Alphaviruses in Latin America and the Introduction of Chikungunya Virus

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Chapter 9
Alphaviruses in Latin America and the Introduction of Chikungunya Virus

Juan-Carlos Navarro, Jean-Paul Carrera, Jonathan Liria, Albert J. Auguste, and Scott C. Weaver

1 Introduction

The *Togaviridae* is a family of enveloped, single-stranded, plus-strand RNA viruses composed of the genera *Alphavirus* and *Rubivirus*. The rubella virus (the cause of German measles) is the only member of the latter genus [129]. The *Alphaviruses* are arthropod-borne viruses (mainly mosquitoes) with a nearly worldwide geographic distribution, having been reported from all continents except Antarctica and from many islands [16].

The genus *Alphavirus* includes 30 species grouped into 10 complexes based on antigenic and/or genetic similarities [75]. The Barmah Forest, Ndumu, Middelburg, and Semliki Forest complexes occur almost exclusively in the Old World. In the

J.-C. Navarro (✉)
Universidad Internacional SEK, Facultad de Ciencias Naturales y Ambientales, Quito, Ecuador

Universidad Central de Venezuela, Lab. Biología de Vectores-IZET, Caracas, Venezuela
e-mail: juancarlos.navarro@uisek.edu.ec; jcnavac@gmail.com

J.-P. Carrera
Gorgas Memorial Institute of Health Studies, Department of Research in Virology and Biotechnology, Panama City, Panama
e-mail: jpcarrera@gorgas.gob.pa

J. Liria
Universidad Regional Amazónica, IKIAM, Tena, Ecuador
e-mail: jonathan.liria@ikiam.edu.ec

A.J. Auguste • S.C. Weaver
Institute for Human Infections and Immunity and Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, TX, USA
e-mail: aj1augus@utmb.edu; sweaver@utmb.edu

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New World, the first alphaviruses to be isolated were western equine encephalitis virus (WEEV) in 1930, eastern equine encephalitis virus (EEEV) in 1933, and Venezuelan equine encephalitis virus (VEEV) in 1938 [129]. Other *Alphaviruses* found in Latin America include Mayaro (MAYV), Aura (AURAV), Una (UNAV), Trocara virus (TROV), and the recently introduced chikungunya virus (CHIKV) (Table 9.1). Others found in North America belonging to the WEE complex, Highlands J (HJV), and Fort Morgan viruses (FMV) [129] are recombinants resembling WEEV derived from ancestral EEEV and Sindbis (SINV) from the Old World.

Many of the New World alphaviruses are widely distributed throughout the Americas. WEEV is found from Canada to Argentina, and EEEV and VEEV occur in both North America and South America. Other viruses such as MAYV and AURAV have a more restricted neotropical distribution [106].

Recent phylogenetic analyses depict the evolution of the alphaviruses (Fig. 9.1) based on structural protein genes. Clades or branches are clearly correlated with the antigenic complexes, host/reservoirs, and disease syndromes: the Semliki Forest virus complex is associated with nonhuman primates and human fever/rash/arthralgia (including chikungunya, Mayaro, Ross River, Semliki Forest). The WEEV/EEEV complexes associate with birds, and the VEEV complex is mostly related to rodents as reservoirs, and all three with human and equine encephalitis.

The most recently described alphavirus, Eilat (EILV), a "mosquito-specific" virus from *Anopheles coustani* mosquitoes in Israel [75], is a sister of the WEEV complex (see Fig. 9.1). In contrast to all other mosquito-borne viruses, it is unable to replicate in vertebrate cell lines. EILV has important implications for arbovirus evolution and may help elucidate the viral factors responsible for the virus–cell interactions of pathogenic alphaviruses, facilitate vaccine development, and help develop strategies to control or prevent alphavirus transmission [28, 74, 75, 138].

Figure 9.2 shows a cartoon of alphavirus transmission cycles. All alphaviruses except EILV are zoonotic: mosquitoes (family Culicidae) are the major vector group, especially the genera *Aedes* (chikungunya), *Culex* subgenus *Melanoconion* (VEEV, EEEV, WEEV), and *Haemagogus* and *Sabethes* for Mayaro [26, 72, 84, 112]. In concordance with the phylogenetic tree, enzootic transmission cycles involve nonhuman primates (chikungunya, Mayaro, others that produce arthralgias), birds (EEEV, WEEV), and rodents (VEEV, possibly Madariaga virus). Spillover transmission to humans occurs mainly in rural areas but can become urban for CHIKV and potentially others. Affected animals (including humans) usually generate insufficient viremia to participate in the transmission cycle (i.e., dead-end hosts). VEEV uses equids (horses, donkeys, mules) as amplification hosts (epizootics) to increase spillover to humans (epidemics) [126]. CHIKV is the only alphavirus known to utilize humans as amplification hosts and the urban mosquitoes [*Aedes (Stegomyia) aegypti* or *Aedes (Stegomyia) albopictus*] for transmission, resulting in major epidemics [47, 129]. Mayaro, similar to CHIKV in Africa, uses nonhuman primates as enzootic hosts, but their role is still not well understood [72].

