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Chapter

Neglected Arboviruses in Latin America

Alfonso J. Rodriguez-Morales and D. Katterine Bonilla-Aldana

Abstract

Over the last decade, there has been an increasing concern for epidemics in Latin America, as well as in other regions, due to arboviruses causing epidemics. Before 2013, dengue and yellow fever were of major preoccupation in urban and rural areas, respectively. But after that year, the emergence of chikungunya (2013) and Zika (2015) with their widespread in the region, affected millions of individuals, especially in tropical countries. Nowadays, other alpha and flaviviruses, but also bunyaviruses, have been circulating in the region causing small outbreaks, as is the case of Mayaro, Madariaga, Rocio, Oropouche, and St. Louis encephalitis, among others. In the current chapter, we address the situation regarding these other arboviruses that have been neglected by also being a differential diagnosis and an etiology of febrile syndrome in the region.

Keywords: Mayaro, Madariaga, Rocio, Oropouche, St. Louis encephalitis, alphavirus, flavivirus, neglected, Latin America

1. Introduction

Vector-borne diseases and many zoonotic diseases remain significantly relevant in tropical areas, such as Latin America. In the specific case of those caused by viruses, arboviruses, this region, as well as Asia, are particularly affected over time, primarily due to the widespread of competent vectors, as is the case of *Aedes aegypti*, but also *A. albopictus*, and more recently *A. vittatus* [1, 2]. Then, as expected, an integrated One Health approach, considering the environment, and animal and human health, is needed for vector-borne diseases [3].

Over the last decades, multiple arboviral diseases caused by alphaviruses and flaviviruses have been a concern in Latin America [4]. However, since the introduction of yellow fever and dengue, the epidemiological landscape in the region has significantly changed [5]. Dutch slave traders brought yellow fever (YFV) to the America from Africa during the mid-seventeenth century.

For the next two and a half centuries, the disease terrorized seaports throughout the America [6]. Reports describe the possible first introduction in 1648 in Mexico [5, 7–9]. Although some studies suggest dengue (DENV) was introduced in the America, through the Caribbean islands in 1635 [5, 10, 11], before 1981, dengue was considered a public health problem only in Asia and posed little or no threat to the region of the America [11, 12]. This scenario shifted with the 1981 Cuban epidemic,

the first significant dengue epidemic in the area. For the following decade, sporadic cases of dengue were observed. Then, in 1990, Venezuela experienced the second major epidemic in the region. These events marked dengue as an emerging disease in the America [11, 12]. As observed, flaviviruses, such as dengue and yellow fever, have been significant concerns regarding morbidity and mortality in the region [4, 13–27]. Additionally, many of them, as observed with Zika (ZIKV) and chikungunya (CHIKV), lead to chronic consequences, such as central nervous system (CNS) compromise (including congenital microcephaly and other complications of congenital Zika syndrome) [28–32], as well as chronic rheumatic and non-rheumatic diseases (CHIKV) [33–39].

