Chikugunya and zika virus dissemination in the Americas: different arboviruses reflecting the same spreading routes and poor vector-control policies

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Purpose of review
This review gathers the most recent investigations about chikungunya and zika viruses in America and would help in creating new research approaches.

Recent findings
Clinical descriptions of chikungunya fever have been performed in the American outbreak observing that fever, polyarthalgia, myalgia and rash are the most common symptoms in the acute phase, while chronic arthralgia has persisted in 37–90% of small cohorts. The Asian origin of American strains of chikungunya virus (CHIKV) and zika virus (ZIKV) evidences a dissemination route in common and both are being transmitted by Aedes aegypti. Regarding zika fever, the association of congenital malformations with previous ZIKV exposure of pregnant women and potential sexual transmission of ZIKV are the most important discoveries in the New World.

Summary
Massive outbreaks of chikungunya fever in 2014 and then followed by zika fever epidemics of lower magnitude in the next year throughout the American continent have their origins in Asia but may have used Pacific Islands as a path of dissemination. Reports of chronic arthralgia have been little described in the continent and more research is needed to measure the economic and health impact in patients who contracted CHIKV before. On the contrary, zika is menacing newborns' health because of its link with congenital microcephaly and sexual health by prolonged presence of viral particles in semen and urine.

Keywords
chikungunya, emergence, transcontinental movement, zika

INTRODUCTION

Although zika virus (ZIKV) is strongly calling attention since the beginning of 2016 due to the World Health Organization international alert, we cannot forget that currently the same Latin-American countries are experiencing more outbreaks and suffering with prolonged joint sequels of past chikungunya fever (CHIKF) epidemics [1▪]. The overlapping circulation of three arboviruses, dengue virus (DENV) included, is an historical opportunity for the academic field of infectious diseases to analyse and to learn the dynamics of public health epidemiology under this dramatic multipathogen scenario [2▪].

From their African original foci and after moving to Asia during several years, both viruses have flourished in naive Latin-American territories impacting with serious incidence rates mostly explained by finding abundant *Aedes aegypti* mosquito populations in urban and rural settings.

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KEY POINTS

- CHIKV emerged in the Caribbean in 2013, but an ancient introduction probably occurred in the nineteenth century and has caused explosive outbreaks accounting for almost two million cases during 2013–2015 in whole America.
- Clinical descriptions of CHIKF include fever, intense poliarthalgia, myalgia and rash in acute phase, while chronic arthralgia has been reported in around 40–90% of past infections.
- Asian–Pacific–American route is the pathway that CHIKV and ZIKV likely used to achieve the transcontinental movement.
- ZIKV appeared for the first time in America in early 2015, causing mild fever, but has been associated with congenital malformations in newborns and sexual transmission has been proposed as a new transmission mechanism.
- Ae. aegypti is the main vector of CHIKV and ZIKV but other arboviruses could be dispersed in the future if the populations of this vector are still inefficiently controlled.

Primary health attention centres now have to face patients showing confusing disease symptoms caused by these three arboviruses, that is haemorrhagic manifestations, painful articular swelling with lasting and debilitating damage and potential microcephaly of newborns, along with neurological symptoms such as Guillian-Barre. The hope of dengue vaccine for mass distribution has been diluted because governments are doubtful of its protecting effectiveness taking into account cocirculation of two viral families with differential immune response, that is *Flaviviridae* and *Togaviridae*.

The Dengue route, a golden triangle of the Caribbean islands, South and Central America (including Mexico), is a known road seeded with continuous epidemics and built after its reemergence in Latin America during the late 1970s [3]; it has remained untouchable since then and has been served now as the chikungunya virus (CHIKV) and ZIKV corridor. It is a geographical pattern matching smoothly with migrant and trade paths; however, these regions also hold perfect *Ae. aegypti* environments wherein poverty, tropical rainy season, including high moisture and temperature interact to rise abundant mosquito vector populations [4]. A serious concern is the fast speed that these two emergent arboviruses have disseminated through Latin America in a period of almost less than 2 years. Lack of herd immunity in Latin America along with enormous poorly controlled *Ae. aegypti* living domestically may have undoubtedly triggered important outbreak of CHIKV and ZIKV, but including a rise of Guillain-Barre syndrome cases and congenital malformations associated with the latter.