Table 9.1 Alphavirus members from those that occur in the New World, including the new introduction of chikungunya virus

Antigenic complex	Virus	Antigenic subtype	Antigenic variety	Clinical syndrome in humans	Distribution
Eastern equine encephalitis (EEE)	Eastern equine encephalitis virus (EEEV)	I–IV		Febrile illness, encephalitis (none recognized in Latin America)	North, Central, South America
Semliki Forest	Mayaro and Chikungunya virus (CHIKV)			Febrile illness, rash, arthritis	South and Central America
	Una virus (UNAV)			None recognized	South America
Venezuelan equine encephalitis (VEE)	Venezuelan equine encephalitis virus (VEEV)	1	AB	Febrile illness, encephalitis	North, Central, South America
			C	Febrile illness, encephalitis	South America
			D	Febrile illness, encephalitis	South America, Panama
			E	Febrile illness, encephalitis	Central America, Mexico
	Mossos das Pedras virus (MDPV)		F	Febrile illness, encephalitis	Brazil
	Everglades virus (EVEV)	II		Febrile illness, encephalitis	Florida (USA)
	Mucambo virus (MUCV)	III	A	Febrile illness, myalgia	South America, Trinidad
			C	Unknown	Peru
			D	Febrile illness	Peru
	Tonate virus (TONV)	III	B	Febrile illness, encephalitis	Brazil, Colorado (USA)
	Pixuna virus (PIXV)	IV		Febrile illness, myalgia	Brazil
	Cabassou virus (CABV)	V		None recognized	French Guiana
	Rio Negro virus (RNV)	VI		Febrile illness, myalgia	Argentina
Western equine encephalitis	Aura virus (AURAV)			None recognized	South America
	Western equine encephalitis virus (WEEV)	Several		Febrile illness, encephalitis	Western North, South America
	Highlands J virus (HJV)				Eastern North America
	Fort Morgan virus (FMV)	Buggy Creek		None recognized	Western North America
Trocara	Trocara virus (TROV)				South America

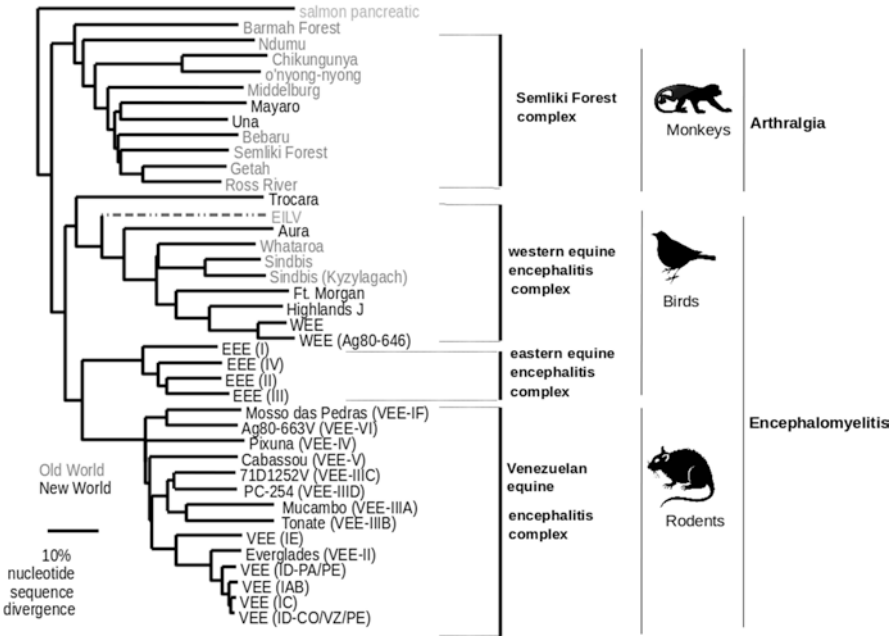
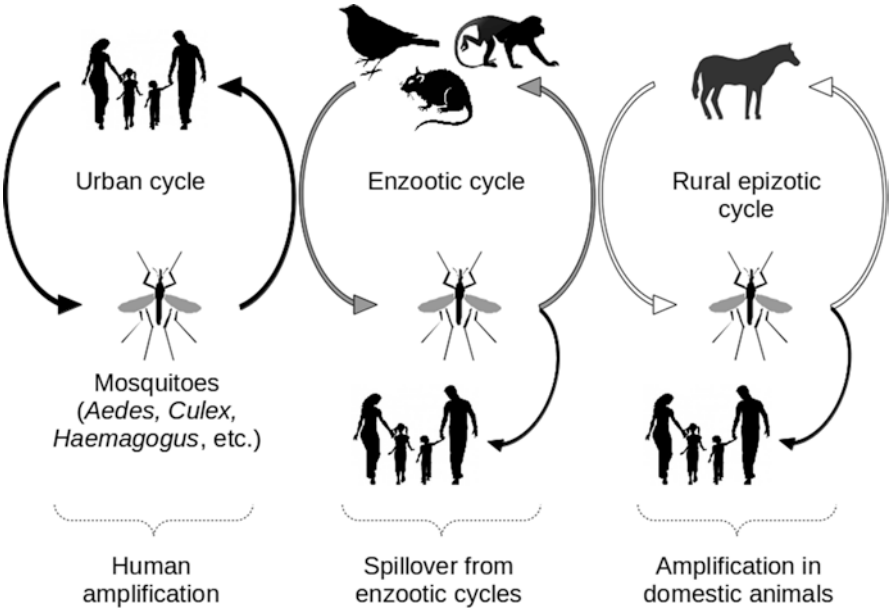


Fig. 9.1 Phylogenetic tree showing the evolutionary hypothesis of *Alphaviruses*. The viruses in *bold* are neotropical and New World viruses; those in *gray* are the Old World viruses (including the mosquito-specific virus Eilat). *Lines* on *right* delimit the clades of viruses associated with a serogroup complex, vertebrate hosts, and symptoms (arthralgia and encephalomyelitis). (Modified from Weaver et al. [129])



The majority of alphaviruses can cause at least mild febrile disease in humans, with several producing severe, life-threatening diseases; however, many remain poorly studied epidemiologically with unknown public health importance.

Recent studies in several Latin American locations of "dengue-like" illness revealed that alphaviruses such as VEEV, EEEV, MAYV, and CHIKV account for a significant number of cases misdiagnosed clinically as dengue. Moreover, with the recent introduction of the Zika virus, diagnosis based only on signs and symptoms is even more complicated in areas where these viruses are circulating simultaneously.

