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REVIEW

Mayaro virus: the jungle flu

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Abstract: Mayaro fever is an emerging acute viral disease endemic in Central and South America. Mayaro virus (MAYV) is classified in the Semliki Forest virus antigenic complex and shares similarities with the alphavirus Chikungunya virus and the flavivirus Dengue virus. MAYV is an arbovirus transmitted by *Haemagogus janthinomys*, with competence also demonstrated in *Aedes aegypti*, *Aedes scapularis*, and *Anopheles quadrimaculatus*. Outbreaks and small epidemics of Mayaro fever have occurred in several countries in northern South America and the Caribbean. In addition, travel-associated cases have been reported in European nationals returning from endemic areas. Clinical features of Mayaro fever include fever, chills, persistent arthralgia, retro-orbital pain, maculopapular rash, itching, dizziness, and, rarely, lymphadenopathy. Methods of control for MAYV are similar to those used for other sylvatic arboviruses. Although MAYV was discovered as long ago as the 1950s and continues to be prevalent in the tropical areas of the Americas, it remains neglected and under-studied. This paper provides a thorough and current review of the published MAYV literature ranging from its original description to modern outbreaks, and from the basic virus characteristics to the clinical and epidemiological aspects of this disease.

Keywords: Mayaro virus, emerging arbovirus, dengue-like virus, arthrogenic virus

An emerging threat to public health in the Americas

Mayaro virus (MAYV) is an alphavirus first described in Trinidad and Tobago, and has commonly been reported in South America, Central America, and the Caribbean.[1] MAYV has mainly been confined to the tropical and subtropical rainforests of the Americas, where it is maintained as an endozoonosis in which non-human primates (including capuchin monkeys [*Sapajus* spp.],[2] howler monkeys [*Alouatta caraya*[2] and *Alouatta seniculus*[3]], and marmosets [*Callithrix argentata*][4]) either are main reservoirs or have been reported to have antibodies against MAYV. MAYV is the etiological agent of Mayaro fever, also known as Mayaro virus disease.[5] However, Mayaro fever has also been imported to Europe, as travelers return home from endemic areas.[6] Considering that MAYV has been co-isolated along with yellow fever virus from the same invertebrate[4,7,8] and that *Aedes* spp. have been reported to be able to transmit MAYV in certain laboratory conditions,[9,10] the urbanization of MAYV is likely and it has the potential to represent a real threat to the region of the Americas, especially if viral changes lead to more effective transmission by anthropophilic, urban mosquitoes.[5]

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Although the number of reported Mayaro fever cases and outbreaks is low compared to other arboviruses, it is possible that considerable misdiagnosis and underreporting might lead to inaccurate estimates of Mayaro's public health burden. Accurate diagnosis of Mayaro fever may be complicated by its clinical similarity to other endemic arboviruses such as eastern equine encephalitis virus, Chikungunya virus, Dengue virus, Oropuche virus, yellow fever virus, and Zika virus.[5,11–15] In addition, co-infection with Dengue virus has previously been described.[15] Moreover, immune cross-reactivity with either other Semliki complex viruses in hemagglutinin inhibition and complement fixation assays[16] or other alphaviruses such as Chikungunya virus in antibody assays (i.e. enzyme-linked immunosorbent assays [ELISAs]) [17] may pose a diagnostic challenge.

The possibility of MAYV expanding its host and vector range represents an additional concern regarding its potential as an emergent threat to public health in the Americas. Molecular epidemiology surveillance in South and Central America suggests that recent recombination events confirmed the preference of MAYV for human hosts over non-human primates with no effect on MAYV adaptation to mosquito vectors such as *Aedes aegypti* and *Culex quinquefasciatus*, to which the virus is nonetheless well adapted.[1] In addition, the emergence of Mayaro fever cases in Mexico[18] and Haiti[15] suggests that the virus is expanding its geographical range of activity. Such geographical distribution could pose a threat to south-eastern and south-western US states (including Florida, Louisiana, Georgia, Alabama, Texas, and California), areas well within the estimated range of aedine mosquitoes.[19] In fact, *Aedes* spp. have been detected in these southern states[20–22] With this mosquito as their vector, will Dengue, Chikungunya, and Zika continue their rampant spread across the continent? Will yellow fever and Mayaro be the new plagues?[23]