Taxonomically speaking, the essential arboviruses are included in the genus alphavirus, family Togaviridae (**Figure 1**), which consists of a total of 32 species; and in the genus flavivirus, family Flaviviridae (**Figure 2**), where 53 species are currently included.
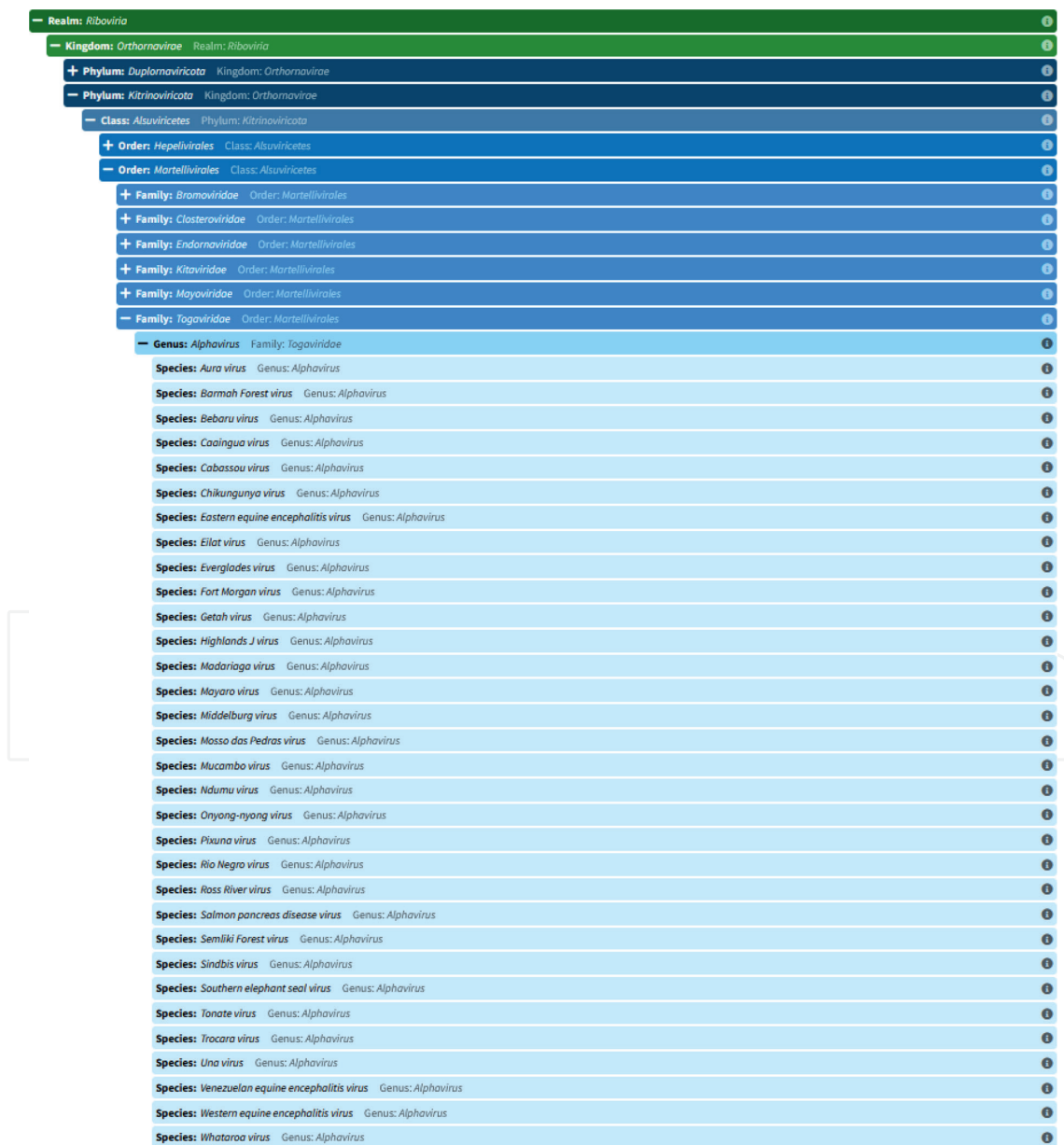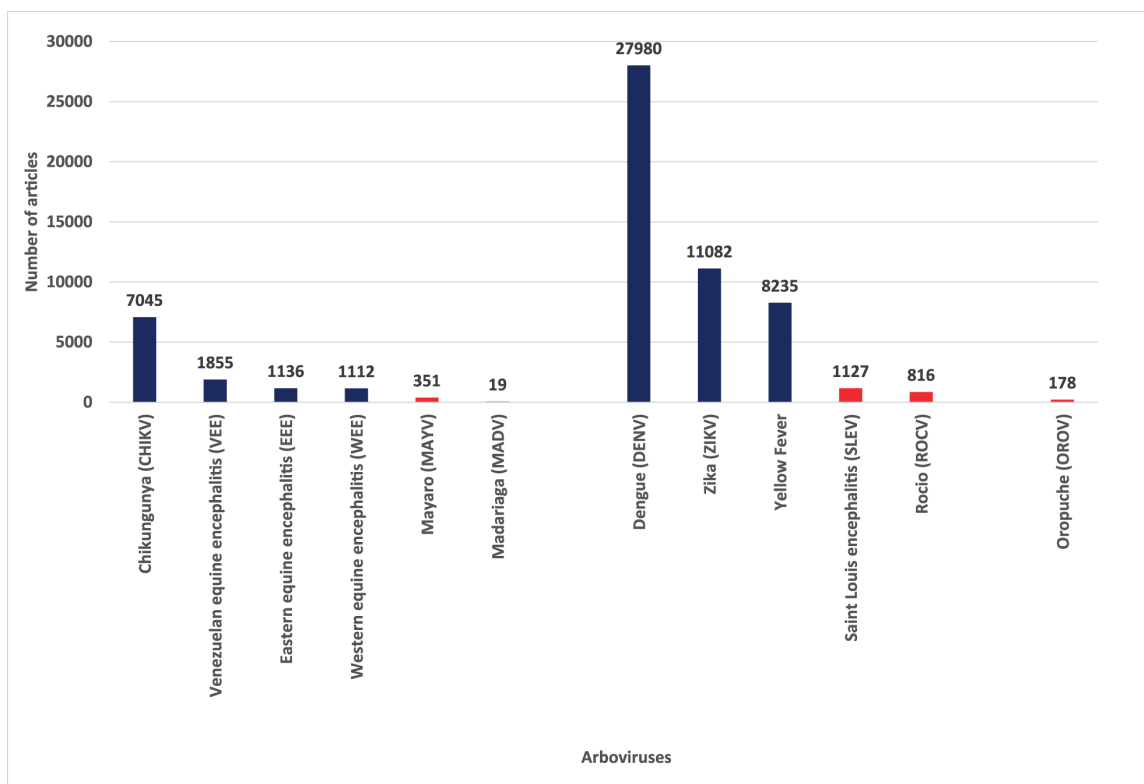