A better understanding of alphavirus transmission cycles, molecular evolution, vector biology, virus–vector–host coevolution, and rapid diagnostics is needed to prevent alphavirus diseases.

Brief descriptions of the most important alphaviruses in Latin America follow.

2 Alphavirus and Encephalitis

2.1 Venezuelan Equine Encephalitis Virus

The Venezuelan equine encephalitis (VEE) complex includes major human and equine pathogens and consequently is the most thoroughly studied in Latin America [126]. VEEV was recognized first in 1936 and isolated soon thereafter from the brains of fatal equids in Venezuela. This virus is transmitted enzootically between mosquitoes and rodents, and equine-amplified epizootic cycles cause large outbreaks of encephalitis in humans and horses [49, 129]. Outbreaks in Mexico and South America (Colombia, Venezuela, and Peru) demonstrated that VEE is a reemerging disease [44] as a naturally emerging pathogen endemic to South and Central America, Mexico, and Florida [126] circulating among wild rodents and mosquitoes. The introduction of horses, a new and susceptible host, into the Americas during the colonial period triggered outbreaks in these animals and increased the exposure of humans.

Fig. 9.2 Transmission cycles and mechanisms of human infection by alphaviruses. At the *center* is an enzootic cycle, typically involving avian, rodent, or nonhuman primates as amplification or reservoir hosts and mosquito vectors. Humans become infected via direct spillover when they enter enzootic habitats or when amplification results in high levels of circulation. Transmission to humans may involve the enzootic vector or bridge vectors with broader host preferences. *Right panel*: Secondary amplification involving domestic animals can increase circulation around humans, increasing their chance of infection via spillover. In the case of VEEV, mutations that enhance equine viremia are needed for secondary equine amplification. *Left panel*: CHIKV can use humans for amplification, resulting in urban epidemic cycles and massive outbreaks. (Modified from Weaver et al. [129] and Muñoz and Navarro [73])

Systematics and Geographic Distribution

The VEE complex is a sister of the eastern equine encephalitis (EEE) complex [90] and includes six subtypes. Only subtypes IAB and IC are traditionally considered epizootic strains that use equids for amplification via high-titer viremias. Other VEEV subtypes (ID and IE) are considered equine-avirulent, enzootic strains, although IE strains from recent Mexican epizootics appear to be equine-neurovirulent but incapable of generating high-titer equine viremia [35]. The remaining subtypes (II–VI) are also enzootic strains that generally circulate in sylvatic or swamp habitats and are considered incapable of equine amplification. In the United States, these include the Everglades virus in Florida and a variant of Tonate virus, Bijou Bridge, isolated in Colorado from cliff swallow bugs during the 1970s [17].

Geographic phylogenetic correlations of VEEV subtypes ID enzootic lineages or genotypes [1, 13, 93, 97, 124] suggest that geographic barriers explain their current distributions.

The major epidemic/epizootic subtype IAB and IC strains are highly pathogenic for horses, with case-fatality rates of 20% to 80%. The last major VEE outbreak occurred in 1995 in Venezuela and Colombia with 75,000 to 100,000 human cases, more than 300 of them fatal. In 1993, equine disease was associated with VEEV-IE in Mexico, and since 1993, human cases of VEEV ID-associated disease have occurred in Peru [33, 126].

VEEV infection usually causes flu-like symptoms, and encephalitis is rare in adults. Although the case-fatality rate is low ($\leq$1%), neurological disease, including ataxia, disorientation, mental depression, and convulsions, can be detected in up to 14% of infected individuals, mainly children. High seroprevalence has been detected in humans in interepidemic/epizootic periods in Argentina [87, 88]. Neurological sequelae in humans are also common [34, 49, 94].

Evolution of Epizootic Strains from Enzootic Ancestors

Phylogenetic analysis of the VEE complex shows a close evolutionary relationship among IAB, IC, and ID strains and delineates six major lineages of enzootic VEEV, including five ID-like lineages and the subtype IE lineage. All epizootic strains from major outbreaks fall into one of three clades nested within one of these lineages, which is otherwise composed of enzootic ID strains from western Venezuela, Colombia, and northern Peru. These phylogenetic data support the hypothesis that epizootic VEEV strains have arisen on at least four occasions by mutation of enzootic ID strains and changes in host range. In further investigations, the occurrence of two mutations involving charge alterations on the surface of the E2 protein implies alterations in cellular receptor usage that influences pathogenesis as a mechanism of epizootic emergence [38, 91, 124–126].

Epizootic Transmission Cycle

The epizootic transmission cycle of VEEV is fairly well understood [91]. A feature common to all major outbreaks is the role of equids as highly efficient amplification hosts. Although the vertebrate host range of epizootic VEEV strains is wide and includes humans, rodents, bats, dogs, sheep, and some birds, major epidemics in the absence of equine cases have never occurred. Despite the repeated occurrence of

epizootics near major cities such as Maracaibo (1995), in western Venezuela, inter-human mosquito-borne transmission has not been detected. However, the potential for urban transmission by a species such as *Aedes aegypti*, which is susceptible to infection after biting humans and exhibits behavioral traits such as multiple host feeding and peri-domesticity that augment its vector competence [43, 54, 80], or the continuous expansion of *Aedes albopictus* should be considered [12, 30, 68, 77], as human populations continue to expand and those of equines decline in rural areas in Latin America [85, 118]. Several small, atypical equine outbreaks were detected in Venezuela in the central llanos (2000–2003) with VEEV sequences showing high genomic stability 10 years after the 1995 outbreak. Cattle sero-surveys indicated the recent circulation of enzootic VEEV strains, and possibly of epizootic strains. Persistence of VEEV subtype IC strains and infection of horses at the end of the rainy season suggested the possibility of an alternative, cryptic transmission cycle involving survival through the dry season of infected vectors or persistently infected vertebrates [76].