Although MAYV was discovered in the tropical areas of the Americas in the 1950s,[5] it remains neglected and understudied. In addition, owing to the relatively poorly understood nature of MAYV, there is a need to conduct more in-depth research and to employ proven control methods that have worked for other arboviruses to prevent epidemics of MAYV.

History of Mayaro fever, the jungle flu

In the Amazonian rainforest, Mayaro fever is commonly known as the "jungle flu."[7] This virus was first isolated in 1954 among five febrile patients from the island of Trinidad.[24] Casals and Whitman characterized MAYV as an arbovirus closely related to the Semliki Forest virus,[25] which was later confirmed by Lavergne et al.[26] Circulating MAYV among humans, vertebrate reservoirs, and non-vertebrate vectors has been reported in Suriname,[25,27] Brazil,[28,29] Panama,[30] Trinidad and Tobago,[25] Bolivia,[6] Ecuador,[7] and Venezuela.[31] In addition, anti-MAYV antibodies have been reported among indigenous populations of Bolivia, Brazil, Colombia, Panama, Peru, Suriname, Trinidad and Tobago, Venezuela, French Guiana, and Mexico.[32–35] MAYV has also been imported into non-endemic areas including France (from French Guiana,[36] and Brazil[37]), Germany (from Bolivia,[6,38] French Guiana,[39] and Ecuador[38]), The Netherlands (from Suriname[17] and Brazil[40]), and Switzerland (from Peru[41]). In addition, Mayaro infection has been frequently identified among colonists of the Trans-Amazonian Highway in South America.[42]

MAYV outbreaks were reported in the Amazonian rainforest of Belterra, Brazil, in 1978.[43] The attack rate of MAYV among immunologically virgin populations has been described in outbreaks among Okinawan settlers in Bolivia[44] and in Dutch military troops in Suriname.[27] The reported attack rate among Dutch soldiers was 5.3 per 100 person/years at risk.[27] MAYV is an important arbovirus in the Amazonian area of French Guiana, with a seroprevalence of 6.3% among humans and 66% among non-human primates.[3] MAYV was first reported in the Amazonian rainforest of Ecuador during the investigation of yellow fever outbreaks in 1997.[7] The syndrome with fever, rash, and severe arthralgias is described by Amazonian native populations as the "jungle flu."[7]

As mentioned earlier, MAYV has been geographically restricted to Central and South America, with a few cases occurring in the Caribbean. Infrequent outbreaks have occurred in Trinidad,[25] Brazil,[28,29] Ecuador,[7] and Venezuela.[31] In addition, sporadic cases have been identified in Bolivia,[44] Haiti,[15] Mexico,[18] and Peru.[45] Finally, a few reports of import/export events exist; these have been summarized in the Epidemiology section.

Characteristics of the virus

MAYV is an enveloped positive-sense single-stranded RNA virus belonging to the genus *Alphavirus* in the family Togaviridae.[5,46] This virus belongs to the Semliki Forest virus antigenic complex, which includes both Old World and New World alphaviruses, including Chikungunya virus, another arbovirus causing similar symptoms.[24,46] The virus encodes four non-structural proteins, dubbed nsP1–nsP4, and five structural proteins, termed C, 6K, E1, E2, and E3 (the last three comprising the viral envelope proteins).[31,47]

Lavergne et al[26] suggested that MAYV could have an Old World origin, based on their analysis of the *E1* gene (directly upstream of the 3′-poly(A) tail). Three distinct genotypes have been identified so far, designated D, L, and N.[5,31] As of the date of writing this article, genotype L has only been recovered from patients in Brazil, while genotype D is distributed more broadly in the Central and South American region.[5,31]

