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Review

Mayaro virus: a forest virus primed for a trip to the city?

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Abstract

Mayaro virus (MAYV) is an emerging arthropod-borne virus (arbovirus).

Infection by MAYV can produce Mayaro virus disease (MAYVD) which is usually a clinically diagnosed, acute, febrile illness associated with prolonged and painful joint inflammation and swelling. MAYVD may be clinically indistinguishable from dengue, chikungunya fever, malaria, rabies, measles or other arboviral diseases. The full spectrum of disease, sequelae, routes of infection, virus shedding and any rarer means of transmission remain undefined.

MAYVD cases in humans have so far been localised to Central and South America, particularly regions in and around the Amazon basin.

MAYV usually circulates in a sylvan cycle of forest mosquitoes and vertebrates, however it has also been found in more urban locations alongside anthropophilic (preferring humans) insect vectors. If transmission via anthropophilic mosquitoes becomes more efficient following viral change, or existing vectors change their habitat and biting habits, the risk of urban establishment and further spread into non-forested areas will grow. Surveillance, testing and vector control remain key to monitoring and preventing global spread and establishment. The possibility of MAYV becoming further urbanized is worthy of note, consideration and action to ensure MAYV does not spread beyond the forests and establish in the world's cities.

Keywords: Mayaro virus (MAYV); Arbovirus; Emerging virus; Mosquito; Arthralgia; Alphavirus

1. What is Mayaro virus?

Mayaro virus (MAYV) is an enveloped RNA virus classified into the family *Togaviridae*, genus *Alphavirus* [1]. Like other alphaviruses, it is arthropod-borne (an arbovirus) and remains mostly tied to a sylvan (forest) cycle involving primate and other vertebrate hosts in addition to mosquito hosts and vectors [2,3]. MAYV is enzootic in Central and South America, mostly around humid, flood-prone and tropical forest areas [4–9]. Strains phylogentically group into three lineages; genotypes D (widely dispersed), L (limited) and N (new) [10,11]. Mayaro virus disease (MAYVD) is most often a clinically diagnosed, acute, febrile illness associated with prolonged arthralgia. The full spectrum of disease, sequelae, routes of infection, virus shedding and any rarer means of transmission remain unknown.

1.1. Virus genome and structure

MAYV has an approximately 11.5 kb single-stranded, positive sense RNA genome which is divided into two open reading frames (ORFs; Fig. 1). The non-structural ORF in the genomic RNA encodes a polyprotein which is proteolytically cleaved into four non-structural (NSP1-4) peptides. The structural ORF from a subgenomic RNA (26S mRNA) encodes a polyprotein cleaved by autocatalysis and cellular proteases into six structural peptides; capsid, envelope 3 (E3), E2, 6K, transframe (TF) and E1 [12]. The ORFs are bracketed

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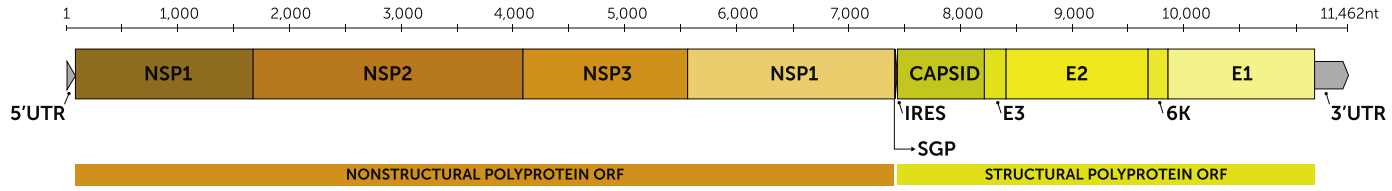

Fig. 1. A scale depiction of a MAYV RNA genome based on GenBank accession no. KX496990. E-envelope peptide; IRES-internal ribosome entry site; NSP-nonstructural peptide; SGP – subgenomic promoter; UTR-untranslated region.

by 5′ and 3′ (including a poly A tract) untranslated regions and capped at the 5′ terminus. The junction between ORFs contains an internal ribosome entry site (IRES) transcriptional promoter for the subgenomic mRNA as well as the start site and leader sequence for 26S mRNA [12]. The 60–70 nm virions are icosahedral, consisting of a nucleocapsid enclosed by a tight envelope comprising host cell membrane embedded with E1-E2 heterodimeric trimers [13–15]. The host cell receptor for MAYV remains unknown [4].