CHIKUNGUNYA: HISTORY OF OUTBREAKS AND LATEST RESEARCH IN AMERICA

CHIKF emergence was announced for the first time in the American Continent with one autochthonous case in the island of Saint Martin in December 2013 [5▪]. However, an ancient introduction of CHIKV in the Caribbean has been proposed in base of its characteristic symptomology according to medical records of the nineteenth century. An outbreak with clinical diagnosis of CHIKF (formerly dengue) was reported in 1827–1828 in the islands of St. Thomas, St. Croix, St. Bartholomew's and Antigua. Then, it advanced towards the US in the cities of New Orleans, Charleston and Savannah at the end of 1828 [6]. After almost two centuries of absence, this alfavirus appeared, probably once again, causing thousands of cases throughout the continent.

Outbreaks in the Caribbean

The first spillover pattern in the Caribbean that CHIKV followed after Saint Martin island introduction occurred probably in Anguilla, St. Bartholomew, Martinique, British Virgin Islands and Guadeloupe, and a few months later, the rest of the Caribbean Islands was affected by CHIKF [7]. After this spreading including all Latin and Non-Latin Caribbean islands, they gathered up to 837 530 cases with an incidence rate of 1898.5 per 100 000 habitants during 2014. The most affected countries were Dominic Republic, Martinique, Guadeloupe, Haiti and Puerto Rico (Fig. 1). In the next year, these numbers considerably decreased to 18 265 cases with an incidence rate of 41.4 per 100 000 habitants being 45.8-fold lower than the previous year [8]. The most likely explanation of the first explosive magnitude of cases in the beginning of the outbreak and then an abrupt reduction in the next year may be due to the reduction of naive population to CHIKV infection after the first wave of cases. A big concern arose in the European community for receiving imported cases from Caribbean Islands because they are a common destination of European tourists [9]. Although the Caribbean outbreak was in its hottest stage in 2014, France and Spain received a considerable amount of imported cases from mainly French Caribbean and Haiti and Dominican Republic, respectively [10,11].