Understanding cell entry of a virus is a key step in understanding infection and, ultimately, in creating an intervention to obstruct viral activity. The mechanisms by which prototype alphaviruses (such as Semliki Forest virus) enter human cells have been known since the early 1990s. However, at present, only one study has investigated the specific cell entry mechanisms of MAYV. The virus achieves cell entry via receptor-mediated endocytosis and fusion with an endosomal membrane through a clathrin-coated pit, a mechanism which it shares with the Semliki Forest virus.[48] This same study revealed an alternative strategy for endocytosis; MAYV has the ability to use a caveolin-coated pit in place of clathrin to reach the endosome.[48]

Clinical signs and symptoms of Mayaro disease

Mayaro fever is a self-limiting Dengue-like acute viral disease that has not been reported to cause human fatalities, but can cause temporal severe incapacity which may lead to chronic arthralgia and, in some instances, interfere with daily activities even 1 year after symptom onset.[45] The onset of the disease is abrupt, with fever (usually between 39°C and 40.2°C),[43] arthralgia, and maculopapular rash.[5] In most patients with Mayaro disease, acute symptoms usually last for 3–5 days.[5,49] Less common symptoms may include dizziness, itching, and cervical and inguinal lymphadenopathy.[28,41]

Along with Chikungunya virus, MAYV is the only alphavirus confirmed to be circulating in the Americas that causes arthralgia, while the others cause encephalitis.[26] In a prospective study of Mayaro fever patients in Peru, 54% of patients reported residual joint pain in the hand, wrist, elbows, knees, and feet 12 months after the initial onset of illness.[45] Axial joint pain was rare.[45]

A typical Mayaro fever rash is shown in Figure 1. This patient was diagnosed during the 1997 yellow fever outbreak investigation in the Amazonian rainforest of Ecuador.[7] The patient presented with fever, rash, headache, and arthralgias.[7] The diagnosis was confirmed by the presence of MAYV-specific immunoglobulin M (IgM) antibodies.[7]

Figure 1 First laboratory-confirmed case of Mayaro disease in Ecuador.
Note: This patient is a native of Montalvo, a community in the Amazonian basin located in Pastaza province.

Clinical signs and symptoms of MAYV are frequently difficult to distinguish from other locally prevalent viruses (both arboviruses and other viruses), bacteria (e.g. leptospirosis), and parasites (e.g. malaria).[5] While persistent joint pain is most common in patients with alphavirus infections, differential diagnosis should include Chikungunya, Dengue, human herpesvirus-6, parvovirus B-19, rubella virus, and Zika virus.[15,28] Clinical presumption should be followed by confirmatory laboratory diagnostic techniques including reverse-transcription polymerase chain reaction, indirect immunofluorescence, and virus neutralization assays.[15,41] In a cross-sectional study of Ecuadorian military personnel, MAYV prevalence was determined by evaluating the presence of immunoglobulin G (IgG) and IgM antibodies via ELISA.[7]

Epidemiology

As mentioned earlier, Mayaro fever outbreaks have been reported most commonly in northern South America and in the Caribbean (Figure 2), in addition to sporadic cases reported in Mexico and the handful of import/export events reported in the literature (Table 1). In these regions, Mayaro fever has been found to be common in people living in rural areas in close proximity to the forest, especially around the Amazon river basin.[49] In addition, MAYV may be able to emerge in urban areas, as demonstrated by its ability to be transmitted by *Ae. aegypti* in a laboratory setting.[9,10] Should MAYV emerge in urban environments, this would present a

