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Examining the Potential for South American Arboviruses to Spread Beyond the New World

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Abstract

Purpose of Review

Zika and chikungunya viruses emerged as public health emergencies in the western hemisphere where previously they had not been reported on a large scale. Millions were infected as the viruses met with virtually no herd immunity upon emergence. We explore the histories of these two recent arbovirus experiences in South America. We then review similar three endemic South American viruses: yellow fever, Oropouche, and Mayaro viruses.

Recent Findings We discuss the commonalities of the transmission systems and the possibility of an atypical emergence, that of the New World virus to the Old World.

Summary We discuss the avenues for research that would increase preparedness and efficiency of response should a South American arbovirus emerge in the eastern hemisphere.

Keywords Emerging viruses · Zika · Chikungunya · Yellow fever · Mayaro · Oropouche

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Introduction

Arthropod-borne viruses (arboviruses) have worldwide distributions. The arboviruses of greatest human and/or animal health importance are grouped into six taxonomic families: *Bunyaviridae*, *Flaviviridae*, *Rhabdoviridae*, *Togaviridae*, *Reoviridae*, and *Orthomyxoviridae*. However, when considering the most recent impacts to human public health, the arboviruses of most concern belong to the *Flaviviridae*, *Bunyaviridae,* or *Togaviridae* families [1]. The greatest number of pathogenic arboviruses originates from Africa and South America, where the relatively high level of biodiversity offers a wide range of both host and vector species [1].

In the western hemisphere, emergent arboviruses like dengue (DENV), chikungunya (CHIKV), West Nile (WNV), and, more recently, Zika (ZIKV) viruses have led to outbreaks of considerable scale, which resulted in high rates of morbidity and mortality [2•]. It is interesting to note that the most significant intercontinental spread of arboviruses, particularly those listed above, appears to originate beyond the Americas rather than within. WNV was introduced via a traveler, likely from Israel; DENV is believed to have originally crossed to South America from Southeast Asia; and evidence suggests that ZIKV and CHIKV were introduced to the Americas from the Pacific region [3]. Presumably, the incursion of an American virus into the urban populations of the eastern hemisphere would encounter a similar lack of widespread herd immunity, yet no such jump has been reported despite increasing global travel and trade [4•].

In this review, we explore the experiences of the most recent incursions of ZIKV and CHIKV into the Americas, as well as the history and most recent outbreaks of yellow fever virus (YFV), an Old World virus already established in the New World. We also review the history and transmission systems of two South American viruses with the potential to

establish within global, urban transmission cycles: Mayaro (MAYV) and Oropouche (OROV) viruses.

Chikungunya (*Alphavirus*)

CHIKV is a member of the *Alphavirus* genus in the *Togaviridae* family. Infection with this virus usually presents as a non-descript febrile disease, but may also be accompanied by rash and severe, debilitating, and often chronic arthralgia, which are its main discriminating characteristics. Historical data regarding CHIKV outbreaks may be confounded by its similarities in clinical presentation and overlapping transmission ecology to DENV and the lack of molecular diagnostic tools that we have today. Still, some authors have suggested that many previous "dengue" records were actually misdiagnosed cases of CHIKV (reviewed in [5]). The first officially recognized outbreak of CHIKV occurred in 1952 in the coastal plateaus of Rondo, Makonde, and Mawia of modern day Tanzania. The etiological agent of this outbreak was isolated and identified as a virus subsequently called chikungunya virus. "Chikungunya" is a Tanzanian word that describes the distinctive posture caused by severe arthralgia in infected people [5]. Shortly after this episode, another outbreak was recorded in Uganda with CHIKV isolated from patients [6] as well as mosquitoes (*Aedes africanus*) [7].