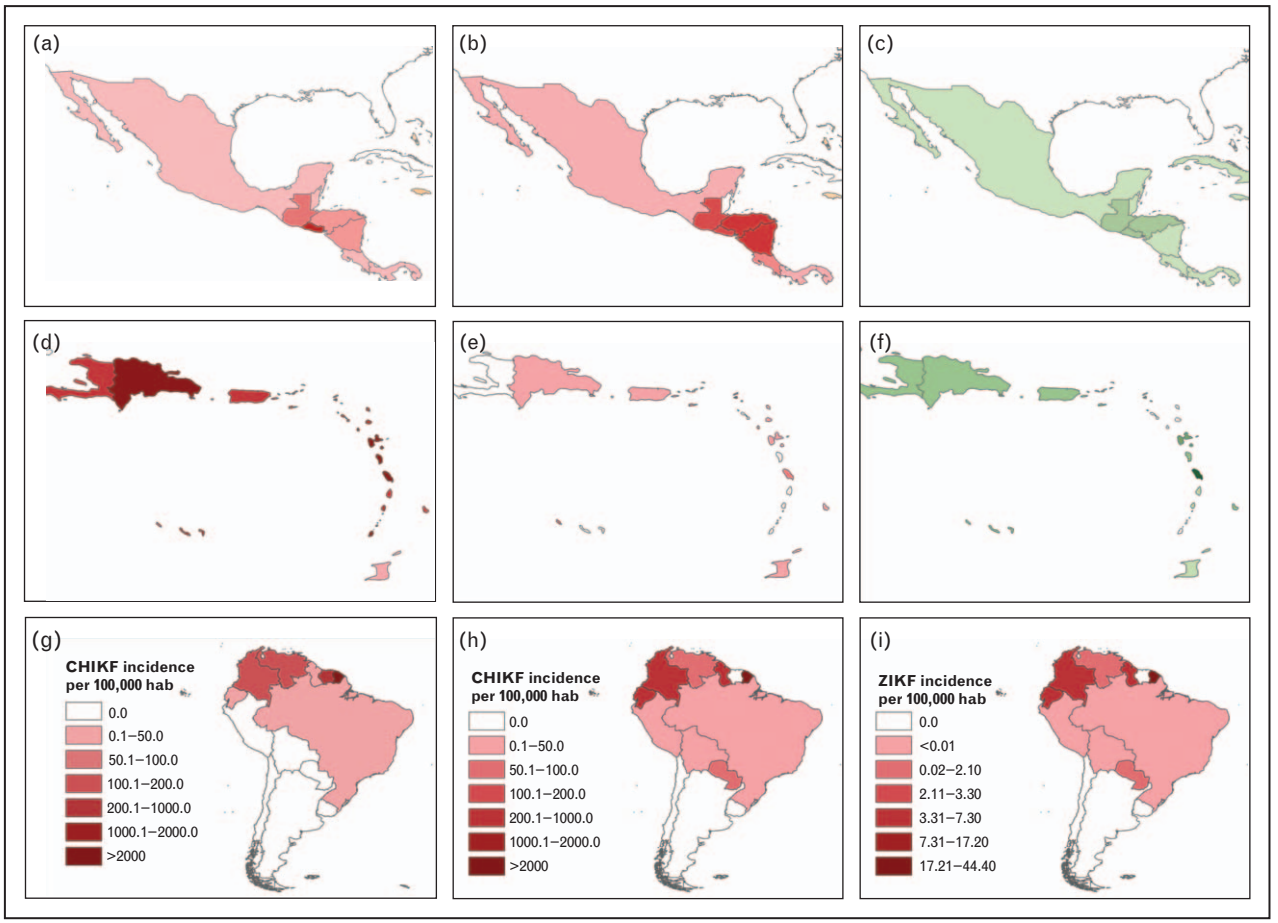

FIGURE 1. Rate incidences of chikungunya and zika virus in America. Central America and Mexico, Caribbean and South America maps displaying rates incidences of CHIKV in the years of 2014 (A, D, G) and 2015 (B, E, H) and ZIKV in the period of March 2015–April 2016 (C, F, I). CHIKF, chikungunya fever; CHIKV, chikungunya virus; ZIKF, zika fever. http://www.paho.org/hq/index.php?option=com_topics&view=article&id=343&Itemid=40931; http://ais.paho.org/phip/viz/ed_zika_cases.asp.

To date, Asian lineage of CHIKV is the only that has been circulating in the Caribbean since its introduction. Viral sequences of this lineage have been obtained from patients who resided in the British Virgin Islands and Trinidad being both closely related [12,13▪]. A theory that may explain the origin of Asian strain in the Americas is that CHIKV was introduced by human movement of tourism travellers and/or maritime trade from Asia. Months previous to the 2014 outbreak, 27.5% of tourism reported in the Caribbean came from China and Philippines [14] and ports in the Caribbean have served as intersections of East–West maritime trade routes linking Asia, America, Europe and the Middle East [15].

Spreading to mainland South and Central America

Although CHIKV had been attacking the Caribbean during the first 6 months since its introduction, the first eight autochthonous cases in the mainland America, specifically El Salvador, were officially reported in June 2014. One month later, Venezuela announced an outbreak of CHIKV with 30 autochthonous cases, and by September, CHIKV reached Colombia and Brazil reporting in both countries 42 and two autochthonous cases, respectively. A further dissemination of CHIKV continued in the rest of Central and South America countries during 2014. As the opposite occurred in Caribbean, the numbers of accumulated cases in Central and South America during 2014 were 172 736 and 133 773, respectively, being lower than 2015 numbers with 262 264 and 438 863 cases, respectively [8]. Brazil, Colombia and Venezuela accumulated most of the cases reported in South America (Fig. 1).

Transmission of CHIKV by Asian lineage has also been reported in Panama, Nicaragua, Colombia and Brazil [16,17,18▪▪,19▪▪], being all closely related to British Virgin Island strain from Caribbean;

however, up this moment, Brazil is the unique country across the continent that ECSA lineage has been circulating. This lineage was reported for the first time in the Feira de Santana State in June 2014, and according to epidemiological and phylogenetic data, it is believed that Brazilian ECSA lineage had an origin from Angola [19▪▪], a former Portuguese colony that is an important trade allied of Brazil and where thousands of Brazilians work for the oil and mining industry [20,21].

