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Review article

Will Mayaro virus be responsible for the next outbreak of an arthropod-borne virus in Brazil?



Danillo Lucas Alves Esposito, Benedito Antonio Lopes da Fonseca*

Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Clínica Médica, Ribeirão Preto, SP, Brazil

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ABSTRACT

Mayaro virus is an alphavirus from the *Togaviridae* family and is transmitted mainly by *Hemagogus* mosquitoes. This virus circulates in high-density tropical forests or rural areas of Central and South America causing a disease characterized by high-grade fever, maculopapular skin rash and marked arthralgia that, in some patients, can persist for long periods after infection and may be misinterpreted as chikungunya. Although only a few outbreaks involving this virus have been reported, in the last years the number of Mayaro virus infections has increased in the central and northern regions of Brazil. In this review, we describe the reported prevalence of this infection over the years and discuss the circumstances that can contribute to the establishment of an urban mayaro virus epidemic in Brazil and the problems encountered with the specific diagnosis, especially the antigenic cross-reactivity of this pathogen with other viruses of the same family.

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Mayaro virus (MAYV; genus *Alphavirus*, family *Togaviridae*) is an arbovirus transmitted primarily by the bite of female mosquitoes of the genus *Hemagogus*, usually from an infected non-human primate (monkeys) to a susceptible human. These tree-dwelling mosquitoes are also the vectors involved in the sylvatic cycle of yellow fever virus, and although MAYV maintenance efficiency in primary reservoirs is not known, it has been detected in nature in several vertebrate hosts such as non-human primates, rodents, birds, sloths, and other small mammals.¹

As for yellow fever virus, MAYV can infect humans who inhabit the rural areas or enter these forested areas either to work or to take advantage of the environmental attractions, leading to a febrile condition characterized by fever,

cutaneous rash, and joint pain. In recent years, there has been an increased number of cases of mayaro fever in several Brazilian states and with the increased circulation of chikungunya virus, there is always a question as to whether a febrile exanthematous disease with severe joint involvement is due to chikungunya or MAYV. In this review, based on epidemiologic and laboratory data, we discuss the variables involved in the possible establishment of outbreaks caused by MAYV.

The virus

MAYV genome is composed of a single-stranded positive-sense RNA of approximately 12 kb in size, flanked by a

* Corresponding author.

E-mail address: baldfon@fmrp.usp.br (B.A. Fonseca).
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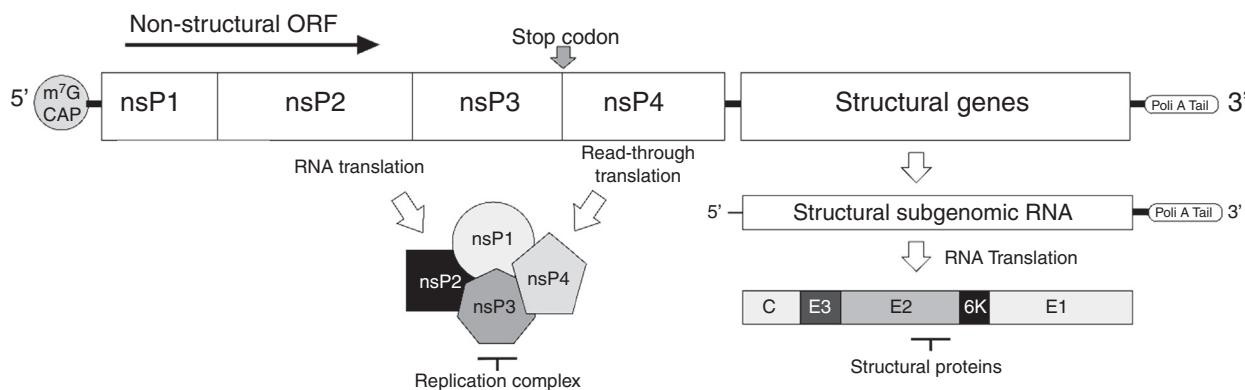


Fig. 1 – A schematic Mayaro virus genome organization and its replication complex.