In 1958, the first confirmed outbreak of CHIKV outside of Africa was reported in Bangkok, Thailand. Importantly, it was also the first report of CHIKV isolation from *Aedes aegypti* and of its co-circulation with DENV, which was also isolated from *A. aegypti* during this episode [8]. Reviews of historical reports suggested that CHIKV was already circulating in those areas at this time and that CHIKV has circulated in Asia since the eighteenth century [9, 10]. Accordingly, phylogenetic analyses indicate three main genotypes: West African, East/Central/South African (ECSA), and Asian, with the West African genotype considered to be the most ancestral [11, 12].

Evidence of CHIKV circulation has continued to the present in Africa and sporadically in Asia. In 2005, a major outbreak of CHIKV took place among the islands of the Indian Ocean, particularly on La Reunion Island where almost a third of the population was infected [13]. From this outbreak, strains were isolated, sequenced, and demonstrated a consistent amino acid change from alanine to valine at position 226 of the E1 (envelope) glycoprotein. This mutation conferred some fitness advantage in the secondary vector, *Aedes albopictus*, while showing little to no advantage in *A. aegypti* [14, 15]. In addition, this outbreak was associated with the first death attributed to CHIKV and the broader nature of the *A. albopictus* habitat may be credited with the explosive expansion of CHIKV during this period [16]. This particular adaptation is specific to a lineage of the ECSA genotype of CHIKV whereas different amino acid shifts in strains of the Asian genotype have also conferred fitness advantages in *A. albopictus* [17]. Studies have shown that the epidemic lineage (often called Indian Ocean lineage [IOL]) is closest to the ECSA lineage, supporting the theory of reintroduction to Asia from Africa [11, 18].

In 2013, CHIKV was detected and isolated for the first time in the western hemisphere on the island of St. Martin. Soon after, the virus spread to 45 countries and territories in the Caribbean and North, Central, and South America [19]. It was determined that this initial epidemic was caused by strains of the Asian lineage and not by the ECSA-IOL lineage [20, 21]. Although some have postulated that molecular elements could play a role in the American epidemic (e.g., a duplication in the 3′ UTR end that led to increased titers of these strains in mosquito cells [12]), it is important to note that ecological, immunological, and environmental factors likely play the dominant role in this explosive epidemic, as the major vector implicated in the Americas was *A. aegypti*, one for which there are no consistent fitness differences among genotypes/lineages [22, 23].

Zika (*Flavivirus*)

ZIKV is a member of the *Flaviviridae* family belonging to the genus *Flavivirus*, which also includes DENV, WNV, Japanese encephalitis virus, and YFV. ZIKV was first identified in a sentinel rhesus monkey caged in the canopy of the Zika forest in 1947 as part of a sylvatic YFV surveillance network in Uganda [24]. A second isolation was achieved in 1948 from *A. africanus* mosquitoes in the same forest [24]. Additionally, while there was evidence of the presence of neutralizing antibodies against ZIKV in humans, the virus was not isolated from a human patient until 1952 in Nigeria [25, 26]. The first isolation in Asia occurred in Malaysia in 1966 from one pool of mosquitoes (*A. aegypti)* collected in Bentong in west central Malaysia [27]. This isolation is particularly important because it was the first demonstration that ZIKV could be transmitted by this urban mosquito species, especially after a failed attempt to experimentally transmit the virus using *A. aegypti* fed on an exposed human [28]. Remarkably, it took 11 years before the first case of human ZIKV disease was reported in Asia when seven patients in Indonesia (1977–78) showed a significant rise in ZIKV antibody titers following presentation with symptoms clinically consistent with ZIKV infection [29]. Phylogenetic analyses have shown that there are two major lineages of ZIKV, the Asian and the African lineages, though some refer to a third lineage (African II); when full genomes are considered, these isolates usually group with the major African lineage [30–32].