Epizootic Vectors

Epizootic strains (subtype IAB and IC) of VEEV are opportunistic in their use of mosquito vectors during outbreaks. Field studies have indicated that more than one principal vector species can be involved in transmission [99, 122, 123, 136]. Although susceptibility to infection is a prerequisite for biological transmission, ecological and behavioral traits can be more important than susceptibility differences in vectorial capacity.

Although several mosquito species have been incriminated as VEEV vectors during epizootics, *Aedes* (*Ochlerotatus*) *taeniorhynchus*, a salt-marsh mosquito, may be the most important epizootic vector. This species is abundant in coastal areas including the Guajira Peninsula (Colombia and Venezuela), where many of the largest outbreaks have occurred, and virus isolations and susceptibility studies have documented its role in transmission [51, 107, 116, 136]. *Culex* (*Deinocerites*) spp. may also be VEEV vectors in coastal areas [37].

Psorophora confinnis and *P. columbiae* were probably important vectors during outbreaks in northern South America and in the 1971 epizootic/epidemic in northern Mexico and Texas [136]. *Aedes* (*Ochlerotatus*) *sollicitans* also exhibited extremely high infection rates in the coastal areas of Mexico and Texas in 1971 [136] and is capable of laboratory transmission following high-titer blood meals [116]. Non-mosquito arthropods (blackflies and ticks) have also been implicated as VEEV vectors but appear to be less important [55–57, 99].

Enzootic Transmission Cycle: Hosts and Vectors

Sylvatic rodents in the genera *Sigmodon*, *Oryzomys*, *Zygodontomys*, *Heteromys*, *Peromyscus*, and *Proechimys* are believed to be the principal reservoir hosts of most enzootic VEE complex viruses because they are frequently infected in nature, have high rates of immunity, and develop moderate- to high-titer viremia [23, 24, 126]. Spiny rats (*Proechimys semispinosus*) and cotton rats (*Sigmodon hispidus*) are the principal reservoir hosts of enzootic subtype ID viruses in Panama and also in Colombia and Venezuela [13, 14, 63, 79, 126]. Comparative studies in Venezuela

and Colombia demonstrated a strong correlation between spiny rat (*Proechimys chrysaeolus* in Colombia) populations and levels of VEEV circulation [13]. Other mammals such as opossums (*Didelphis marsupialis*) are also frequently infected, and bats and shorebirds may be involved in the dispersal of enzootic viruses.

The most important enzootic vectors are members of the genus *Culex*, subgenus *Melanoconion*, Spissipes section [9, 25, 31, 71, 78, 101, 123, 126, 134], a diverse and taxonomically difficult group [78, 83, 98, 112]. The Spissipes section [98, 104, 112] includes most vectors of enzootic VEEV and EEEV in Latin America [18, 126], and seven species are proven vectors of VEE complex viruses. Studies of enzootic VEEV ecology have incriminated a single species or multiple species as the principal vector in a given location [9, 13, 31, 69, 123, 134]. A combination of enzootic vectors (transmission within forests) and epizootic vectors (potential exporters of the virus to open agricultural areas) were also studied in enzootic areas of the Catatumbo region in Venezuela [5, 67].

The restriction of most *Melanoconion* arbovirus vectors to the Spissipes section raises the question of what genetic, physiological, or ecological characteristics are shared by the members of this section that predispose them to transmit arboviruses. Recently, the use of ribosomal DNA sequences and phylogenetic methods have revealed evolutionary relationships among the Vomerifer and Pedroi groups of Spissipes [78]. Navarro and Weaver also detected two cryptic potential vector species under *Culex pedroi* supporting the hypothesis of differential vector capacity for VEEV and EEEV [31, 117].

Control and Prevention of VEE Outbreaks

Equine vaccination in enzootic countries, where progenitors of epizootic strains circulate and where recent outbreaks have been documented, can be effective if VEEV circulation is anticipated or recognized quickly during outbreaks. However, governmental responses to epizootics are often slow for reasons of veterinary and public heath surveillance deficiencies. The live-attenuated TC-83 vaccine is the most effective way to prevent and control epizootic VEEV transmission, and it is available throughout most of Latin America. However, some equids in South America are vaccinated with inactivated, multivalent alphavirus vaccines marketed in the United States. Immunity from these vaccines is slower to develop, is less durable, and requires frequent boosters. Therefore, public and veterinary health officials should strongly discourage the use of these inactivated vaccines in regions of Latin America with a history of VEE [126]. The protection of human populations relies principally on personal protection and avoidance of mosquito bites by limiting physical exposure and applying repellants containing the active ingredient diethylmethylbenzamide (DEET). Applying permethrin to clothing to enhance protection of individuals who reside or work near equine herds during epizootics, who contact tropical forest or swamp habitats where enzootic VEEV circulates, or during outbreaks is also effective. The rural–sylvan behavior of enzootic VEEV vectors renders the usual control based on ULV insecticide methods inappropriate and largely ineffective.

2.2 *Eastern and Western Equine Encephalitis Viruses*

2.2.1 Eastern Equine Encephalitis

Eastern equine encephalitis virus (EEEV) (*Alphavirus*, *Togaviridae*) is an single-stranded RNA mosquito-borne zoonotic pathogen transmitted throughout the Americas [105, 135]. In North America, EEEV circulates principally along the east cost of United States and Canada, and related strains have been also detected in northern Mexico and the Caribbean region. In North America, sporadic human cases averaging approximately five or six per year occur in swamp habitats where the enzootic cycle is involved mainly among birds of the Passeriformes order and the ornithophilic mosquito *Culiseta melanura* and *Culex* subgenus *Melanoconion* species in the southeast [105, 135]. EEEV infections in domestic animals are common; the case-fatality rates in both human and equine cases average about 50% to 70% or more.