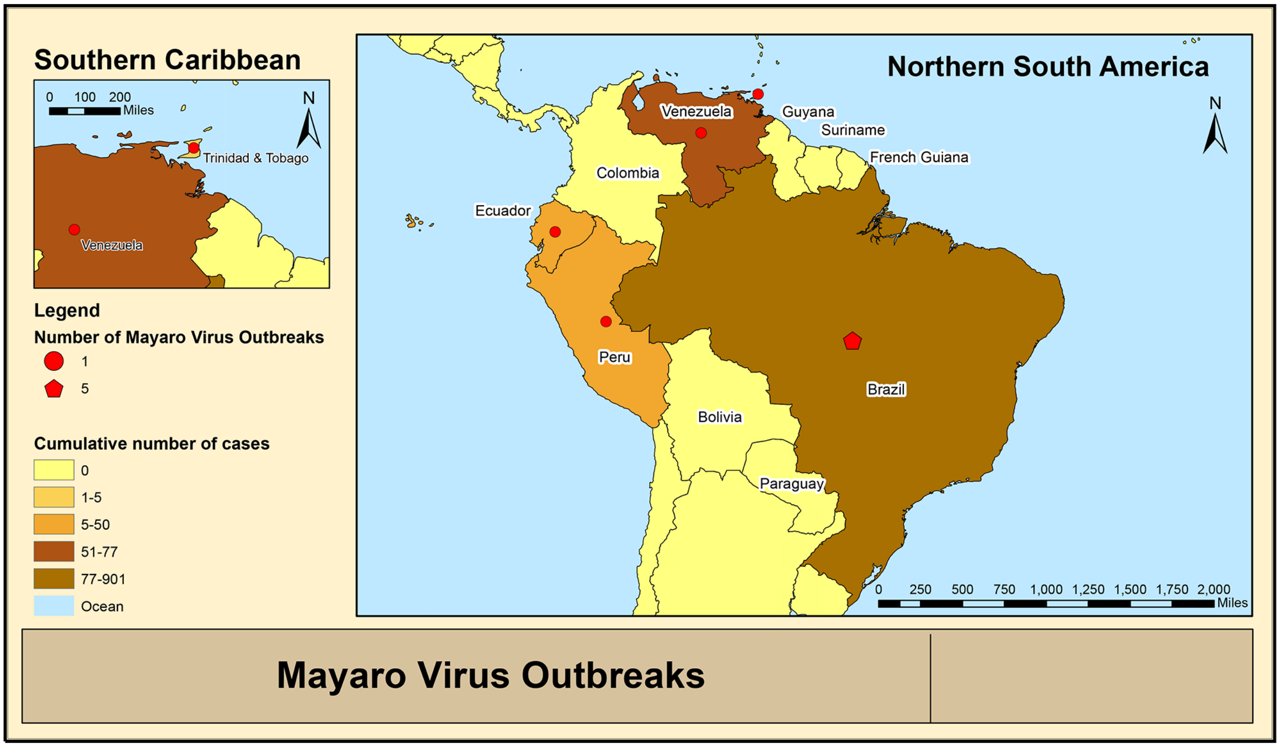

Figure 2 Geographical distribution of Mayaro virus outbreaks.
Note: Data from these studies.[7,24,28,31,43,49,51,64,65]

Table 1 Mayaro virus fever import/export events by year of event

Year of event	Exporting country/region	Importing country	Reference
1996	Peru	USA	49
1997	Peru	USA	49
2008	Suriname	The Netherlands	17
2010	Brazil	France	37
2011	Peru	Switzerland	41
2012	Bolivia	Germany	6
2013	French Guiana	Germany	39
2013	Brazil	The Netherlands	40
2014	Bolivia	Germany	38
2014	Ecuador	Germany	38
2015	French Guiana	France	36

significant threat to public health.[5] Since MAYV is endemic in areas of the world where Dengue and/or yellow fever virus circulate, and Dengue often produces large-scale urban epidemics, this may lead clinicians to suspect Dengue instead of MAYV fever, possibly contributing to misdiagnosis. Moreover, co-infection and immune cross-reactivity (as discussed in the section "An emerging threat to public health in the Americas"), may also contribute to misdiagnosis and underreporting of MAYV, leading to Mayaro fever's true public health impact being misestimated.