Figure 1.
Taxonomical classification of viruses belonging to the genus alphavirus (family Togaviridae, order martellivirales, class alsuviricetes). (https://ictv.global/taxonomy).

Figure 2.
Taxonomical classification of viruses belonging to the genus flavivirus (family Flaviviridae, order amarillovirales, class flasuviricetes). (https://ictv.global/taxonomy).

Alphaviruses, originally endemic in Latin America, such as the Venezuelan equine encephalitis (VEE) and the eastern equine encephalitis; were described in 1920 in Venezuela and 1972 in Trinidad and Tobago, respectively [5]. Mayaro virus, another

3

Figure 3.
The number of articles published about arboviruses (alphaviruses, flaviviruses, and orthobunyaviruses) in Latin America, cumulated until November 1, 2022, in PubMed-indexed journals. (https://pubmed.ncbi.nlm.nih.gov/).

alphavirus from Trinidad and Tobago, was described in 1954. In Trinidad and Tobago, an endemic orthobunyavirus, the Oropouche virus, was described in 1955 [5].

Then, as observed in the number of published articles available in PubMed (**Figure 3**), many of these arboviruses in Latin America, such as Mayaro (MAYV), Madariaga (MADV), Saint Louis encephalitis (SLEV), Rocio (ROCV), and Oropuche (OROV) are neglected. Nevertheless, according to the World Health Organization (WHO), only DENV and CHIKV are formally included as neglected tropical diseases (https://www.who.int/health-topics/neglected-tropical-diseases).

Even the total of articles of them (1364) is much lower than the total of DENV (20.5 times higher), ZIKV (8 times), YFV (6 times), CHIKV (5 times), or VEE (1.4 times) (**Figure 3**). So then, MAYV, MADV, SLEV, ROCV, and OROV may be considered neglected. As a consequence, such arboviruses will be analyzed in the current chapter.

2. MAYV, MADV, SLEV, ROCV, and OROV: neglected arboviruses

Both alphaviruses and flaviviruses included neglected arboviruses. Nevertheless, given the importance of DENV and YFV, flaviviruses have been studied more, and even vaccines for a long time have existed for YFV [25] and recently for DENV [40]. However, there are no vaccines against alphaviruses for humans. Nevertheless, after epidemics of CHIKV in 2014–2015 in the America, their importance increased. However, as a group, the situation is worse regarding investigating orthobunyaviruses. Epidemics of CHIKV and ZIKV, as well as periodical outbreaks of YFV, especially in Brazil and Venezuela, have influenced the attention and research on these alphaviruses and flaviviruses [26, 27].

The region's MAYV, MADV, SLEV, ROCV, and OROV can be considered neglected arboviruses [41–44]. Even in most countries, such arboviruses are not under regular surveillance, laboratory investigation, and confirmation.

