, Latin America, and Africa. The main viruses transmitted by the vectors are Mayaro (MAYV), chikungunya (CHIKV), Zika (ZIKV), yellow fever (YFV), and dengue (DENV) [4].

MAYV is an emerging pathogen in the Togaviridae family, genus Alphavirus, and is the cause of Mayaro fever, a disease that is similar to CHIKV infection. Infected patients show an acute febrile episode of variable severity, usually self-limited (typically 3–5 days), accompanied by a clinical course of arthralgia with or without arthritis [5,6]. Arthropathy is usually frequent and is a cause of temporary or permanent disability of a significant sector of the population. This, in turn, represents a substantial economic burden for the countries affected by this phenomenon. In this article, a narrative literature review was done in order to synthesize the information currently available on epidemiology, pathophysiology, osteoarticular and muscular manifestations, diagnosis, and treatment of people infected with MAYV.

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KEY POINTS

- There is a high risk of MAYV outbreaks, given the inadequate vector control (*Aedes* mosquitoes) in tropical countries of Latin America.
- Mayaro virus arthropathy may be severe and leads to disability.
- Prevention of MAYV as a public health threat would be achieved by integrating vector control with vaccines (still under development).

EPIDEMIOLOGY

The first reported cases of MAYV infection occurred in 1954 in Trinidad and Tobago, where the virus was isolated for the first time in five people [7]. However, there is evidence that, during the construction of the Panama Canal in the 1910s, the workers were infected by the same virus [8]. After that, the virus was found in six patients from Belem, Brazil, in April 1955 [9]. Later in Bolivia a strain of MAYV, previously known as Uruma, was associated with 15 of the 'fevers of the jungle' of that time [10]. Furthermore, between 1958 and 1960 in Santander, Colombia, of 12 strains of arboviruses that had been isolated, 4 strains corresponded to MAYV [11]. In 1964, in Suriname, a fever illness was reported in Dutch soldiers and, although it was not identified serologically, the presence of MAYV was suspected [12]. Later in 1965, the virus was isolated in serum from Peruvian patients through neutralization tests on Vero cell cultures [13]. In 1997, an outbreak of hemorrhagic fever was reported in Ecuador. A seroprevalence of 46% was documented in the Equatorial Amazonian natives [14]. One year later, the virus was reported in French Guiana with a seroprevalence of 6.3% [15]. In Venezuela, the first cases, in four relatives with specific IgG and IgM titers against the virus, were reported in 2000 [16].

Then, 10 years later, 77 cases were reported in what was the biggest outbreak reported in Latin America [17]. In 2001, two cases of MAYV were documented in Mexico, one of which resulted in a fatal outcome with liver failure and encephalopathy [18]. In Bolivia and Peru, between 2000 and 2007, the virus was found in rural areas in those countries [19]. In a study done between 2010 and 2013 in 4 Peruvian cities, the virus was reported in 0.8% of the people [20]. In 2015, the virus was isolated in an 8-year-old patient in Haiti [21]. In 2018 and 2019, Peru have reported 37 cases, in the Cuzco and Ayacucho regions. According to the Pan American Health Organization (http://www.paho.org/), in 2019, in Ecuador, five cases of MAYV among 34 samples that were negative for DENV, CHIKV and ZIKV, were reported. Two of the confirmed cases occurred in Guayaquil, its largest city.

With respect to imported cases, some from Peru and Bolivia were reported in the United States [22,23]. Furthermore, two cases in Europe, one from Suriname in 2008 and one from Brazil in 2013 were imported into the Netherlands [24,25]. In 2016, a case was imported into France from French Guiana [26], whereas another case was imported into Switzerland from Peru [27]. In Germany, in 2012, one case was reported in a woman with a fever who had been in Peru and in whom serology specific for MAYV was confirmed [5]. A few years later, in the same country, a case was reported that had been imported from French Guiana [28]. These reports have made it possible to describe the wide distribution of the virus throughout Latin America and abroad through travel. However, it is necessary to create public health policies that would prevent an epidemic, as well as to include MAYV in the surveillance, integrated with other arboviruses.

TRANSMISSION

The main epidemic outbreaks of vector-borne infections have shown that the epidemiological behavior follows a seasonal pattern related to a higher incidence of cases in the rainy season, a situation that varies between countries, as also occur with other arboviruses. The MAYV transmission occurs with the bite of a female hemophagous mosquito. Vector function has been described in different species of mosquitoes, such as: *Aedes, Culex, Mansonia,* and *Psorophora*, each of which has a different vector capacity. Of these, the *Aedes* genus is the most important because it feeds primarily on humans. It frequently bites several human beings in a single meal, and its habitat is close to people [11,29].