Earlier reports have shown that MAYV has been detected in São Paulo (among three people who visited the forested state of Mato Grosso do Sul)[28,50] and Manaus,[51] two important cities of the coastal and Amazonian regions of Brazil, respectively. Similarly, people living in the Amazon basin in Ecuador were 23 times more likely to contract an infection by MAYV than people in other regions of the country.[7] In the same study, 46% of people living in the Amazon basin in Ecuador had IgM- or IgG-specific antibodies to MAYV, compared with only 2% of people residing in other regions of Ecuador.[7] These findings support the notion that people living near the rainforest or those whose occupations require them to work near the rainforest are more likely to be exposed to MAYV mosquito vectors; this can be thought of as a sylvatic cycle of transmission similar to those observed for other arboviruses such as Dengue or yellow fever.[5]

The transmission cycle of MAYV is complex. Although the main mosquito vector for MAYV has been identified (i.e. *Haemagogus* spp.),[52] some studies suggest that *Ae. aegypti*,[9,10,52] an important urban vector, would be able to transmit the virus. Additional studies exploring the competence of other mosquito species to transmit the virus are needed. Similarly, since other arboviruses (specifically flaviviruses) have demonstrated the ability to persist in bodily fluids and transmit sexually,[53] future studies should investigate other possible routes of transmission for MAYV, along with persistence in bodily fluids, especially synovial liquid. With extensive future studies examining key factors in MAYV infection, we may have a unique opportunity to intervene before this emerging virus becomes a more serious threat to public health.

Seroprevalence of antibodies against MAYV

The presence of antibodies against MAYV in humans provides epidemiological evidence of its transmission in the Americas. An investigation in Valença, Bahia, in the coastal area of Brazil, reported that only one subject (who had a previous residence of 3 years in the Amazonian rainforest) among 288 sampled individuals had antibodies against Mayaro.[54] This subject reported that during his residence in the Amazonian rainforest, he had developed a febrile disease with exanthema and arthralgias.[54] Serological surveys of other populations in northern South America have found antibodies against MAYV in rates that range from 1% to 60%.[44,55] A study carried out in Belterra, Brazil, between 1977 and 1978 showed that 10.3% of the 161 people tested had antibodies against MAYV. No sampling frame was described in selecting subjects for study. In a parallel study conducted by the same team in 1978, during the peak of the MAYV outbreak, 327 people were tested. The sample represented all ages of susceptible people and all residential areas. Seventy-one (22%) were found to have MAYV antibodies.[56] During the Belterra outbreak, five fatal cases and one non-fatal case of yellow fever were reported between January and April 1978. In the parallel seroepidemiological survey, 11 people (3.3%) had antibodies against yellow fever. Four of these 11 subjects (36%) reported having had an acute febrile episode during the preceding 2 months.[56] Thus, in the subsequent study, the prevalence of MAYV exposure rose to 30% in the autochthonous population. One observation of this study, which is similar to the findings of the 1954 study in Trinidad and Tobago,[24] is the strong association of MAYV and yellow fever virus. This finding, in addition to the fact that yellow fever, similarly to MAYV, is associated with *Haemagogus* spp. mosquitoes[57] and *Alouatta* spp. monkeys,[57] supports the assumption that these diseases have similar transmission cycles in the rainforest.