North America: migration, spillover in Southern Mexico, local transmission in Florida and potential risks for the rest of us

By September 2014, one month after the beginning of the El Salvador outbreak, CHIKV appeared in Guatemala Republic reporting just eight cases, one from Escuintla city that is located approximately 200 km from the Mexico–Guatemala border. CHIKV took only 1 month to reach a border community in Chiapas, Southern Mexico, causing an outbreak of 94 patients [22], but this was confirmed months later by the official announcement of one CHIKF case in November by Mexican Ministry of Health [23]. Illegal migration from Central America and commerce may have led the movement of infected patients to Chiapas through the Mexico–Guatemala border. During 2015, the outbreak was moving northward along Pacific and Gulf of Mexico Coast and towards Yucatan Peninsula causing hundreds of cases, but stagnated in Northern Mexico with few cases near the US–Mexico border [24]. An unusual prolonged heatwave in midsummer and a short rainy season afterwards may explain the low number of cases in this region because of the poor environmental conditions for *Ae. aegypti* breeding [25].

With regard to the US scenario, this country was the only one that had an appropriate surveillance system to collect CHIKV cases before 2013. The US reported 164 imported CHIKV cases between 1995 and 2013 mainly from travellers who visited Asia and Africa [26,27]. After CHIKV emergence in America, imported cases arose up to 400, which probably most of 236 reported during June 2014 had a history of travel to Caribbean [28]. Finally, Florida through CDC reported officially two autochthonous cases in July 2014, but similarly as Mexico, 1 month before, 11 autochthonous cases were collected but reported until December by Florida Department of Health [29▪]. The final figure of locally transmitted cases of CHIKF during 2014 was 12 cases, and since then, no autochthonous cases have been notified. The absence of local transmission of CHIKV in the US may be explained due to effective labour of vector control services performed by mosquito control districts throughout Southern US [30,31]. In addition, a strong heatwave in midsummer and a short period of rains afterwards in Northern Mexico during 2015 could have hold back the CHIKV outbreaks outside the US.

Clinical and entomological investigations during American outbreak

Clinical and epidemiological information generated in ongoing CHIKV epidemics in America has been limited to specific outbreaks, but clinical data have adjusted to previously report in clinical guides from PAHO and La Reunion outbreak investigations. Overall attack rate is unknown in the whole continent, but research in a children cohort in Nicaragua gave an estimate of 2.9%. However, it may be underestimated, as this age group usually presents symptoms of an undifferentiated fever [16].

Trinidad and Tobago, Colombia and Mexico have published the first clinical findings of their outbreaks in the continent during the 2014–2015 outbreaks [13▪,17,32]. All reported that the main symptomatology was fever (100%), headache (64–94%), sever polyartharlgia (83–88%), rash (33–66%) and myalgia (28–94%). Biochemical parameters have been barely measured during these outbreaks, being coagulation tests in normal ranges but leukopenia was observed in the Mexican study during the first 2 days of symptomatology onset. The clinic of CHIKF and dengue has been compared and was clearly observed that haemorrhagic symptoms and low platelet levels were more frequent in dengue than in CHIKF patients, and inversely, severe polyarthralgia and leukopenia were more common in CHIKF patients [32].

In regard of persistent arthralgia that has been observed in chronic phase of CHIKF, little information has been described within 2 years since its introduction in America. Preliminarily in Colombia, a follow-up of two cohorts of 39 and 131 CHIKV-confirmed patients from Sincelejo and Tolima, respectively, has reported the postchikungunya chronic arthralgia (pCHIK-CRA) in 89.7 and 44.3% and with median time of duration of 37 and 24 weeks, respectively [33▪,34▪]. Another brief report of pCHIK-CPA in imported cases from the US has found that 37% of travellers who had contracted CHIKV in the Caribbean had persistent arthralgia and myalgia [35]. These results have their sample size limitations and are not conclusive for the rest of American outbreaks, but lead to further investigations about the health and economic impact of prolonged arthralgia in the Continent using quantitative methodologies such as applying DAS-28 and WHODAS 2.0 to assess the articular damage and the health and disability, respectively.