South American eastern equine encephalitis virus (EEEV/SA) was first characterized in Argentina in 1933 [70]. New evidence shows that North American EEEV (EEEV/NA) and EEEV/SA variants have developed differences in the ecological, epidemiological, pathogenic, antigenic, and genetic profiles that allowed the classification of EEE/SA into a new species called *Madariaga virus* (MADV), named after the place of its first collection in Argentina. Consequently, MADV is composed of three distinct genetic lineages: one that circulates in Guatemala, Brazil, and Peru; a second lineage in Argentina, Brazil, Colombia, Ecuador, Guyana, Panama, Peru, Venezuela, and Trinidad; and a third represented by a single location isolated in Brazil [8].

Early reports suggest that MADV virus was human avirulent and causes equine epizootics with high mortality averaging approximately 70%; despite human exposure during epizootics, cases have never been detected in Panama and Argentina despite active surveillance [27, 70, 96]. Studies in Peru revealed that although the isolation of MADV in mosquitoes known to feed on humans was not uncommon, no MADV was isolated in acutely febrile patients [3]. Only three human cases of MADV infection had been recognized in Brazil (one) and in Trinidad (two) [21, 32] before the first documented epidemic was detected in Panama during 2010 [18].

Vector and Host

Culex (Melanoconion) taeniopus and *Cx. (Mel.) pedroi* are recognized as the main enzootic vectors of MADV in Central and South America, respectively [108, 117]. Forest-dwelling rodents and marsupials have been implicated as possible hosts based on serosurveys, although birds may also serve as hosts in the Amazon and southern regions of South America. Lizards have also been suggested as MADV hosts in Panama [22]. Recent serological studies in Panama suggest that the short-tailed cane mouse (*Zygodontomys brevicauda*) is a host for MADV, and humans active in pastures and farms where this rodent is abundant are at increased risk of infection [121].

Epidemiology

Human MADV infections in Panama are recognized after equine cases have been detected early in the rainy season (May–June). The distribution of cases is typically clustered in the Province of Darien close to the Colombian border. Severe cases are observed principally in children with a median age of 5.1 years, with a case-fatality rate around 10% [18].

With the exception of Panama, there is no report of human disease outbreaks attributed to MADV, and the lack of human cases in the rest of Latin America may result from (a) cross-protective immunity by heterologous alphavirus antibodies such as VEEV or (b) intrinsic characteristics of MADV strains, such as the inability to evade the interferon response [2, 3]. In addition to previous studies, in Panama recent evidence supports the effect of cross-protective immunity, as areas of high VEEV transmission appear to have reduced MADV transmission [121].

Clinical Characteristics

Symptomatic MADV cases present a prodromal phase, principally with fever and headache; vomiting and diarrhea occur less frequently. A neurological stage follows accompanied by disorientation, somnolence, seizures, and coma. Patients typically show elevated white cell counts and protein elevation in the cerebrospinal fluid (CSF). Severe cases can develop long-term neurological sequelae including seizures, hemiparesis, psychomotor retardation, and coma [18, 61].

Laboratory Diagnosis

Laboratory diagnosis is a challenge in endemic countries, where a high level of training to perform the viral isolation and serological assays is required. Co-circulation of multiple alphaviruses and antibody cross-reactions are common in Latin America. Furthermore, in endemic regions where multiple alphaviruses such as VEEV and EEEV (MADV) that cause similar clinical presentations are circulating, the interpretation of laboratory results is complex. The alphavirus IgM antibody response lasts around 2 to 3 months, and multiple diagnostic tools such as viral isolation, antibody tests, and viral RNA detection should be implemented [18, 62]. Although incidental laboratory infections with MADV have not been reported, diagnostic confirmation in endemic regions may require the use of live VEEV and EEEV in biosafety level 3 containment. In this case, neutralization tests for MADV and VEEV can be performed with EEEV chimeric viruses and TC-83 live-attenuated vaccine VEEV strain in biosafety level 2 facilities with results similar to those obtained with the wild-type strains [48, 121].

2.2.2 Western Equine Encephalitis

Western equine encephalitis virus (WEEV) is a recombinant alphavirus descended from Sindbis- and EEEV-like ancestors [40]. WEEV causes sporadic epizootics in the western United States and Canada, associated with increased rainfall in early spring followed by warmer-than-normal temperatures. *Culex tarsalis* is recognized as the principal vector in North America, and *Aedes albifasciatus* has been implicated in South America; passerine birds are the main enzootic hosts.

Circulation of WEEV in Latin America has been recognized during epizootics in Argentina, Uruguay, and Cuba [128]. A human fatal case was reported in Uruguay during 2009. However, the available evidence suggests that WEEV circulation is declining, with the last human case in North America reported during 1994, and the last detection in mosquito pools in 2008 [15].

3 Alphavirus and Arthralgias

3.1 Mayaro Virus

Mayaro virus (MAYV) is a unique, exceptional New World alphavirus, and, before the introduction of chikungunya virus (CHIKV) in 2013, represented the sole arthralgic alphavirus endemic to the Western Hemisphere. MAYV was first detected in forest workers in the county of Mayaro, Trinidad, in 1954 [6]. Since then, there is evidence of MAYV infection, either by serological detection or virus isolation, in several regions of Latin America, including Brazil, Colombia, Ecuador, Peru, Surinam, Bolivia, French Guiana, Trinidad, and Venezuela [4, 10, 11, 33, 39, 46, 50, 59, 66, 72, 81, 109–111, 113, 120, 137]. Although MAYV has not recently emerged sufficiently to result in major outbreaks, several acute undifferentiated febrile illness surveillance studies have clearly shown that the virus commonly infects humans, and that those infected most are infected as a result of occupational exposure [33, 120].