A study using blood bank sera to test for antibodies against MAYV by hemagglutinin inhibition was conducted in French Guiana in 1996.[3] A total of 1962 sera samples were tested from 896 women and 1066 men.[3] Antibodies against MAYV were found in 124 (6.3%) with no significant differences in the seroprevalence rates between women (5.8%) and men (6.8%).[3] However, seroprevalence increased significantly with age: <10 years old, 0%; 10–19 years, 5.5%; 20–29 years, 5.9%; 30–39 years, 8%; 40–49 years, 13%; and ≥50 years, 20%.[3] Similar to other studies,[7] seroprevalence differed according to the place of residence.[3] The highest rates were found in the areas closest to the Amazonian rainforest along the Maroni and Oyapock Rivers,[3] echoing the findings by Izurieta et al.[7] A comparison among ethnic groups found that Noir-Marrons and Amerindians had the highest prevalence after adjusting for age. Differences that appear to be based on ethnicity may be attributable to the geographical place of residence. The increased prevalence among older groups was explained by the authors as a consequence of: 1) older people being more likely than young children to go hunting in the forest and 2) an epidemic that occurred about 10 years ago, with the circulation of MAYV being only sporadic since then. In addition, a fairly constant transmission risk with increased cumulative incidence over time may explain the age-specific rates, given the smaller sizes in each age stratum.[3] The same pattern was observed in monkeys, suggesting that MAYV epidemics may occur from time to time with a low endemicity linked to an endozoonosis.[3]

Ecology of the virus

Sylvatic vertebrates are the principal reservoirs for MAYV maintaining the zoonosis in the rainforest.[5] Epizootics and epidemics of the disease occur periodically as the virus is spread. Humans become infected through mosquito bites. Based on the only research conducted during an ongoing outbreak, epidemics seem to begin with the onset of the wet season and end with the onset of the dry season. This correlates with the rise and fall of the mosquito population in the rainforest.[56]

Vectors

The main mosquito vector for MAYV in its sylvatic cycle of transmission has been identified as *Haemagogus janthinomys*.[5,8] Along with *Ae. aegypti*, *H. janthinomys* has also been identified as a vector for yellow fever virus.[48] Because MAYV is still emerging and is likely to develop into a more significant public health concern, it is important to identify other species of mosquito that may also transmit the virus.

Because of its prevalence in urban environments and the existence of several urban centers in countries where Mayaro fever is endemic, *Ae. aegypti* was an excellent candidate for competence studies. Long et al determined that *Ae. aegypti* is competent in transmitting MAYV at a rate of 70% in a laboratory setting.[9] Soon after the initial discovery of MAYV, it was demonstrated that *Anopheles quadrimaculatus* and *Aedes scapularis* were also moderately competent in transmitting MAYV, although no further experiments have been conducted to confirm these results.[24,58] More contemporary studies exploring additional species present in tropical urban environments have not been conducted. MAYV has been isolated from several genera of mosquitoes, including *Culex* spp., *Haemagogus* spp., *Mansonia* spp., *Aedes* spp., *Psorophora* spp., and *Sabethes* spp., with *H. janthinomys* being considered the main vector.[5,9,59,60]

Based on all these observations, we propose a potential three-cycle transmission dynamic for MAYV, similar to the one observed for Dengue and yellow fever, whereby the virus is transmitted in the jungle by *Haemagogus* spp. in a sylvatic cycle which may then reach urban areas through people living in urban or periurban areas and working in or visiting the forest fringe (intermediate cycle); once in the urban setting, the mosquito could potentially be spread by *Ae. aegypti* in an urban cycle (Figure 3). We posit that it is likely that these three dynamic transmission cycles occur currently and that MAYV is likely to be currently misdiagnosed as Dengue virus (or another locally transmitted pathogen) given their close clinical and immunological profiles, as discussed earlier (see "Epidemiology").

In 1977 and 1978, the epidemic that occurred in Belterra, Pará, Brazil, was the first to be successfully studied. During the Belterra outbreak in Brazil, *H. janthinomys* yielded the only positive isolate for both MAYV and yellow fever virus.[4] This vector is found in abundance in the forest canopy, especially around 1 pm, followed by a decline in activity around 4 pm.[4] At nightfall (6 pm), *H. janthinomys* activity had ceased.[4] Approximately 12,000 potential biting vectors were captured in a 1 month trapping that coincided with the peak of a MAYV epidemic. MAYV was recovered from *H. janthinomys*, *Limatus flavisetosus*, and *Wyeomyia aporonoma*. Pooled samples of *H. janthinomys* yielded nine