Previous CHIKV emergence in America and vector populations from this continent were evaluated to prove their ability to transmit CHIKV under laboratory conditions. *Ae. aegypti* was competent for Asian and ECSA genotypes; however, the transmission efficacy of the emerging Indic Ocean Lineage (strain CHIKV_0621), which is derived from ECSA genotype, was higher in American populations of *Ae. albopictus* [36,37▪▪]. The most important vector during the American epidemic is probably *Ae. aegypti* because its distribution is extensive and wider than *Ae. albopictus* in tropical and subtropical regions from America [38]; it has been incriminated during outbreaks in Chiapas and Yucatan States [39▪,40▪] and has been found infected in domestic populations from Guerrero State, Mexico [41]; the transmission of Asian genotype is constrained mainly to *Ae. aegypti* [42]; and at the time of writing this manuscript, there is no evidence of the appearance of adaptive mutations to become *Ae. albopicuts* as an effective vector [43▪▪]. Countries with temperate regions where tiger mosquito breed, such as US and European countries, cannot discard a future role of *Ae. albopictus* as a CHIKV vector. The proven ability of CHIKV to evolve and adapt to a new vector should maintain surveillance activities focused on this mosquito.

ZIKA VIRUS: AN UNEXPECTED GUEST IN THE MIDDLE OF CHIKF PANDEMIC

While chikungunya outbreaks were affecting thousands of persons throughout America, another arbovirus unexpectedly emerged in the continent in spite of all efforts for vector control activities: zika virus. In the beginning of 2015, local transmission of ZIKV occurred in the Northeast of Brazil causing eight cases [18▪▪]. From this moment, the virus spread to South America (except Chile, Argentina, Uruguay and Peru), Caribbean, Central America and finally Mexico during 2015. Currently, the US and Canada have been free of ZIKV transmission, but the risk is latent. To date, a total of 227 929 suspected and 7698 confirmed cases of zika fever (ZIKF) have been reported in the whole continent. The countries that gather the most amount of cases are Brazil (30.4%), Colombia (29.1%), Venezuela (13.4%), Honduras (7.7%), Martinique (7.6%) and El Salvador (4.7%) (Fig. 1). Genetic evidence from some American strains exhibits that Asian genotype of ZIKV is currently circulating in America and the strains were most closely related to a 2013 isolate from French Polynesia into Asian clade. In the base of molecular evidence, the introduction of ZIKV could have taken place from infected patients who travelled since Pacific Islands had ongoing ZIKV outbreaks until Brazil [44▪▪].

In Mexico, only 239 cases have been reported since its introduction in November 2015 [45]. The majority of cases (235) were observed in Southern States of Mexico: Chiapas, Guerrero, Tabasco, Veracruz, Yucatan, Oaxaca, Michoacan, Jalisco and Nayarit. The Northern State of Nuevo Leon, which is part of the Mexico–US border, reported just four cases in 2015, but during 2016, none of the Border States with the US have had a ZIKV case. In the same way observed in the behaviour of CHIKV outbreak, ZIKV epidemic remained in Southern States of Mexico probably for the same reason of long heatwave during midsummer 2015 in Northern Mexico.

Vectorial and sexual transmission

ZIKV, like another member of genus *Flavivirus*, is a vector-borne disease transmitted mainly by *Aedes* mosquitoes. Sylvatic species of these genera have been involved in enzootic transmission and it is believed that urban vectors *Ae. aegypti* and *Ae. albopictus* have participated in the urban cycle of transmission in Africa and Asia before 2008. In Pacific epidemics of 2007–2013, *Ae. helsiinii* and *Ae. aegypti* were probable vectors of ZIKV because of their high presence in household environments during outbreaks [46▪]. The first incrimination of Ae. aegypti under natural transmission conditions was demonstrated at the end of 2015 in Southern Mexico. During the ZIKV outbreak in Tapachula, Chiapas, this vector was found infected in houses with ZIKV-confirmed patients. Partial NS5 sequences derived from sera of these patients had no more than one nt difference from the mosquito strains, confirming a transmission link. Suspicious role of Culex quinquefasciatus as a ZIKV vector has recently arisen but in this study was not found infected [47▪▪]. Entomological situation in America has offered to ZIKV the perfect scenario for rapid dissemination throughout the continent as similarly observed for CHIKV [24].