MAYV causes sporadic outbreaks, which have been localized primarily to regions of Brazil [11, 53, 64, 82, 120, 137], but has also been detected in Bolivia and Peru [33]. A pediatric infection was recently detected in Haiti, suggesting local enzootic (although no wild monkeys are present) or endemic circulation [139]. Typically, infection with MAYV is not fatal but cases usually present with fever, headache, retro-orbital pain, myalgia, vomiting, diarrhea, rash, and often persistent (<1 year) severe arthralgia [41, 100]. In this regard, MAYV may be more incapacitating than other common arboviruses such as dengue virus (DENV). Given the low economic impact of MAYV, there is very little vaccine development effort, the exception being an IRES-based attenuated live-attenuated vaccine [133]. The largest documented MAYV outbreak occurred in Belterra, Brazil, in 1978, with approximately 790 persons possibly affected and 55 confirmed cases: the virus was isolated from 43 cases [53, 86]. Since then, outbreaks have been very limited, until recently in Venezuela in 2010, where there was an outbreak of 77 suspected cases, of which 6 were detected by virus isolation from acute-phase sera [10].

Given the extent of the most recent MAYV outbreak in Venezuela, it is important to consider the possibility that *Aedes (Steg) aegypti* was involved in virus transmission, in addition to its enzootic vectors. *Ae. aegypti*-vectored arboviruses are among the most important arboviral pathogens, and previous studies suggest this is a moderately competent MAYV vector [60]. *Ae. albopictus* is a competent vector for several arboviruses [131], and in contrast to *Ae. aegypti*, it is found in periurban areas and more temperate regions. *Ae. albopictus* competency for MAYV has been examined experimentally, and results suggest it is not a competent vector unless bloodmeals are taken from highly viremic mice (>7 logs). If MAYV were to adapt for more efficient *Ae. aegypti* or *Ae. albopictus* transmission, it can present a significant global threat [140].

Phylogenetic studies of MAYV sequences show that the viruses can be further delineated into three genotypes, designated genotype D, L, and N [10, 89]. Genotype D includes isolates from Trinidad, Brazil, French Guiana, Surinam, Peru, and Bolivia; genotype L contains isolates from Brazil, but it is unclear if this genotype is still in circulation because it has not been detected since 1991; and genotype N consists of a single strain isolated from Peru in 2010 [10]. The single genotype N sequence is intermediary in phylogeny between genotypes D and L. It would be interesting to determine the prevalence of this strain in Peru and fully characterize its pathogenicity in mice relative to the other genotypes.

There is no evidence that the MAYV phylogeny is temporally structured, but it appears to be influenced to some extent by geography. Genotype D strains can be further delineated into smaller clades based on the geographic region of collection [10, 89]. Given this geographically structured phylogeny, we cannot exclude the possibility that there may be potential restrictions associated with vector competence, vector distributions, or alternative vertebrate amplification hosts that might affect this apparent population subdivision. However, sampling bias and the difficulty associated with isolating MAYV should be considered when proposing these conclusions. Additionally, recent studies provide evidence that MAYV strains concurrently circulating within Venezuela are undergoing regionally independent evolution, suggesting the absence of a single panmictic viral population, at least in Venezuela [10].

The MAYV ecological niche model based on localities of virus isolations [10, 89], vector distributions, and 19 climatic variables [58] predicts the suitable MAYV habitats in the following order of importance: eco-regions, followed by *Haemagogus (Hg.) leucocelaenus*, *Hg. celeste*, and *Hg. clarki* distributions. Figure 9.3 presents a

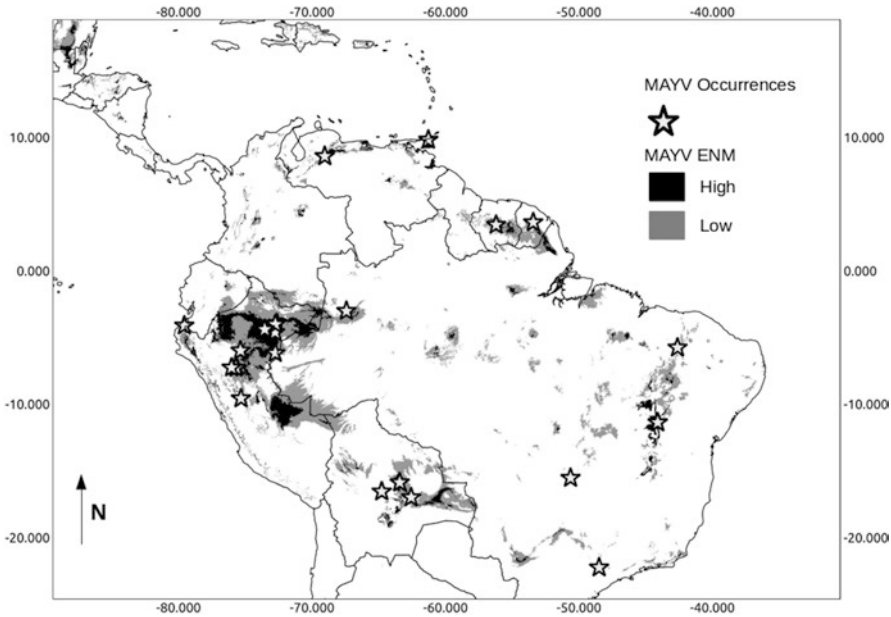


Fig. 9.3 Ecological niche model for Mayaro viruses (MAYV) based on virus isolation localities, seropositivity records, primary vector distribution (*Haemagogus* spp.), and 19 climatic variables

map of the predicted geographic distribution of the virus. MAYV presents six distributional patterns across South America related to terrestrial eco-regions showing the high and low probabilities of predicted areas.

Previous findings suggest that MAYV circulates between canopy-dwelling *Haemagogus* mosquitoes and nonhuman primates [45, 72, 89], but very little is known about the enzootic transmission cycles that perpetuate MAYV.