The emergence of Zika as a major public health problem began in 2007 on the island of Yap, Federated States of Micronesia. It was estimated that 73% of residents over the

age of 3 years were infected by ZIKV, and the main vector identified was *Aedes hensilli* [33]. This outbreak was the first time ZIKV had been reported outside Africa and mainland Asia. In 2013, ZIKV was reported in French Polynesia where more than 5800 cases were recorded and a total of 19,000 suspected [34]. Subsequently, the virus spread to New Caledonia, Cook Islands, and Easter Island [35]. In 2013–2014, the virus arrived in the Americas, particularly in Brazil, where numerous world sport championships were held including the Fédération Internationale de Football Association (FIFA) Confederations Cup 2013, the International Va'a Federation's world sprints 2014, and the 2014 FIFA World Cup. There is some disagreement on exactly when the virus arrived, with some arguing 2013 [36] while others propose 2014 [37, 38] due to its first detection and rapid spread in this year. ZIKV spread to other states of Brazil in 2014 [39, 40], and in 2015, the circulation of ZIKV was reported in 12 countries of South America, Central America, and the Caribbean (reviewed in [41]). Previously, ZIKV infection was characterized by a flu-like illness, often asymptomatic or manifested as a mild clinical syndrome that may include fever, rash, arthralgia, conjunctivitis, pruritus, muscle pain, headache, and malaise. In these recent outbreaks, ZIKV was newly associated with severe manifestations, most notably the Guillain-Barré syndrome, microcephaly, and ocular scarring [42–45]. Characterization of these recent outbreaks revealed that the circulating strains were from the Asian lineage [34, 36].

Yellow Fever (*Flavivirus*)

YFV infections can be mild, but severe and often fatal disease which includes chills, fatigue, nausea, vomiting, and jaundice. The first New World YFV epidemics are believed to have occurred between 1647 and 1649 in Barbados, Cuba, Guadeloupe, and Mexico before spreading to the USA [46]. YFV continued to infect people in the tropical and subtropical areas of Americas and Africa, with additional outbreaks reported in Europe [47]. Josiah Nott was the first to present the idea that mosquitoes may transmit both yellow fever and malaria, and Carlos Finlay of Cuba formally described the theory of transmission in 1881, proposing, but not directly demonstrating, that a *Culex* mosquito was the vector [46, 48]. At the end of the nineteenth century, Walter Reed demonstrated that *A. aegypti* was the likely vector [49]. Work in the late nineteenth to early twentieth centuries led to successful YFV reduction campaigns in Havana and Panamá [50, 51], but it was not until post-WWI that researchers expanded the characterization of YFV to Africa with the intention of connecting it to the disease in the Americas and Africa [52]. Stemming from these efforts, Max Theiler eventually attenuated the virus and thereby created the strain 17D, which

is still the basis of the yellow fever vaccine [53]. Despite the existence of an effective vaccine, outbreaks have still been the cause of significant morbidity and mortality, especially in populations where vaccination levels are low [54, 55].

Phylogenetic analyses have demonstrated that YFV originated in Africa and was brought to America by slave trade hundreds of years ago [56]. One of the first comprehensive phylogenetic studies on YFV showed four main genotypes that included two genotypes from Africa and two from America [57]. Later, the existence of five genotypes in Africa was demonstrated: West African genotypes I and II and the East African, the East and Central African, and the Angola genotypes [58]. In America, two genotypes have been described: genotype I (grouping viruses from Brazil, Panamá, Venezuela, Colombia, Trinidad, and Ecuador) and genotype II (grouping viruses mainly from Perú and some from Trinidad) [56, 57].