Apart from the vector–human–vector transmission cycle, a suspicion of another potential transmission mechanism has arisen in a report of US native who came back from Senegal sick of ZIKF and likely transmitted the virus to his wife through sexual intercourse [48]. In addition, viral particles have been detected in semen and urine in patients who had been infected by ZIKV days or weeks before [49▪▪,50▪▪,51▪]. It is unknown how this transmission mechanism is currently influencing ZIKV outbreaks in America.

Associated microcephaly: case reports and prelaminar case–control study in Brazil

Unexpectedly, an alarming rise of newborns with microcepahly begun to be observed during 2015.

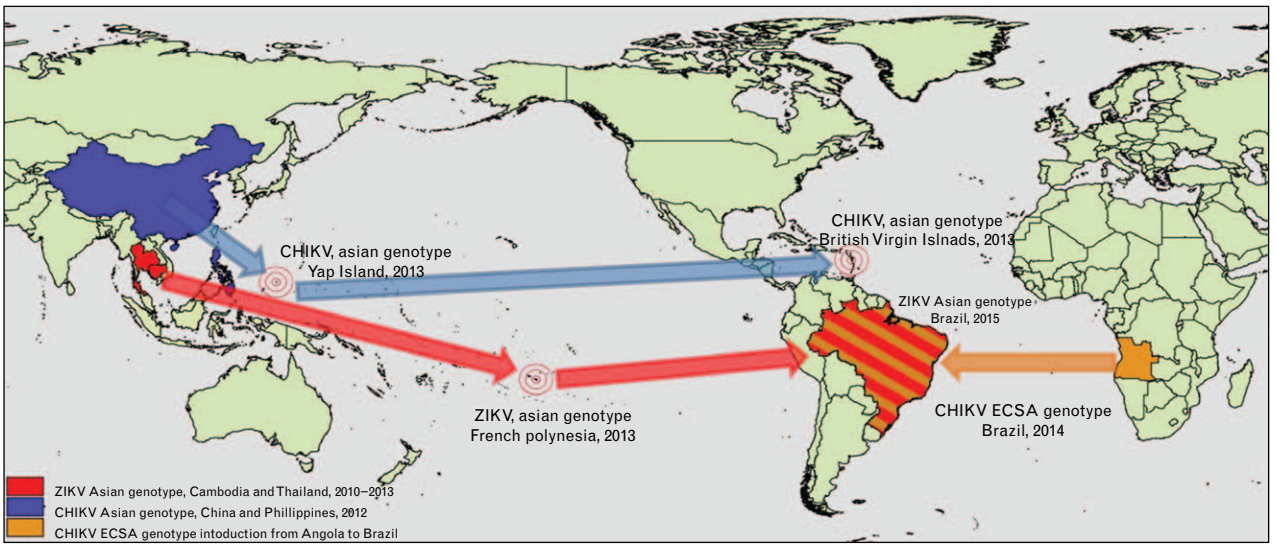

FIGURE 2. Probable pathway of the transcontinental movement of CHIKV and ZIKV through Asia–Pacific–America route and additionally the CHIKV ECSA genotype introduction from Africa according to recent phylogenetic analysis [19▪▪,43▪▪,56▪▪]. CHIKV, chikungunya virus; ZIKV, zika virus.

Early 2016, the incidence rate of microcephaly incremented 20-fold reaching 99.7 cases per 100 000 newborns of whom 76 have died [52▪]. At this moment, 5640 microcephaly cases have been reported of whom only 583 were born from a mother with a previous infection of ZIKV during her pregnancy [53]. Report cases have been described seeking ZIKV infection in pregnant women, miscarried foetus and deceased newborns with microcephaly. One study detected and sequenced the virus that was found in amniotic fluid from two pregnant Brazilian females who carried foetus with microcephaly [52▪]. Another report describes a Slovenian woman, who had sickened of ZIKF in the 13th week of gestation in Brazil, with interrupted pregnancy at the eighth month and the miscarried foetus with microcephaly showed evidence of infection in brain tissue [54▪▪]. Similar report of two foetal losses and two congenital ZIKV-infected newborns from Brazil confirmed the infection in brain tissue and also placental tissue had evidence of ZIKV infection from early miscarriages [55]. A preliminary case–control study was carried out in Brazil in a prospective cohort of 88 women of whom 72 (82%) were ZIKV-positive, but foetal ultrasonography was performed only in 42 women (58%). From these patients, foetal abnormalities were observed in 12 (29%) and none in ZIKV-negative pregnant woman. The abnormalities included foetal death, foetal growth restriction and mainly central nervous system (CNS) injuries [56▪▪]. Despite these evidences suggesting a likely association of ZIKV infection during pregnancy and microcephaly in foetus, full case–control studies are necessary to establish finally the causality of congenital malformations in the CNS by vertical transmission of ZIKV [57].