The MAYV genome is highly conserved (i.e., 96.4%–100% nucleotide sequence identities and 97.7%–100% amino acid sequence identities), across the complete genome, among genotype D strains [10]. Given this level of sequence conservation, it is unlikely that there may be significant phenotypic variation among strains, but recent work has shown the presence of five positively selected sites across the genome and nonsynonymous mutations that delineate various genotypes as well as the Venezuelan 2010 outbreak strains [10]. Reverse genetic studies are necessary to determine if any of these substitutions can cause phenotypic alterations. These studies can also be used to compare virulence among historical and contemporaneous isolates.

3.2 Chikungunya Virus

Chikungunya virus (CHIKV) is an alphavirus in the family *Togaviridae* and a relative of other neotropical viruses such as Venezuelan, western, and eastern equine encephalitis (although most strains in Latin America are part of the species *Madariaga* virus) viruses, as well as Mayaro (MAYV) and Una viruses, its closest relatives in the New World [132].

As does MAYV, CHIKV causes an acute febrile disease typically accompanied by severe arthralgia that can persist for years [130]. However, differing from MAYV wherein human infections are thought to result mainly from direct spillover of enzootic strains, CHIKV causes disease via direct spillover as well as by entering a human–mosquito–human cycle in urban areas, typically involving transmission by the anthropophilic mosquito *Aedes ae.* and recently also by *Ae. albopictus*; this leads to major epidemics involving millions of persons with efficient spread via infected air travelers during recent outbreaks. Although CHIKV is rarely fatal, newborns infected during birth, as well as the elderly, especially those with complicating, underlying medical conditions, can have severe neurological disease,. However, in addition to CHIKV being a direct cause of extensive morbidity in all age groups because of its typically high attack rates, the debilitating and often chronic arthralgia results in extensive economic impacts when infected persons cannot work or care for their families [102].

Chikungunya virus is believed to have originated in sub-Saharan Africa in enzootic cycles involving nonhuman primates and sylvatic *Aedes* spp. mosquito vectors, and these cycles continue in many regions of that continent. The history of CHIKV in Latin America probably began centuries ago when sailing ships carried it from Africa to port cities around the world, including the Caribbean and Latin America [127]. In fact, the term “dengue” may have originally described CHIKV infections, with the terminology becoming confused over the centuries with what is now known as dengue fever [42]. During modern scientific history since CHIKV was first

isolated and associated with febrile illness in 1952 [65, 95], CHIKV is believed to have emerged from the enzootic African cycle to initiate urban transmission on several occasions, beginning about a century ago when the Asian lineage was introduced into South and Southeast Asia and caused outbreaks first recognized in 1958 (Fig. 9.4) [127]. This Asian lineage, transmitted primarily by *Ae. aegypti*, has continued to cause sporadic outbreaks in Asia and Oceania ever since. The next major emergence of a strain into a stable urban cycle began in 2004 when an outbreak began in coastal Kenya [20] and spread into the Indian Ocean basin as well as into Asia to infect millions of persons. Following the importation of this Indian Ocean lineage (IOL) strain by tens of thousands of infected travelers, outbreaks were also detected in Italy [92] and France [36]. However, despite importations into permissive (naïve human populations and abundant *Ae. aegypti*) dengue-endemic regions of the Americas, no local transmission was detected in the Western Hemisphere until late 2013, when an Asian lineage strain was implicated in human infections on the island of St. Martin in the Caribbean. Subsequently, this strain spread to nearly all Caribbean islands and throughout tropical and subtropical regions of Latin America during 2014, with continued circulation in many regions as of 2016. Then, in 2014, another CHIKV strain was introduced into northeastern Brazil directly from Africa (a member of the East/Central/South African, or ECSA, lineage). The distributions of the two CHIKV strains (Asian and ECSA lineages) are not completely known, but the Asian strain has been detected by sequencing in the Caribbean, Central America, Mexico, Florida in the United States (briefly following introductions in 2014), and northern South America, whereas the ECSA strain has not been reported outside Brazil. Determination of the geographic ranges of the two strains could be important because many ECSA strains have the ability to adapt for more efficient transmission by *Ae. albopictus* via mutations in the E1 and E2 envelope glycoprotein genes [114], although Asian lineages are epistatically constrained from such adaptation [115]. However, the ECSA strain circulating in Brazil and possibly beyond may have a different epistatic constraint based on a different E2 residue (position 211) [115]. Reverse genetic studies are needed to more definitively assess this adaptive potential of the Brazilian ECSA strain because the ability to use *Ae. albopictus* as an efficient vector could allow CHIKV to extend its geographic range into rural and temperate regions of Latin America.

Control of CHIKV in Latin America represents the same challenges imposed by dengue and now Zika viruses. Until a vaccine can be licensed (and several promising candidates are in late preclinical or early clinical stages of testing), vector control represents the only means of preventing infection and limiting spread. Although CHIKV has already spread extensively to many regions of Latin America and the Caribbean, and high seroprevalence [52, 103] as well as a drop in reported cases since 2014 (PAHO data) suggest that the epidemic has peaked in many regions, CHIKV infections continue to occur and outbreaks have not been reported in some areas with a history of dengue, suggesting continued spread. Unfortunately, past failures with the control of *Ae. aegypti* because of the wide range of challenges posed by this species do not bode well for this approach to CHIKV control [29]. The presence of MAYV in many parts of South America could also influence further