2.1 Mayaro (MAYV)

MAYV, an enzootic virus [44, 45], is an alphavirus that shares epidemiological features with YFV, having sylvatic cycles involving animal reservoirs and with sylvatic and urban mosquito vectors. Clinically, MAYV shares characteristics with its genus and family. It is an arthritogenic alphavirus, as occurs with CHIKV, able to generate immune-mediated chronic disease [46, 47] but overlaps in symptoms during the acute phase with other arboviruses [48]. A few years ago, the ChikDenMaZika syndrome was proposed as a mnemotechnic rule to keep in mind Mayaro and other more frequently observed arboviruses, such as CHIKV, DENV, and ZIKV [48]. That would help decrease the negligence of Mayaro, to be considered in the differential diagnosis of febrile syndrome in the tropics or possibly caused by an arbovirus. MAYV is more frequently detected in other countries, in addition to Trinidad and Tobago, Brazil, and Peru. It has also been identified in Panama, French Guiana, Colombia, Argentina, Venezuela, and Paraguay [49, 50]. Studies have reported MAYV positivity in wild mammals, birds, or reptiles, as well as in domestic animals. Also, 12 orders of wild-caught vertebrates, most frequently in Charadriiformes and primate orders, have been identified with MAYV. This alphavirus has been detected in wild-caught mosquito genera, including *Haemagogus*, *Aedes*, *Culex*, *Psorophora*, *Coquillettidia*, and *Sabethes* [49]. Although MAYV has been identified in urban vectors, there is no evidence of sustained urban transmission. MAYV's enzootic cycle could become established in forested areas within cities, similar to the yellow fever virus [51]. Arboviruses in mosquito body pools sampled during the rainy season of 2018 in 21 bird-watching points of Cuiabá and Varzea Grande, south central Mato Grosso, Brazil, highlights the possibility of MAYV detection in urban areas of Latin America [52]. An investigation of arboviruses in patients with acute febrile illness (n=453) for less than 5 days in Mato Grosso state during the period of ZIKV and CHIKV dissemination in Brazil found multiple other neglected arboviruses [53]. Alphaviruses were detected in 2 (0.4%) patients infected with CHIKV genotype ECSA, 1 (0.2%) with Madariaga (EEEV) lineage III, and 34 (7.5%) with Mayaro (MAYV) genotype L. Four (11.4%) patients presented dual infections with DENV-1/ZIKV, DENV-1/DENV4, DENV-4/MAYV, and ZIKV/MAYV. The majority—13/34 positive for MAYV, one for Madariaga virus—are residents in Várzea Grande, the metropolitan region of Cuiabá, the capital of Mato Grosso [53]. Up to June 2015, only 121 articles were published in PubMed-indexed journals, based on a bibliometric analysis [47]. After 7 years, only 230 additional papers have been published on MAYV (**Figure 3**).

In countries, such as Peru, MAYV has become more critical in epidemiological terms; even MAYV is under surveillance in that country (**Figure 4**). Although that, there is still a lack of research from that country in MAYV (only 28 articles, <8% of the total on MAYV in PubMed). Especially in jungle areas in the country's north and south border with Brazil, Peru has endemic areas where MAYV and other arboviruses cause infection.