Once the mosquito feeds on an infected person, the virus infects the mosquito's intestinal epithelial cells where it replicates until it reaches the hemolymph stage after which it will live in the salivary glands of the mosquito and reinitiate the cycle of infection with the next meal [30]. Like other alphaviruses, there is the possibility of other transmission routes, which are still a matter for research [30].

CLINICAL FINDINGS AND OSTEOARTICULAR MANIFESTATIONS

After a bite from a mosquito infected with MAYV, the onset of symptoms occurs at 8 days according to some authors. However, MAYV's incubation period has not been well established [5,6,31]. The clinical course is usually similar to and shared with that of

Table 1. Main clinical findings in chikungunya virus, dengue virus, Mayaro virus, and Zika virus

Clinical findings	Viruses			
	MAYV	CHIKV	DENV	ZIKV
Fever	(++++)	(+++)	(++++)	(++/−)
Myalgia/arthralgia	(+++)	(++++)	(+++)	(++)
Edema in limbs	−	−	−	(++)
Rash	(++)	(++)	(++)	(+++)
Retro-ocular pain	(++)	(+)	(++)	(++)
Conjunctivitis	−	(+)	−	(+++)
Lymphadenopathies	(+)	(++)	(++)	(+)
Hepatomegaly	(+)	(++)	−	−
Thrombocytopenia	(++)	(++)	(+++)	(−/+)
Hemorrhages	−	(+)	(+++)	(−/+)

+, presence; −, absence; MAYV, Mayaro virus; CHIKV, chikungunya virus; DENV, dengue virus; ZIKV, Zika virus.

other arboviruses. However, there are relevant clinical differences between the infections (Table 1). An infection by alphaviruses like MAYV usually starts with fever, arthralgias/arthritis, myalgias, maculopapular exanthema, and retro-ocular pain. Dizziness, vomiting, anorexia, lymphadenopathy, and jaundice are also frequent [6]. Debilitating acute and chronic musculoskeletal disease accompanied by high-intensity fever (>39 °C) may be observed in up to 100% of affected individuals. Headaches have been found in 60–100% of those infected, arthralgia in 50–89%, myalgias in 75%, joint edema in 58%, retro-ocular pain in 44–63%, and rash in up to 49% of cases [32].

The clinical characteristics of joint manifestations are usually similar to those present in other alphavirus infections. They generally coincide with the onset of febrile symptoms and rash (3–5 days after the mosquito bite). All the symptoms may disappear within a couple of weeks after they had started except for the arthralgia. The main joints affected are ankles, wrists, toes, fingers, elbows, shoulders, and knees (Fig. 1). The arthralgias have a prolonged course in more than 50% of the cases [33]. In addition, the arthralgias present a symmetrical pattern associated with morning stiffness and nocturnal worsening of symptoms.

In the study by Santiago *et al.* [33], it was found that up to 54% of MAYV cases had persistent arthralgias. The appearance of anti-MAYV antibodies correlated with better clinical results except for persistent arthralgias [33]. The appearance of neutralizing antibodies occurs in 100% of the cases, and they are a fundamental part of the recovery of these patients. However, the magnitude of this response did not differ between patients who developed persistent arthralgia and those who recovered completely, thus suggesting that neutralizing antibodies alone cannot completely protect individuals from the development of persistent arthralgia [33].

PATHOGENESIS OF OSTEOARTICULAR MANIFESTATIONS

Currently, there are few studies that demonstrate the pathophysiological mechanism of the MAYV in relation to osteoarticular complications. However, there are studies of alphaviruses that can shed light

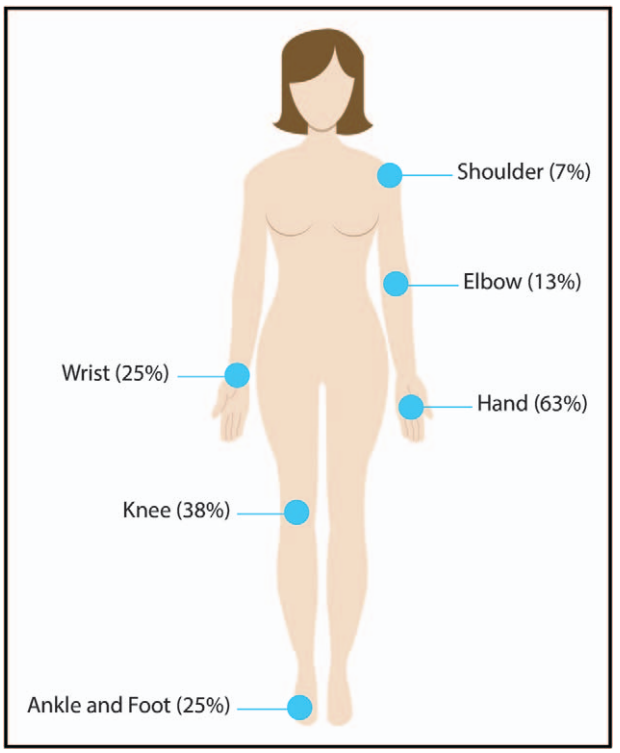

FIGURE 1. Distribution of arthralgia in Mayaro virus infection. Any joint 69%.