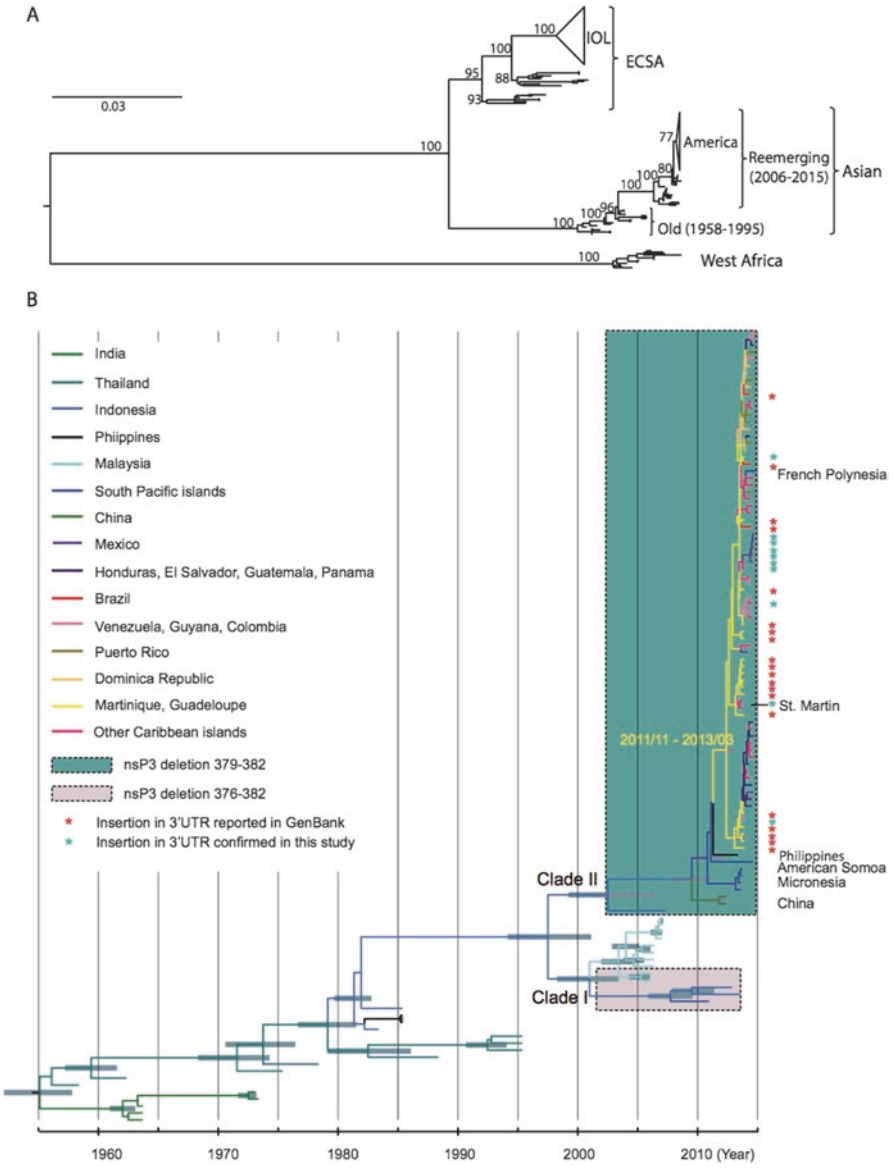


Fig. 9.4 Evolution of CHIKV. **a** Maximum-likelihood tree of major CHIKV lineages based on concatenated open reading frames (ORFs). Branch lengths reflect genetic distance. Bootstrap values are labeled for major lineages and clades. **b** Maximum clade credibility (MCC) tree of the Asian CHIKV lineage based on the Skyride population model using all Asian lineage strains. Branch length is scaled to the sampling and divergence time, and the branches are color coded for sample location. *Node bars* representing 95% highest probability density (HPD) value of the node height are shown only for those with a posterior probability of 90 or higher. (Modified from Chen et al. [19])

CHIKV spread and possibly disease manifestations. These two alphaviruses exhibit some antigenic cross-reactivity [16] that could reduce viremia to affect pathogenesis and possibly vector transmission, which should be evaluated in the near future.

4 Challenges of Future Research

In VEEV, there are four major challenges that we believe can be solved using new approaches: (1) rapidly estimating the origin of a newly discovered VEEV strain; (2) estimating its equine and/or human amplification and thus epidemic potential; (3) predicting the human virulence phenotype of a newly discovered VEEV strain. Phylogenetic relationships of a diverse collection of VEEV strains have proved useful for identification of the genetic features leading to epidemic spread to humans and livestock of this zoonotic pathogen. Also, (4) search for synapomorphic genetic, physiological, or ecological factors shared by Spissipes mosquitoes could explain their important role in transmitting arboviruses [34, 126].

Meanwhile, in EEEV several advances in the understanding of MADV pathogenesis have been achieved in the recent year. However, the available evidence is limited to in vitro studies. Genetic determinants of virulence are still unclear: animal models have failed to reproduce the natural history of disease, although cotton rats seem to be a promising model for evaluation of this question [7]. Basic epidemiological investigations are needed to understand the potential of MADV emergence in other Latin American countries; evaluation of cross-protective immunity is also important for vaccine design.

For MAYV and CHIKV, the degree and longevity of such cross-protection between both viruses should be further assessed not only to assist with predicting interactions that might limit circulation and spread but also to determine if an effective CHIKV vaccine could also limit disease caused by MAYV, which is probably indistinguishable from CHIKV infection and appears to be grossly underreported in Latin America [119].

Further work is warranted to truly understand the ecology of MAYV as a potentially emergent alphavirus. Of particular interest are (i) which vectors maintain enzootic transmission, (ii) what species are competent bridge vectors that facilitate transmission to humans, (iii) which nonhuman primate species serve as the primary amplification host, and last (iv) do other canopy-dwelling vertebrates, rodents, or birds have a role in transmission, or act as dead-end hosts only. These questions can be addressed through experimental infections in the laboratory or via field studies aimed at virus isolation and serological detection of MAYV among vectors and vertebrates in known endemic areas.

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