During 2017–2020, a total of 36 cases were reported by Peru (**Table 1**), most of them (29, 81%) in 2017 and predominantly in the Madre de Dios department (16, 44%) that year (**Table 1**). At least seven departments of Peru, from a total of 24, reported at least one case of MAYV during that period.
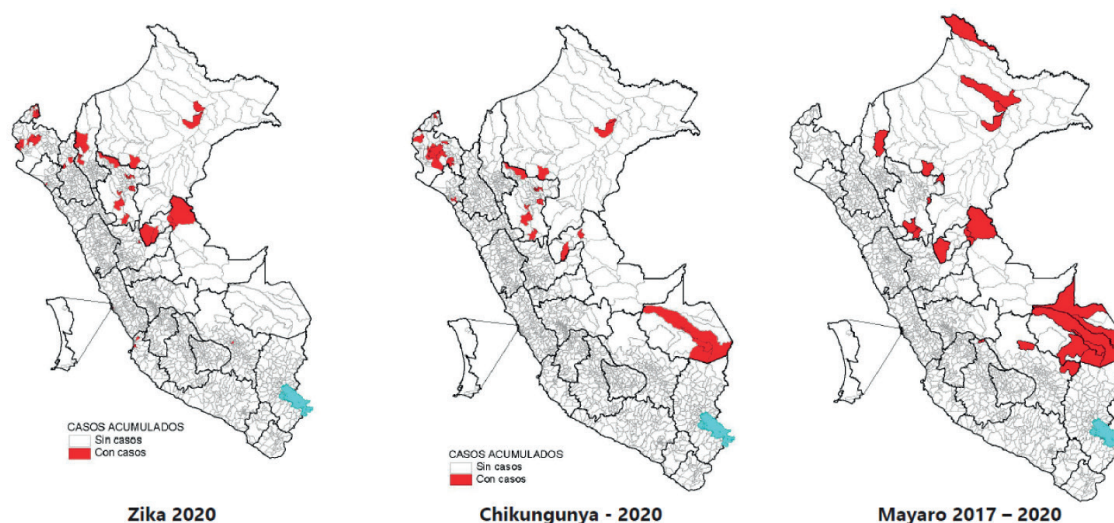
Figure 4.
Geographical distribution of ZIKV, CHIKV, and MAYV in Peru, 2020. (Modified from https://www.dge.gob.pe/ epipublic/uploads/boletin/boletin_202043.pdf).

2.2 Oropouche (OROV)

In Peru, there is limited detection of OROV, an orthobunyavirus. But in 2016, at least in three districts of Madre de Dios (2) and Cusco (1), OROV outbreaks were detected (Tambopata, Iñapari, and Ocobamba).

OROV is another neglected arbovirus [54]. OROV is a species in the genus orthobunyavirus, the family Peribunyaviridae (**Figure 5**). That genus includes 103 species, but only OROV is considered of medical importance in Latin America. More relevant in North America, this genus contains the La Cross virus (LACV), which has not yet been identified in Latin America [55].

In another bibliometric study performed in June 2015 [54], only 83 articles were recovered from PubMed (43% from Brazil, 18% from the United States of America, and 6% from Peru) [54]. On May 2016, the Ministry of Health of Peru reported 57 cases of OROV [54]. Cases of OROV have also been reported in nearby countries, such as Panama, Ecuador, French Guiana, Haiti, Suriname, Trinidad and Tobago, Brazil, and Venezuela [56–60]. As occurs with MAYV, OROV is under surveillance in Peru but not in most countries of Latin America. After 7 years of the unique bibliometric assessment of OROV so far [54], only 95 additional articles have been published, showing clearly the lack of research on this orthobunyavirus.

Nevertheless, recent studies (2021–2022) in Colombia have identified OROV as an emerging cause of acute febrile illness in the country [61]. In a study with 2,967 individuals, OROV was identified in 87 of 791 (10.9%) viremic cases, where an RT-qPCR dual-target assay was possible. Those cases were from Cali (the third largest city in the country) (3/53), Cucuta (border with Venezuela) (3/19), Villavicencio (easter lowlands) (38/566), and Leticia (Amazon jungle) (43/153). In parallel, an automated anti-nucleocapsid antibody assay detected IgM in 27/503 (5.4%) and IgG in 92/568 (16.2%) patients screened, for which 24/68 (35.3%) of PCR positives had antibodies [61]. Such findings confirm OROV as an emerging pathogen and recommend increased surveillance to determine its burden as a cause of acute febrile illness in Colombia [61]. A previous assessment in Colombia diagnosed OROV in a woman 28 years of age from Turbaco, Bolivar department (near Cartagena), by viral isolation, quantitative reverse transcription PCR, and phylogenetic analysis of the small,

	Cases per year				%				Incidence (cases/100,000 pop.)			
Departments	2017	2018	2019	2020	2017	2018	2019	2020	2017	2018	2019	2020
Madre de Dios	16	0	0	0	55.17	0	0	0	11.14	0	0	0
Loreto	3	0	3	1	10.34	0	50	100	0.28	0	0.28	0.1
San Martin	5	0	0	0	17.24	0	0	0	0.06	0	0	0
Ucayali	4	0	0	0	13.79	0	0	0	0.08	0	0	0
Cusco	0	0	2	0	0	0	33.33	0	0	0	0.15	0
Amazonas	1	0	0	0	3.45	0	0	0	0.24	0	0	0
Ayacucho	0	0	1	0	0	0	16.67	0	0	0	0.14	0
Total	29	0	6	1	100	0	100	100	0.09	0	0.02	0.003

(Modified from https://www.dge.gob.pe/epipublic/uploads/boletin/boletin_202043.pdf).