Discussion I: Learning From Experience

The recent emergence of ZIKV and CHIKV first in the Pacific regions and then in the Americas caused millions of infections and prompted a public health emergency [19, 59]. During these experiences, the body of knowledge regarding these viruses grew exponentially but also uncovered needed, unexplored avenues for better understanding of transmission and ultimately control. While the explosive nature of the epidemics was, in part, due to a lack of herd immunity, additional questions regarding transmission remain and the answers have significant impact on public health response and decision-making. First, which are the vector species most likely to play a role in transmission? Even with the adaptation of CHIKV to *A. albopictus,* the traditionally more competent vector *A. aegypti* was implicated in its emergence in Brazil. Additionally, *A. albopictus*, which was shown to be highly competent for ZIKV in Singapore [60], is only moderately competent for ZIKV in the Americas [61]. Still, the mosquito most implicated in this ZIKV outbreak is *A. aegypti* [62, 63]. This suggests that other elements of the human-*aegypti*-virus interaction are equally or more important to understanding emergence potential than just vector competence in tropical regions [64]. Second, how similar must two ecologies be to support the maintenance of a newly emerged virus in an enzootic cycle? The long-term success of YFV is, in part, driven by the establishment of a robust enzootic cycle involving the sylvatic *Haemagogus* spp. mosquito vectors and a different set of non-human primates from its assumed African origins [65]. Thus, is there a similar consideration for South American viruses that may establish sylvatic cycles in similar, but geographically distinct, regions? Lastly, there is a need for proactive, specific, and consistent diagnostics for the detection of new viruses and the discrimination from related, endemic viruses. Because many members of the genus *Flavivirus* have

historically circulated in similar ecologies and the geographic regions of these viruses overlap with the zone of emergence of ZIKV, there has been some difficulty in diagnostic development. Serological and immunological diagnostics like hemagglutination and neutralization assays have significant cross-reactivity with other flaviviruses, specifically DENV [66]. Additionally, there is antibody cross-reactivity among alphaviruses of the Semliki forest group, suggesting a similar problem may occur when differentiating CHIKV from MAYV [67]. This lack of diagnostic specificity confounded efforts to quickly and definitively diagnose ZIKV patients in the Americas and may lead to future issues in distinguishing disease etiologies.

Mayaro (*Alphavirus*)

The Mayaro virus (MAYV) was isolated for the first time in 1954 in Trinidad from five patients [68] and was identified as closely related to the Semliki forest seroroup of viruses [69]. Like CHIKV, MAYV is a member of the genus *Alphavirus*. MAYV has been recorded from many countries in Latin America (Bolivia, Brazil, Colombia, Costa Rica, Ecuador, French Guiana, Guatemala, Guyana, Honduras, Mexico, Panamá, Perú, Suriname, Trinidad and Tobago, and Venezuela (reviewed by Mota and colleagues, 2015 [70])). Clinical presentation of MAYV is non-descript and "flu-like," similar to other arboviruses such as dengue or chikungunya [71]. Due to the clinical similarities, some have estimated that ~ 1% of dengue-like illness cases in northern South America may be caused by MAYV, but are misdiagnosed [72]. However, there have been three major epidemics documented to be caused by MAYV. First, in the mid-twentieth century, an outbreak of febrile illness occurred 120 miles from Belem, Brazil, with subsequent isolation of MAYV from six samples and further evidence of MAYV seroconversion in 18.9% of those sampled [73]. Second, an epidemic occurred in 1955 in Bolivia and killed 15 visiting Japanese pioneers. The etiologic virus was originally named Uruma, but phylogenetic analysis revealed this to be a strain of MAYV [74, 75]. Lastly, in 1977–1978, another outbreak in Belterra, Brazil, was reported with approximately 20% of residents infected and more than 43 isolates collected [71, 76]. It was during this final outbreak that *Haemagogus janthinomys* was described as a possible vector and that marmosets (*Calithrix argentata*) were described as the potential enzootic reservoir [77]. Importantly, experimental transmission of MAYV by *A. aegypti* has been demonstrated, raising the possibility of urban transmission of MAYV in a system similar to DENV, CHIKV, and ZIKV [78].

MAYV is not as well characterized as dengue, CHIKV, or ZIKV. However, historically, two phylogenetic groups have been described: genotypes D and L. Most strains group into genotype D and are geographically clustered with isolates from Trinidad, Brazil, French Guiana, Surinam, Perú, and Bolivia. Genotype L, on the other hand, is comprised mostly of isolates from the north central region of Brazil [75, 79, 80]. Additionally, Auguste and co-workers suggest the existence of a third lineage called N (New) and further phylogenetic analysis from Llagonne-Barets supports this assertion [81, 82].