on the action of this virus at the osteoarticular level. Dissemination occurs through the lymphatic system [34], affecting the liver, spleen, and other sites, where most viral replication happens. The acute phase of the disease occurs in the muscle, bone, and joints [35]. In murine models, it has been observed at the level of joints and muscles, inflammatory infiltrates, macrophages, natural killer cells, and both CD4+ and CD8+ T lymphocytes [36,37,38]. In in-vitro studies, it has been observed that MAYV infection is associated with apoptosis [39]; tumor necrosis factor (TNF)-α is produced and induces the appearance of arthritis and fever. An increase in the generation of reactive oxygen species, which was confirmed in infected HepG2 cells, has also been observed [40▪▪]. The production of IL-6, IL-7, IL8, IL-12p70, IL-15, IP-10, and MCP-1 has been described during the acute phase. In particular, MCP-1 is crucial during the migration of monocytes in the acute phase of the infection [33]. Moreover, the presence of IL-2 and IL-9 favors cellular proliferation whereas IL-7 and IL-13 may remain elevated for up to 3 months after infection. In the chronic phase, high levels of IL-1β, IL-5, IL-10, IL-12p70, IL-17, interferon (IFN)-γ, and TNFα are characteristic. Finally, chronic arthropathy as a secondary infection is associated with high levels of G-CSF, IL-1Ra, IL-8, IL-17, IFN-γ, MCP-1, PDGF-BB, and TNF-α [33].

DIAGNOSIS

MAYV infection should be suspected in patients with rash, fever, polyarthralgia, and a history of living or having recently been in areas where the virus is endemic. MAYV shares many serological characteristics with other viruses in the alphavirus genus, and this leads to a high degree of cross-reactivity with serological tests [31].

The diagnosis of MAYV can be done with viral RNA determination through real-time reverse transcription-PCR (RT-PCR) or through serology for MAYV. A complete review of the diagnosis of MAYV was published elsewhere [41▪▪].

TREATMENT AND PREVENTION

Currently, there is no approved treatment for diseases caused by alphaviruses [20,42]. Due to the similarity of the clinical and biochemical findings for arthritis secondary to alphavirus and rheumatoid arthritis (RA), it was initially thought that the treatment of MAYV arthropathy could be similar to that used for RA. However, the use of steroids has been tried on patients with polyarthritis with dubious results under a risk–benefit assessment [31]. Furthermore, the use of antimalarials has been shown be beneficial for the prolonged polyarthralgias of these patients [43].

Another medication that could be useful in the near future could be Harrigntonine. This compound is isolated from trees belonging to the family *Cephalotaxus* (Coniferous) [44]. It improves arthritis in murine models and is able to inhibit the replication of CHIKV. However, studies are needed to assess its effectiveness in MAYV infection [44]. Recently, the use of two drugs with antiviral effect, thienopyridine derivatives and epicatechin, on MAYV replication raised expectations for their use in clinical trials [45▪▪,46]. In extreme cases of thrombocytopenia or hemorrhage, blood transfusion is indicated. In mild cases, it is possible for the patient to remain at home. In some cases, the patient is hospitalized for a study and diagnostic protocol. Few cases have been described that require admission to the intensive care unit.

To prevent transmission, greater integrated control of the vector is required. Fumigation programs of urban and rural areas are recommended, together with avoiding exposure in areas of high mosquito activity, using repellents, impregnating clothing with permethrin, using appropriate clothing (pants and long-sleeved shirt), and using mesh and mosquito nets [42,47]. There is no vaccine available yet although a live-attenuated vaccine is under study in murine models [48].

CONCLUSION

Tropical diseases have been neglected by governments and the pharmaceutical industry, although they represent a significant economic burden for the affected developing countries. Emerging viral infections are not the exception. They have a major potential to spread and significant morbidity. The ecology of the mosquito has changed with the passing of time and is covering more and more of the northern and southern regions of the planet as well as reaching altitudes beyond the historical maximums and affecting populations previously considered exempt from the problem because of their height above sea level. That is why it is necessary to increase efforts to control the spread of mosquitoes as well as to enhance the surveillance, including this arbovirus.

The main clinical manifestations of MAYV infection are arthralgia fever and maculopapular rash. Arthralgias can be self-limiting or become chronic. Further studies are needed to evaluate the long-term outcome for patients affected by MAYV and their treatment.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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