Table 1.
Cases of MAYV in Peru, 2017–2020.
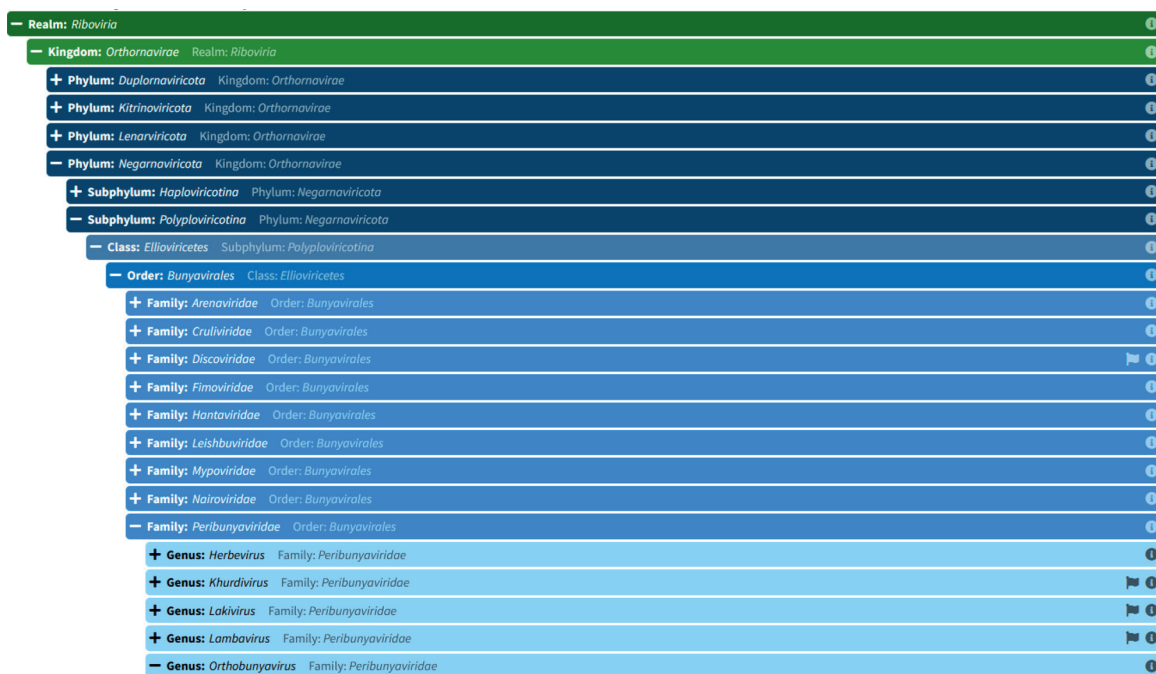
Figure 5.
Taxonomical location of the genus orthobunyavirus (family Peribunyaviridae). (https://ictv.global/taxonomy).

medium, and large genomic segments. That virus was related to a strain isolated in Ecuador in 2016 [62]. That means that in countries, such as Colombia, OROV should be considered in the differential diagnosis of fever and investigated as part of the surveillance [45, 63], especially in possibly endemic areas.

2.3 Saint Louis encephalitis virus (SLEV)

Saint Louis encephalitis virus (SLEV) is a flavivirus, a member of the Japanese encephalitis virus serogroup, initially identified in 1933 in Saint Louis, Missouri, USA, as encephalitis lethargica [64], during an outbreak involving 475 cases with 71 deaths (14.9%) [65]. The encephalitis lethargica occurred in Saint Louis in 1919, 1924, and 1932 [65]. Studies on SLEV in Latin America also lack, regardless of its epidemiological situation [66]. In a bibliometric study performed in December 2016 [64], only 955 articles were recovered from PubMed (44% from the United States of America, 4% from Brazil, and 4% from Argentina) [64]. After 6 years of that bibliometric assessment of SLEV, only 172 additional articles have been published, clearly showing the lack of research on this flavivirus.