Oropouche (*Bunyavirus*)

The Oropouche virus (OROV) is a member of the genus *Orthobunyavirus*, which belongs to the family *Bunyaviridae*, and its geographic distribution is restricted to the Americas. OROV was isolated for the first time in 1955 from a febrile human in Vega de Oropouche, Trinidad, and again from a pool of mosquitoes (*Coquillettidia venezuelensis*) [83]. In the same study, antibodies against OROV were detected in forest workers and non-human primates [83]. In 1960, OROV was isolated in Brazil from the blood of a sloth (*Bradypus tridactylus*) in the proximities of Belem [84]. In 1961, the first known outbreak of OROV was recorded in the Pará state of Brazil, where an estimated 11,000 people were affected by the flu-like illness [84]. At least six other outbreaks of OROV were recorded in Pará over the next decades with *Culex paraensis* implicated as the main vector and biting midges (*Culicoides*) have been indicated as competent vectors [85–88]. After 1981, additional outbreaks were reported outside of Pará, including the Brazilian states of Amazonas, Amapá, Acre, Rondônia, Maranhao, and Tocantins [89–93]. In 1989, the virus was detected in Panamá during an outbreak in Bejuco, located approximately 60 km west of Panamá City [94]. In 1992, OROV was diagnosed in five patients from Iquitos, Perú, who were previously suspected of having DENV [95]. A subsequent serosurvey showed 35% antibody prevalence in urban residents and confirmed infection in a further 28% of residents of rural communities and 2% of urban and forest communities [96]. Since then, there have been consistent reports of OROV infections in Brazil, Panamá, and Perú, and there is evidence of OROV circulation in Ecuador, Bolivia, and Argentina [72, 97, 98].

OROV has a tri-segment, negative-sense RNA genome consisting of the large (L), medium (M), and small (S) segments [99]. Initial phylogenetic analyses of OROV have identified at least three lineages named I, II, and III. Lineage I grouped isolates from Trinidad with most of the Brazilian strains. Lineage II contained Peruvian strains and some from Brazil. Finally, lineage III comprised Panamanian strains [100, 101]. Later, with the three initial lineages conserved, a fourth lineage (IV) was introduced consisting of Brazilian strains isolated in Amazonas [102, 103]. In addition, a reassortant of OROV (Madre de Dios Virus) was isolated in Venezuela [104].

Table 1 Exports of Zika, chikungunya, yellow fever, and Mayaro viruses due to returning travelers as reported in ProMed Mail