1.2. Sequencing and genetic variation

Other alphaviruses include Ross River virus (RRV), Barmah Forest virus (BFV), chikungunya virus (CHIKV), eastern/western/Venezuelan equine encephalitis virus (EEEV/WEEV/VEEV), Semliki Forest virus (SFV) and Una virus (UNAV). Serologically, MAYV falls into the SFV antigenic complex, defined by serological cross-reactivity patterns [2]. Sequencing studies also classify MAYV as part of the SFV group, indicating that genotypic and phenotypic data agree (Fig. 2) [12].

Analysis of genome sequences in 2013 concluded that MAYVs diverged from their nearest ancestral virus between 1760 and 1860 [11]. However to date there are just three dozen complete MAYV genomes in the public domain, to represent approximately 60 years of observed viral evolution. More genomes are required to robustly estimate viral evolution and to better understand virus spread and change. The limited number of MAYV genomes is not surprising with sporadic, small outbreaks available for study, and few that have occurred recently enough to be within the modern realm of extensive genomic sequencing, as happened after a Venezuelan outbreak in 2000 [11]. In comparison, there are over 250 complete CHIKV genomes online.

There have been no studies comparing the phenotypic impact of sequence differences to date and so it is unclear what viral changes will be important to watch for as indicators of increased risk of transmission in different mosquito species. A single amino acid change in a CHIKV variant resulted in a virus better adapted to a mosquito species not normally considered to be the primary CHIKV vector [16,17]. Micro-evolutionary changes can produce a disproportionately large impact on transmission to humans and these are amplified by urbanization and lapses in vector management [18]. It is essential to develop a genetic "baseline" for MAYV – for any emerging viruses in fact – from which contemporary genetic changes can be observed and targeted for functional and comparative virological studies to inform models, diagnostic, drug and vaccine designs and to predict and manage future epidemics.

2. MAYVD: signs, symptoms and treatments

MAYV infection usually causes MAYVD, an acute, usually non-fatal and non-specific febrile rash, often accompanied by arthralgia [19]. No studies to date have specifically looked for asymptomatic infection. Disease is often clinically indistinguishable from dengue, chikungunya fever, malaria, poliomyelitis, rabies, measles, rubella, hepatitis, leptospirosis, Oropouche fever or other arboviral diseases [4,20,19]. Indeed a study that examined acute sera from those clinically diagnosed with dengue fever, during a dengue outbreak in Brazil, found that only 20% were dengue virus positive and that 3% were found to be positive for MAYV [20].

2.1. Signs, symptoms and underlying mechanism of disease

MAYVD occurs abruptly with a three to five day spiking fever, a nonpruritic maculopapular rash that may appear on the legs and arms within a week after onset and may spread to the trunk, neck and face. Dizziness, chills, headache (sometimes severe and frontal), myalgia, retro-orbital pain, photophobia, inguinal lymphadenopathy, myalgia, epigastric pain, vomiting and diarrhoea are also reported and arthralgia which can affect ankles, wrists, fingers, elbows and toes and less often, other joints, sometimes prior to fever can be severe [9,21,19,22–27]. MAYVD can include a four day viraemia that reaches approximately 10^5 plaque-forming units (PFU)/ml of whole blood [19]. Rash reportedly occurs more often in children less than five years old [19]. Leucopenia and thrombocytopenia have been identified in a number of cases [25,20,19]. Death attributed to MAYV infection is rare [28].

A feature of MAYVD is the often long-lasting polyarthralgia which involves virus-induced inflammation and pain that may also be accompanied by effusions in the joints [24,25]. Joint pain may persist for weeks to months, even in the presence of neutralizing antibody, it can be debilitating and may recur [6,19,4,29,5,30–32].

Few investigations of the underlying cellular and molecular mechanisms specific to MAYVD have been undertaken and so extrapolations have been made from studies of RRV, CHIKV, sindbis virus (SINV) and other alphaviruses [33,34]. Because monocytes and macrophages are key cells in the body's defences against pathogens, their ability to replicate MAYV was an important finding. Macrophages are already known to host