Culex species generally transmit SLEV as vectors and birds as animal hosts. Most SLEV infections are asymptomatic, but clinical manifestations range from nonspecific febrile syndrome to febrile headache, aseptic meningitis, and encephalitis, with fatality ranging from 3 to 30% [67]. In the case of Latin America, SLEV is one of the flaviviruses that circulate in Brazil [68]. Reports from Argentina [69, 70], Colombia [71], Cuba [72], Ecuador [73], French Guiana [74], Guatemala [75], Mexico [76], Panama [67, 77], Peru [78], and Uruguay [79] have also been published, among other possible identifications in other Latin countries. The primary SLEV mosquito vectors in some endemic areas include *Culex tarsalis*, *C. pipiens*, and *C. quinquefasciatus* [80, 81]. Like most arboviruses that cause central nervous system (CNS) disease in humans, most SLEV infections are asymptomatic or mild, with symptom onset 5–15 days after exposure and exhibiting a broad range of clinical presentations [80].

	Arboviruses				
Clinical findings	**MAYV**	**MADV**	**ROCV**	**OROV**	**SLEV**
Fever/chills	++++	+	++	++	+++
Myalgia/arthralgia/fatigue	+++	++	0	++	+/0
Edema in limbs	0	0	0	0	0
Maculopapular rash	++	0	0	0	0
Retro-ocular pain	++	0	0	0	+/0
Conjunctivitis, non-purulent	0	0	+	0	0
Lymphadenopathies	+	0	0	0	0
Hepatomegaly	+	0	0	0	0
Leukopenia/thrombocytopenia	++	0	0	0	0
Encephalitis	0	++	++	0	++++
Meningitis	0	0/+	++	0	+++
Headache	0	++	++	++	+++
Photophobia	0	0	0	+++	++
Hemorrhages	0	0	0	0	0

MAYV, Mayaro; MADV, Madariaga; ROCV, Rocio; OROV, Oropouche; SLEV, St. Louis Encephalitis.

Table 2.
Clinical findings of neglected arboviruses in Latin America and the proposed mnemotechnic of **MAMA-ROS** *syndrome (***MA***yaro,* **MA***dariaga,* **R***ocio,* **O***ropouche and* **S***t. Louis encephalitis).*

The discussed neglected arboviruses may overlap clinically, then, initial differentiation between them, may be complex (**Table 2**). Unfortunately, major infectious and tropical diseases books do not cover some of them (e.g., MADV) [82, 83].

2.4 Madariaga (MADV)

Recent ecologic and genetic studies of eastern equine encephalitis virus (EEEV; togaviridae: alphavirus) have demonstrated clear separation between North and South American EEEV strains: North American EEEV cluster in a single genetic lineage—lineage I, in the system proposed by Arrigo et al. [84]—with South American EEEV strains (now known as Madariaga virus [MADV]) clustering in EEEV lineages II, III, and IV. Although there is a reasonable understanding of North American EEE's clinical and epidemiologic features, much less is known about MADV infections. MADV is neglected in multiple ways [85]. Contrasting with other neglected arboviruses, MADV has no previous bibliometric assessments nor for EEE. As shown before, there is a significant lack of studies about it [85–94]. Recent studies in Panama have clinically characterized this emerging encephalitis (**Table 2**) [90]. Studies from that central American countries suggest that the lack of additional neurological cases may indicate that severe MADV infections occur only rarely. Field studies suggest that over the past five decades, alphavirus infections, such as MADV and VEEV, have occurred at low levels in eastern Panama, but that MADV and VEEV infections have recently increased-potentially during the past decade. In some of eastern Panama, the endemic diseases and outbreaks of MADV and VEEV appear to differ spatially [95].

These neglected arboviruses are usually neglected; in the past, the ChikDenMaZika syndrome helped to decrease the neglect of thinking on Mayaro. Nevertheless, still, that alphavirus, as well as others, and the rest of discussed arboviruses, should be considered for an additional mnemotechnic, as **MAMA-ROS** syndrome (**MA**yaro, **MA**dariaga, **R**ocio, **O**ropouche and **S**t. Louis encephalitis) (**Table 2**) to think in them as differential diagnoses, as also to assess their clinical presentations.