Virus	Imported to	Exported from	Link
Zika	Australia	Cook Islands	https://www.promedmail.org/post/2378034
	Canada	Thailand	https://www.promedmail.org/post/1744108
	Chile (Easter Island)	Tahiti	https://www.promedmail.org/post/2804821
	Germany	Malaysia	https://www.promedmail.org/post/3367412
	Germany	Thailand	https://www.promedmail.org/post/2139786
	Mexico	Columbia	https://www.promedmail.org/post/3818813
	Japan	French Polynesia	https://www.promedmail.org/post/2126046
	Japan	Thailand	https://www.promedmail.org/post/2716731
	Micronesia: Guam	Yap	https://www.promedmail.org/post/15805
	Netherlands	Suriname	https://www.promedmail.org/post/3858300
	New Caledonia	French Polynesia	https://www.promedmail.org/post/2082225
	New Zealand	Cook Islands	https://www.promedmail.org/post/2762121
Chikungunya	New Caledonia	Tonga	https://www.promedmail.org/post/2409660
	Portugal	Angola	https://www.promedmail.org/post/2338670
	Australia	Papua New Guinea	https://www.promedmail.org/post/1974825
	Japan	Cambodia	https://www.promedmail.org/post/1909917
	Australia	Indonesia	https://www.promedmail.org/post/1798136
	Australia	Papua New Guinea	https://www.promedmail.org/post/1798136
	Australia	Papua New Guinea	https://www.promedmail.org/post/1675486
	New Guinea, Australia	Indonesia (Bali)	https://www.promedmail.org/post/1594512
	Germany	Indonesia (Bali)	https://www.promedmail.org/post/1562598
	Malaysia (SL)	Malaysia (PK)	https://www.promedmail.org/post/1040110
	New Caledonia	Indonesia	https://www.promedmail.org/post/663016
	France	Benin	https://www.promedmail.org/post/631448
	Brazil	India and Indonesia	https://www.promedmail.org/post/601534
	France	Reunion	https://www.promedmail.org/post/423855
	Taiwan	Indonesia	https://www.promedmail.org/post/390011
	France	Maldives	https://www.promedmail.org/post/388657
	Germany	Maldives	https://www.promedmail.org/post/297273
	Belgium	Thailand, India	https://www.promedmail.org/post/212872
	Germany	SE Asia	https://www.promedmail.org/post/170276
	Japan	Malaysia	https://www.promedmail.org/post/153351
	Australia	Malaysia (Johor)	https://www.promedmail.org/post/141130
	Singapore, Italy	Sri Lanka	https://www.promedmail.org/post/102398
	Singapore	Indonesia, India (Kerala)	https://www.promedmail.org/post/78513
	Taiwan	Indonesia	https://www.promedmail.org/post/75879
	Hong Kong	Sri Lanka	https://www.promedmail.org/post/54478
	Taiwan	Indonesia	https://www.promedmail.org/post/47575
	France	Madagascar	https://www.promedmail.org/post/8163
	Japan	Sri Lanka	https://www.promedmail.org/post/2209612
	Taipei	Singapore	https://www.promedmail.org/post/4792
	USA	Asia, Africa	https://www.promedmail.org/post/4759
	France (Bourdeau)	Senegal	https://www.promedmail.org/post/4622
	French Guiana	Madagascar	https://www.promedmail.org/post/2209424
Yellow fever	China	Angola	https://www.promedmail.org/post/4179477
	China	Angola	https://www.promedmail.org/post/4136699
	Mauritania	Angola	https://www.promedmail.org/post/4119691
	China	Angola	https://www.promedmail.org/post/4119422
	China	Angola	https://www.promedmail.org/post/4109684

Table 1 (continued)

Virus	Imported to	Exported from	Link
	China	Angola	https://www.promedmail.org/post/4106312
	China	Angola	https://www.promedmail.org/post/4105105
	Kenya	Angola	https://www.promedmail.org/post/4104819
	Kenya	Angola	https://www.promedmail.org/post/4097945
	China	Angola	https://www.promedmail.org/post/4089857
	Senegal	Gambia	https://www.promedmail.org/post/545254
	Brazil (MG)	Brazil (RS)	https://www.promedmail.org/post/152217
	Paraguay	Argentina (MN)	https://www.promedmail.org/post/146084
	Belgium	Gambia	https://www.promedmail.org/post/2201007
	Belgium	Gambia	https://www.promedmail.org/post/2200994
	Belgium	Gambia	https://www.promedmail.org/post/2200990
	Brazil (Brasilia)	Brazil (W. Central)	https://www.promedmail.org/post/2197496
	Netherlands	Suriname	https://www.promedmail.org/post/2197331
	Netherlands	Suriname	https://www.promedmail.org/post/2197328
	Netherlands	Suriname	https://www.promedmail.org/post/2197319
	Brazil (Brasilia)	Brazil (W central)	https://www.promedmail.org/post/2197244
	Brazil (Brasilia)	Brazil (W central)	https://www.promedmail.org/post/2197216
	USA	Venezuela	https://www.promedmail.org/post/2196966
	USA	Venezuela	https://www.promedmail.org/post/2196947
	Germany	Cote D'ivoire	https://www.promedmail.org/post/2196220
Mayaro	France	Brazil	https://www.promedmail.org/post/444435
	France	Brazil	https://www.promedmail.org/post/423267