5'-7-methylguanylate (m^7G) cap and a 3'-poly-A tail. It encodes four nonstructural proteins (nsP1–4) and five structural proteins (C-E3-E2-6k-E1).² Similar to other alphaviruses, MAYV RNA has a stop codon at the end of nsP3 gene, and at a low frequency (5–20%), a read-through translation can occur, resulting in nsP1–4 product (Fig. 1). Structural proteins are produced after translation of a subgenomic RNA transcript, synthesized from the negative-sense RNA used for replication, a common feature of the *Togaviridae* family³ (Fig. 1). Following the expression of structural proteins, the virus RNA is complexed to the capsid protein and the envelope proteins, processed during their traffic through the Golgi apparatus, are inserted into the plasma membrane from where the virus acquires its envelope, releasing infectious particles able to infect susceptible cells.

Phylogenetically, MAYV is considered a monophyletic group, divided in two similar genotypes—genotype D, which includes most of the isolates, from 1954 to 2003, and genotype L, limited to the Brazilian isolates.⁴ MAYV is part of the Semliki Complex, a serological group inside *Alphavirus* genus that shares some common antigenic sites, which can generate cross-reactivity with polyclonal immune sera among the species, when analyzed by conventional serological tests, such as Hemagglutinin Inhibition (HI) and Complement Fixation (CF). The Semliki Complex is composed by eight viruses (Bebaru, Chikungunya, Mayaro, Getah, Semliki Forest, Ross River, O'nyong-nyong, and Una viruses) of veterinary and medical importance, usually causing human disease characterized by fever, arthritis and skin rash⁵ (Fig. 2 – the strain of MAYV used to assemble this phylogeny was BeAr20290⁶). As mentioned before, the fact that these viruses belong to the same serological complex, the correct diagnosis of these infections can be difficult to achieve, usually only carried out in well-equipped research laboratories. Specifically, of importance to Brazil, chikungunya and mayaro fever can exhibit the same clinical manifestations and both viruses are co-circulating in the country.

Clinical manifestations and specific diagnosis

Little is known about the pathophysiology of mayaro fever, but once the infection has established the virus goes through

an intrinsic incubation period, which can range from 3 to 11 days, when a high-rate replication takes place followed by a short viremia lasting while the symptoms are present (usually 5–7 days). The symptoms of MAYV infection are often an exanthematous rash, fever, myalgia, retro-orbital pain, headache, diarrhea, and arthralgia, the latter may persist for months or even years.⁷ There are several reports on the literature of persistent or recurrent arthralgia resulting from MAYV infection,^{8–10} which could be a result of an inefficient neutralizing antibody response against this virus associated with the continuous expression of some pro-inflammatory immune cytokines.¹¹ However, there is a need for more studies evaluating the broad spectrum of the clinical manifestations of the acute phase of the disease, including unusual presentations, if present, as well as the possible chronic clinical manifestations, and also, the viral and immunological parameters involved in the causation of each form of this disease.

As for most arboviral infections, the diagnosis of alphavirus infection, such as Mayaro fever, is more efficient if performed during the acute phase of the disease, either by virus isolation or RT-PCR to detect viral RNA. At a convalescent phase of infection, antibody cross-reactivity has been shown to occur when using traditional serological tests, such as ELISA. High cross-reactivity between mayaro and chikungunya has been described,^{12,13} and either side-by-side tests aiming at the comparison of serum reactivity to each virus or neutralization tests should be performed to correctly establish the specificity of an antibody reaction, and provide a correct diagnosis of the disease.

Epidemiology

The epidemiologic history of MAYV infection begins in 1954 with its first report in Trinidad and Tobago, when the virus was isolated from blood samples of five rural workers that presented with a febrile disease. The virus received its name after Mayaro County, a southeastern region of Trinidad, where the cases were reported.¹⁴ Since then, the virus has been reported in some countries in Central and South America, usually in places with tropical forests, such as French Guiana, Bolivia, Peru, Suriname, Costa Rica, Guatemala, Venezuela, Mexico, Ecuador, Guyana, Panama, and Brazil. Imported cases are not very frequent, but some have been reported: North Americans

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