ASIAN–PACIFIC–AMERICAN ROUTE: THE PATHWAY OF CHIKV AND ZIKV

A similar transcontinental route has been traced by ZIKV and CHIKV according to recent phylogenetic studies. Although both viruses found in America belong to CHIKV and ZIKV Asian genotypes, they are more related with Pacific Islands of Yap strain (2013) and French Polynesia strain (2013), respectively [44▪▪,58▪▪]. Thus, both viruses crossed from Asia to Western Hemisphere using the Pacific Islands as a bridge (Fig. 2). Massive sport events such as World Cup Soccer and canoe tournaments have been proposed as the cause of ZIKV introduction to Brazil, but recent molecular findings suggest that large-scale patterns of human mobility explain better the introduction of ZIKV in America [59]. Therefore, human movement among continents serves as the appropriate pathway for CHIKV and ZIKV dissemination.

A LOOK INTO THE FUTURE: OTHER ARBOVIRAL THREATS, SAME VECTORS, SAME PATHS

During the annual outbreaks of DENV in the last two decades, CHIKV and ZIKV received little attention in that time. The magnitude of pandemics of these last

arboviruses was not expected and the consequences have been little encouraging: long-term disability by prolonged arthralgia, congenital malformations (microcephaly) and neurological disorders such as Guillain-Barré. Which is the scenario of vector-borne diseases in the following years? The horizon is shady, but there are other arboviruses waiting in the line. The Rockefeller Foundation granted surveillance programs of Yellow fever virus (YFV) and other arboviruses until 1970 and this initiative achieved important goals discovering new arboviruses, their ecology and human activity in Africa [60▪▪]. Potential emerging flavivirus, alfavirus and orthobunyavirus that probably cocirculated with ZIKV, CHIKV and YFV in the past would be the strongest candidates to become the most important vector-borne diseases in the future [61–72]. Within *Flavivirus,* Uganda S virus (UGSV), Wesselsbron virus (WESSV) and Kedougou virus (KEDV) were most commonly found in seroprevalence studies and they group into clades of *Aedes*-associated flavivirus [73]. Similar studies of *Alfavivurs*, Semliki Forest virus (SFV) and epidemic polyarthritis Ross-River virus and Barmah Forest viruses are potential arthalgic-virus transmitted by *Aedes*. Finally, the most common seroprevalent virus belonging to *Orthobunyavirus* genus is Bunyamwera virus (BUNV) and potentially transmitted by *Aedes* mosquitoes too [74]. Despite these studies being not conclusive because of the low specificity of serologic techniques used, ZIKV was also reported along these arboviruses.

In addition, there is an American arbovirus that has sporadically turned up from its enzootic cycles in Trinidad and Amazonas rainforests: Mayaro virus (MAYV). Another arthralgic virus related to CHIKV and SFV has recently emerged in Panama in 2016 and has the same urban potential to be dispersed [75]. A last question is in the air: will any of these known arboviruses have the same potential to be spread in urban transmission cycles worldwide such as DENV, CHIKV and ZIKV? What about unknown arboviruses? Only time will tell us.

CONCLUSION

Chikungunya and zika viruses, both transmitted by *Aedes aegypti,* have become an important public health issue favoured by lack of vaccines and efficient vector control methods. A new scenario of three different arboviruses cocirculating in the same regions has alarmed the academic community and new strategies should be proposed for the control of this vector. No matter how many vaccines could be developed, the risk of introduction of new arboviruses is always latent.

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Conflicts of interest

There are no conflicts of interest.

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- ▪▪ of outstanding interest

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