There have been no reports of Oropouche virus exports

Discussion II: Needed Research for Enhanced Preparedness

MAYV and OROV have been thus far restricted to the Americas and are responsible for sporadic epidemics nowhere near the scale of ZIKV or CHIKV, likely due to at least a modest level of herd immunity. However, YFV, which is maintained in a sylvatic cycle in South America, has caused smaller outbreaks, including a significant outbreak in 2016–2017 [105, 106]. This outbreak was successful even in the face of an effective vaccine and likely at least some pre-existing immunity of the population. Thus, we must conclude that either there are factors that preclude these viruses from establishing in regions where they have not been recorded or that there is a real possibility that these viruses will pose public health threats in the future. The critical information needed to accurately predict and plan responses to possible emergences of these viruses mirrors those questions brought up during the ZIKV and CHIKV experience.

1. Has there been undetected circulation of these viruses, and are current diagnostics capable of differentiating related viruses? The combination of often non-specific symptoms, potential for high rates of asymptomatic infections, and a lack of infrastructure for definitive diagnosis may confound the detection of these viruses. Thus, while the detection of South American viruses outside the Americas has not been widespread, it does not necessarily indicate the absence of their spread. In Africa, for example, etiologies have been misdiagnosed with the assumption that febrile illnesses are most likely to be malaria [107], and reports have shown cross-reactivity between MAYV and CHIKV, at least. Human-led movement of OROV from Brazil to Peru has been hypothesized via the Amazon river traffic, which subsequently seeded a series of self-contained outbreaks [72]. The MAYV outbreak that occurred in 1955 which involved 200 foreign workers was in a time where travel was not as fast. Today, travel from South America to Japan is a matter of hours, well within the incubation time for this and most other viruses.

2. What are the vector species most likely to be involved in emergence, and what factors make these vectors likely? The presence of a competent species is of course necessary, but it may not be sufficient. For example, while DENV has been endemic to Southeast Asia, YFV has not spread to that region, even though the two share a common urban vector, *A. aegypti*. Perhaps this is because

to establish a robust transmission cycle, other factors are necessary. Identification and assessment of the relative importance of elements driving regional transmission must be investigated, such as biting behavior, contact rates with human/zoonotic hosts, and the variability in vector competence among strains of the same species across geographic distances.

3. What are the sufficient and necessary elements of an urban and/or sylvatic ecology that would encourage maintenance of these viruses? For example, when a virus is introduced into new regions or ecosystems, new species of mosquitoes may be involved in transmission, resulting in different transmission patterns [108]. Certainly, the presence of a robust sylvatic maintenance system has contributed to the long-term success of YFV in South America. Is it a lack of the necessary elements of a robust sylvatic transmission system that hinders YFV spread to Asia, and does a similar hurdle preclude the spread of MAYV and OROV across the ocean? The role of different ecologies, potential vector species, and human urban migration patterns should be the focus of predictions for the movement of viruses across the globe and their ultimate transmission trajectories [109]. Understanding of the existing urban and ecological factors of endemic viral success as well as investigations into the alterations of transmission cycles that promote successful expansions is needed to predict and then respond to emerging arboviral pathogens for global public health security.

Conclusions

As CHIKV and ZIKV indicate, emergent viruses are a serious and ongoing threat to global public health. Table 1 shows the reports of exportation of the viruses herein as reported to ProMed Mail (https://www.promedmail.org). Currently, understanding the factors of international arbovirus emergence is paramount for reasons such as vector expansion corresponding to climate change, global trade and travel, and increased urbanization and land use changes such as deforestation [110]. More than likely, these viruses may not have emigrated from the Americas, meaning that populations outside of the western hemisphere likely exhibit widespread susceptibility. For that reason, MAYV and OROV have the potential to cause large-scale epidemics in these susceptible populations on the scale of ZIKV and CHIKV. Critically, not only is the community unprepared from a detection standpoint, but also the ecological determinants of emergence success are not understood. Studies of these neglected South American diseases are needed so that the community is prepared for a data-informed response in case of emergence.

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