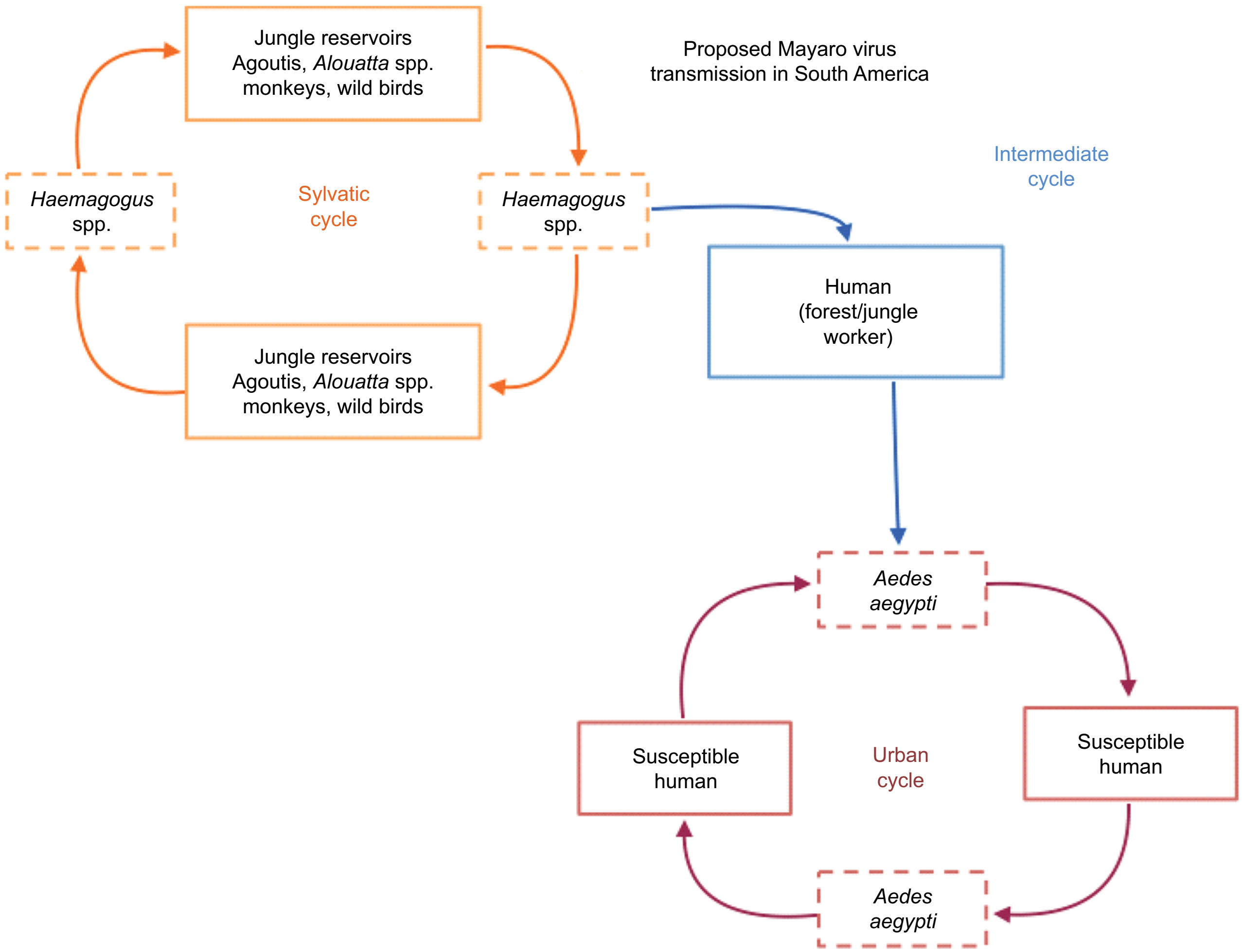

Figure 3 Proposed Mayaro virus transmission cycles for northern South America. Dashed boxes represent mosquito vectors for the virus.