2.5 Rocio (ROCV)

ROCV emerged as a cause of outbreaks of encephalitis in Brazil during 1975–1976. However, as another neglected arbovirus, there are less than 1,000 articles in PubMed (**Figure 3**), with no bibliometric studies.

After initial descriptions, sporadic reports have been identified; nevertheless, no additional outbreaks have been reported. ROCV is probably circulating among wild birds and transmitted by *Psorophora ferox* and *Aedes scapularis* [82, 83]. It has an incubation period of 7–14 days, and illness begins with headache, fever, nausea, and vomiting, sometimes with pharyngitis and conjunctivitis (**Table 2**). Meningitis or encephalitis follows in many, with altered mental state and cerebellar tremor. Convulsions are uncommon. The case fatality rate is about 10%. Death occurs in patients of all ages with neurological sequelae. Gait disturbances may appear in survivors [1, 2]. Some of these neglected viruses are commonly detected during dengue outbreaks, as with other arboviruses. Patients result negative for DENV and are investigated for multiple other flaviviruses and alphaviruses. Recent seroprevalence studies in animals detected ROCV in regions of Brazil, indicating risk for reemergence of this pathogen. A recent study identified ROCV RNA in samples from two human patients for whom dengue fever was clinically suspected but ruled out by laboratory findings. Then, such results suggest that testing for infrequent flavivirus infections should be considered, including ROCV [96, 97].

A group of maps showing the distribution by countries where neglected arboviruses have been reported (**Figure 6**). Theses maps do not necessarily reflect the real distribution, but just countries that have published cases or studies showing arboviral circulation. In the case of countries, such as Bolivia and Paraguay, is particularly curious that they have not reported most of the neglected arboviral pathogens, although have been described in most of their neighboring countries.

Figure 6.
Distribution map of MAYV, MADV, ROCV, OROV, and SLEV in Latin America. This distribution indicates just circulation in the country, but not necessarily that has been detected nationwide.

		Vector						
		Aedes	*Culex*	*Culicoides*	*Haemagogus*	*Psorophora*	*Coquillettidia*	*Sabethes*
Arbovirus	MAYV	x	x		x	x	x	x
	MADV	?	x			x		
	ROCV	x	?			x		
	OROV	x	x	x				
	SLEV	?	x					

x, studies have reported the detection of the arbovirus; ?, potential vector.

Table 3.
Main reported vectors of neglected arboviruses in Latin America.

A significant problem in the diagnosis of these arboviruses includes the clinical and epidemiological overlapping [4], even with possible coinfections [16, 22, 98], but also the problems derived from potential antibody cross-reactivity that may yield serological false-positive results, now even, including coinfections and cross-reactivity with SARS-CoV-2 [18, 99–102]. Then, molecular diagnosis of them is critical, including multiplex testing to search simultaneously many arboviruses and perform more specific serological testing, using better antigens, such as plaque reduction neutralizing antibody testing (PRNT) [103], especially in patients with risks for severe or complicated disease.

For the control of these neglected arboviruses, vector control is key, especially on *Aedes* and *Culex* species that represent the main mosquito genuses related to their transmission (**Table 3**).

As expected, no vaccines nor antivirals have been developed for these neglected arboviruses [104–106], although there is hope for them in the future. Therefore, symptomatic treatment is indicated with them after establishing a specific and confirmed molecular diagnosis.

3. Conclusions

Vector-borne diseases, particularly those involving virus transmission, continue to be a significant public health problem, especially in tropical countries, but even with climate change in also in subtropical countries. Still, in multiple countries, problems related to accurate diagnosis of the etiology of febrile syndrome are complex. That is in large magnitude related to arboviral pathogens, many of them neglected, as the case of MAYV, MADV, ROCV, OROV, and SLEV, among others. Therefore, after considering major arboviral diseases, such as DENV, CHIKV, ZIKV, YFV, VEE, and EEE, among others, epidemiological and clinical suspicion of them is critical to establishing a differential diagnosis, detecting them, and even identifying possible coinfections. At the same time, as there is a significant gap in knowledge about neglected arboviruses in Latin America, more research is needed to understand their implications and acute and non-acute clinical consequences and impacts.

Conflicts of interest

AJRM has been a consultant/advisor for Takeda, Sanofi Pasteur, Merck Sharp and Dohme, Valneva, and AstraZeneca.

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