isolates of MAYV and two isolates of yellow fever virus. The minimum field infection rate of *H. janthinomys* was 1:82 for MAYV and 1:368 for yellow fever virus.[4]

Vertebrate reservoirs

In addition to humans, MAYV infects several species of non-human primates and birds.[4,61] In Panama, agoutis (*Dasyprocta punctata*) and howler monkeys (*Alouatta villosa*) have been reported to have antibodies against MAYV.[30] The median positive titer was 1:128 (range 1:32 to 1:512).[30] Another finding of that study was that yellow fever antibodies were also detected.[30] Among the 14 *A. villosa* primates, nine had antibodies against yellow fever virus.[30] Based on these findings, the authors concluded that in the Americas, sylvatic yellow fever was a monkey virus.[30] Seymour et al also hypothesized that MAYV and yellow fever virus may have a similar transmission cycle, based on their finding that antibodies against both viruses were highly prevalent among *A. villosa*.[30] MAYV has also been isolated from other vertebrates, including lizards and wild birds. Calisher et al reported the isolation of MAYV in a migrating bird, *Icterus spurius*, captured in Louisiana in 1967.[62] The isolation of MAYV in one bird among 1300 studied may suggest that the finding was a rare and incidental infection with no meaning for the transmission of the disease. Nevertheless, the study conducted in Belterra, Brazil, showed a seroprevalence that ranged from 0.4% to 5% in seven families of birds. In a previous study, the same authors showed that during 1959 and 1960, 34 out of 119 doves (29%) in Belém forest, Brazil, had Mayaro antibodies.[4]

Antibodies against MAYV have been detected in the one Cebidae studied and in 32 out of 119 Callitrichidae (27%).[4] Yellow fever virus was also isolated in the only Cebidae studied and was found in five out of 119 Callitrichidae (4%).[4] In the same study, two howler monkeys (*Alouatta belzebul*) were collected during the Mayaro epidemic; however, the test could be performed in only one, which was confirmed positive for yellow fever virus.[4] In another study, two-thirds of studied howler monkeys (*Alouatta seniculus*) tested positive for MAYV antibodies.[3] Gender was not correlated with seroprevalence, but increased age and weight of the monkeys was correlated with increased seroprevalence. The prevalence of MAYV antibodies increased to 84% in older monkeys. Sera were also collected from 44 tamarins (*Saguinus midas*), which showed a lower MAYV seroprevalence of 18.2%.[3]

Proposed control methods

Methods of control are similar to those employed for other arboviruses, particularly for other alphaviruses and flaviviruses. Prevention at its most basic level should consist of the application of insect repellent to repel daytime biters when spending time in endemic areas, especially if working in forested areas. If mosquito density is high, the use of personal nets or long-sleeved shirts and pants may be more appropriate. This prevention strategy should also be employed by people who may have occupational exposure to insect vectors, not simply travelers. In terms of vaccination, two experimental MAYV vaccines are currently being tested in animal experiments and are expected to continue into clinical experimentation.[16]

Epidemiologically, contact tracing and isolation are important control strategies. Contact tracing can be a useful strategy to identify unreported cases of MAYV disease since people living in the same conditions as the patient during the same timeframe are likely to have a similar exposure to the mosquito vector.[59] In patients who have contracted MAYV fever, reverse isolation (using bed nets and screened rooms to prevent forward transmission) as well as avoiding areas where mosquito vectors are prevalent should be implemented.[60] Unlike Dengue fever, MAYV fever has not yet produced large-scale urban epidemics. Still, locating and eradicating mosquito vector habitats around human homes should prove useful to obstruct further progression of an epidemic.[59,60]

Disclosure

The authors report no conflicts of interest in this work.

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